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A Peer-Reviewed Journal Tracking and Analyzing Disease Trends Vol.7, No.2, Mar–Apr 2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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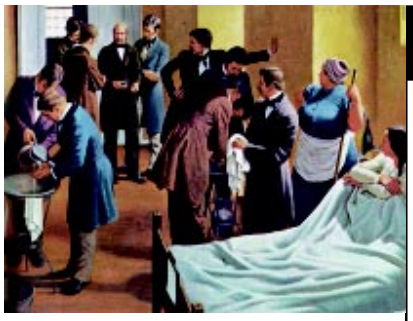

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4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections

Prevention is Primary

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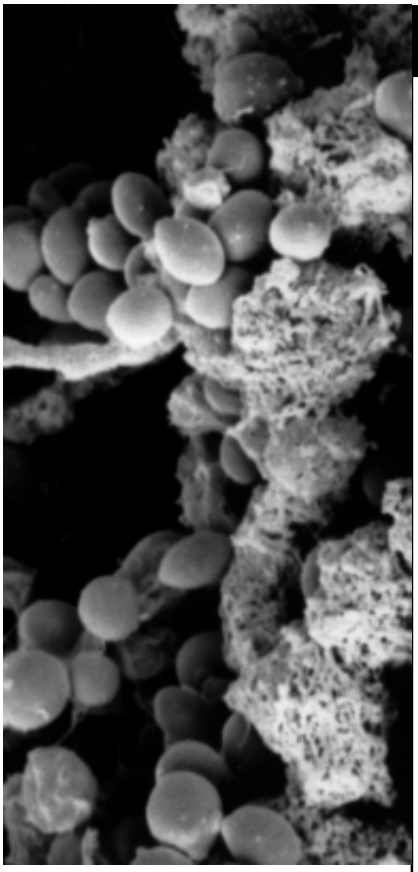

Electron micrograph of infected catheter (detail). See p. 343.

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Decennial Conference, cont'd.

About the 4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections

Steven L. Solomon
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

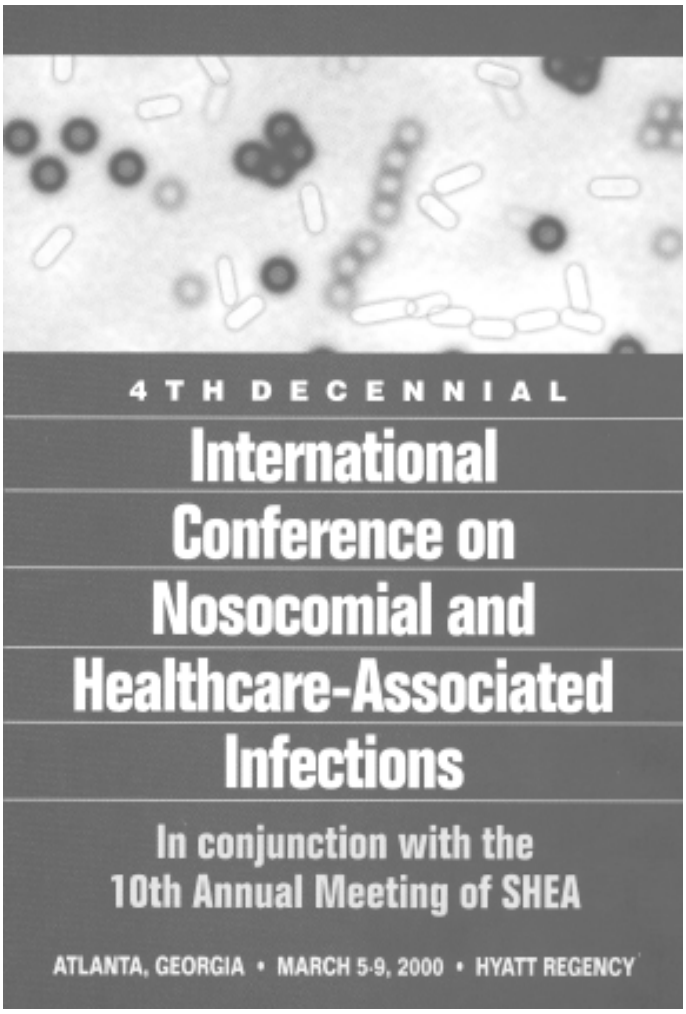
On March 5-9, 2000, 2,500 infection control professionals, epidemiologists, microbiologists, physicians, nurses, laboratory scientists, and other medical professionals from 55 countries convened in Atlanta for the Fourth Decennial International Conference on Nosocomial and Healthcare-Associated Infections. The goals of this conference, like those of its predecessors in 1970, 1980, and 1990, were to provide the latest scientific information in the field and help shape the agenda for research and prevention activities in the coming decade.

The theme of the conference was "Prevention Is Primary." More than 800 scientific papers, abstracts, and lectures were presented in 50 plenary sessions, symposia, panels, slide presentations, and poster sessions during the 5 days of the conference. The epidemiology, microbiology, and prevention of antimicrobial-drug resistant infections were recurring topics, as were new knowledge and current research on bloodstream infections, surgical site infections, and pneumonia associated with health care. Areas of particular emphasis included infection prevention in special populations, including pediatric, geriatric, and immunocompromised patients; infection control in nonhospital settings, including long-term care, home health care, and ambulatory care; preventing infections in health-care personnel; and new technologic developments in microbiology, the design and use of medical devices, facilities engineering, and information systems.

Each of the four decennial conferences has documented remarkable scientific advances and achievements in preventing and controlling infections associated with health care. Each conference has also presented the emerging challenges brought by each decade's changes in the epidemiology and microbiology of pathogens, the growing numbers of patients with increased susceptibility to infection, the rapidly increasing complexity of medical care itself, and the dramatic developments in the organization, structure, and financing of health care. Many speakers addressed topics that have evolved over three decades but continue to be vital areas of research and investigation, such as antimicrobial-drug resistance, device-associated infections, and surveillance. Also featured were presentations on subjects that have grown in prominence only in recent years: information technology, patient safety, health-care economics, outcomes research, and managed care.

In publishing the conference presentations in this journal, the organizers hope to capture the extraordinary breadth of the science in this area; maintain the ongoing record of advances in infection prevention and control during these past 30 years; and help promote research, demonstration, and evaluation efforts to improve health-care quality and to protect patients and health-care personnel from this continuing threat to their safety.

The conference was organized and sponsored by the Centers for Disease Control and Prevention, the Association for Professionals in Infection Control and Epidemiology, the Society for Healthcare Epidemiology of America, and the National Foundation for Infectious Diseases.



Acknowledgments

The organizers of the conference thank the Conference Publications Committee members: Steven L. Solomon (Chair), Elaine Larson, Loreen Herwaldt, J. Michael Miller, and William J. Martone, as well as CDC staff Machel Forney, J Shaw, and Denise Cardo, for their work in assembling the conference proceedings.

Infection Control and Changing Health-Care Delivery Systems

William R. Jarvis
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In the past, health care was delivered mainly in acute-care facilities. Today, health care is delivered in hospital, outpatient, transitional care, long-term care, rehabilitative care, home, and private office settings. Measures to reduce health-care costs include decreasing the number of hospitals and the length of patient stays, increasing outpatient and home care, and increasing long-term care for the elderly. The home-care industry and managed care have become major providers of health care. The role of specialists in health-care epidemiology has changed accordingly.

Over the past two decades, there has been a revolution in health-care delivery systems in the United States. The number of acute-care facilities has decreased, the proportion of patients requiring intensive care in acute-care facilities has increased, and the number of surgical procedures performed in outpatient settings or surgical centers has increased. Not only has there been a shift to the outpatient setting, but the long-term care, home-care, and managed-care industries have grown dramatically. I will provide an overview of recent changes in the U.S. health-care delivery system and describe the challenges for health-care epidemiology and infection control departments in the new millennium.

Changing Spectrum of Health-Care Delivery

In the 1970s and 1980s, the acute-care facility was the center of the hospital infection and infection control universe (1) (Figure 1). Most health care was delivered in the acute-care setting, and outpatient, long-term, and home care were relatively small, in number of facilities and patients. The growth of the U.S. gross domestic product (GDP) and the proportion spent on health care reflect changes in health-care delivery (Figure 2). From 1960 to 2000, the GDP grew nearly 15-fold, from approximately $526 billion to nearly $8,000 billion. At the same time, the proportion of the GDP expended on health care increased 41% to approximately $1,120 billion. This growth, together with the introduction of the prospective payment plan based on diagnostic-related groups, led to marked changes in hospitalization (Table 1). From 1975 to 1995, the number of hospitals decreased from 7,126 to 6,291, the number of hospital beds decreased from 1.47 million to 1.08 million, patient admissions decreased by 5%, hospital stay decreased by 36%, the average length of patient stay decreased by 33%, and the number of inpatient surgical procedures decreased by 27%. These trends have resulted in fewer and smaller hospitals, more and larger intensive care units, and greater severity of illness in the hospitalized population. At the same time, reports of nursing shortages and downsizing of infection control departments have been increasing, despite the fact that nearly 2 million hospital-acquired infections occur each year. Thus, the challenge for infection control departments in acute-care settings will be to focus surveillance activities on populations at high risk, calculate risk-adjusted rates of hospital-acquired infection,

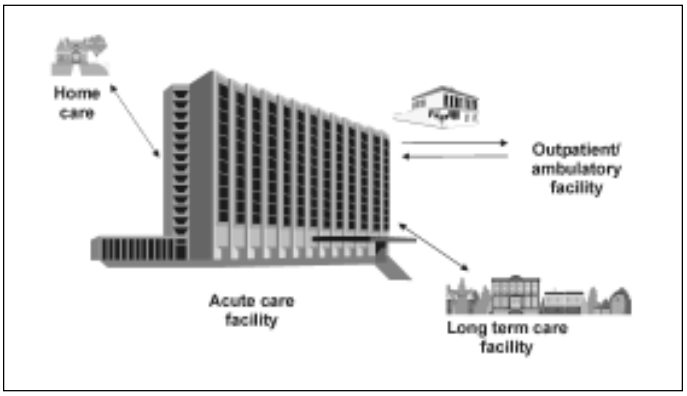

Figure 1. Health-care system of the past, 1970–1980

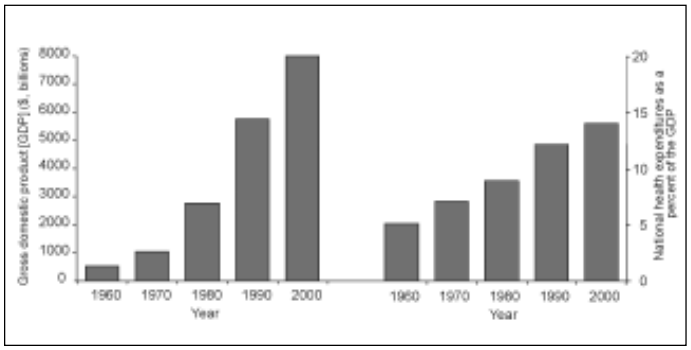

Figure 2. Distribution of U.S. gross domestic product (GDP) and proportion of GDP distributed as national health-care expenditures, 1960-2000. (Adapted from reference 5).

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Table 1. Changing epidemiology of health care in acute-care facilities

Characteristic	Year 1975	1995
Admissions	37,700,000	35,900,000
Patient-days	299,000,000	190,000,000
Length of stay	7.9 days	5.3 days
Inpatient surgical procedure	18,300,000	13,300,000

Adapted from reference 6 and unpublished data (CDC, Hospital Infections Program)

and provide feedback to appropriate personnel so that integrated prevention programs can be implemented and interventions evaluated to ensure quality health care (2-4).

Effects of the Aging Population

Since 1950, the number of persons >65 years of age in the United States has nearly tripled, from 12.2 million to 36 million. To accommodate this growth, the number of nursing homes increased from 16,091 in 1986 to 17,208 in 1996, and the number of beds in these facilities increased from 1.298 million to 1.839 million (Figure 3) (5). By 2035, the population of persons 65 years of age will exceed 80 million. In 1997, 1.6 million persons lived in long-term care facilities; by 2005, this figure will increase to an estimated 5 million. Since 3%-15% of such patients acquire an infection in these facilities each year, the 48,000 to 240,000 infections estimated to have occurred in 1997 will increase to an estimated 150,000 to 750,000 in 2005.

Challenges for infection control in long-term care facilities include the following: First, many facilities have no dedicated infection control personnel to conduct surveillance and lead prevention, education, and intervention programs. Second, uniform definitions and surveillance protocols are needed for infections acquired in long-term care facilities. Third, further studies are needed to determine the best numerator (e.g., number of infections, colonization, positive cultures, symptomatic or asymptomatic residents) and denominator (e.g., number of residents, number of resident-days, number of residents with a specific device or device-days) to use for infection rate calculations to facilitate inter- and intrafacility comparisons. Fourth, for many reasons, including lack of availability of laboratory facilities, failure of clinicians to order appropriate diagnostic work-ups, and inadequate reimbursement for diagnostic testing for infections, patients in long-term care facilities often are not evaluated for infection when they are symptomatic. (Rather, antimicrobial drugs are initiated on an empiric basis.) The influence of this reduced testing on detection of infections acquired in long-term care facilities needs to be assessed.

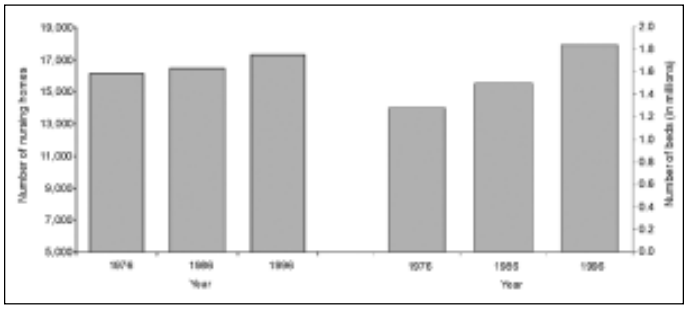

Figure 3. Number of nursing homes and nursing-home beds in the United States, 1976–1996. (Adapted from reference 5).

Emergence of Home Health-Care Delivery

The fastest-growing segment of the health-care delivery system has been the home health business. In 1988, the Health Care Financing Administration expended approximately $2 billion for home health. By 1999, approximately $20 billion was expended. Today, almost as many persons receive health care in the home (an estimated 34 million annually) as in acute-care settings.

Infection control in home-care settings poses the following challenges: 1) Few home health-care companies have dedicated infection control personnel. 2) No uniform definitions of infection or protocols for infection surveillance have been agreed upon. 3) Often health-care delivery in the home is uncontrolled and may even be provided by family members. 4) Health Care Financing Administration reimbursement schedules largely determine policies on the frequency of home health-care visits. 5) For some infection rates, such as central venous catheter-associated bloodstream infections, device-adjusted rates are needed for intra- and interfacility and company comparisons. Who will collect these data? How will the numerator (number of infections) be captured when the data may come from various sources, including the hospital, private physician offices, or private laboratories? Often these data are not reported to the home health-care company and thus may be very difficult to obtain. Although collecting these data from a single home health-care company is easier, many acute-care facilities contract with 10 to 20 home health-care companies and do not require in their contracts that such data (numerator, denominator, or rates) be provided. Thus, further studies are necessary to determine the data critical for measuring the quality of home health-care delivery and to identify which components of our infection control programs are essential.

At least initially, home health care and other infection control personnel should focus their efforts on high-risk infections, e.g., urinary tract, bloodstream, pneumonia, or skin and soft tissue infections. For specific infections, e.g., urinary tract and bloodstream infections, device-specific infection rates should be calculated. Uniform definitions applicable to home care, uniform surveillance protocols, and a national nonpunitive reporting system should be established so that rates can be compared.

Growth of Health Maintenance Organizations

Since 1976, managed care and health maintenance organizations in the United States have grown explosively. In 1976, there were approximately 174 health maintenance organizations in the United States (Figure 4) (5). By 2000, that number had grown to >700. Concomitantly, the number of persons enrolled in such plans increased from 6 million to >75 million, and the percentage of the U.S. population enrolled in such plans increased tenfold, from 2.8% to 29%. Because managed-care organizations focus their efforts on cost containment, the challenge for infection control personnel will be to demonstrate to administrative personnel that both quality care and cost containment are facilitated by improving infection surveillance and control programs.

Outpatient and Ambulatory Care

From 1993 to 1996, the annual number of visits to hospital outpatient clinics increased from 62.5 million to 67.1 million, the number of hospital emergency department visits remained stable at approximately 90 million, and the number

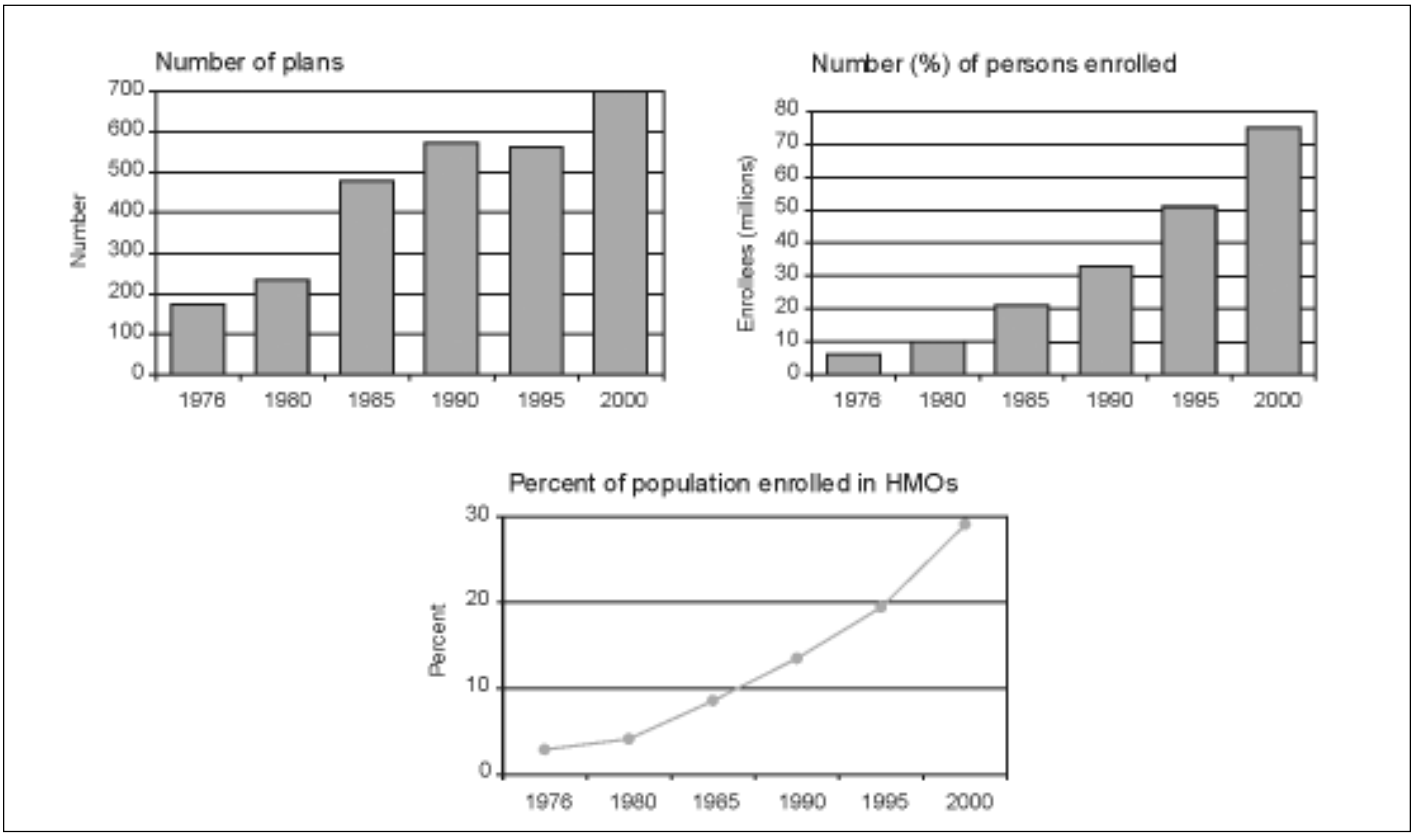

Figure 4. Growth of health maintenance organization (HMO) plans, enrollees, and percent of U.S. population enrolled in HMOs, 1976-2000. (Adapted from reference 5).

of physician office visits increased from 717 million to 734 million. Challenges for infection control personnel in outpatient and ambulatory-care settings include determining for which infections to conduct surveillance, what definitions to use, who will conduct the surveillance, to whom the data will be reported, and who will be responsible for implementing the changes. Often infection control personnel are not aware of what populations of patients are being seen or what procedures are being performed in outpatient settings. Furthermore, no systems are in place to collect the needed numerators (infections or adverse events) and denominators (e.g., number of patients with central venous catheters being seen in the clinic) data. To collect the data for these rate calculations, it will be necessary to identify methods, including electronic databases, whereby such data can be captured and used. Calculating infection or adverse event rates in outpatients and reporting them to ambulatory care and specialty personnel (e.g., the director of the oncology clinic) will be useful for improving education programs for health-care workers, as well as the quality of patient care.

Role of the Infection Control Professional

Infection control personnel play a critical role in preventing infections and medical errors. They conduct infection surveillance in acute-care facilities, apply standard definitions and surveillance protocols, calculate infection rates, report these data to essential personnel, implement prevention interventions, and evaluate their impact. Most importantly, as the Study of the Efficacy of Infection Control Programs (SENIC) has documented, the infection surveillance and prevention efforts of these infection control personnel are cost-effective (6).

Increasingly, infection control personnel have been expanding their activities to include prevention of infection and other adverse events in long-term care, home-care, and outpatient settings. If we are to prevent infections and other adverse events associated with the delivery of health care in the entire spectrum of health-care settings, we will need to expand the infection control departments in all these settings (Figure 5).

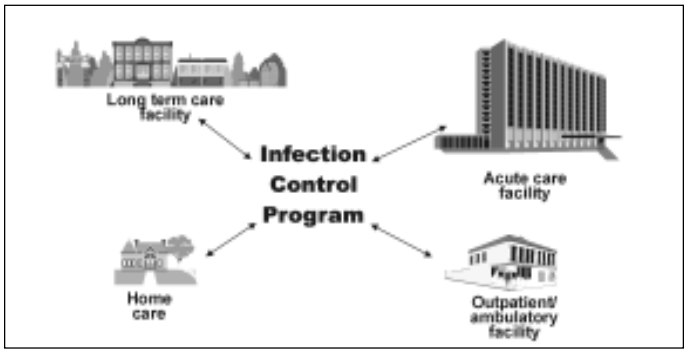

Figure 5. Model for comprehensive surveillance and prevention of health-care associated adverse events in the United States.

Conclusions

Over the past two decades, acute-care facilities have become smaller and fewer, but the hospitalized patient population has become more severely ill and more immunocompromised and thus at greater risk for hospital-acquired infections. At the same time, the proportion of the U.S. population ≥65 years of age has increased, as have the number of long-term care facilities and the number of beds in these facilities. This trend is expected to continue for the next 50 years. Similarly, delivery of health care in the home has become the most rapidly growing sector of the health-care system. Currently, nearly as many patients are receiving care in the home as in the inpatient setting. Provision of health care in managed-care and outpatient and ambulatory-care settings continues to expand. Thus, the spectrum of health-care delivery in 2000 is larger than ever before. Because of the severely ill and immunocompromised populations in these settings, prevention of infections and other adverse events is a major component of providing quality care.

In each of these settings, challenges need to be addressed. In acute-care settings, where the responsibilities of infection control departments already have markedly expanded (e.g., occupational health, prevention exposure to bloodborne pathogens, prevention of *Mycobacterium tuberculosis* or multidrug-resistant bacterial transmission, medical errors) during the past 2 decades, emphasis will need to be on conducting surveillance of populations at high risk, calculating device-specific infection rates, and educating health-care workers on infection control. In long-term care facilities, infection control personnel need to establish infection surveillance systems, determine baseline infection rates for comparison, improve device and antimicrobial drug use, and educate staff about prevention. In managed-care settings, infection control personnel will need to expand their efforts toward cost-effective infection surveillance and control programs. In the outpatient and ambulatory setting, infection control personnel will need to work with computer systems and clinic personnel to design information systems to improve collection of data about infections and other adverse events so that rates can be calculated and trends monitored. Because of their expertise in epidemiologic methods, infection control personnel can assist infection control, quality assurance, and medical error reduction programs in all these health-care system components.

Infection control personnel will need to expand their efforts to match the expansion of the health-care delivery system. Enhanced administrative support for programs to prevent infections and medical errors will be needed if we are to reduce the risk of infection and other adverse events and improve the quality of care in the entire spectrum of health-care delivery. Now, instead of the acute-care facility being the center of the infection control universe, the infection control department has become the center of the diverse health-care delivery system. Infection control departments will need to expand their surveillance of infections and adverse events and their prevention efforts to all settings in which health care is delivered.

Dr. Jarvis is associate director for program development, Division of Healthcare Quality Promotion* (formerly Hospital Infections Program), CDC, and president of the Society for Healthcare Epidemiology of America (SHEA).
*proposed

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The Impact of Hospital-Acquired Bloodstream Infections

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Nosocomial bloodstream infections are a leading cause of death in the United States. If we assume a nosocomial infection rate of 5%, of which 10% are bloodstream infections, and an attributable mortality rate of 15%, bloodstream infections would represent the eighth leading cause of death in the United States. Because most risk factors for dying after bacteremia or fungemia may not be changeable, prevention efforts must focus on new infection-control technology and techniques.

Vital statistics outlining the major causes of death in a population are an important measure of public health. Ranking disease agents according to the number of deaths they cause can be used for strategic planning and public health resource allocation. In the United States, vital statistics support efforts to control coronary artery disease, cancer, cerebrovascular diseases, and infections (Table 1) (1). A listing of causes of death, however, provides little insight on how the diseases were acquired or managed or how they might have been prevented. Infections acquired in the hospital are an important cause of death, especially those involving the bloodstream or lung (2).

If hospital infection and death occur at high rates, we can examine the process of institutional care: access to infection control personnel, systems for prevention and early recognition, and early and appropriate therapy. With improved care, improved outcome could be anticipated. We explore the impact of hospital-acquired infections, with a focus on bloodstream infections.

Baseline Data

Population-based surveillance studies of nosocomial infections in U.S. hospitals indicate a 5% attack rate or incidence of 5 infections per 1,000 patient-days (3-5). With the advent of managed care and incentives for outpatient care, hospitals have a concentrated population of seriously ill patients, so rates of nosocomial infections are probably correspondingly higher (6). For many larger institutions, the nosocomial infection rate may be closer to 10%.

Table 1. Deaths and death rates in the United States, 1997 (1)

Cause of death	No. of deaths (x 10^3)	Crude death rate (per 10^5)	% of all deaths
Heart disease	725.8	271.2	31.4
Malignancies	537.4	200.8	23.2
Cerebrovascular disease	159.9	59.7	6.9
Pneumonia and influenza	88.4	33.0	3.8
Septicemia	22.6	8.4	0.97

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If 35 million patients are admitted each year to the approximately 7,000 acute-care institutions in the United States, the number of nosocomial infections—assuming overall attack rates of 2.5%, 5%, or 10%—would be 875,000, 1.75 million, or 3.5 million, respectively. If 10% of all hospital-acquired infections involve the bloodstream, 87,500, 175,000, or 350,000 patients acquire these life-threatening infections each year.

Crude and Attributable Mortality Rates

The overall or crude rate of death does not distinguish the contribution of the patients' underlying diseases from the contribution of bloodstream infections. Recent data from the Surveillance and Control of Pathogens of Epidemiologic Importance [SCOPE] surveillance system of nosocomial bloodstream infections in U.S. hospitals identified a crude mortality rate of 27% (7), with great variation by pathogen (Figure 1).

The direct contribution of nosocomial infection, after the contribution of the underlying illnesses is accounted for, is the attributable mortality rate (8). For example, if a crude mortality rate for nosocomial candidemia of 40% is assumed (as in the SCOPE surveillance system [7]) and three-eighths of the deaths are directly due to the underlying diseases (15% of the 40%), the mortality rate attributable to candidemia would be 25% (40%-15%). Thus, candidemia would contribute five-eighths (25% of the 40%) of the crude mortality rate.

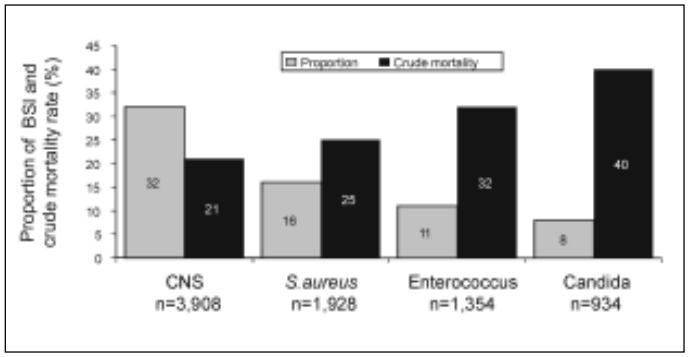

Figure 1. Variation in mortality rate by organism causing nosocomial bloodstream infection (7). The leading four organisms and crude mortality rate are illustrated.

Number of Deaths from Nosocomial Infections

Several assumptions may be examined simultaneously regarding the attack rate and both crude and attributable mortality rate estimates (Figure 2). By doing so, deaths directly attributable to nosocomial bloodstream infections can be calculated, with a range of very conservative to more liberal estimates based on available data. For example, with a hospital infection rate of 5%, of which 10% are bloodstream infections, and an attributable mortality rate of 15%, 26,250 deaths can be directly linked to nosocomial bloodstream infections. However, if a 20% attributable mortality rate is assumed, the number of deaths is from 17,500 (with a 2.5% nosocomial infection rate) to 70,000 (with a 10% total nosocomial infection rate).

With various assumptions about total nosocomial infection rates and attributable mortality rate, the ranking of nosocomial bloodstream infections among leading causes of death can be estimated (Figure 3). This ranking reflects the total number of deaths compared with the reported numbers of leading causes of death in the United States (1). From the above estimates, if nosocomial bloodstream infections alone were counted, they would represent the fourth to thirteenth cause of death in the United States.

The impact of nosocomial bloodstream infections can also be examined in terms of years of life lost. SCOPE (M. Edmond, pers. comm.) indicates that the median age of patients dying of nosocomial bloodstream infections is 57 years. If these patients are 60 years of age, without bloodstream infection they would have lived to age 70. This assumption is reasonable since only attributable deaths are included in the calculations (Figure 4). As an example, if the attributable mortality rate is 20% and the total nosocomial infection rate is 5%, the total number of years of life lost in the United States would be 350,000 annually. If the attributable mortality rate were only 10%, the number of years of life lost annually would be 87,500 to 350,000, depending on the total infection rate.

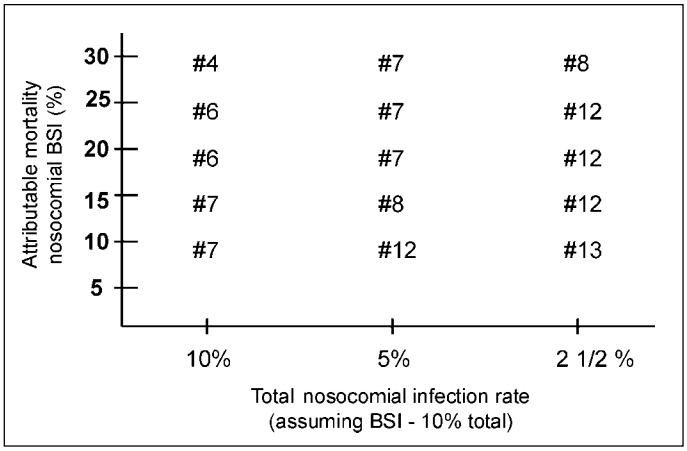

Figure 3. Leading causes of death are ranked according to attributable mortality rate and compared with number of deaths from leading causes in the United States (1).

Conclusions

The arguments above justify a major effort with substantial resources for preventing and controlling serious hospital-acquired infections. We suggest a quality assessment approach for hospital-based programs of infection control: structure, process, and outcome. The Study of the Efficacy of Nosocomial Infection Control (SENIC), published in 1985, showed that both structure (expertise) and process (surveillance, feedback and protocols) predicted lower infection rates (9). A subsequent analysis suggested that infection control programs represented one of the most cost effective of current public health efforts (10).

Access to improved infection-control technology is one of the promises at the dawn of the 21st century. Another is

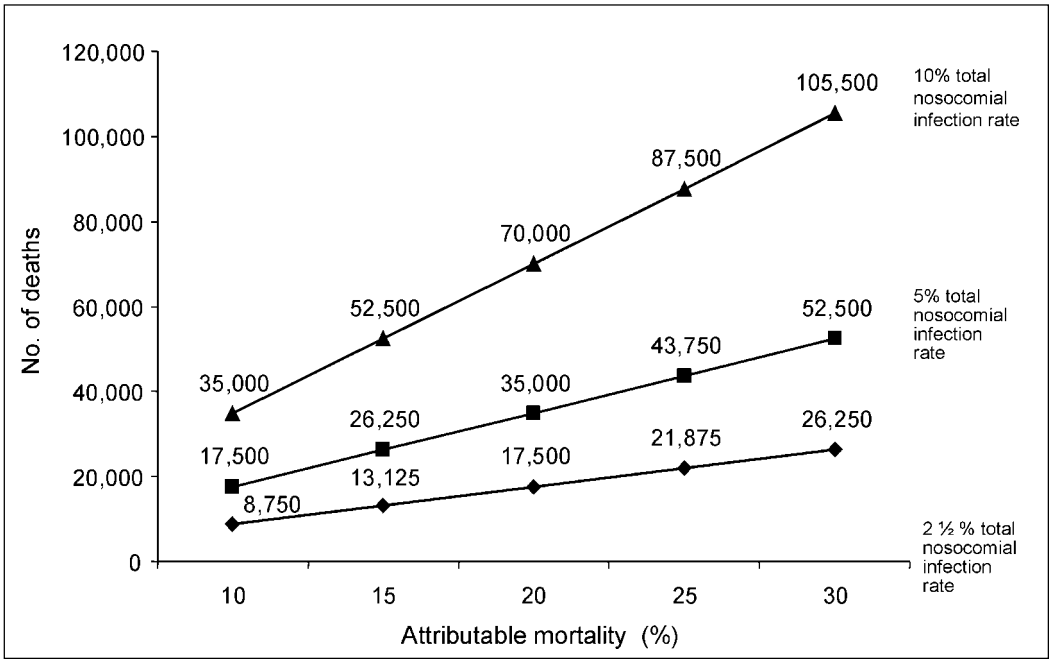

Figure 2. Estimated number of deaths caused by nosocomial infections in the United States each year. Attributable mortality rates are 10% to 30% on the X axis, and the three curves assume overall nosocomial infection rates of 2½%, 5%, or 10%.

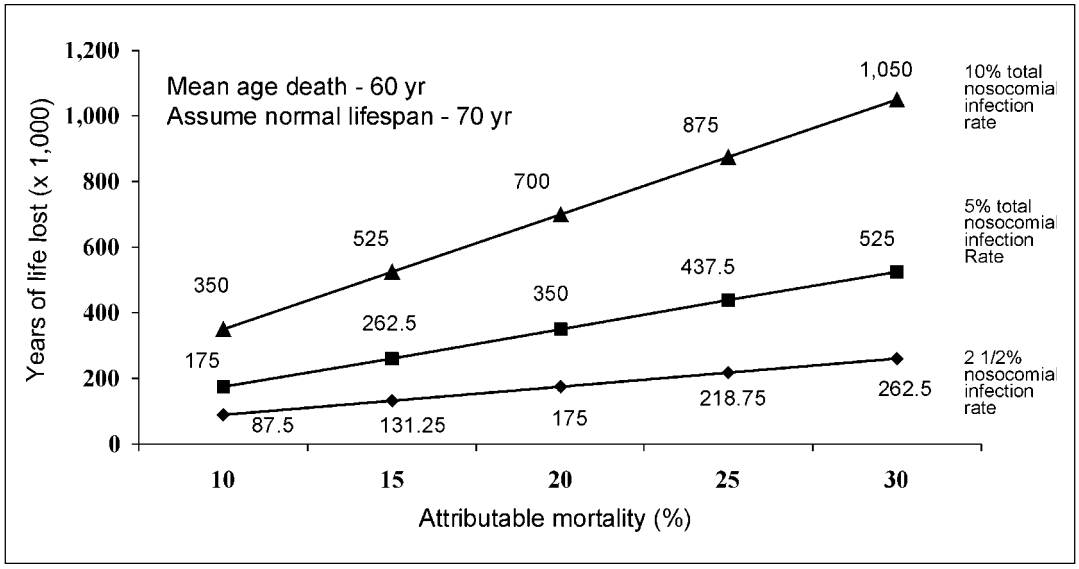

Figure 4. Years of life lost annually in the United States from nosocomial infections. Attributable mortality rates are 10% to 30% on the X axis, and the three curves assume overall nosocomial infection rates of 2½%, 5%, or 10%.

improved handwashing compliance associated with more attractive and accessible products. Two recent factors influencing infection control are use of antibiotic-bonded vascular catheters and access to alcohol hand-cleansing materials that improve handwashing compliance. In a multicenter study reported by Darouiche and colleagues, bloodstream infections were significantly reduced when patients received catheters bonded with rifampin and minocycline (11). Estimates of nosocomial bloodstream infections from the SCOPE database indicate that 70% occur in patients with central venous catheters (12). Furthermore, the study by Darouiche et al. showed that 90% of central venous catheter-associated infections could be prevented by antibiotic-bonded catheters. Assuming 200,000 total nosocomial bloodstream infections of which 35% are attributable to central venous catheters and assuming that 45% could be prevented with a catheter bonded with minocycline and rifampin, the number of lives saved according to varying attributable mortality rate estimates would be 4,745 to 9,450 (Table 2).

In a study of handwashing compliance by Bishoff and colleagues, handwashing frequency in a medical intensive-care unit (ICU) increased with access to an alcohol-based product (13). Previously, Doebbeling and colleagues showed that medicated soap solutions were more popular than alcohol preparations and thus were associated with reduced infection in intensive care units (14). The study by Doebbeling et al. showed that a 28% increase in handwashing frequency (with a higher volume of use of antiseptic soap) resulted in a substantial reduction in the rate of nosocomial bloodstream infections of 56/10,000 ICU admissions, by 45% for the attack rate and by 22% when incidence density was calculated (Table 3). In SCOPE, 49.4% of all nosocomial bloodstream infections occurred in intensive-care units. However, if 25%-50% of all

Table 2. Central venous catheter technology and nosocomial bloodstream infections and deaths

Attributable mortality rate (%)	Expected CVC[a]-related deaths from bloodstream infections[b]	No. of deaths remaining if new catheters prevent 45% of deaths	No. of lives saved
15	10,500	5,755	4,745
20	14,000	7,700	6,300
25	17,500	9,625	7,875
30	21,000	11,550	9,450

[a]CVC = Central venous catheter.
[b]Assumptions in this analysis: 200,000 bloodstream infections/year, 35% attributed to CVCs, 45% prevented with antibiotic-bonded catheters. Previous studies showed 175,000-350,000 nosocomial bloodstream infections/year, 70% of which were related to central venous catheters; 90% of central venous catheter-related bloodstream infections prevented with antibiotic bonded catheters (11).

Table 3. Handwashing and nosocomial bloodstream infections and deaths

Attributable mortality rate (%)	Expected deaths	No. of lives saves if 25% of BSI[a] occur in ICUs[b]	No. of lives saved if 50% of BSI occur in ICUs
15	1,875	469	938
20	2,500	625	1,250
25	3,125	781	1,562
30	3,750	937	1,874

[a]BSI = Bloodstream infections; ICU = Intensive-care unit.
[b]Assumptions in this analysis: 50,000 (25%) or 100,000 (50%) of BSI occur in ICUs, and a 25% increase in handwashing prevented 25% of BSIs. Known (14): In ICUs, a 28% increase in handwashing was related to a reduction of risk of BS1 of 56/10,000 ICU admissions, a reduced attack rate of 45%, and a reduced incidence density rate of 22%.

bloodstream infections occur in intensive-care units and a 25% increase in handwashing would prevent 25% of bloodstream infections in ICUs, the number of lives saved would be 469 to 1,874, depending on assumptions of attributable death rate (Table 3). The emerging concept is that increased handwashing frequency will result in an improved outcome. Perhaps most striking is that in this selected comparison of the impact of changes in technology with changes in behavior, the former will likely be 5 to 10 times more effective, but at substantially increased cost. Neither, however, is mutually exclusive, and both need to be in place.

In summary, vital statistics list the major causes of death yet give little insight into environmental risk factors for disease or outcomes. Estimates of hospital-acquired bloodstream infections derived from the attributable mortality rate show the impact of the specific environment where many life-threatening infections occur. By modifying the institutional environment to improve hospital care and infection control, the outcomes for patients will greatly improve. Technological advances will likely have a greater impact on health than theoretical advances in behavior, such as improved handwashing frequency.

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The Changing Epidemiology of *Staphylococcus aureus*?

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Strains of methicillin-resistant *Staphylococcus aureus* (MRSA), which had been largely confined to hospitals and long-term care facilities, are emerging in the community. The changing epidemiology of MRSA bears striking similarity to the emergence of penicillinase-mediated resistance in *S. aureus* decades ago. Even though the origin (hospital or the community) of the emerging MRSA strains is not known, the prevalence of these strains in the community seems likely to increase substantially.

Recent reports of strains of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from children in the community have led to speculation that the epidemiology of *S. aureus* is changing (1-3). Epidemiologic features of the cases described in these reports show a major departure from features typically associated with MRSA colonization or infection. Traditionally, MRSA infections have been acquired almost exclusively in hospitals, long-term care facilities, or similar institutional settings (4). Risk factors for MRSA colonization or infection in the hospital include prior antibiotic exposure, admission to an intensive care unit, surgery, and exposure to an MRSA-colonized patient (4,5).

Humans are a natural reservoir for *S. aureus*, and asymptomatic colonization is far more common than infection. Colonization of the nasopharynx, perineum, or skin, particularly if the cutaneous barrier has been disrupted or damaged, may occur shortly after birth and may recur anytime thereafter (6). Family members of a colonized infant may also become colonized. Transmission occurs by direct contact to a colonized carrier. Carriage rates are 25% to 50%; higher rates than in the general population are observed in injection drug users, persons with insulin-dependent diabetes, patients with dermatologic conditions, patients with long-term indwelling intravascular catheters, and health-care workers (7). Young children tend to have higher colonization rates, probably because of their frequent contact with respiratory secretions (8,9). Colonization may be transient or persistent and can last for years (10).

When cases of MRSA infection have been identified in the community, a thorough investigation usually reveals a history of recent hospitalization; close contact with a person who has been hospitalized; or other risk factors, such as previous antimicrobial-drug therapy (11,12). In the 1980-1981 outbreak of community-acquired MRSA infections in Detroit (13,14), approximately two thirds of the patients affected were injection drug users. Previous antimicrobial therapy was associated with infection by a strain of MRSA. Recent hospitalization, defined as within 4 months (which may not have been long enough, given that hospital-acquired MRSA colonization may last years [10]), was not a predictor of MRSA infection in the drug users; however, the epidemic strain had the same phage type as a strain of MRSA responsible for an outbreak in a burn unit in Minnesota in 1976 (15). The source of the Detroit outbreak was not identified. Frequent needle sharing was speculated to be the mode of transmission in the community. In contrast to infection in injection drug users, MRSA infection in nonusers was strongly associated with recent hospitalization, which suggests that drug users had become colonized during a previous hospital admission. In turn, patients (and probably health-care workers, who become colonized with MRSA as a consequence of their exposure to colonized patients) in a hospital or other health-care setting can then transmit MRSA strains to close associates and family members by direct contact.

Direct or indirect exposure to an institutional health-care setting in which MRSA is likely to be found and other risk factors typically associated with MRSA colonization are strikingly absent from the recently described cases in which MRSA seems to have been acquired from a community reservoir. The antimicrobial susceptibility patterns observed for these MRSA strains are further evidence of a possible community origin. Unlike hospital strains, which typically are resistant to multiple antibiotics and can be shown by typing schemes to be related to other hospital strains, these so-called community strains have tended to be susceptible to other antibiotic classes and often are resistant only to beta-lactam antibiotics (1,2,9). The lack or loss of resistance to multiple antibiotics suggests a community origin because antibiotic selective pressure is much lower within the community than in hospitals, and the survival advantage of multiple-drug resistance is lower. Typing by pulsed-field gel electrophoresis (PFGE) also suggests that these strains are distinctive.

Emergence of Penicillinase-Producing *S. aureus*

Whether their appearance in the community and their susceptibility to antibiotics other than beta-lactams are fundamental changes in MRSA epidemiology is debatable. The epidemiology of MRSA and the factors driving resistance bear strong similarities and parallels to those occurring with

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penicillin-resistant strains of *S. aureus* in the 1940s and 1950s. When Kirby's first description of penicillinase-producing strains of *S. aureus* was published in 1944 (16), resistance was infrequently encountered, with only a handful of strains available for study. As with MRSA, penicillinase-producing strains first were isolated from hospitalized patients (17). Community strains tended to be penicillin susceptible. The prevalence of penicillinase-producing strains of *S. aureus* within hospitals soon began to rise as penicillin became readily available after World War II. Within a few years, most hospital isolates were resistant to penicillin (17). As was observed decades later with MRSA, previous treatment with a beta-lactam antibiotic, in this case penicillin, increased the chances of isolating a penicillin-resistant strain. Colonization of hospital staff by penicillin-resistant strains and their role in transmission also were notable features of these early reports.

Although penicillinase-producing strains were universally present in hospitals by the early 1950s, community isolates of *S. aureus* were considered to be largely penicillin susceptible. Penicillin continued to be recommended as an effective anti-staphylococcal agent as late as the early 1970s (18). However, then as now, there was no systematic surveillance for antibiotic resistance among *S. aureus* isolates circulating within communities. The first comprehensive description and accurate assessment of the epidemiology of drug-resistant strains of *S. aureus* were published in 1969 by Jessen et al. (19). Examination of more than 2,000 blood culture isolates of *S. aureus* received at the Statens Seruminstitut in Copenhagen for 1957 to 1966 for which detailed information on the origin of infection (hospital or community) was available confirmed a high prevalence of penicillin resistance (85% to 90%) for hospital isolates of *S. aureus*. Somewhat unexpected was that penicillinase-producing strains were almost as common in the community, with 65% to 70% of isolates resistant to penicillin. The community-acquired isolates often were resistant only to penicillin, whereas nosocomial strains typically were resistant to multiple antibiotics.

By the 1970s, it was apparent that the high prevalence of penicillin resistance among community isolates was not limited to Denmark. A remarkably constant 70% to 85% prevalence of penicillinase-producing strains was found regardless of location in inner cities, suburbs, rural areas, within and outside the United States (8,20,21). A population-based study conducted in 1972 revealed that 47% of healthy school-aged children under 10 years of age were carriers of *S. aureus* and that 68% of colonizing strains were penicillin-resistant (8).

Staphylococcal resistance was reported shortly after penicillin was introduced, and within approximately 6 years, 25% of hospital strains were resistant (Table 1). One to two decades later, 25% of community isolates were penicillin resistant (22, 23). Although the rates are only approximate because they are based on reports from numerous locations, a clear correlation exists between the prevalence of penicillin-resistant strains of *S. aureus* reported in hospitals and rates in the community (Figure). The upswing in community rates followed soon after nosocomial rates exceeded 40% to 50%, and by the 1970s, the two rates were practically equal.

Table 1. Time required for prevalence rates of resistance to reach 25% in hospitals

Drug	Year drug introduced	Years to report of resistance	Years until 25% rate in hospitals	Years until 25% rate in community
Penicillin	1941	1-2	6	15-20
Vancomycin	1956	40	?	?
Methicillin	1961	<1	25-30	40-50 (projected)

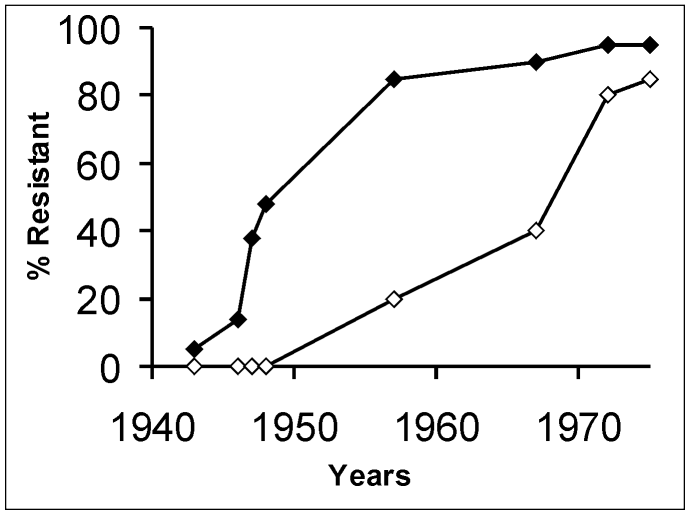

Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

Community-Acquired MRSA

In the past two decades, the prevalence of MRSA strains has steadily increased in hospitals in the United States and abroad. National Nosocomial Infections Surveillance (NNIS) data collected by the Centers for Disease Control in the early to mid-1980s indicated that MRSA was limited mainly to relatively large urban medical centers and that rates were 5% to 10%. Smaller, nonreferral centers were relatively free of MRSA, with prevalence rates well below 5%. By the 1990s, rates among these smaller (<200-bed) community hospitals had increased to 20%, and twice that rate was found in the larger urban centers. More recent surveillance data from NNIS indicate that rates have continued to rise, with the prevalence of MRSA isolates from intensive care units approaching 50% by the end of 1998. Unless this upward trend has reversed, the prevalence rate of MRSA in U.S. hospitals likely has reached 50%. At these high rates, the emergence of correspondingly high rates of MRSA strains in the community can be anticipated. Because no systematic, population-based surveillance of community isolates of *S. aureus* exists, the true prevalence of MRSA cannot be determined. One hospital-based study found that up to 40% of MRSA infections in adults were acquired before admission to the hospital (24). Published reports of MRSA colonization and infection among study participants who lack traditional risk factors indicate that community prevalence rates are rising. For the period 1976 through 1990, a Medline search identified 10 articles in which key words "methicillin-resistant *Staphylococcus aureus*" and "community" appeared in the

title (Table 2). For the period 1991 through 1999, 39 articles were identified; 29 were published from 1996 through 1999. A community-based survey of injection drug users in the San Francisco Bay area communities found that up to 35% of *S. aureus* carriers harbored MRSA (Table 3).

In early reports, community isolates of MRSA had affected persons with known risk factors for colonization (contact with health-care facilities, previous antimicrobial therapy), whereas more recent reports describe colonization and transmission in populations lacking risk factors. A recent study of methicillin-resistant *S. aureus* carriage in children attending day-care centers is reminiscent of Ross's survey of healthy children colonized with penicillin-resistant *S. aureus* strains two decades earlier (9). This survey of two day-care centers in Dallas, Texas, each of which had an index case of MRSA infection, revealed that 3% and 24% of children in the respective centers were colonized. The isolates generally were susceptible to multiple antibiotics, which is in contrast to the typical, multiple-drug-resistant hospital isolate. Forty percent of the children colonized had had no contact with a health-care facility or a household member with such contact within the previous 2 years, which suggests that sustained transmission and colonization of MRSA in children were occurring in the community. A study from Chicago found a 25-fold increase in the number of children admitted to the hospital with an MRSA infection who lacked an identifiable risk factor for prior colonization (1). These MRSA strains, also presumably transmitted and acquired in a community setting, tended to be susceptible to multiple antibiotics. Two examined strains had PFGE patterns that were distinct from the common nosocomial isolates.

Table 2. Estimated prevalence of methicillin-resistant *Staphylococcus aureus* strains in U.S. hospitals and publications[a] pertaining to community-acquired methicillin-resistant *S. aureus*

Years	Hospital prevalence rate (%)	Total no. of articles	No. of articles pertaining to children	No. of articles pertaining to other groups
1996-1999	40	29	8	3 (seniors, rugby team, wrestlers)
1991-1995	28	10	0	0
1986-1990	20	5	1	0
1981-1985	5	5	0	4 (addicts)
1976-1980	<5	0	0	0

[a]Identified by Medline search.

Table 3. Outpatient population-based prevalence of *Staphylococcus aureus* carriage and percentage of carriers with methicillin-resistant (MRSA) strains among injection drug users

Location	*S. aureus* carriage (%)	Carriers with MRSA (%)
San Francisco		
Western addition	25	16
Tenderloin	20	21
Mission	34	35
Bayview	23	12
East Bay		
Oakland	18	12
Richmond	20	6

The deaths of four children from rural Minnesota and North Dakota caused by infection with community-acquired MRSA strains brought the problem to national attention in 1999 (2). These children, like those in the Chicago study, lacked risk factors for MRSA infection. The infections were caused by strains susceptible to several antibiotics, except beta-lactams. The PFGE patterns of these strains indicated that they were related to one another but differed from typical nosocomial isolates circulating in local hospitals.

These reports of infection and colonization by strains of MRSA in children provide compelling evidence that MRSA strains, like penicillinase-producing strains almost 30 years ago, have gained a foothold in the community and are emerging as important outpatient pathogens. Based on the experience with penicillin-resistant strains, prevalence of MRSA among community isolates may be as high as 25% within the next 5 to 10 years (Table 1).

Origins of Community-Acquired MRSA

The origins of these community-acquired strains are subject to debate. One possibility is that they are feral descendants of hospital isolates. If so, these isolates must have undergone considerable change because they possess distinctive PFGE patterns and have lost resistance to multiple antibiotics. Another possibility is that the community isolates arose as a consequence of horizontal transfer of the methicillin-resistance determinant into a formerly susceptible background. This possibility could also account for the unique PFGE patterns and lack of resistance to multiple drugs. In the case of penicillinase-mediated resistance, dissemination of strains from the hospital and horizontal transfer of the penicillinase gene into susceptible recipient strains were both likely to have contributed to emergence of penicillin-resistant strains in the community. Penicillinase typically is plasmid encoded and can be readily transferred by transduction or conjugation. These characteristics account for methicillin-susceptible, penicillinase-producing strains being genetically diverse and polyclonal.

Unlike plasmid-encoded penicillinase, the methicillin resistance determinant, *mec*, is chromosomally encoded. Horizontal transfer of *mec* is thought to be relatively rare; only a handful of ancestral strains account for all clinical isolates worldwide (25). Ribotyping (a genotyping scheme that uses Southern blot analysis to identify DNA restriction enzyme polymorphisms of the five to six ribosomal RNA genes distributed throughout the *S. aureus* chromosome) and cluster analysis indicate that *mec* has integrated into at least three distinct methicillin-susceptible chromosomal backgrounds, A, B, and C (26, 27). *mec* itself is polymorphic; three types have been identified: I, II, and III. These polymorphs differ in number of base pairs, genetic organization, number of insertion sequences, and resistance determinants (Table 4). All three mec types have been found integrated into ribotype cluster A. Type II *mec* has also integrated into cluster B and C ribotype backgrounds. Thus, five distinct clones of MRSA have been identified worldwide since the first strain was isolated in the United Kingdom in 1961; even if more clones were identified, the relatively low number pales in comparison to the large number of distinct clones of methicillin-susceptible clones.

Table 4. Elements found within three types of *mec*-associated DNA

Genetic feature[a]	*mec* types I	II	III
Size	32 kb	52 kb	60 kb
mecA	+	+	+
mecR1-mecI	-	+	+
ccrAB	+	+	+
pUB110	-	+	-
IS431 (number)	1	2	4
Tn554 (number)	0	1	2
Tc, Hg resistance	-	-	+

[a]mecA = gene encoding PBP 2a, the penicillin-binding protein with low binding affinity that mediates methicillin resistance; *mecR1-mecI* = sensor-transducer and repressor genes that regulate production of inducible PBP 2a; *ccrAB* = cassette chromosome recombinases A and B that mobilize the *mec* element; pUB110 = integrated plasmid that encodes tobramycin and kanamycin resistance; IS431 = insertion sequence; Tn554 = erythromycin-resistance encoding transposon; Tc = tetracycline-resistance determinant; Hg = mercury-resistance determinant.

Unlike the mechanisms responsible for horizontal transfer of penicillinase resistance, the mechanism by which *mec* might be mobilized and transferred had not been understood until recently. Hiramatsu and co-workers have identified two genes, *ccrAB* (cassette chromosome recombinase genes A and B), which are homologous to DNA recombinases of the invertase-resolvase family and can mobilize *mec* (28). The proteins encoded by these genes catalyze precise excision and precise site-specific and orientation-specific integration of *mec* into the *S. aureus* chromosome. Thus, *mec* is somewhat analogous to the pathogenicity islands found in gram-negative bacilli, except that this locus encodes resistance determinants instead of virulence factors. How an element as large as *mec* is transferred from donor to recipient is not known. Nevertheless, as the prevalence of MRSA strains has increased, so has the abundance of *mec* DNA. Even though transfer of *mec* occurs rarely, the chances that it might occur have correspondingly increased. The community-acquired strains could possibly have arisen as a consequence of one of these rare transfers of *mec* from a nosocomial donor into a susceptible recipient. With appropriate analysis of *mec* DNA and the recipient chromosome, researchers should be able to determine whether these newly identified community-acquired strains are feral or freestanding. Regardless of the origins, which are likely to become obscured as clones move back and forth between hospital and community over time, emergence of MRSA within the community is a major threat with several important clinical implications: treatment failure with accompanying complications or death may result if an antistaphylococcal beta-lactam antibiotic is used and the infecting strain proves to be resistant; infections caused by methicillin-resistant strains may be more difficult to manage or more expensive to treat, perhaps because vancomycin is inherently less efficacious (29-33); and the increasing prevalence of MRSA will inevitably increase vancomycin use, adding further to the problem of antibiotic-resistant gram-positive bacteria.

Antimicrobial resistance to penicillin, methicillin, or vancomycin is an unavoidable consequence of the selective pressure of antibiotic exposure. Although the details of the epidemiology of staphylococcal drug resistance may change, the fundamental forces driving it are similar. The question is not whether resistance will occur, but how prevalent resistance will become. Minimizing the antibiotic pressure that favors the selection of resistant strains is essential to controlling the emergence of these strains in the hospital and the community, regardless of their origins.

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Emergence of Vancomycin-Resistant Enterococci

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Vancomycin and ampicillin resistance in clinical *Enterococcus faecium* strains has developed in the past decade. Failure to adhere to strict infection control to prevent the spread of these pathogens has been well established. New data implicate the use of specific classes of antimicrobial agents in the spread of vancomycin-resistant enterococci (VRE). Extended-spectrum cephalosporins and drugs with potent activity against anaerobic bacteria may promote infection and colonization with VRE and may exert different effects on the initial establishment and persistence of high-density colonization. Control of VRE will require better understanding of the mechanisms by which different classes of drugs promote gastrointestinal colonization.

Enterococci are important nosocomial pathogens (1,2). Their emergence in the past two decades is in many respects attributable to their resistance to many commonly used antimicrobial agents (aminoglycosides, aztreonam, cephalosporins, clindamycin, the semi-synthetic penicillins nafcillin and oxacillin, and trimethoprim-sulfamethoxazole) (3). Exposure to cephalosporins is a particularly important risk factor for colonization and infection with enterococci (4-6). Thus, the era in which safe and effective cephalosporins became widely available has also been an era of enterococcal ascendance.

Ampicillin Resistance

Ampicillin is the therapy of choice for enterococcal infections. Ampicillin MICs for *Enterococcus faecalis*, the most commonly isolated enterococcal species from clinical cultures, generally are 0.5 to 4.0 µg/mL, whereas for the less commonly isolated *E. faecium*, MICs are 4 to 8 µg/mL. *E. faecalis* and *E. faecium* account for >95% of enterococcal isolates from clinical cultures. Low-level ampicillin resistance in enterococci is attributable to the production of a low-affinity penicillin-binding protein (PBP), PBP 5 (7). PBP 5s have been identified in several enterococcal species. Those of *E. faecalis*, *E. faecium*, and the closely related *E. hirae* demonstrate <75% nucleic acid identity, but the fact that antibodies raised against one bind to all three suggests substantial structural similarity (8).

Increased ampicillin resistance in enterococci is attributable to either the production of beta-lactamase or alterations in the expression or structure of PBP 5. Beta-lactamase production has been described almost exclusively in *E. faecalis* and is attributable in most cases to the acquisition of the *Staphylococcus aureus* beta-lactamase operon (9-11). Beta-lactamase production occurs at a low level in enterococci, conferring a minor increase in MIC at standard inoculum. MIC increases more dramatically at high inoculum, however, and animal studies suggest that expression of this determinant may affect the outcome of endocarditis (12).

Ampicillin resistance resulting from changes in PBP 5 is primarily a clinical problem in *E. faecium*. The first detailed information about PBP 5-mediated ampicillin resistance arose from several lines of investigation. Williamson et al. noted that penicillin resistance expressed by *E. faecium* was related to the amount and the affinity of PBP 5 (13). The observation that enterococci could grow normally in penicillin concentrations enough to saturate all the PBPs, except PBP 5, suggested that PBP 5 was capable of carrying out all the functions necessary for cell-wall synthesis. Eliopoulos et al. derived a hypersusceptible mutant of a clinical *E. faecium* strain and noted that it no longer produced detectable amounts of PBP 5 (14). Subsequent studies confirmed that the lack of PBP 5 expression in this mutant was due to loss of the *pbp5* gene (15). Fontana et al. described in vitro mutants of *E. hirae* 9790 that expressed increased levels of resistance to ampicillin (MIC 64 µg/mL) (16). These mutants were found to produce increased quantities of PBP 5. In the initially analyzed strain, increased PBP 5 production was associated with a deletion within an upstream open reading frame that was characterized as a penicillin-binding protein synthesis repressor (psr) (17). A more recent study suggests that psr may serve as a global regulator of cell-wall synthesis genes in enterococci (18).

E. faecium strains expressing very high levels of ampicillin resistance (MIC >128 µg/mL) emerged in U.S. medical centers in the late 1980s (19). Molecular analysis of these strains suggested that the increase was attributable to mutations within the *pbp5* gene, which decreased the binding affinity of PBP 5 for ampicillin (20,21). One clinical study associated colonization with ampicillin-resistant *E. faecium* and prior therapy with extended-spectrum cephalosporins (22).

During the late 1980s, the prevalence of methicillin-resistant staphylococci was also increasing in U.S. hospitals (1), resulting in increased use of vancomycin. The discovery that antibiotic-associated diarrhea and pseudomembranous colitis were due to *Clostridium difficile* further fueled vancomycin use (23).

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Vancomycin Resistance

Vancomycin-resistant enterococci (VRE) were first reported in 1986, nearly 30 years after vancomycin was clinically introduced. The primary inciting factor was likely the use of orally administered vancomycin for treating antibiotic-associated diarrhea in hospitals. Vancomycin resistance is conferred by one of two functionally similar operons, VanA or VanB (Figure) (24). The VanA and VanB operons are highly sophisticated resistance determinants, which suggests that they evolved in other species and were acquired by enterococci. The difference in the guanine-cytosine (G-C) content of the genes of the VanB operon (roughly 50% G-C) (25) in comparison to typical enterococcal genes (35% to 40% G-C) (3) is compelling evidence for this acquisition. The conditions that would favor substantial colonization by naturally glycopeptide-resistant species (probably streptomycetes) and persistence of enterococci include high vancomycin concentrations in the gastrointestinal tract. Substantially high levels of glycopeptides in the gastrointestinal tract are achievable by oral administration, since these agents are not absorbed, resulting in fecal vancomycin concentrations high enough to favor colonization with vancomycin-resistant streptomycetes, but not high enough to kill the notably tolerant enterococcus. Hence, it is reasonable to presume that oral administration of glycopeptides to humans was a major factor in the emergence of vancomycin resistance in enterococci. The European VRE outbreak's apparent origin in animals (who were fed oral glycopeptides as growth promoters) further supports this scenario.

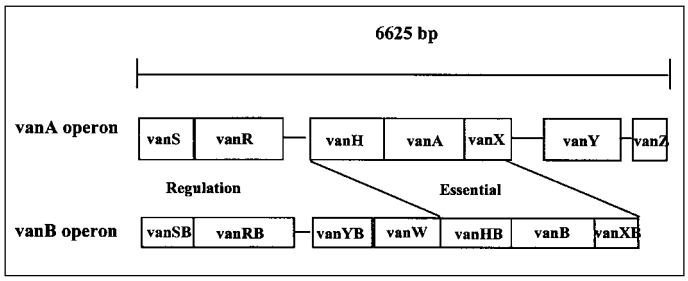

Figure. Comparison of arrangements of the VanA and VanB glycopeptide resistance operons. Essential genes and those involved in regulation of expression of the resistance determinant are marked.

Risk Factors for Multidrug-Resistant Enterococci

More than 95% of VRE recovered in the United States are *E. faecium*; virtually all are resistant to high levels of ampicillin. The phenotypic association of ampicillin and vancomycin resistance is in some instances due to genetic linkage. We reported transferable ampicillin and VanB-type vancomycin resistance from *E. faecium* strains isolated in northeast Ohio (26). Both *pbp5* and the *vanB* operon were located in the chromosome and linked as a result of the insertion of a VanB transposon (Tn*5382*) immediately downstream of *pbp5* (15). Both determinants were located within a larger mobile element that was able to transfer between *E. faecium* strains. This larger transposon is widely disseminated; it is found in clonally unrelated *E. faecium* isolates from New York, Pennsylvania, Florida, Missouri, Ohio, and Hawaii (27).

E. faecium is less pathogenic than *E. faecalis*; in fact, many VRE infections resolve without active antimicrobial-drug therapy (28). However, in specific patient populations, notably in liver transplant patients and patients with hematologic malignancies, VRE cause serious and often fatal disease (29,30). Therefore, it is well worth understanding the factors that promote the emergence and spread of multidrug-resistant VRE.

Frequently identified risk factors for VRE colonization and infection include prolonged hospital stays, exposure to intensive care units, transplants, hematologic malignancies, and exposure to antibiotics (31). The epidemiology of VRE spread in the hospital involves both person-to-person transmission and selective antibiotic pressure. Very specific practices designed to prevent the person-to-person spread of VRE have been recommended by the Hospital Infection Control Practices Advisory Committee to the Centers for Disease Control and Prevention and are in place in many hospitals (32). These measures include surveillance for colonization, identification of colonized and infected patients, isolation or cohorting of colonized persons, strict use of gloves and gowns by people coming into contact with the patient, thorough room cleaning after patient discharge, and efforts to limit use of vancomycin in hospitals. In geographically limited outbreaks caused by the dissemination of a single VRE clone, these practices have successfully eliminated the organisms from the hospital (33-35). In larger, more disseminated outbreaks caused by several different VRE clones, infection control measures and control of vancomycin use have shown only limited efficacy, suggesting selection pressure by antimicrobial drugs other than vancomycin (36,37).

Antibiotics other than glycopeptides have been linked with increased risk for colonization and infection with VRE, most prominently, the extended-spectrum cephalosporins and antibiotics with potent activity against anaerobic bacteria (26,31,38,39). These associations have been noted in retrospective, uncontrolled studies.

Nonglycopeptide Antibiotics and VRE

Are there compelling reasons to believe that cephalosporins or antibiotics with potent activity against anaerobic bacteria increase risk for VRE? Early studies reported VRE strains in which exposure to vancomycin increased the susceptibility to beta-lactams (40). It was hypothesized that PBP 5 was unable to process peptidoglycan precursors terminating in D-lactate. Therefore, expression of vancomycin resistance, whose mechanism in both VanA and VanB strains involves the substitution of D-lactate for D-alanine at the terminus of the pentapeptide precursors, would need to involve other PBPs in cell-wall synthesis. These other PBPs would be susceptible to beta-lactams, including cephalosporins. However, mutants resistant to synergism are relatively easy to select in vitro, and strains resistant to such synergism are commonly found in the clinical setting (41).

The cephalosporin association may be related to the fact that virtually all VRE in the United States express high-level ampicillin resistance. The high-level ampicillin-resistant strains express even higher degrees of resistance to extended-spectrum cephalosporins (>10,000 µg/mL) (26). The concentrations of cephalosporins achievable in bile (as high as 5,000 µg/mL for ceftriaxone) (42-44) can inhibit or kill virtually all upper gastrointestinal bacterial flora, except for VRE. On the

other hand, antienterococcal penicillins such as piperacillin, which appear to be protective against VRE in some clinical studies, achieve biliary concentrations in excess of 1,000 µg/mL in human bile after standard doses (45). These concentrations exceed the MIC of most VRE for piperacillin (256 to 1024 µg/mL). It is therefore within reason that the potentially protective effect observed with piperacillin is explainable by its direct inhibition of VRE in the upper gastrointestinal tract.

We tested this hypothesis in an animal model in which subcutaneous doses of different antimicrobial agents were administered to mice for 2 days, followed by intragastric injection of small numbers (ca. 100 CFU) of a highly ampicillin-resistant VRE strain B *E. faecium* C68 (46). Stool samples were subsequently collected over a 2- to 3-week period to determine whether high-level VRE colonization was established. In this model, subcutaneous administration of piperacillin-tazobactam was found to protect against high-level VRE colonization, whereas ceftriaxone and ticarcillin-clavulanic acid (with antienterococcal activity equivalent to the cephalosporins) promoted high-level VRE colonization (Table 1). These results are consistent with a model in which piperacillin is protective because of direct inhibition of VRE in the upper gastrointestinal tract, whereas ceftriaxone and ticarcillin promote colonization because they inhibit everything but VRE, thereby permitting high-level colonization.

Table 1. Pretreatment with antibiotics and vancomycin-resistant enterococci (VRE) colonization after gastric administration of 10^2 CFU vancomycin and ampicillin-resistant *Enterococcus faecium* C68 (46)

	Approximate $\log_{10}$ CFU VRE/g stool				
	Day 3	Day 6	Day 9	Day 13	Day 16
Saline	2	2.5	3	2.5	2.5
Piperacillin-tazobactam	2	2	2	2	2
Ticarcillin-clavulanic acid	>9	>9	8.2	6.8	6.8
Ceftriaxone	>9	8.8	8.4	7.2	6

A direct activity of antianaerobic antibiotics against VRE is more difficult to understand, since some of these antibiotics are among the most active antienterococcal agents (ampicillin-sulbactam, piperacillin-tazobactam), and most of the extended-spectrum cephalosporins have relatively weak activity against anaerobes. Conceivably, however, these antibiotics exhibit potent activity against species that successfully compete with enterococci for colonization of the gastrointestinal tract, thereby promoting persistence of high-level VRE colonization once it is successfully established. We tested this hypothesis in a separate animal model in which high-level VRE colonization was established by intragastric injection of 10^6 CFU of C68 after administration of oral vancomycin (47). This technique established colonization of mouse stool with 10^9 CFU of VRE in all animals. When oral vancomycin was discontinued, colonization levels declined at a regular and predictable rate; most animals had no detectable colonization after 3 weeks. We tested the effects of subcutaneous administration of different antibiotics on the persistence of high-level VRE colonization (Table 2). Vancomycin and antibiotics with potent activity against anaerobic bacteria (ampicillin-sulbactam, cefoxitin, clindamycin, metronidazole, piperacillin-tazobactam, and ticarcillin-clavulanic acid) promoted persistence of high-level VRE colonization, even though some had excellent activity against enterococci and had been shown to prevent VRE colonization in the other model (see above). In contrast, antibiotics with relatively poor antianaerobic activity (aztreonam, cefepime, ceftriaxone, ciprofloxacin) did not promote high-level colonization.

Table 2. Antibiotic treatment and persistence of high-level colonization with vancomycin and ampicillin-resistant *Enterococcus faecium* C68 (47)

	Approximate $\log_{10}$ CFU VRE/g stool[a]				
	Day 0	Day 4-5	Day 9-10	Day 14-15	Day 19-20
Saline	9.5	8.3	6	3.8	3.5
Vancomycin (SQ)	>9	>9	>9	>9	>9
Vancomycin (oral)	>9	>9	>9	>9	>9
Antibiotics with potent antianaerobic activity					
Piperacillin-tazobactam	>9	>9	>9	>9	>9
Ticarcillin-clavulanic acid	>9	>9	>9	>9	>9
Clindamycin	>9	>9	>9	>9	>9
Cefotetan	>9	>9	8.8	7.8	8
Metronidazole	>9	>9	>9	>9	>9
Ampicillin	>9	>9	8	7.2	7
Ampicillin-sulbactam	>9	>9	>9	7.8	7.7
Antibiotics with relatively poor activity against anaerobic bacteria					
Cefepime	>9	>9	6.2	5	4.8
Ceftriaxone	>9	8.8	8.4	7.2	6
Aztreonam	>9	9	4.3	4.2	3.8
Ciprofloxacin	>9	8.8	6	5.2	5

[a]VRE = vancomycin-resistant enterococci; SQ = subcutaneous.

Antibiotics and VRE Colonization and Infection

The above results suggest a model for antibiotic influence on the spread of VRE. Commonly used antibiotics that achieve high gastrointestinal concentrations but are inactive against enterococci, such as the cephalosporins, ticarcillin, and perhaps vancomycin, favor colonization with high levels of VRE in the stool. Antibiotics active against anaerobic bacteria, which are the primary competitors of enterococci for colonizing the gastrointestinal tract, favor the persistence of high levels of VRE in stool but may or may not (depending on their intrinsic antienterococcal activity) favor colonization in uncolonized patients. Antibiotics that meet both criteria, such as ticarcillin-clavulanic acid, should be particularly associated with VRE. In a citywide analysis of hospitals in the greater Cleveland area, the use of ticarcillin-clavulanic acid was associated with higher hospital rates of clinical VRE (26). A positive, although not statistically significant, association was noted for extended-spectrum cephalosporins, while a negative but statistically insignificant association was noted for the combination of ampicillin, ampicillin-sulbactam, piperacillin, and piperacillin-tazobactam.

The frequent association of cephalosporins with VRE colonization and the failure to associate piperacillin-tazobactam with VRE suggest that the most important

driving force for the emergence and spread of these organisms within institutions may be the predilection for establishing new colonizations. This is not to say that antimicrobial agents that promote persistence of high-level colonization will not be important for promoting VRE outbreaks, but that this effect is less pronounced if high-volume use of cephalosporins (or ticarcillin-clavulanic acid) does not create receptive new environments for establishing new colonization.

These data also suggest that refined strategies can be developed to limit the emergence and spread of VRE within hospitals. Commitment to serious infection control practices and limitation of vancomycin use must remain the cornerstones of any successful strategy. However, it is possible to envision settings where surveillance-culturing systems are taken seriously and patients who are colonized with VRE are routinely identified. In such settings, the choice of which empiric antibiotic to administer for a presumed nosocomial infection would be affected by the colonization status of the patient. In patients known to be colonized with VRE, broad-spectrum agents that lack significant activity against anaerobes (such as extended-spectrum cephalosporins of fluoroquinolones) would be preferred, on the assumption that potent anaerobic activity would not be required for treating the infection. If the patient is not colonized with VRE, administration of a potent antienterococcal broad-spectrum agent such as piperacillin-tazobactam may be preferred. In this manner, both the establishment of new colonization and the level of colonization of those already colonized could be minimized.

Conclusions

Multidrug-resistant enterococci continue to pose problems in U.S. medical centers. The best available evidence suggests that the emergence and spread of these pathogens are promoted by poor infection control techniques and by antibiotic selective pressure. Antibiotic selective pressure favoring the emergence and spread of VRE may involve more than simply the extent of vancomycin use. Specifically, extended-spectrum cephalosporins and similarly active beta-lactams and drugs with potent activity against anaerobes appear to predispose to VRE colonization and infection. On one hand, data from animal models suggest that the cephalosporins predispose to establishment of VRE colonization through their potent activity against many bacteria and essential lack of activity against ampicillin-resistant enterococci. On the other hand, antianaerobic antibiotics appear to favor persistence of high levels of VRE colonization through their activity against competing flora. A more detailed understanding of the impact of different antibiotics on the upper and lower gastrointestinal flora will be an important step in controlling the emergence and spread of VRE.

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Controlling Antimicrobial Resistance in Hospitals: Infection Control and Use of Antibiotics

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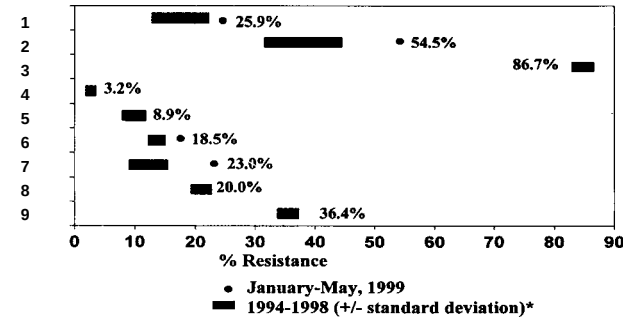
Antimicrobial-drug resistance in hospitals is driven by failures of hospital hygiene, selective pressures created by overuse of antibiotics, and mobile genetic elements that can encode bacterial resistance mechanisms. Attention to hand hygiene is constrained by the time it takes to wash hands and by the adverse effects of repeated handwashing on the skin. Alcohol-based hand rubs can overcome the time problem and actually improve skin condition. Universal glove use could close gaps left by incomplete adherence to hand hygiene. Various interventions have been described to improve antibiotic use. The most effective have been programs restricting use of antibiotics and computer-based order forms for health providers.

The forces that drive antimicrobial-drug resistance (failures of hospital hygiene, selective pressures created by overuse of antibiotics, and mobile genetic elements that can encode bacterial resistance mechanisms) have been discussed at length (1-4). Despite this extensive knowledge base, exhortations about resistance, and formal control guidelines (5), drug resistance has continued to emerge, especially in intensive care units (ICUs) (Figure 1).



1 = Vancomycin/enterocci
2 = Methicillin/*S. aureus*
3 = Methicillin/CNS
4 = 3rd Ceph/*E. coli***
5 = 3rd Ceph/*K. pneumoniae***
6 = Imipenem/*P. aeruginosa*
7 = Quinolone/*P. aeruginosa*
8 = 3rd Ceph/*P. aeruginosa*
9 = 3rd Ceph/*Enterobacter* spp.

Note: *S. aureus* = *Staphylococcus aureus*; CNS = coagulase-negative staphylococci; 3rd Ceph = reistance to third-generation cephalosporins (ceftriaxone, cefotaxime, or ceftazidime); *P. aeruginosa* = *Pseudomonas aeruginosa*; Quinolone = resistant to either ciprofloxacin or ofloxacin.
*Percentage (%) increase in resistance rate of current period (January-December 1999) compared to mean rate of resistance over previous 5 years (1994 through 1998): [(1999 rate - previous 5-year mean rate)/previous 5-year mean rate] X 100.
**Resistance for *Escherichia coli* or *Klebsiella pneumonia* is the rate of nonsusceptibility of these organisms to either 3rd Ceph group or aztreonam.

Figure 1. Rates of resistance in nosocomial infections reported in ICU patients, National Nosocomial Infections Surveillance System, CDC. Comparison of data from January-December 1999 with historical data.

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In a survey in four U.S. medical centers (a public hospital, a community hospital, a long-term care facility, and a university hospital), 85% of 424 physicians noted that antimicrobial-drug resistance was a major national problem; 55% thought that resistance was an issue for their patients (6). At the root of the resistance problem are health-care workers, who, although generally willing to do the right thing to control antimicrobial-drug resistance, undervalue the problem, do not know what the "right thing" is, or need an easier way to do it. This review summarizes a "facilitated right thing" approach to the problems of failed hygiene and antibiotic pressures.

Hand Hygiene

In a recent survey of physicians (6), 45% considered poor handwashing practices an important cause of antimicrobial-drug resistance in hospitals, perhaps a reflection of health-care workers' markedly inflated view of their attention to hand hygiene (Table 1) (7). In fact, in most surveys of handwashing adherence, in various patient-care settings, personnel have practiced appropriate hand hygiene in only 25% to 50% of opportunities. As we pass the sesquicentennial of Semmelweis' seminal observations on the importance of hand hygiene in reducing the incidence of nosocomial childbed fever, why does handwashing remain the most breached infection control measure in hospitals? Two frequently cited reasons are the large time commitment (up to

Table 1. Hospital personnel self-reported and observed handwashing rates[a]

	Handwashing after patient contact N (%)
Self-reported rate (n=123)	104 (85)
Estimate of co-workers' rate (n=123)	63 (51)
Observed rate (n=173)	48 (28)

[a]From Chicago Antimicrobial Resistance Project and from data adapted from Vernon et al. (7).

90 minutes per work shift if performed as recommended by the Centers for Disease Control and Prevention [CDC]) and the adverse effects of repeated handwashing on the skin (8).

Alcohol-Based Hand Rubs

If given a choice of changing human behavior (e.g., improving attention to hygiene and asepsis) or designing a technologically foolproof device to control infections, go for the device. For hand hygiene, we have the opportunity to fulfill the infection control "prime directive": use technologic advances to improve behavior. How? Alcohol-based sinkless hand rubs (Table 2) can overcome the time problems of handwashing (9) and actually improve skin condition (10). Handwashing requires approximately 45 to 90 seconds to access and use a sink with running water, soap, and hand-drying facilities; an alcohol-based hand rub can degerm hands in less than 30 seconds and enhance killing of transient hand flora.

Although use of alcohol for handwashing or scrubbing is perceived as leading to dry skin, use of alcohol hand rubs, without rinsing, is beneficial to skin, presumably because the protective fats and oils remain on the hands as the alcohol dries and because alcohol rubs contain emollients. In a study comparing an alcohol gel hand rub to soap and water handwashing, Boyce et al. reported that health-care workers found that alcohol hand rub causes less skin dryness, is accessible and convenient to use, and has a pleasant odor. After the study, 92% of test participants agreed to use the hand rub routinely (11).

Table 2. Potential benefits of alcohol-based sinkless hand degerming agents

	Soap and water handwashing	Alcohol hand rub
Time required	30-120 seconds	10-30 seconds
Efficacy in degerming	Good to very good	Excellent
Acceptance by personnel	Historically poor	Good to excellent

Colonization Pressure and Universal Glove use

While alcohol-based hand rubs appear promising, maintaining adherence may require ongoing educational reenforcement, compliance monitoring, and feedback to personnel. With such aggressive campaigns, hand hygiene rates of 60% to 80% can be achieved. But is this enough? For uncommon pathogens that may colonize or infect only a small proportion of patients, indirect patient-to-patient cross-transmission by the hands of health-care workers may be interrupted readily by such adherence rates. However, when "colonization pressure" is greater because of a large number of colonized patients, such rates may not be sufficient. For example, when 30% to 50% of patients are colonized with vancomycin-resistant enterococci (VRE), even occasional lapses in hand hygiene may be enough to sustain cross-transmission (Figure 2) (12,13).

A "belt and suspenders" approach to the colonization pressure dilemma has been to encourage use of disposable examination gloves during contacts with patients and their environment (2,14,15). In one study, the rate of nosocomial

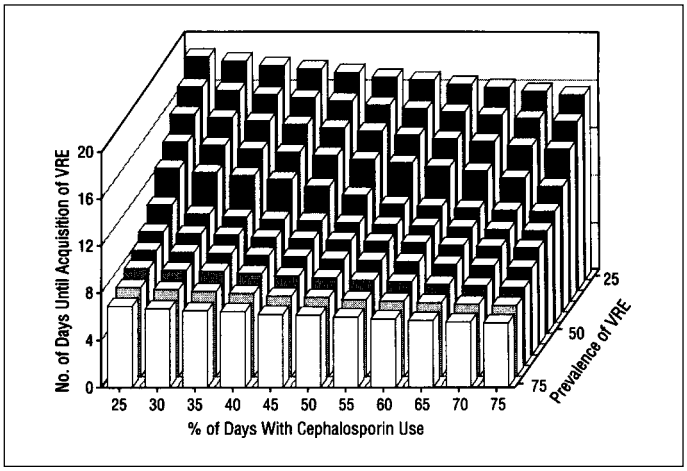

Figure 2. Median number of days until acquisition of VRE in a medical ICU; prevalence of VRE ("colonization pressure") exerted a greater effect on acquisition than did antibiotic use, i.e., time to acquisition of VRE was shorter with high colonization pressure and low antibiotic use than with the converse conditions (13).

Clostridium difficile-associated diarrhea was threefold lower on "universal glove use" wards than on control wards (16). In a study of VRE, 39% of personnel had contamination of examination gloves by VRE after even brief contact with infected or colonized patients; personnel hand contamination was reduced 71% by use of gloves (17). Because even intact upper body skin may be colonized by resistant bacteria such as VRE (18) and environmental contamination by VRE is common (19), we recommend that disposable examination gloves be worn for all contact, even with intact skin or the environment of at-risk patients. Gloves must be changed and hands disinfected by an alcohol hand rub between patients, because gloves are not a total barrier (17,20). In one observational study of universal glove use, 96% of gloved personnel removed gloves after leaving the patient's room (21). In that study, personnel cited a marked preference for universal glove use over traditional contact precautions.

Because of the huge resistance iceberg (Figure 3), with as many as 5 to 10 patients colonized with resistant bacteria for every patient known to be infected, universal glove use may be a more preferable infection control strategy than contact precautions, which are applied only to the tip of the iceberg. With universal glove use, gowning of personnel is recommended only for self-protection, e.g., from blood and body fluid exposures. In a study of the epidemiology and control of VRE in a medical ICU and in a study of control of VRE, methicillin-resistant *Staphylococcus aureus,* and ceftazidime-resistant *Escherichia coli* and *Klebsiella pneumoniae*, gowns did not add value to universal glove use (21,22). However, gowns may be of value for motivation (they have increased compliance in some studies) (22), in outbreak control (23), or in some heavily contaminated environments such as burn units.

Prescription of Antibiotics

Antibiotic pressures may be more amenable to intervention than hygiene practices. Prescribers want to do

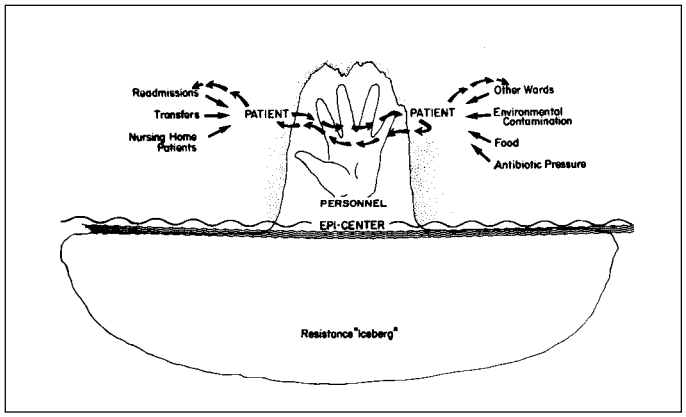

Figure 3. The dynamics of nosocomial resistance. Resistance iceberg floating in an epicenter (2).

the right thing but may not always remember recommendations. Even though most health-care workers see inappropriate use of antibiotics as an important cause of drug resistance, many consider use of broader-spectrum antibiotics for longer periods the way to stamp out resistant bacteria (6).

To simplify prescription of antibiotics, most hospitals use "closed" formularies that limit prescribing options, often based on competitive bidding, to one or two drugs per antibiotic class. Clinical guidelines have become popular, especially for common infections, such as community-acquired pneumonia. Such guidelines may improve antibiotic use, especially if results are audited, and feedback is provided to prescribers. Use of order forms (24) and concurrent feedback to prescribers or next-day review of antibiotic appropriateness (25) also can improve prescriptions. The most effective antibiotic interventions have been restriction programs and computer-based order forms (so-called provider-order entries).

Restrictions to Use of Antibiotics

Restricting use of antibiotics has been especially effective in reducing cost and excess empiric use of broad-spectrum drugs (26). In one large study of the effect of prior authorization for selected drugs, a 32% decrease in expenditure for parenteral antibiotics was accompanied by increased susceptibility of bacterial isolates to beta-lactam and quinolone antibiotics. There were no adverse effects on clinical outcomes as measured by time to receipt of appropriate antibiotics, survival, and discharge from hospital for patients with bacteremia caused by gram-negative bacilli (27).

Computer Order Entry

Computer-based order entry for medical providers uses technology to direct and improve prescription behavior and thus fulfills the infection control prime directive (28). Order entry systems for antibiotics (and other drugs) provide simple messages to prescribers, such as the hospital's suggested indications for, or the local resistance patterns of, a selected antibiotic. More sophisticated systems integrate results of microbiology and other laboratory tests into decision-support algorithms (29). Because they provide prescribing information when it is needed, in a neutral, nonjudgmental, fact-based format, computer order forms are efficient and well accepted and can change prescribing behavior dramatically, almost overnight.

Rotating Use of Antibiotics

The most recent intervention in antibiotic prescribing has been renewed interest in rotating use, or cycling, of antibiotics (30). Over 20 years ago, in a series of studies at the Minneapolis Veterans' Administration Hospital, the substitution of amikacin for gentamicin and tobramycin as the aminoglycoside of choice produced sustained decreases in the prevalence of aminoglycoside-resistant gram-negative bacilli (31). The higher serum levels of amikacin, and the infrequent appearance in U.S. hospitals of amikacin-modifying enzymes that could confer amikacin resistance in gram-negative bacilli, were the underpinnings of the success of this strategy.

The more recent reports on cycling describe replacement (or switch) therapy for empiric antibiotic choices (30,32-34). Replacing ceftazidime with ciprofloxacin for empiric treatment of suspected gram-negative bacterial infections in a cardiac surgery ICU was associated with decreased incidence of ventilator-associated pneumonia and bacteremia caused by antibiotic-resistant gram-negative bacilli (33). In another hospital, use of beta-lactam/beta-lactamase inhibitor combinations to replace use of third-generation cephalosporins and clindamycin was associated with decreased rates of colonization by VRE (34); a follow-up study reported that these formulary manipulations were associated with decreasing numbers of patients from whom methicillin-resistant *S. aureus* and ceftazidime-resistant *K. pneumoniae* were cultured but increased rates of resistant *Acinetobacter* (35). Rotating use of fourth-generation cephalosporins, quinolones, carbapenems, and beta-lactam/beta-lactamase inhibitor combinations is being studied in several hospital ICUs.

Cycling of antibiotics is most likely to be effective for limited periods in closed environments, such as ICUs, but this approach requires careful microbiologic monitoring because of the monotonic selective pressure of a single agent and the possible emergence of resistance to unrelated classes of drugs caused by genetic linkage of resistance mechanisms (30,36). As the size of the patient population under study increases, availability of various classes of drugs may be more effective at reducing the risk of emergence of resistance and may be a better strategy than cycling (37).

Conclusions

Control of antibiotic resistance requires aggressive implementation of several strategies (2): ongoing surveillance of resistance; molecular typing of isolates, usually using pulsed-field gel electrophoresis (38,39) when rates of resistance increase; using hygiene controls to limit spread of single (clonal) strains and antibiotic controls to limit spread of multiple (polyclonal) strains of resistant bacteria; and enlisting administrative support. Monitoring adherence of health-care workers to control measures and feedback of individual and ward rates of hygiene adherence and antibiotic resistance are central components of health-care worker education and motivation. Mathematical modeling has been used to judge the value of infection control activities. In these calculations, screening and cohorting of infected and colonized patients are the most effective control measures (11), although creating and maintaining cohorts are often logistically and technically difficult.

Current infection control strategies are aimed at the hygiene and antimicrobial engines that drive resistance. To ulfill the infection control prime directive, we must harness technology to improve and direct adherence to these

strategies. Future approaches may control or eliminate the bacterial events that underlie evolution of resistance.

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Impact of Hospital Care on Incidence of Bloodstream Infection: The Evaluation of Processes and Indicators in Infection Control Study

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The Evaluation of Processes and Indicators in Infection Control (EPIC) study assesses the relationship between hospital care and rates of central venous catheter-associated primary bacteremia in 54 intensive-care units (ICUs) in the United States and 14 other countries. Using ICU rather than the patient as the primary unit of statistical analysis permits evaluation of factors that vary at the ICU level. The design of EPIC can serve as a template for studies investigating the relationship between process and event rates across health-care institutions.

Comparing Clinical Performance

Health-care organizations are increasingly expected to provide clinical outcomes data as measures of clinical quality to accrediting bodies, purchasers, and the public, under the premise that outcome variations indicate quality differences across organizations. Variation in clinical performance can result from variation in any number of factors, some relevant to improving the quality of care but many not. The best-studied source of variation in clinical performance measures is patient characteristics. Hospitals differ widely in the severity of illness and extent of coexisting illnesses in their patients, and much research has been devoted to developing risk adjustment methods to permit interhospital comparisons not confounded by patient characteristics (1). Hospitals also differ in methods of data abstraction and data management (2). Even subtle differences in definitions can introduce measurable variation in clinical performance(3).

Variations in patients, data collection, and definitions distract from collecting comparative data for quality improvement. To be useful, an indicator must be linked to variations in the processes of care provided since these processes are within the scope of control of the health-care organization. Furthermore, the "signal" must be separable from the "noise" of extraneous variation. Despite pressure to collect and disseminate clinical performance data as instruments of quality improvement, relatively little research has been done to establish their validity by demonstrating an association with process differences between hospitals.

In 1993, the Society for Healthcare Epidemiology of America (SHEA) responded to a growing concern among its membership about the sudden increase in the use of clinical performance comparisons to measure quality of health care. At the same time, the Joint Commission on Accreditation of Healthcare Organizations announced a plan to require all hospitals to collect an identical set of comparative indicators as part of its Agenda for Change Initiative. In 1994, the Joint Commission and SHEA formed a collaboration called the Project to Monitor Indicators (4) to foster the science of comparative indicators for the benefit of both organizations and the health-care community. The initial demonstration project, called the Comparison of Hospital Performance Indicators, was completed in 1997 (3). The second project, which is nearing completion, is called Evaluation of Processes and Indicators in Infection Control (EPIC). EPIC's area of

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focus is bloodstream infections, specifically those in intensive-care unit (ICU) patients.

Because hospital epidemiology is a mature discipline, infection control indicators offer excellent opportunities to demonstrate how processes of care relate to infectious disease outcomes. Hospital epidemiology has long addressed surveillance techniques, disease definitions, patient risk factors, and process factors that may influence disease rates (5-7).

EPIC Study Design

EPIC is two investigations under one name. The first investigation is designed to answer the following question: do the relative rankings of hospitals change, with indicators of bloodstream infection used for comparison? The design is relatively straightforward. With the assistance of the Centers for Disease Control and Prevention's Hospital Infections Program, the project identified six vendors offering different bloodstream infection indicators. A sample of 36 hospitals is collecting the data necessary to calculate these six indicators. When completed, the relative rankings of the hospitals across the set of indicators will be compared. The second investigation is designed to answer the following question: can variation in hospital care process explain variation in bloodstream infection rates across a sample of ICUs? The design for answering this question differs considerably from traditional epidemiologic designs (e.g., cohort and case-control designs).

Patient Risk vs. Unit Rates

EPIC relates process performance to variation in bloodstream infection rates across ICUs. Traditional epidemiologic designs focus on the prediction of disease risk for the individual patient. In a traditional cohort study, the processes of care under scrutiny would be documented in ICU patients with central venous catheters. Primary bloodstream infections are relatively rare, even in this vulnerable population; however, this rarity presents practical problems in study design. Given an average 3% risk to each patient, prospective cohorts would have to include approximately 2,500 patients to have 80% power to detect as statistically significant a twofold relative risk associated with an exposure common to 25% of ICU patients. The case-control design was developed to address situations in which the outcome under study is uncommon; however, case-control studies establish exposure status after the disease has occurred. Therefore, not all varieties of exposure can be studied. In hospital epidemiology, exposures that are reliably documented in the medical record (coexisting diseases, for example) can be studied by a case-control approach. However, relevant aspects of the process of care are not always documented (e.g., the experience of the central venous catheter inserter or the number of attempts at insertion) and may be difficult to establish retrospectively.

Even if all relevant process factors could be documented in advance, some factors cannot be studied within a single ICU or even across a small number of ICUs. In many instances, process exposures are mandated by hospital, ICU, or infection control policy. In this situation, all patients within an ICU may have catheters inserted with specific types of barriers or have a similar skin preparation before catheter insertion. If there is no variation in the process under study within an ICU, that process cannot be evaluated by examining patients within that ICU. One would need to examine many ICUs with varied processes to relate the process to disease risk.

Ultimately, traditional designs cannot address the variation in unit rates because they focus on the wrong unit of analysis, i.e., the patient rather than the ICU. To study variation in ICU bloodstream infection rates, the ICU is the appropriate unit of analysis. The ICU rate is an aggregate measure that represents the average risk for bloodstream infection. Strong but infrequent determinants of patient risk have relatively little influence on the unit rate. A certain process factor, like gross contamination at the insertion site, may be related to a marked increase in bloodstream infection risk for individual patients but may occur so rarely that the overall rate of infection is not noticeably influenced. Even if a strong determinant of risk were relatively common, it would not necessarily be an important determinant of differences in bloodstream infection rates across ICUs. For an exposure to affect variation in rates between ICUs, two criteria must be met. First, the condition must be common enough to influence the bloodstream infection rate, i.e., it must have a fairly high attributable risk. Second, there must be variation between ICUs in the proportion of patients affected. Even a strong factor will not explain differences if every ICU has the same proportion of patients affected. Conversely, a relatively modest determinant of patient risk could account for a substantial proportion of the variation between ICU infection rates if ICUs varied greatly in the proportion of patients exposed. The average patient and average process determine the ICU infection rate since the ICU rate is a function of the average patient risk. The difference between individual risk and population rates has been extensively explored elsewhere (8).

When the ICU is the unit of analysis, important difficulties in evaluating process can be resolved. First, factors that vary at the level of the ICU can be studied appropriately. Factors not routinely charted can also be studied efficiently. Since the goal of the evaluation is to relate the average process to the ICU rate, only data sufficient to adequately characterize the average process are required. Therefore, every insertion in an ICU does not have to be followed; a random sample of insertions allows characterization of typical performance. On the other hand, many ICUs must be studied, since the sample size of the project is not the number of patients in ICUs but the number of ICUs being compared.

EPIC Process Assessment Design

In 1998, the membership of SHEA and other interested persons were solicited to support participation of their respective hospitals in the study. Initially, 58 hospitals volunteered to participate (Table) (four were added later and eight withdrew). Data collection began in November 1998 and continued through January 2000, and data from 54 ICUs have been forwarded to the coordinating unit. The number of ICUs was determined by the willingness of epidemiologists and infection control personnel to participate in the study. However, the sample size is sufficient to evaluate important determinants of variation in ICU bloodstream infection rates. With a sample of 54 ICUs, a factor that explains 7% of the variance in the ICU rates would be statistically significant (alpha=0.05).

Because of its precise definitions and long history of use in the field, the National Nosocomial Infections Surveillance

Table. Hospitals participating in EPIC

Characteristic	n	%
Major teaching hospital	33	61.1
NNIS participant	18	33.3
Location		
United States*	40	74.0
International	14	26.0
ICU selected		
Medical	12	22.2
Surgical	4	7.4
Medical/surgical	34	63.0
Other	4	7.4
Study ICU bed size		
1-9	12	22.2
10-14	24	44.4
15-19	8	14.8
≥20	10	18.5

(NNIS) System's central venous catheter-associated primary bloodstream infection indicator in ICU patients was used (9). To establish the rate, each ICU reported all qualifying infections to the coordinating unit throughout the study period. Units also reported their central-line days throughout the study period. Using these data elements, the coordinating unit calculated the NNIS indicator rate for each hospital.

Data on process and patient characteristics were collected for a random sample of central venous catheter insertions in patients admitted to the study ICUs. All hospitals were provided with the same list of five randomly selected dates and times each month. The study volunteers identified the first catheter insertion occurring after each random date and time and recorded a number of patient and process factors and interviewed the line inserter to document details of the insertion. Interviews were conducted within 48 hours of the insertion. It was not necessary for the insertion to have occurred in the study ICU; any patient who was admitted to the ICU within 8 hours of central venous catheter insertion qualified. Up to 65 insertions were documented during the study in each ICU. Each patient was monitored for bloodstream infection for 2 days after discharge from the ICU.

The higher the number of insertions assessed, the more precise the assessment of process. However, the increase in precision with sample size is not linear. The increase in precision in the estimate of the mean is a function of the standard error, which in turn is a function of the inverse of the square root of the sample size. Therefore, the return from increasing the sample size by a given amount decreases as the sample size increases. For example, adding 45 new observations to an initial sample of 20 observations increases the relative precision in the estimate of the mean by approximately 80%. Adding 45 new observations to an initial sample of 55 increases the precision only by approximately 30%. The value of 65 was selected because it was large enough to provide acceptably precise performance estimates but was not so large as to preclude voluntary participation in the study.

Data elements collected in EPIC are as follows: 1) Factors related to the patient: age, sex, primary and secondary diagnoses, length of ICU stay, dialysis, neutropenia, active treatment for cancer involving either chemotherapy or radiotherapy, albumin <3 g/L, burns involving >10% of body surface area, HIV/AIDS, current immunosuppressive therapy, and surgery under general anesthesia within 2 weeks before insertion. 2) Factors related to the line: type of central line, number of lumens, coating with antimicrobial material, anatomic site of insertion, location of insertion, urgency of insertion, use of the line for hyperalimentation, line exchange over a guide wire, and duration of the line. 3) Factors related to the insertion of the line: use of barrier precautions (sterile gown, mask, large drape, small drape), type of dressing applied, time from initial needlestick until line secured, number of sites attempted before completion, number of attempts made at the final insertion site, experience of the inserter (years inserting and number of lines inserted in the past 6 months), professional background of the inserter, and unusual occurrences during the insertion. 4) Factors related to the organization: number and kinds of ICUs within the hospital, presence of an infection control committee, length of time tracking bloodstream infection rates, experience tracking central line-days, NNIS participation, number of blood cultures done in the previous year, staffing for ICU surveillance, percentage of lines managed by a team, percentage of lines using a needleless systems, and number of in-service training sessions provided to the ICU staff in the previous 6 months. 5) Factors related to the study ICU: number of hours devoted to surveillance in the study ICU, experience and training of the infection control staff doing surveillance, total of registered nurse hours in the ICU, number of agency nurse hours used for staffing, number of "float" nurse hours used for staffing, total number of patient days, and minimum experience required for a new ICU nurse.

Conclusions

The goal of comparative measurement for quality improvement is to identify opportunities for improvement by showing which organizations have superior processes. However, a clear link between process and indicator needs to be established before the indicator can be confidently used for this purpose. The design of EPIC provides an opportunity to relate the typical care process directly to bloodstream infection rates in ICUs. Because the ICU is the unit of analysis, EPIC can evaluate process factors that could not be addressed by studies within a single ICU, specifically processes and policies that apply to all patients within an ICU. In addition, because the sample of patients in each ICU are followed for the development of bloodstream infections, the study affords a unique opportunity to compare an analysis based on patient risk with one based on unit rates.

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New Technologies to Prevent Intravascular Catheter-Related Bloodstream Infections

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Most intravascular catheter-related infections are associated with central venous catheters. Technologic advances shown to reduce the risk for these infections include a catheter hub containing an iodinated alcohol solution, short-term chlorhexidine-silver sulfadiazine-impregnated catheters, minocycline-rifampin-impregnated catheters, and chlorhexidine-impregnated sponge dressings. Nontechnologic strategies for reducing risk include maximal barrier precautions during catheter insertion, specialized nursing teams, continuing quality improvement programs, and tunneling of short-term internal jugular catheters.

Intravascular catheter-related bloodstream infections are an important cause of illness and excess medical cost. In prospective studies, the relative risk (RR) for a catheter-related bloodstream infection is 2 to 855 times higher with central venous catheters than peripheral venous catheters (1-3). Approximately 80,000 catheter-related bloodstream infections occur in U.S. intensive-care units each year, at a cost of $296 million to $2.3 billion (4,5). These infections are associated with 2,400 to 20,000 deaths per year. The focus of this article is on preventive strategies aimed at central venous catheters.

Chlorhexidine-Silver Sulfadiazine-Impregnated Catheters

Catheters impregnated with chlorhexidine-silver sulfadiazine are commercially available. In prospective, randomized studies of catheters left in place for an average of ≤11 days (6-14), the incidence of catheter-related bloodstream infections was reduced by using chlorhexidine-silver sulfadiazine-impregnated catheters (RR 0.4, confidence interval [CI] 0.2-0.8) (4). These catheters are cost-effective if the incidence of bloodstream infections is greater than 3.3/1000 catheter-days (6) or greater than 1% (15). In addition, if chlorhexidine-silver sulfadiazine-impregnated catheters in place for ≤10 days reduce infections from 5.2% to 3%, then for every 300 catheters used, approximately $60,000 would be saved and seven catheter-related bloodstream infections and one death would be prevented (15). Published studies of chlorhexidine-silver sulfadiazine-impregnated catheters were performed with catheters impregnated extraluminally. However, the U.S. Food and Drug Administration (FDA) has recently approved the use of catheters impregnated intraluminally with chlorhexidine, in addition to chlorhexidine-silver sulfadiazine extraluminal impregnation. Use of chlorhexidine-silver sulfadiazine-impregnated catheters has been associated with serious anaphylactoid reactions in Japan (16), and these catheters are not commercially available in that country. One such reaction in the United States has been reported to the FDA (as of April 2000). Resistance to the antiseptic components of this device has not been demonstrated in clinical studies (6). However, in vitro studies of *Pseudomonas stutzeri* exposed to slowly increasing concentrations of chlorhexidine, in the absence of silver sulfadiazine, have demonstrated the development of resistance to chlorhexidine and associated resistance to several classes of therapeutic antimicrobial agents (17). Although the conditions in these experiments do not simulate clinical practice, the experiments demonstrate the potential for resistance associated with use of these devices.

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Minocycline-Rifampin-Impregnated Catheters

Catheters impregnated with minocycline and rifampin are commercially available. In a prospective, randomized clinical trial of catheters in place for an average of 6 to 7 days, minocycline-rifampin-impregnated catheters were associated with lower incidence of infection than chlorhexidine-silver sulfadiazine-impregnated catheters (RR 0.1, CI 0-0.6) (18). The active ingredients of the minocycline-rifampin-impregnated catheters were on the extraluminal and intraluminal surfaces of the device, whereas the active ingredients of the chlorhexidine-silver sulfadiazine-impregnated catheters were only on the extraluminal surface. Therefore, the difference in the incidence of infection may reflect the extent of impregnation on the catheters, in addition to the difference in active ingredients. If minocycline-rifampin-impregnated catheters reduce infections from 5% to 0%, then for every 850 catheters used, approximately $500,000 would be saved (19). Resistance to active antimicrobial components of the minocycline-rifampin-impregnated catheters has not been demonstrated in clinical studies (18,19). However, when these catheters were implanted for 7 to 14 days in laboratory animals and then removed and placed on agar plates injected with *Staphylococcus aureus*, microbial growth was detected in the zones of inhibition (20); this growth may represent subpopulations of *S. aureus* with reduced susceptibility to minocycline or rifampin. In additional experiments, minocycline-rifampin-impregnated catheters were implanted in animals for 7 days, after which rifampin-resistant, minocycline-susceptible *S. epidermidis* was introduced into the insertion site and tunnel tract. In this animal model, the

minocycline-rifampin-impregnated catheters were not protective (20). These studies suggest the potential for resistance against the antimicrobial agents used to impregnate these catheters as their clinical use becomes more widespread.

Catheter Hubs Containing Iodinated Alcohol

A catheter hub containing an antiseptic chamber filled with 3% iodinated alcohol is commercially available in Europe but not in the United States. In a prospective, randomized trial of catheters in place for an average of 15 to 16 days, use of a hub with the antiseptic chamber reduced the incidence of infection (RR 0.2, CI 0.1-0.7) (21). A formal cost-benefit analysis has not been published. However, use of this device led to fourfold reduction in the incidence of infections, and the device would most likely be cost-effective when used with central venous catheters in place for approximately 2 weeks. A minute amount of iodine (0.024 mg) is estimated to enter the bloodstream each time the hub containing the antiseptic chamber is punctured (21). However, the currently marketed device has been modified, and entry of iodine into the bloodstream with daily use has not been reported.

Chlorhexidine-Impregnated Sponge Dressings

Use of a commercially available chlorhexidine-impregnated sponge dressing at the insertion site of central venous and arterial catheters led to a threefold reduction in catheter-related bloodstream infections in a recent prospective, randomized study (22).

Nontechnologic Interventions

Several strategies reduce the risk for catheter-related bloodstream infection. In a prospective, randomized study of central venous catheter insertion, use of maximal barrier precautions (large sterile sheet drape; long-sleeved sterile gown; sterile gloves, mask, and hat) resulted in lower incidence of infections, 0.08/1,000 catheter-days, compared with use of minimal precautions (small sterile drape and sterile gloves), 0.5/1,000 catheter-days (23). In another prospective, randomized trial of peripheral catheter insertions, the catheters inserted and managed by a specialized nursing team had a lower incidence of infection than catheters inserted and managed by house officers (odds ratio 0, CI 0-0.6 [24]). In prospective, cohort studies, continuing quality improvement programs aimed at appropriate insertion and maintenance of catheters substantially reduced the incidence of infection (25-29). In a prospective, randomized trial of catheters not used for blood-drawing, tunneling of short-term internal jugular central venous catheters was associated with lower incidence of infection than nontunneling of catheters (RR 0.2, CI 0.1-0.7 [30]).

Some of the nontechnologic interventions aimed at reducing the risk for catheter-related bloodstream infection, such as quality improvement programs, depend on changes in human behavior. Once implemented, whether they remain effective over the long term remains to be seen.

Future Strategies

Greater understanding of the pathogenesis of intravascular-related infections will help prevent such infections. For example, *S. aureus* binding to the catheter surface in vivo involves fibronectin-specific adhesions (31). Identification of epitopes in the *S. aureus* fibronectin-binding protein for the generation of adhesion-blocking antibodies (32) may aid in preventing future infections. The development of bacterial biofilms on the surface of foreign bodies involves cell-to-cell signaling by acyl homoserine lactone-based chemical messengers that control bacterial gene expression (33,34). Prevention of microbial growth on the surface of future intravascular catheters may be mediated by inhibitors of these chemical messengers (35).

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Ventilator-Associated Pneumonia or Not? Contemporary Diagnosis

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Ventilator-associated pneumonia (VAP) is pneumonia in patients who have been on mechanical ventilation for ≥48 hours. VAP is most accurately diagnosed by quantitative culture and microscopy examination of lower respiratory tract secretions, which are best obtained by bronchoscopically directed techniques such as the protected specimen brush and bronchoalveolar lavage. These techniques have acceptable repeatability, and interpretation of results is unaffected by antibiotics administered concurrently for infection at extrapulmonary sites as long as antimicrobial therapy has not been changed for <72 hours before bronchoscopy.

Ventilator-associated pneumonia (VAP) is defined as nosocomial pneumonia in a patient on mechanical ventilatory support (by endotracheal tube or tracheostomy) for ≥48 hours. For many years, VAP has been diagnosed by the clinical criteria published by Johanson et al. in 1972, which include the appearance of a new or progressive pulmonary infiltrate, fever, leukocytosis, and purulent tracheobronchial secretions (1); however, these criteria are nonspecific (2). In the mechanically ventilated patient, fever may be caused by a drug reaction, extrapulmonary infection, blood transfusion, or extrapulmonary inflammation. Pulmonary infiltrates may be due to pulmonary hemorrhage, chemical aspiration, pleural effusion, congestive heart failure, or tumor. Both fever and pulmonary infiltrates occur in the fibroproliferation of late acute respiratory distress syndrome, atelectasis, and pulmonary embolism, as well as in VAP. Cultures of tracheal aspirates are not very useful in establishing the cause of VAP (2). Although such cultures are highly sensitive, their specificity is low even when they are cultured quantitatively (3).

VAP can be accurately diagnosed by any one of several standard criteria: histopathologic examination of lung tissue obtained by open lung biopsy, rapid cavitation of a pulmonary infiltrate in the absence of cancer or tuberculosis, positive pleural fluid culture, same species with same antibiogram isolated from blood and respiratory secretions without another identifiable source of bacteremia, and histopathologic examination of lung tissue at autopsy (4). However, these criteria are based on invasive procedures for obtaining lung tissue or on uncommon manifestations or complications of VAP. Given the invasive nature of lung biopsy and the infrequent occurrence of other manifestations used as standard criteria, another approach is needed for the definitive diagnosis of VAP. In 1979, a fiberoptic bronchoscopic technique was introduced for obtaining uncontaminated lower respiratory tract secretions, which were cultured quantitatively (5). The causative microorganisms were recovered at $\geq 10^3$ CFU/mL from six patients with clinical evidence of lower respiratory tract infection.

In 1987, a correlation was observed between pneumonia and $\geq 10^5$ CFU/mL in bronchoalveolar lavage (BAL) fluid (6,7). Kahn and Jones noted that BAL fluid with $\geq 10^5$ CFU/mL and ≤1% squamous epithelial cells had 100% sensitivity and specificity for the diagnosis of bacterial pneumonia.

Two bronchoscopic techniques have been introduced for the accurate diagnosis of VAP in the absence of standard criteria. The protected specimen brush (PSB) collects 0.001 mL of lower respiratory tract secretions and has a diagnostic threshold of $\geq 10^3$ CFU/mL (8). BAL, an unprotected technique, samples approximately one million alveoli and has a diagnostic threshold of $\geq 10^4$ CFU/mL (8). A protected BAL technique with a balloon-tipped catheter has also been described (9). Detection of ≥5% of neutrophils or macrophages with intracellular organisms on a Wright-Giemsa stain of a smear of cytocentrifuged BAL fluid is also diagnostic of VAP (10).

Bronchoscopically Directed Techniques for Diagnosis of VAP

The accuracy of quantitative culture and microscopic examination of lower respiratory tract secretions for the diagnosis of VAP was validated by Chastre et al. (10,11), who compared the results of quantitatively cultured lower respiratory tract secretions with those of culture and histopathologic examination of simultaneously obtained lung tissue. In the first study, quantitative culture of secretions obtained by PSB was compared with histopathologic examination and quantitative culture of lung tissue (11). Of six patients with pneumonia confirmed by histologic criteria, all had at least one microorganism obtained at a concentration of $\geq 10^4$ CFU/g of lung tissue. Compared with the results of histologic examination and quantitative culture of lung tissue, quantitative culture of secretions obtained by PSB using a diagnostic threshold of $\geq 10^3$ CFU/mL had a sensitivity of 100%, specificity of 60%, positive predictive value of 43%, and negative predictive value of 100%.

In the second study, the results of PSB, BAL, and ≥5% intracellular organisms were compared with simultaneously obtained lung tissue (Table) (10). Patients were included in

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Table. Quantitative cultures and microscopy examination of lower respiratory tract secretions in the diagnosis of ventilator-associated pneumonia[a]

Diagnostic techniques	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PSB[b] cultures ($\geq 10^3$ CFU/mL)	82%	89%	90%	89%
BAL cultures ($\geq 10^4$ CFU/mL)	91%	78%	83%	87%
Microscopic examination of BAL fluid (≥5% intracellular organisms)	91%	89%	91%	89%

[a]From ref 10.
[b]PSB = protected specimen brush; BAL = bronchoalveolar lavage.

the study only if they had never had pneumonia or had acquired it during the terminal phase of their illness. Bronchoscopy was performed within 1 hour after death, while mechanical ventilation was continued and PSB and BAL samples were taken. Immediately after bronchoscopy, a left thoracotomy was performed, and lung tissue specimens were taken from the areas of lung where the bronchoscopic samples had been obtained. All but two patients had been receiving antibiotics before death, but antibiotic therapy had not been changed for ≥3 days. All lung segments judged to have moderate to severe pneumonia by histologic criteria yielded $\geq 10^4$ CFU/g of tissue.

Four other published studies have concluded that bronchoscopically directed techniques were not more accurate for diagnosis of VAP than clinical and X-ray criteria combined with cultures of tracheal aspirates (12-15). In one study, quantitative cultures of lower respiratory tract secretions obtained by PSB and BAL were compared with quantitative culture and histopathologic examination of lung tissue taken from the same areas sampled by PSB and BAL (12). These investigators used $\geq 10^3$ CFU/g of lung tissue as a threshold for positive cultures of lung tissue; in addition, patients were enrolled at any time during mechanical ventilation, so that pulmonary infiltrates could have been included from earlier pneumonia or current pneumonia with bacteria previously eradicated from some foci and still present in other areas of the lung. When multiple inflammatory foci of varying ages are present in the lungs, histopathologic examination and culture of lung tissue may not correlate with results of quantitative cultures of simultaneously obtained lower respiratory tract secretions.

Other investigators compared the results of quantitative culture and microscopic examination of lower respiratory tract secretions obtained by PSB and BAL with histopathologic examination of lungs at autopsy performed within 3 days of bronchoscopic sampling of the lower airways (13). Specificity and positive predictive values for cultures of secretions collected by PSB and BAL were comparable with those observed by Chastre et al. (10,11); however, substantially lower sensitivities of 57.8% and 47.3% and negative predictive values of 51% and 48% were observed for PSB and BAL, respectively. These discrepant findings may be due to the study design, in which sampling of lower airways and examination of lung tissue were separated by up to 3 days, the areas from which PSB and BAL samples were taken could not be precisely matched with the same areas examined histopathologically, and lung tissue could not be cultured because lungs were examined at autopsy.

In a comparative study, quantitative culture and microscopic examination of lower respiratory tract secretions were compared with histopathologic examination and quantitative culture of lung tissue obtained from the same area of the lung from which samples of secretions were taken (14). These investigators observed 70% specificity and 65% positive predictive value for bronchoscopically guided PSB and 63% sensitivity and 79% negative predictive value for bronchoscopically guided BAL. These patients were on mechanical ventilation for a mean of 14 days and a median of 8 days and could have acquired one or more episodes of pneumonia at any time while on mechanical ventilation. In addition, 38 of 39 patients received antibacterial or antifungal therapy in the 48 hours before death. However, duration of therapy or change of antimicrobial therapy in the 72 hours before death was not stated. If antimicrobial therapy had been changed, bacteria susceptible to the newly instituted antimicrobial agents might not have been recovered on culture of respiratory secretions and lung tissue of patients who had histopathologic evidence of pneumonia.

In another study, the results of quantitative culture and microscopic examination of lower respiratory tract secretions were compared with histopathologic examination and quantitative culture of simultaneously obtained lung tissue in 25 patients on mechanical ventilation immediately after death (15). Whether patients on antibiotic therapy at the time of death had any changes in therapy in the 72 hours before death or whether they had earlier episodes of VAP before the episode of pneumonia diagnosed at the time of death was not stated. In addition, these workers used $\geq 10^3$ CFU/g of tissue rather than $\geq 10^4$ CFU/g as the threshold for positive lung cultures, which may account for the lower sensitivity, specificity, and positive and negative predictive values for quantitative culture of secretions obtained by bronchoscopically directed PSB and BAL.

Nonbronchoscopically Directed (Blind) Diagnostic Techniques

Because of the invasive nature and cost of bronchoscopy, investigators have evaluated other techniques for collecting lower respiratory tract secretions. These nonbronchoscopic techniques involve passage of a catheter or telescoping catheters through the endotracheal tube with advancement to a wedged position in the lung. Samples may be taken by telescoping catheters containing a brush (blind PSB) (16-18), aspiration of secretions into a distally wedged catheter (19,20), or BAL through a distally wedged catheter (21-24). BAL may be performed by using a balloon-tipped catheter with the balloon inflated after the catheter has been advanced to the wedged position (protected BAL) (21), by using telescoping catheters (22,24), or by placing a catheter into the wedged position with a guide wire (23).

Although nonbronchoscopic or blind techniques for obtaining lower respiratory tract secretions appear promising, additional validation studies are needed before these techniques are widely adopted and can be used in place of bronchoscopically directed sampling techniques. Studies of nonbronchoscopic sampling techniques have recently been reviewed (25). Another indication of the need for further study of the nonbronchoscopic sampling techniques is the absence of

standardized diagnostic thresholds for quantitative culture of lower respiratory tract specimens obtained by these techniques.

Quantitative Cultures To Predict VAP Onset and Monitor Therapy

To predict the onset of VAP in patients with adult respiratory distress syndrome (ARDS), Delclaux et al. used quantitative culture of lower respiratory tract secretions obtained blindly by passing a plugged telescopic catheter through the endotracheal tube (26). They observed that in 16 of 18 patients lower respiratory tract colonization ($<10^3$ CFU/mL) evolved to pneumonia within 2 to 6 days. Colonizing microorganisms were the same as those that caused subsequent pneumonia. The 89% positive predictive value of lower respiratory tract colonization for pneumonia further substantiates the accuracy of quantitative culture of lower respiratory tract secretions for the diagnosis of VAP.

Quantitative culture of lower respiratory tract secretions can also be used to monitor the progress of antimicrobial therapy for VAP. Montravers and co-workers diagnosed VAP in 76 patients by using quantitative culture of lower respiratory tract secretions obtained through bronchoscopically directed PSB and recovered 135 isolates at $\geq 10^3$ CFU/mL (27). When a second PSB was performed by bronchoscopy 3 days after start of therapy, 126 (93%) of the initial 135 isolates were not recovered by the second PSB, 7 (5.2%) were recovered at $<10^3$ CFU/mL, and 2 (1.5%) were still present at $\geq 10^3$ CFU/mL. The last two isolates were the only bacteria resistant to initial treatment because of errors in selection of antibiotics. Thus, results of quantitative cultures of respiratory secretions obtained by repeat PSB were consistent with the antimicrobial susceptibilities of isolates obtained by the first PSB. The authors noted that when follow-up PSB cultures were negative, the patients' conditions improved. This study further supports the accuracy of quantitative culture of lower respiratory tract secretions for the diagnosis of VAP.

Repeatability of PSB and BAL

Repeatability, which is defined as the variation in repeated measurements of the same quantity (28), is one measure of the accuracy of a technique in diagnosing the diseases(s) for which it was developed. Marquette and associates performed a study in which a single investigator performed bronchoscopy on 22 patients with suspected VAP (28). At each bronchoscopy, five successive PSB samples were taken from the same area of the lung. All PSB specimens were cultured quantitatively by the same technologist. In each patient, all five PSB procedures identified exactly the same microorganisms. In 59% of the patients, there was more than a 1-log variation in quantitative culture of the five PSB specimens; in 3 (13.6%) of the 22 patients, quantitative culture results were spread out on both sides of the 10^3 CFU/mL breakpoint. Thus, in spite of the substantial variability of the quantitative cultures, all five PSB procedures for 19 (86.4%) of 22 patients gave results on the same side of the breakpoint, indicating acceptable repeatability.

The repeatability of BAL was assessed in a study in which two BALs were performed in the same lobe 30 minutes apart in 44 patients (29). The bronchoscope was sterilized between procedures in each patient. The investigators observed that both BALs yielded negative results in 28 patients and that the same microorganism was recovered from both BALs in 14 of 16 patients. Thus, 40 of 44 pairs of BAL samples yielded the same results, for a repeatability of 90.9%. Results of duplicate BALs for 4 (25%) of the 16 patients with positive cultures were spread out on both sides of the 10^4 CFU/mL diagnostic threshold. Overall, BAL appears to have an acceptable (75%) level of repeatability in patients with positive cultures. Additional studies of the repeatability of PSB and BAL are needed.

Antibiotics and Diagnosis of VAP by Quantitative Culture of Lower Respiratory Tract Secretions

When patients with pneumonia are receiving antimicrobial agents at the time lower respiratory tract secretions are obtained for diagnosis of VAP, cultures may be negative, and concentrations of bacteria may be below the diagnostic threshold. Such uncertainty about the interpretation of culture results from patients on antibiotics has prompted study of the effect of antibiotics on the diagnosis of VAP. Timsit and co-workers assessed the impact of antimicrobial therapy on the diagnosis of VAP by collecting lower respiratory tract secretions by bronchoscopically directed PSB and BAL from patients with suspected VAP (30). Ninety-six patients had not received antimicrobial agents for ≥3 days before bronchoscopy, while 65 patients had been on antibiotics for ≥3 days at the time PSB and BAL samples were obtained. Sensitivity and specificity did not differ for PSB, BAL, and percentage of intracellular organisms in patients receiving and not receiving antibiotics. The authors concluded that when patients acquire pneumonia while on antibiotics for infections at extrapulmonary sites, the microorganisms are resistant to these antibiotics and the diagnostic yields of PSB and BAL are unaffected.

Souweine et al. (31) confirmed and extended the observations of Timsit and co-workers. In 63 episodes of suspected VAP, 12 patients had received no antibiotics in the 4 days before bronchoscopy, 31 had been treated with antibiotics for >72 hours, and 20 had begun antibiotics or had their antibiotic regimen modified within the 24 hours before bronchoscopy. The diagnosis of VAP was made by bronchoscopically directed PSB, BAL, and microscopic examination for intracellular organisms. The sensitivity for the diagnosis of VAP by percentage of intracellular organisms did not differ in the three groups. Nor did the sensitivity of PSB and BAL differ in the group not receiving antibiotics and the group receiving antibiotics for >72 hours. In the group of patients with initiation or change of antibiotics in the 24 hours before bronchoscopy, the sensitivity of PSB and BAL decreased substantially but was restored by reducing the threshold for PSB to 10^2 CFU/mL and for BAL to 10^3 CFU/mL. These studies suggest that the sensitivity of PSB and BAL for the diagnosis of VAP is unchanged in patients who acquire VAP while on antibiotics for >72 hours for treatment of an extrapulmonary infection. Therefore, for such patients lower respiratory tract secretions should be obtained for quantitative culture and microscopic examination before any changes are made in antimicrobial therapy.

Diagnosis of VAP in Patients with ARDS

VAP is more common in patients with ARDS than in those with other causes of respiratory failure (26,32,33); it occurs later and is caused by more resistant microorganisms. The diagnosis of VAP is more difficult in such patients because ARDS and VAP have very similar clinical

manifestations. Chastre et al. observed no significant differences in temperature, leukocyte count, Pao_2/Fio_2 ratio, or radiologic score in patients with ARDS with and without VAP (32). Since clinical criteria for VAP lack both sensitivity and specificity in patients with ARDS, microbiologic data are thought to play a prominent role in the diagnosis of VAP that complicates ARDS (26). In a study of the use of bronchoscopically directed BAL to diagnose VAP in patients with ARDS, bronchoscopic findings modified antibiotic therapy in 91% of patients with positive BAL cultures and prevented the use of new antibiotics in 54% of patients with insignificant growth (33). Given the severity of illness of patients with ARDS, particularly when complicated by VAP, and the great difficulty in differentiating VAP from ARDS on clinical and radiographic grounds, the most effective approach to diagnosis of VAP in patients with ARDS is quantitative culture and microscopic examination of lower respiratory tract secretions.

Data Quality in the Diagnosis of VAP

Quantitative culture and microscopic examination of lower respiratory tract secretions are most effective when attention is paid to the quality of specimens from the lower respiratory tract (8,34,35). The following practices are recommended: 1) Antibiotics should not be started or changed until after lower respiratory tract secretions have been obtained. 2) When bronchoscopically directed techniques are used, secretions should not be suctioned nor anesthetic injected through the working channel of the bronchoscope. 3) Less than 10% return of instilled fluid during BAL probably represents inadequate sampling of the lower respiratory tract. 4) When lower respiratory tract sampling is performed by PSB, the brush must be placed into exactly 1 mL of fluid. 5) Specimens should be delivered immediately to the laboratory. 6) Fewer than 10 cells per field at a magnification of 500x in fluid obtained by PSB probably represents an inadequate sample; resampling should be considered. 7) The presence of >1% epithelial cells indicates an unreliable sample; additional samples should be obtained.

In conclusion, in the absence of gold standard criteria for the diagnosis of VAP, the diagnostic test of choice is quantitative culture and microscopic examination of lower respiratory tract secretions. This approach provides the most accurate diagnosis of VAP and identification of the causative microorganism(s), can predict the onset of VAP and provide the identity and susceptibility of the causative microorganism(s) at the time clinical manifestations of VAP appear, can be used to assess the cause of therapy failure, provides the most effective modality for diagnosis of VAP that complicates ARDS, minimizes misclassification of cases of VAP for studies on the epidemiology of VAP, and minimizes the selective pressure for development of resistant microorganisms. Whether this approach to the diagnosis of VAP has an effect on outcome and reduces deaths is yet to be determined.

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Preventing Infections in Non-Hospital Settings: Long-Term Care

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Infection concerns in long-term care facilities include endemic infections, outbreaks, and colonization and infection with antimicrobial-drug resistant microorganisms. Infection control programs are now used in most long-term care facilities, but their impact on infections has not been rigorously evaluated. Preventive strategies need to address the changing complexity of care in these facilities, e.g., the increased use of invasive devices. The anticipated increase in the elderly population in the next several decades makes prevention of infection in long-term care facilities a priority.

In the United States, more patients are in long-term than in acute-care facilities. Long-term care facilities deliver various services to persons with a range of functional disability and disease. While some of these facilities provide care to young as well as elderly persons and psychiatric as well as medical care, most are nursing homes, which provide care to the elderly. The approach to preventing infection in nursing homes will vary with characteristics of the population.

Infections in Long-Term Care Facilities

Infections are common in long-term care facilities (1). Major areas of concern are endemic infections, outbreaks, and colonization and infection of residents with antimicrobial-drug resistant microorganisms.

The most frequent endemic infections are respiratory tract, urinary tract, skin and soft tissue, and gastrointestinal infections (primarily manifesting as diarrhea) (Table 1). Respiratory tract infections include upper tract infections, such as pharyngitis and sinusitis, and lower tract infections, such as bronchitis and pneumonia. Pneumonia is the only infection in this setting that is often fatal (1). Urinary tract infections are the most frequent infections; while most patients are asymptomatic, the prevalence rates of bacteriuria are 25% to 50% (2). Skin and soft tissue infections include decubitus ulcers, infected vascular or diabetic foot ulcers, erysipelas, and other types of cellulitis. Nonbacterial causes of skin infection include oropharyngeal or intertriginous candidiasis, as well as herpes zoster.

Table 1. Common endemic infections in long-term care facilities (1)

Site of infection	Frequency/1,000 patient days
Urinary tract	0.46 – 4.4
Respiratory tract	0.1 – 2.4
Skin, soft tissue	<0.1 – 2.1
Gastrointestinal tract	0 – 0.9

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Many bacteria, fungi, viruses, and parasites cause outbreaks in nursing homes (Table 2). The most common are outbreaks of respiratory infection caused by influenza A (3). However, parainfluenza and respiratory syncytial viruses also cause respiratory outbreaks. Gastrointestinal outbreaks, including those caused by bacteria such as *Escherichia coli* O157:H7 and *Salmonella* species, as well as small round enteric viruses, are also common. Skin outbreaks with scabies are frequent.

Nursing home residents are at risk for colonization with antimicrobial drug-resistant microorganisms (1,4,5), including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), penicillin-resistant *Streptococcus pneumoniae*, gram-negative microorganisms with extended-spectrum beta-lactamases, and increasingly, quinolone-resistant Enterobacteriaceae. Some U.S. facilities have reported rates of colonization with MRSA as high as 30% (1). Colonization with resistant microorganisms usually occurs in the acute-care facility, and transmission within the long-term care facility is uncommon in the nonoutbreak situation.

Table 2. Microorganisms reported to cause outbreaks in long-term care facilities (1)

Viruses	Bacteria	Parasites ectoparasites
Influenza A,B	Group A *Streptococcus*	*Giardia lamblia*
Parainfluenza	*Staphylococcus aureus*	*Entamoeba histolytica*
Respiratory syncytial virus	*Streptococcus pneumoniae*	*Sarcoptes scabiei*
Caliciviruses	*Haemophilus influenzae*	
Adenovirus	*Bordetella pertussis*	
Rhinovirus	*Salmonella* spp.	
Coronavirus	*Shigella* spp.	
Rotavirus	*Campylobacter jejuni*	
	Aeromonas hydrophila	
	Escherichia coli O157:H7	
	Clostridium perfringens	
	Bacillus cereus	
	Mycobacterium tuberculosis	

Considerations Unique to Long-Term Care Facilities

While the reasons for preventing infections are the same in long-term and acute-care facilities, several considerations relevant to prevention of infection differ in long-term care populations (6). For most long-term care residents, the facility is their domicile. All members of society experience infections within their homes; to what degree are unusual measures appropriate or realistic to prevent the usual infections in this setting? When is it reasonable to limit mobility or social interaction of persons in their usual residence to prevent transmission of infection?

Long-term care residents also are often highly functionally impaired. Many are incontinent, immobile, and confused or demented. The worse the functional status, the greater the likelihood of infection or colonization with resistant microorganisms (1,4,7). For example, incontinence and impaired mental status have consistently been associated with asymptomatic urinary tract infection (2). MRSA colonization is more likely to be identified in residents with pressure ulcers or fecal incontinence or who are bed bound or require feeding tubes or urinary catheters (7). In most cases, impaired functional status is a determinant of admission to long-term care and is not modifiable. If the major predictors of infection in long-term care facilities are poor functional status and co-existing chronic illness, and these conditions cannot be altered, to what extent is it realistic to anticipate that endemic infections can be prevented in such residents? In addition, with the number and severity of existing conditions, how much illness or death is attributable to infections per se, rather than to underlying chronic disease? Assessing the impact of infection on patient outcome in evaluating interventions to prevent infection is, thus, often problematic. An example is a decision to provide comfort care but not to treat pneumonia with antibiotics in severely impaired patients.

Diagnostic uncertainty is also a major issue in identifying infections and assessing interventions to prevent them. Standard clinical guidelines for surveillance of infection have been developed for long-term care facilities (8), but many barriers to diagnostic accuracy exist (9). Communication is impaired because of dementia, blindness, or deafness, and clinical assessment is complicated by symptoms associated with chronic conditions, such as cough or incontinence. The very high prevalence of asymptomatic bacteriuria means that, in a patient with nonspecific deterioration in clinical status, a positive urine culture has a low predictive value for identifying symptomatic urinary infection (10). Similarly, the high prevalence of oropharyngeal colonization with gram-negative microorganisms indicates that isolation of Enterobacteriaceae from the sputum of a person with lower respiratory tract infection has a low predictive value for identifying the infecting microorganism (2).

Infection Control Programs

In the last 2 decades, an increasing number of long-term care facilities have developed infection control programs with surveillance and control activities (11,12). A major contribution to this development was the publication of guidelines by the Association for Professionals in Infection Control and Epidemiology (APIC) in 1991 (13). These were updated in 1997 as the Society for Healthcare Epidemiologists of America (SHEA)-APIC position paper on infection prevention and control in long-term care facilities (6). The document reviews infections in such facilities and makes specific recommendations for a feasible and relevant control program.

Differences between acute-care and long-term care facilities affect the development and management of infection control (6). Generally, long-term care facilities have fewer resources. Part-time employees or employees with many other responsibilities are often responsible for infection control, and the secretarial and computer resources may be limited. The educational level of the staff is often lower than in acute-care facilities. Radiologic and laboratory facilities are often not on site (9). Diagnostic tests may not be obtained because access to such tests requires patient transfer. Return of test results on microbiologic specimens may be prolonged. The medical record often is inadequate and access to physician resources is limited. As observation without intervention may be the more appropriate management approach in some cases, this physician shortage may lead to overuse of empiric antibiotics. Finally, limited clinical research is available to validate either an overall infection control program or specific components of a program in the long-term care facility.

SHEA-APIC infection control guidelines are evidence based (6). They categorize recommendations as A (having good evidence to support the recommendation), B (moderate evidence to support a recommendation), and C (poor evidence to support the recommendation). The quality of evidence is designated as follows: I (at least one randomized controlled trial), II (at least one well-designed clinical trial without randomization), or III (opinions of respected authorities). The infrequency of evidence designations in the guidelines demonstrates the limitations of available research (6). Only five recommendations are AI, BI, AII, or BII: for handwashing, tetanus-diphtheria immunization, annual influenza immunization, and hepatitis B and influenza immunizations for employees. All other recommendations are AIII or BIII, i.e., based on opinions of respected authorities. Thus, further evaluation of the effectiveness of specific interventions is needed.

Clinical Trials of Interventions to Prevent Infections

Results of several recent clinical trials in long-term care settings (Table 3) have been uniformly negative with respect to the interventions assessed but are helpful in addressing the question of the extent to which endemic infections are preventable in such facilities (14-17). Many other issues relevant to specific interventions in care in long-term care facilities require assessment, particularly with the increasing use of invasive devices. For example, appropriate care needs to be explored for patients with chronic tracheostomies and respirator therapy, dialysis therapy, central lines, and percutaneous feeding tubes to limit infections and minimize cost.

Management of Drug-Resistant Microorganisms

Antimicrobial drug-resistant microorganisms may cause illness and death in acute-care facility residents (1,4). However, it is not clear that a high prevalence of colonization with these microorganisms is associated with excess illness or death (7). In addition, no evidence supports the use of stringent barrier precautions to decrease illness or death from antimicrobial drug-resistant microorganisms in long-term care facilities (5,7). Nevertheless, such facilities have repeatedly raised barriers to admission of patients colonized

Table 3. Assessing effectiveness of selected interventions in decreasing infections in long-term care facilities

Study question (reference)	Outcome
Does vitamin A supplementation decrease the frequency of infection? (14)	No decrease in overall occurrence of infection with vitamin A supplementation
Do outcomes differ with routine percutaneous feeding tube changes compared with as-needed changes? (15)	No difference in infection or other relevant outcomes with routine tube changes
Does treatment to eradicate MRSA[a] colonization decrease the frequency of MRSA infection? (16)	No decrease in infection with antimicrobial therapy
Does the frequency of symptomatic urinary infection differ with clean or sterile intermittent catheterization? (17)	No difference in frequency of infection or antimicrobial use

[a]MRSA = methicillin-resistant *Staphylococcus aureus*.

with drug-resistant microorganisms, and management of patients colonized or infected with resistant microorganisms has sometimes been inappropriate.

Observational studies suggest that the intensity of barrier precautions, isolation or cohorting, or environmental cleaning does not decrease the likelihood of transmission of MRSA or VRE (7). Thus, additional precautions are recommended for patients colonized with these microorganisms only when the patients are a documented source of transmission to other patients (4,5) (e.g., MRSA patients with extensive skin lesions that cannot be covered or VRE patients with diarrhea and incontinence).

Conclusions

There are many complex, unanswered questions in the prevention of infection in long-term care facilities. Priority issues for evaluation include determining the most appropriate surveillance strategies for endemic infections and identifying outbreaks early and efficiently. Recommendations for influenza A have been made (3). However, when should cultures be obtained from patients with diarrhea? What is appropriate surveillance for endemic infections, and should it be focused only in areas where an opportunity for prevention exists?

The feasibility of preventing endemic infections requires further study. In addition, the feasibility of decreasing or preventing high colonization rates with drug-resistant microorganisms in long-term care facility residents needs to be assessed, since most patients acquire these microorganisms in acute-care facilities. Practices related to antimicrobial-drug use are key to this question. In addition to controlled comparative trials to identify appropriate antimicrobial-drug use, patients who do not require treatment need to be identified. The role of drug therapy in preventing infections is also not adequately studied. Finally, an infection control program may be costly. What are the benefits of such a program? Decreased length of stay, for example, will not usually be a meaningful outcome. Thus, while substantial progress has been made in the past decade in managing infection prevention, many issues still need to be answered. As the elderly population will increase in the next two decades, addressing these problems must be a priority.

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Infection Control in Home Care

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Although home care has expanded in scope and intensity in the United States in the past decade, infection surveillance, prevention, and control efforts have lagged behind. Valid and reliable definitions and methods for surveillance are needed. Prevention and control efforts are largely based upon acute-care practices, many of which may be unnecessary, impractical, and expensive in a home setting. Infectious disease control principles should form the basis of training home-care providers to assess infection risk and develop prevention strategies.

Efforts to decrease length of hospital stay and shift care to ambulatory settings, as well as patient and family preference to receive care at home, have contributed to the substantial growth of home care in the past decade. As life expectancy in the U.S. population continues to increase and patients with chronic illnesses live longer, home care will continue to expand.

Home care has also broadened in type and scope in the past decade. Most patients are elderly and have chronic conditions requiring skilled nurses and aides. High-tech home care is provided to patients of all ages and may include home infusion therapy, tracheotomy care and ventilator support, dialysis, and other highly invasive procedures. In addition, home-care nurses provide assessment, education, and support to post-acute-care patients who might have spent several additional days in the hospital but are now discharged to cut costs. This category of patient may include postoperative patients, postpartum mothers and their newborns, and patients with acute medical conditions such as newly diagnosed diabetes and recent strokes.

In the United States, 9,655 agencies (1998 data) (1) provide home care to patients. Infection control and health-care epidemiology have not kept up with the needs of the home-care providers or their patients. As this segment continues to expand and services provided in the home increase, the infection control community must address the risks and needs of home care.

Infection Surveillance, Prevention, and Control in Home Care

Infection surveillance, prevention, and control have constituted a discipline that has been acute-care based and oriented for the past 40 years. However, as the health-care system continues to shift delivery of care from hospitals to other settings, surveillance, prevention, and control programs must respond. Since efforts to measure the incidence of home-care acquired infections, study the associated risk factors, and adapt prevention and control measures for home care are nascent, available studies provide minimal information and little guidance. A few articles have appeared in non-U.S. publications. Overall, the literature is sparse, but expanding slowly (2-22).

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Systems of Surveillance: Definitions and Methods

Without valid data on the incidence of home-care acquired infection and analysis of risk factors, developing control efforts is difficult. Thus, initial resources must be directed toward developing measurement systems. Definitions and methods for the surveillance of nosocomial infection cannot be readily applied to home care. First, definitions, such as those developed by the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infection Surveillance (NNIS) system (23), rely heavily on laboratory data, including cultures and serologic tests. In home care, the diagnosis of infection for clinical purposes is frequently made on an empiric basis with substantial reliance upon physical signs and symptoms. In fact, physicians routinely rely on the assessment skills of home-care nurses and may not see a patient before making a presumptive diagnosis and writing prescriptions. The current reimbursement system does not support the use of cultures and laboratory tests used for hospitalized patients. For example, cultures are not routinely obtained to diagnose or confirm infections of the urinary tract, respiratory tract, or wound or skin sites. Cultures are more frequently obtained to confirm and appropriately treat bloodstream infection in patients undergoing home infusion therapy.

Definitions of home-care acquired infection developed for surveillance will need to rely more heavily on clinical signs and symptoms and tests that can be performed by the home-care nurse at the bedside (e.g., urine dipstick testing). A scheme that includes probable home-care acquired infection (i.e., clinical signs and symptoms of pneumonia) as well as definite home-care acquired infection (i.e., confirmed by chest X ray and sputum culture) may be considered. Once developed, definitions must be examined for validity, sensitivity, and specificity. However, methods to identify patients at risk and apply the definitions are also critical.

Surveillance methods routinely used in acute care, such as cultures and other laboratory tests, are not practical in home care (24) so other sources of information and methods of screening must be developed. In addition, a system that relies on a designated person(s) to review medical records and assess patients for infection, such as infection control

professionals do in hospitals, is impractical in home care because of the logistics of patients, staff, and medical records.

A more suitable approach is a two-tiered system, which relies on home-care nurses to identify and report patients with clinical signs and symptoms of infection and on an infection control nurse to review evidence and ascribe a definition (Table). Screening criteria for home-care nurses would include fever, new antibiotic order, purulent drainage from a wound, change in color or odor of urine, change in consistency or color of sputum, respiratory rales and rhonchi, and increased serum leukocytes. Once made aware of these patients, a designated nurse can review the evidence (e.g., clinical signs and symptoms, available laboratory data, nursing and physician progress notes) and apply the definition of home-care acquired infection. This approach should enhance both sensitivity (more nurses observing and reporting patients with clinical signs and symptoms of infection) and specificity (one nurse applying the definition of infection). The use of a single infection control nurse should also improve the reliability of data.

What Is Needed

To achieve a system to measure and study the incidence and risks for home-care acquired infection, infection control must develop valid definitions for home-care acquired infection and practical methods for surveillance. These definitions and methods must be developed through a broad, national effort that includes participation by home-care professionals as well as infection control practitioners. These professionals must take a very practical approach to this endeavor and may have to forego rigid application of epidemiologic techniques for a more suitable surveillance system. The Association for Professionals in Infection Control and Epidemiology has recently published draft definitions for surveillance in home care (25). In parallel, home-care professionals must engage in learning the epidemiologic principles of surveillance systems (26) and apply or adapt them as faithfully as possible.

Once consensus is reached on definitions and methods and we describe the epidemiology of home-care acquired infections, we can study specific risk factors for infection. Home-care professionals need the assistance, support, and practical guidance of infection control professionals. Because of substantial financial challenges in home care, one nurse is often responsible for quality improvement, safety, risk management, and infection control. These professionals can apply and manage surveillance systems but will need substantial guidance and support in developing them.

Efforts to initiate surveillance systems do exist. The Missouri Home Care Alliance began a program in 1997 to develop definitions and collect data from home-care agencies in that and other states. With assistance from CDC's Hospital Infections Program, the alliance has made progress in developing a surveillance system and sharing data. The Florida Hospital Association also sponsored a surveillance project for hospital-based home-care agencies (6) in which they studied the incidence of urinary tract infections and central-line infections. The Arizona Association for Home Care also described its methods and results in a cooperative study to measure and compare rates of urinary tract infections (7). Similar efforts were undertaken in a collaborative effort to determine device-related rates of urinary tract and bloodstream infections in California, Kentucky, and Indiana (8). These studies provide initial descriptions of incidence of home-care acquired infections. Authors report catheter-related urinary tract infection rates

Table. Criteria for inclusion in definitions of home-care-acquired infection[a]

Site of infection	Clinical data	Laboratory data
Catheter-related UTI[b]	Change in characteristics of urine, fever, pain	Elevated serum leukocytes, evidence of UTI in urinalysis, evidence of leukocytes in urine dipstick test, positive urine culture (>10^5 CFU of a single organism per mL urine)
Postoperative pneumonia	Change in character of sputum, decreased breath sounds, increase in rales and rhonchi, fever, shortness of breath, pain	Elevated serum leukocytes, sputum Gram-stained smear with evidence of respiratory infection, positive sputum culture, positive chest X ray
Catheter-related bloodstream infection	Fever with chills and rigors, redness, tenderness, or pain at insertion site, purulent drainage at site	Elevated serum leukocytes, positive blood culture, positive catheter culture (after catheter removal)
Skin and soft tissue infection	Pain, swelling, tenderness at site, inflammation and warmth, purulent drainage, fever	Gram-stain smear with leukocytes and organisms, positive culture, elevated serum leukocytes
Endometritis in postpartum patients	Uterine tenderness and abdominal pain, purulent vaginal drainage (lochia), foul-smelling lochia, fever	Positive Gram-stain smear of lochia, positive culture of lochia, remarkably elevated serum leukocytes

[a]Source: Rhinehart E, Friedman M. Infection control in home care. Gaithersburg (MD): Aspen Publishing, Inc.;1999 (22).
[b]UTI = urinary tract infection.

of 2.8 per 1,000 catheter days (6) to 4.5 per 1,000 catheter days (8). Measures of intravenous catheter-related bloodstream infections range from 1.1 per 1,000 catheter days (8) to 4.2 per 10,000 catheter days (2). Data from these studies must be interpreted with caution, however, since surveillance in this area is in its initial stages and definitions and methods are not uniform. More studies are in progress, and eventually there will be consensus on such issues.

Prevention and Control of Home-Care Acquired Infection

Even without reliable surveillance data, we know that infection prevention and control in home care is quite different from that in acute care. In acute care, a patient's risk for nosocomial infection is related not only to the severity of illness and exposure to invasive interventions and devices but also to environmental risks, including exposure to other patients and inanimate reservoirs of nosocomial pathogens. The home-care patient may have less clinical "acuity" (i.e., intensity or degree of care needed) but may have substantial host risk factors, including advanced age, chronic illness, or immunosuppression. Much of home care is provided by family members in a setting that is much less structured and controlled than the hospital environment. Plumbing, sanitation, and ventilation may be poor or absent. Nonetheless, basic principles of prevention and control can be adapted and applied with large doses of realistic risk assessment and common sense.

Because written resources for home-care practice are lacking, many home-care providers have adopted unnecesssary infection control practices to reduce risk for patients, including the ritual of nursing bag technique (i.e., placing a newspaper under the nursing bag), policies that require the routine disinfection of noncritical devices (e.g., stethoscopes and blood pressure cuffs) after every use, and procedures that require handwashing based on seemingly arbitrary criteria (e.g., upon entering the home). Some of these practices are not only unnecessary but also costly (e.g., routine changing of urinary drainage bags every 30 days).

Patient-care practices to reduce the risk for home-care acquired infection must be based on the basic science embodied in the chain of infection model. Actual risk and appropriate prevention and control strategies must be incorporated in recommendations for policy and procedure. Using this simple approach to determine actual risk and implement the appropriate prevention and control strategies will lead to more reasonable and less ritualistic practices for patient care and use of precautions to prevent the spread of infections to others. Infection control professionals should approach their responsibility to guide home-care providers by first addressing educational needs. Knowledge of infection control principles enables home-care providers to develop their own approaches to patient care and make decisions about infection risk and its reduction.

Patient-Care Practices

Infection prevention strategies in home care should focus on home infusion therapy, urinary tract care, respiratory care, wound care, and enteral therapy. Most recommended practices on intravenous therapy (27) do not require adaptation for the home. However, in care involving other sites, the risk may be lower, allowing for adaptation of practices designed for hospitalized patients. For example, use of indwelling urinary catheters creates an inherent risk for infection. In the hospital, considerable efforts are exerted to maintain an intact, closed urinary drainage system (28); however, in home care the system is frequently interrupted when an ambulatory patient uses a leg bag. Drainage bags may also be disinfected in the home, a procedure rarely (if ever) seen in a hospital. Guidance provided to accomplish this procedure is empiric (21,22). Similarly, empiric approaches have been developed for home wound care. Surgical site infection should rarely, if ever, be a home-care acquired infection if the wound is primarily closed and no drains are left in place. However, if a surgical patient is sent home with drains, a surgical site infection may develop, and wound-care procedures must address this risk. More frequently, home-care patients have other types of wounds, such as stasis ulcers and pressure sores, which are commonly colonized with gram-negative flora and may become infected with the patient's own organisms. Again, procedures for care of these wounds must be based on the genuine potential for contamination and infection. Arbitrary instructions to discard irrigation fluids at set intervals (e.g., every 24 or 48 hours) are not helpful. Procedures must be practical, with guidance to use containers of fluid that will be used up in two to three visits (i.e., no more than a 500-mL bottle) and incorporate methods to avoid contamination of fluids (e.g., proper handling of the cap, storage away from children and pets) (22).

Many home-care patients receive enteral therapy, introducing the risk for gastrointestinal infection. Again, to reduce this risk, focus must be placed on refrigeration of the enteral feeding and meticulous care of kitchen appliances and tools, such as blenders, used in its preparation. Cleaning blender parts, measuring cups, and spoons in a dishwasher after use is probably sufficient; sterilizing them is probably not necessary (22).

Use of Barrier Precautions

The rationale and strategy for use of precautions in home care differ substantially from those applied in hospitals (29). In most cases, the use of gowns, gloves, and masks in the care of homebound patients is recommended to protect the health-care provider, not the patient. In addition to standard precautions, care givers in the home may need to use masks only when caring for patients with pulmonary tuberculosis. The exception to this rule may be the home-care patient who is colonized or infected with multidrug-resistant organisms (16,30). Although these organisms are not known to be a risk to providers, they may be transmitted to other home-care patients through inanimate objects or hands. Thus, home-care patients known to have a multidrug-resistant organism should be cared for through use of appropriate barriers. Reusable equipment such as stethoscopes and blood pressure cuffs should remain in the home. If practical, such patients should be seen as the last appointment of the day. If this is not possible, visits should be scheduled to avoid seeing patients at risk, such as those requiring wound care, after seeing a patient with multidrug-resistant organisms.

The Future of Infection Control in Home Care

The next several years will be critical for developing surveillance systems for home care. Additional studies and reports are needed to improve knowledge of the risk factors for home-care acquired infections. We also need to study the

effects of the current empiric practices for preventing such infections. Hospital-based infection control professionals must support and guide their home-care colleagues to develop an evidence-based approach to infection control in home care. A scientific approach will help identify valid risks and successful risk-reduction strategies, as well as improve the quality of care and preserve resources.

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Automated Methods for Surveillance of Surgical Site Infections

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Automated data, especially from pharmacy and administrative claims, are available for much of the U.S. population and might substantially improve both inpatient and postdischarge surveillance for surgical site infections complicating selected procedures, while reducing the resources required. Potential improvements include better sensitivity, less susceptibility to interobserver variation, more uniform availability of data, more precise estimates of infection rates, and better adjustment for patients' coexisting illness.

The Centers for Disease Control and Prevention (CDC) recommends routine surveillance for surgical site infections (1); accrediting agencies such as the Joint Commission for Accreditation of Healthcare Organizations require it. Surveillance identifies clusters of infection, establishes baseline risks for infection, provides comparisons between institutions or surgical specialties, identifies risk factors, and permits evaluation of control measures (2). Achieving these goals requires health-care systems to have access to different information types (Table 1).

An ideal surveillance system should have several attributes, including meaningful definitions of infection, consistent interpretation of classification criteria, applicability to procedures performed in both inpatient and ambulatory facilities, ability to detect events after discharge, sufficient precision to distinguish small absolute differences in attack rates, ability to adjust for different distribution of severity of illness across populations, and reasonable cost. Most current systems lack at least one of these attributes; for example, the system recommended by CDC's Hospital Infection Control Practices Advisory Committee (HICPAC) (3) is excellent for clinical decision-making, but some elements are difficult to apply for surveillance purposes. Information required to apply some of its criteria may not be available for all cases; for example, the criterion of recovery of microbial growth from a normally sterile site may be affected by variation in obtaining specimens for culture. Some elements of CDC's National Nosocomial Infections (NNIS) System definition require substantial judgment or interpretation. An example is determining whether purulent drainage is present: An attending physician's diagnosis is sufficient, although the way physicians record or confirm their diagnoses may differ.

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Table 1. Goals and needs of surgical site infection surveillance (2)

Goal	Principal needs
Control of clusters	
Identify clusters of infection.	Real-time detection of events. Attack rates and case-mix adjustment are not a high priority. Should include all patients.
Support of quality improvement programs	
Establish baseline infection rates.	Sufficient precision to identify absolute differences of a few percent. Typically includes all patients.
Comparison of institutions or surgical specialities.	Case-mix-adjusted attack rates. Identical detection methods that are applied and interpreted identically across sites. Sufficient precision.
Evaluate control measures (in the usual situation no randomized trial).	Comparably ascertained rates of over time.
Research on epidemiology of infection	
Identify risk factors.	Detailed data on many attributes of patients and procedures. Population can be small, but must be representative.

For these reasons, case ascertainment is affected by considerable interobserver variability (4).

Although most surgical site infections become manifest after the patient is discharged from the hospital (5-12), there is no accepted method for detecting them (13). The most widely described method of conducting postdischarge surveillance is questionnaire reporting by surgeons. This method has been shown to have poor sensitivity (15%) and

[1]The CDC Eastern Massachusetts Prevention Epicenter includes Blue Cross and Blue Shield of Massachusetts, CareGroup, Children's Hospital, Harvard Pilgrim Health Care, Partners Healthcare System, Tufts Health Plan, and Harvard Medical School. Investigators include L. Higgins, J. Mason, E. Mounib, C. Singleton, K. Sands, K. Kaye, S. Brodie, E. Perencevich, J. Tully, L. Baldini, R. Kalaidjian, K. Dirosario, J. Alexander, D. Hylander, A. Kopec, J. Eyre-Kelley, D. Goldmann, S. Brodie, C. Huskins, D. Hooper, C. Hopkins, M. Greenbaum, M. Lew, K. McGowan, G. Zanetti, A. Sinha, S. Fontecchio, R. Giardina, S. Marino, J. Sniffen, E. Tamplin, P. Bayne, T. Lemon, D. Ford, V. Morrison, D. Morton, J. Livingston, P. Pettus, R. Lee, C. Christiansen, K. Kleinman, E. Cain, R. Dokholyan, K. Thompson, C. Canning, D. Lancaster.

positive predictive value (28%), even when surgeons are compliant in returning the questionnaires (5). Moreover, a questionnaire-based surveillance system requires substantial resources. Reporting by patients via questionnaires also has poor sensitivity (28%) because many patients do not return questionnaires mailed to them a month after surgery. Telephone questionnaires have been used effectively but are too resource intensive for routine use.

Many procedures must be monitored to allow confident conclusions that relatively small differences in observed attack rates do not reflect chance variations. Identifying these small differences, understanding their cause, and undertaking quality improvement programs to reduce their occurrence would have large consequences when applied to the >45 million surgical procedures performed annually in the United States (14). Reducing the overall infection rate by a quarter of a percent would prevent >100,000 infections per year. For coronary artery bypass surgery alone, a one percentage point decrease in the risk for infection would prevent >3,500 infections per year in the United States (15). Because of the need to observe large numbers of procedures, conducting surveillance for the entire surgical population is desirable. However, to conserve scarce resources, some programs survey only a fraction of their procedures or rotate surveillance among different procedure types.

Determining whether relatively small differences in infection rates result from differences in care rather than in patients' susceptibility to infection requires robust risk-adjustment methods that can take into account different case-mixes in different institutions. Available methods do not have optimal resolution and depend in part on the Anesthesia Society of America (ASA) score (3,16). The ASA score, a subjective assessment of the patient's overall health status, may reflect interobserver variability (17) that can adversely affect stratification of risk for surgical infection (18).

Automated methods to augment current surveillance methods should improve the quality of surveillance for surgical site infections and reduce the resources required. To achieve these goals, surveillance should be based on the growing body of data that health-care systems, including hospitals, physicians' offices, health maintenance organizations (HMOs), and insurance companies, routinely collect during care delivery. Many types of automated data are now or will soon become widely available, including information about patients, surgical procedures, and patients' postoperative courses (Table 2). Three ways to use these data to support surveillance programs are inpatient surveillance, postdischarge surveillance, and case-mix adjustment.

Table 2. Automated health-care data potentially useful for surgical site infection surveillance

Type of information	Availability of this information in specific locations: Hospitals[a]	Automated medical records in physicians' offices	Payors (HMOs, insurers)
Demographic/ personal information			
Sex	Usually	Usually	Usually
Age	Usually	Usually	Usually
Smoking status	Rarely	Sometimes	Rarely
Body mass index	Rarely	Sometimes	Rarely
Preoperative health status			
Diagnoses	Sometimes	Usually	Usually
Procedures	Rarely	Sometimes	Usually
Drug therapy	Sometimes	Sometimes	Usually
ASA score	Sometimes	Rarely	Rarely
Procedure data			
Type (ICD-9, CPT)	Usually	Sometimes	Usually
Duration	Sometimes	Rarely	Rarely
Inpatient postoperative care			
Diagnoses	Usually	Sometimes	Usually
Reoperation	Usually	Rarely	Usually
Incision and drainage	Usually	Rarely	Sometimes
Microbiology data	Usually	Rarely	Rarely
Antibiotic therapy	Usually	Rarely	Rarely
Postdischarge care			
Diagnoses	Rarely	Usually	Usually
Reoperation in another hospital	Rarely	Sometimes	Usually
Incision and drainage	Rarely	Usually	Usually
Microbiology data	Rarely	Usually	Sometimes
Antibiotic therapy	Rarely	Sometimes	Usually

[a]Excludes hospital-based physicians' offices.

Inpatient Surveillance for Surgical Site Infections

One of the most widely available types of automated data useful for inpatient surveillance is antibiotic exposure data from pharmacy dispensing records. Studies have indicated that antibiotic exposure is a sensitive indicator of infection (19,20), since relatively few serious infections are managed without antibiotics. Poor specificity (too many false positives) has been a major problem, however, because antibiotics are so widely used after surgery for extended prophylaxis, empiric therapy of suspected infection, and treatment of infections other than surgical site infections.

One way to improve the usefulness of postoperative antibiotic exposure as a marker of infection is to consider the timing and duration of administration, rather than just its occurrence. Quantitative antibiotic exposure is a measure that reduces the number of false positives by excluding patients who receive a brief course; however, there is a trade-off between sensitivity and specificity. Constructing receiver-operating characteristic curves helps to identify the amount of treatment with the best combination of sensitivity and specificity. For example, acceptable identification of infections after cesarean section was achieved by requiring a criterion of at least 2 days of parenteral antibiotic administration (21). In that study, the sensitivity was 81% and the specificity was 95% compared with infections identified by NNIS surveillance.

Quantitative inpatient antibiotic exposure is useful for identifying infections in coronary artery bypass surgery patients (22). Receiver-operating characteristic curves were used to demonstrate that patients with infections were best identified as those who received postoperative antibiotics for at least 9 days, excluding the first postoperative day. This criterion included both oral and parenteral antibiotics and ignored gaps in administration. This approach has two important implications for surveillance systems: It allows this mechanism to identify patients readmitted for treatment

of infection within 30 days of surgery, and automated programs to identify patients who meet this threshold are substantially easier to implement. The 9-day exposure cutoff resulted in greater sensitivity (approximately 90%) for identifying surgical site infections than conventional prospective surveillance (approximately 60%) conducted in the same hospitals. A disadvantage of the antibiotic threshold criterion is that it identifies events that are not surgical site infections, including problematic wounds that do not meet the HICPAC criteria for infection, other types of hospital infections, and other long durations of antibiotic use.

Studies under way will determine the utility of this approach in a larger number of hospitals. Preliminary data from nine hospitals suggest that surveillance for antibiotic use provides useful information. For cesarean section, prospective comparison of a quantitative antibiotic exposure threshold to conventional prospective NNIS surveillance and International Classification of Diseases, 9th Revision (ICD-9), discharge diagnosis codes indicates that antibiotic surveillance has considerably better sensitivity (89%) than either NNIS surveillance (32%) or coded discharge diagnoses (47%). This difference was consistent across hospitals (23).

Quantitative thresholds for antibiotic exposure should be chosen individually for specific surgical procedures, since the value for cesarean section (2 days) differs from that for coronary artery bypass grafting (9 days) and there may be no useful threshold for some procedures. These values may also need to be reassessed as medical practice evolves. It will be important to understand the discrepancies between the results of formal NNIS surveillance and antibiotic surveillance. In some cases, patients who receive more than the threshold duration of antibiotic therapy appear to have clinically relevant infectious illness, such as fever and incisional cellulitis with no drainage.

Postdischarge Surveillance for Surgical Site Infection

Because most infections become manifest after discharge and many patients with infections never return to the hospital where the surgery was performed (5), traditional inpatient surveillance methods are not sufficient. In addition, conventional methods for postdischarge surveillance, including surgeon questionnaires, are highly inaccurate, with both low sensitivity and specificity.

Information about postdischarge care is available in office-based electronic medical records of coded diagnoses, procedures, tests, and treatments from the automated billing and pharmacy dispensing data maintained by most HMOs and many insurers. Pharmacy dispensing information is typically available for insured patients who have a pharmacy benefit. Together, these automated data elements identified >99% of postdischarge infections that occurred after a mixed group of nonobstetric surgical procedures (5). This high sensitivity came at the cost of low specificity (many false positives requiring manual review of medical records).

Recursive partitioning, logistic regression modeling, and bootstrap methods have made it possible to preserve good sensitivity while improving specificity by combining automated data from inpatient and ambulatory sources. The resulting algorithms use these automated data to assign to each patient an estimated probability for postoperative infection. These probabilities of infection, based on postoperative events that indicate infection has occurred, must be distinguished from predictions based on personal risk factors such as diabetes or obesity or on characteristics of the procedures such as the duration of surgery.

Choosing a lower probability threshold results in higher sensitivity and lower specificity, whereas a higher threshold improves specificity at the expense of sensitivity. For example, using automated data from both HMOs and ambulatory medical records permitted a sensitivity of 74% and a specificity of 98%, for a predictive value positive of 48%. A higher sensitivity, 92%, was achieved at the expense of lowering the specificity to 92%, for a predictive value positive of 21% (Figure) (24).

This work has been extended to surveillance for inpatient and postdischarge surgical site infections following coronary artery bypass surgery in five hospitals (25). That study found that HMO data alone identified 73% of 168 infections and hospital data alone identified 49% of the same infections. Separate algorithms have been developed to identify postpartum infections occurring after discharge (26).

The utility of automated data sources might be improved in several ways: 1) A procedure-specific algorithm will likely perform better than a general one. 2) Algorithms can be improved to further reduce the number of false positives (e.g., by excluding codes for infection that occur on the same day as a surgical procedure or for antibiotics dispensed before the second postoperative day). 3) These algorithms should be made robust enough for general use by including all ICD-9 and Current Procedural Terminology codes that might be used for surgical site infections.

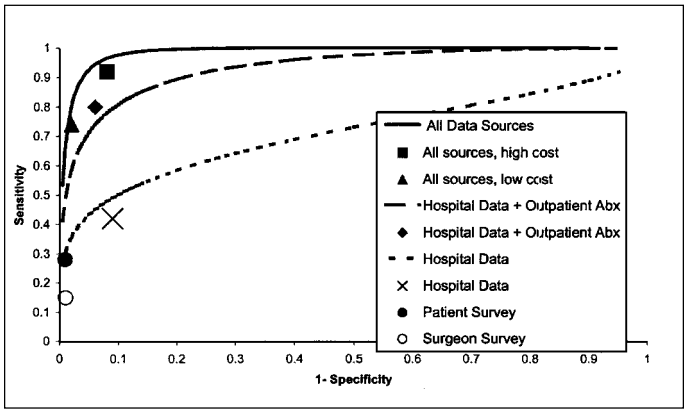

Figure. Performance of various methods for detection of postdischarge surgical site infections for 4,086 nonobstetric surgical procedures with no inpatient infection. Lines represent fitted receiver operating characteristic (ROC) curves for three logistic regression models, which differ by data sources available for generating probabilities. Points represent performance of four different recursive partitioning models and data from patient and physician surveys. For analyses limited to hospital data and outpatient antibiotic (Abx) dispensing data, the logistic regression model had equivalent performance to classification trees at the points shown. The fitted ROC curve falls below this point because most procedures clustered around a few discrete probabilities and limited data points cause approximation of the ROC curve to be less accurate. The recursive partitioning high-cost model accepts 15 false-positives at the margin to capture one true infection; the low-cost model accepts 5 false positives at the margin (24). (Figure originally published in Sands et al. Journal of Infectious Diseases 1999;179:434. Copyright 1999, University of Chicago Press. Reprinted with permission.)

Improved Case-Mix Adjustment Methods

As quality improvement and patient safety programs evolve, there are likely to be many more opportunities and incentives for comparing infection rates within and across institutions. However, such comparisons will require case-mix adjustment that accounts for coexisting illnesses, to avoid penalizing hospitals that care for patients at higher risk. As discussed, the NNIS risk index is based on the ASA score, which has several undesirable features. Although the ASA score has five possible values, the NNIS index collapses them into two levels so that all information about coexisting illness is summarized, in effect, as high or low. There is often little heterogeneity of ASA score in patients within a surgical procedure class, for instance, cesarean sections. In addition, the ASA score is subject to considerable interobserver variation, is not available for many ambulatory procedures, is usually not captured in automated form by hospital databases, and is not available in administrative or claims data systems.

As an alternative to the ASA score, the chronic disease score has been proposed to adjust data for coexisting illness in surgical patients. This score is based on the premise that dispensed drugs are markers for chronic coexisting illness; for example, dispensing of hypoglycemic agents strongly suggests the presence of diabetes. Approximately 24 conditions are represented in the chronic disease score, which is computed from ambulatory pharmacy dispensing information and can predict death and overall resource use (27-30). The chronic disease score has theoretical advantages over the ASA score: it can be computed automatically for the approximately 90% of the population that has prescription drug coverage, and it is completely objective. In its first application to a mixed group of surgical procedures, the chronic disease score performed at least as well as the ASA score (30). In addition, a modified chronic disease score, based on data for drugs dispensed on hospital admission, performed with substantially better sensitivity and specificity than the ASA score. The chronic disease score, based on admission medications, can also be computed by health-care facilities without the need for ambulatory drug-dispensing data.

The chronic disease score might be considered as a substitute when the ASA score is not available or as a supplement to the ASA score to provide better risk stratification. In addition, the chronic disease score might be modified to optimize its prediction of surgical site infections, rather than all causes of death and resource utilization. For example, data on psychotropic drugs, which are important contributors to the overall chronic disease score, might detract from the prediction of infection. Improved scoring systems will need to be developed through formal modeling programs applied to large, heterogeneous datasets.

Potential Uses of Electronic Data for Surgical Site Infection Surveillance

Electronic data have the potential to provide better information about infections while reducing the effort required to conduct surveillance. The outcome measures (e.g., quantitative antibiotic exposure or combinations of coded diagnoses) are meaningful, although they differ from the NNIS definition. The medical profession must decide whether a surveillance definition of surgical site infection might coexist with a clinical definition, with the understanding that the two serve related but different purposes (for example, the surveillance definition for influenza epidemics depends on hospitalizations with a coded diagnosis of pneumonia or influenza rather than virologically confirmed infections or specific clinical signs and symptoms).

Implementation of systems that use these data requires consensus on the part of the medical profession about outcome definitions, surveillance algorithms, and reporting standards. Even if consensus is reached, impediments will remain to the widespread adoption of electronic surveillance systems. The disparity in the electronic systems currently in use is one of these. While more sophisticated systems will permit better surveillance, most of the results described above depend on data elements such as drug dispensing information or financial claims data that are already available or are among the first to become automated. Thus, it will not be necessary to wait for fully automated medical records or more advanced hospital information systems. Although the costs of developing and validating systems based on electronic data are substantial, much of the development can be centralized, and validation need only be conducted in a few sites to establish generalizability. These reporting systems require a moderate investment by hospitals, HMOs, and insurers, most of which is the fixed cost for creating automated reporting functions. While some of this cost can be defrayed through the use of standard, shared computer code, this code usually must be customized to make it compatible with existing automated systems. Organizations that have electronic data typically create similar reports for other purposes and will not need new skills. In addition, the costs of maintaining and using the periodic reports that will constitute a new surveillance system are negligible.

Data sharing between hospitals, HMOs, and insurers is important, since very few single entities possess enough information to implement a self-sufficient surveillance system. Furthermore, in many locales, hospitals contract with several HMOs and insurers. In that case, HMOs and insurers must share information among themselves as well as with the hospitals, since no one hospital is likely to have enough patients to achieve the necessary precision. Data sharing will require development of systems that protect both patients' confidentiality and the organizations' proprietary interests.

If such surveillance becomes widely available, two types of uses might coexist. One would be to improve traditional prospective surveillance; for example, sensitivity of inpatient surveillance could be maintained with greatly reduced effort by restricting traditional (NNIS) review to the <10% of records that meet the quantitative screening criterion for antibiotic exposure. Similarly, for the postdischarge surveillance system, one could review as little as 2% of records (including ambulatory records in physicians' offices) while greatly increasing the sensitivity of detection.

A second way to use these surveillance systems is to apply them to the entire surgical population, including patients or procedures that are not being evaluated because of resource constraints. Tracking the proportion of inpatients who exceed the antibiotic threshold or the number of patients who exceed a prespecified computed probability of surgical site infection after discharge might be sufficient, as long as that proportion is within agreed-upon limits. When the rates are below this limit, no further evaluation would be needed, since important problems in the delivery system are unlikely to have escaped detection. However, when the proportion or number exceeds

the prespecified limit, more rigorous examination of the data would be triggered.

Electronically assisted surveillance for infections could be performed at modest expense by many organizations that have administrative claims and pharmacy data. These groups include the providers of care for most of the U.S. population, including essentially all HMO members, many of those with traditional indemnity insurance, Medicaid recipients, and most Medicare beneficiaries who have pharmacy benefits.

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New Surgical Techniques and Surgical Site Infections

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Technologic advances in surgery include a trend toward less invasive procedures, driven by potential benefits to patients and by health-care economics. These less invasive procedures provide infection control personnel opportunities for direct involvement in outcomes measurement.

"Pray before surgery, but remember
God will not alter a faulty incision."
Arthur H. Keeney

The 21st century advancements in genetics, nanotechnology (mechanical engineering on a molecular scale), and robotics could revolutionize medical therapy and diagnostics. I will review current and future directions of minimally invasive surgery, with an emphasis on cardiac surgery, and surgical site infections after minimally invasive valve procedures.

Minimally Invasive Surgery

Since the first endoscopic cholecystectomy was performed in France in 1988, minimally invasive surgical techniques have dramatically affected many surgical subspecialties, driven by advances in port access and video instrumentation and the desire to lessen incision pain and length of hospital stay. Advances in laparoscopic kidney and adrenal surgery now include 2-mm needle optics and instruments, which have resulted in decreased postoperative illness and superior cosmetic results (1). The challenge is to evaluate the safety and efficacy of these new techniques as they are widely introduced in the United States.

Minimally invasive cardiac surgery was predated by innovations in general surgery and is increasingly applied to cardiac procedures (30,000 worldwide in 1998). Coronary artery bypass grafting (CABG) through a median sternotomy incision with cardiopulmonary bypass support remains standard because it provides the surgeon with good exposure, a bloodless and motionless field, and myocardial protection, with graft patency rates of 90% at 10 years (2). However, cardiopulmonary bypass support may have adverse physiologic consequences, including a 6% incidence of central nervous system events (3).

There is no internationally accepted case definition for minimally invasive cardiac surgery, but two approaches to revascularization have been developed: the off-pump (beating heart) CABG, or minimally invasive direct coronary artery bypass (MIDCAB), and the endoscopic (port access technique) CABG (HeartPort, Redwood City, CA) (4).

Coronary artery anastomosis on a beating heart was first described by Kosselov in 1967 and has been modified with the MIDCAB technique to an 8-cm right or left anterior thoracotomy incision that allows direct visualization of the beating heart through small incisions. The primary candidate for this procedure is a patient with single anterior vessel disease; an estimated 1 of 3 coronary revascularization procedures (CABG or percutaneous coronary artery angioplasty) meet this criterion. The technical constraints of the MIDCAB procedure include a moving surgical field and a turgid heart on which to perform grafting. Stabilizers to control heart movement are used to facilitate anastomosis of the target grafts during suturing.

The port-access operation involves a mini-thoracotomy (8 cm) on an arrested heart by using percutaneously inserted endovascular occluder balloons in the ascending aorta. Unlike port-access surgery in noncardiac surgical subspecialties, almost all cardiac operations on adult patients are reconstructions that are technically more demanding when performed through an endoscope. In addition, the laparoscopic approach with an insufflated peritoneum provides better exposure than open techniques (5).

Surgical site infections after minimally invasive cardiac surgery pose a challenge to the clinician. Physical findings of sternal instability and sternal click of the median sternotomy cannot be applied to many incisions used in minimally invasive cardiac surgery (Figure 1). The initial experience of

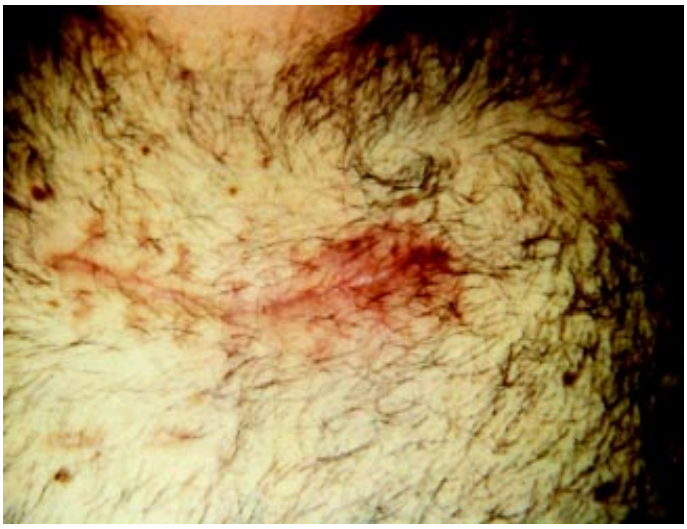

Figure 1. Surgical site infection following minimally invasive valve surgery.

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1,400 minimally invasive cardiac surgery procedures at the Cleveland Clinic showed no significant difference in the incidence of deep or superficial wound infections (Table).

Table. Rates[a] of surgical site infections in patients undergoing minimally invasive compared with traditional open heart surgery, Cleveland Clinic Foundation, 1996–98

	Traditional (n=9,633)	Minimally invasive (n=1,400)	p value >0.05
Overall rate[a]	3.3	2.9	Not significant
Deep infection	1.7	1.9	Not significant

[a]per 100 procedures

An important quality indicator for minimally invasive surgical procedures is the conversion rate to open procedures. A surgeon's decision to convert from a minimally invasive procedure to an open procedure may be determined by poorly defined anatomy or surgical complications. Conversion is not necessarily a failure but may be used as a quality indicator, and conversion rates for minimally invasive cardiac surgery procedures have declined substantially with increasing experience at our institution (Figure 2). The introduction of

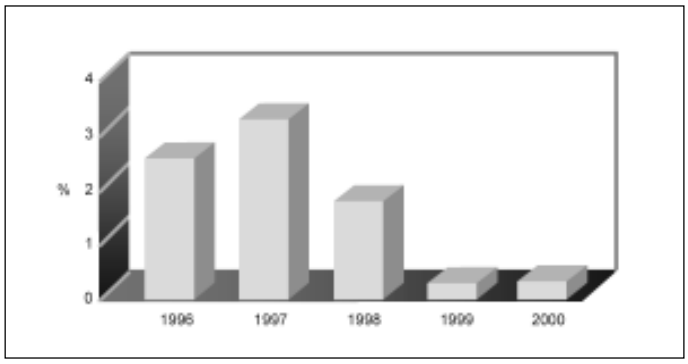

Figure 2. Conversion rates to open procedures among patients undergoing minimally invasive heart surgery, Cleveland Clinic Foundation.

any new surgical technique involves a learning curve, and increased experience may be translated into reduced illness and death. Examples of the relationship between surgeon-specific volume and death associated with CABG procedures have been published (6-8).

The association of outcome with case volume may not depend on a single person but on the collective abilities of the clinical team (9). High volumes may also reflect selection bias by patient referrals to institutions and surgeons with good outcomes. Health-care consumers are increasingly interested in outcome measurements, and one consumer advocate group (the Center for Medical Consumers) has compiled 1998 data from the New York State Department of Health for 21 surgical procedures, stratified by volume, hospital, and individual practitioner (available at URL www.medicalconsumers.org).

Solid Organ Transplantation

The greatest challenge facing solid organ transplantation in the United States is a shortage of donors, with approximately three persons awaiting transplantation for every organ donated. Organs from pigs may alleviate the shortage, but the challenge of xenotransplantation is in replacing xenogenic epitopes (antigens) recognized as foreign by the immune system. An additional concern is trans-species transmission of endogenous retroviruses from donor animals, such as porcine endogenous retrovirus (PoERV). Two cases of successful extracorporeal hepatic support with transgenic pig livers have been reported with no evidence of human PoERV infection at 5 and 185 months of follow-up (10).

Another alternative to cardiac allotransplantation is the implantable ventricular assist device (11). The two types approved by the U.S. Food and Drug Administration (HeartMate left ventricular assist device, ThermoCardiosystems, Woburn, MA, and the Novacor left ventricular assist device, World Health, Inc., Oakland, CA) are both electrical pulsatile devices, implanted through a median sternotomy with an inflow cannula in the apex of the left ventricle and an outflow tube anastomosed to the ascending aorta. A single drive line containing the electrical cable and the atmospheric air vent leads transcutaneously from the implanted pump to an external power pack (Figure 3).

Recipients of implantable left ventricular assist devices are vulnerable to device-related infections because the extracorpeal drive line (13.5 mm to 15 mm in diameter) breaches normal cutaneous defenses against infection, providing a portal of entry for pathogens (12). The incidence of infection increases with duration of ventricular assist device support (a mean of 120 days for patients awaiting heart transplantation at the Cleveland Clinic in 1999). As recipients are often malnourished or debilitated, it is not surprising that 32% of patients had a device-associated infection and 55% had a hospital-associated bloodstream infection during support (13). Patients with ventricular assist devices commonly receive antibiotic therapy, both for prophylaxis or treatment of infections and on an empiric

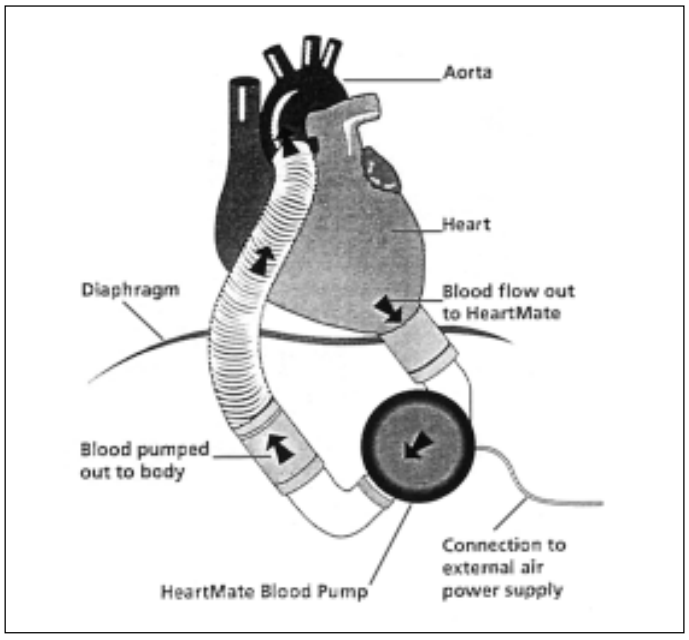

Figure 3. Implantable left ventricular assist device.

basis. The use of antibiotics may lead to development of infections with fungi and drug-resistant pathogens. Despite these implications, infections associated with ventricular assist devices do not preclude successful transplantation. Strategies for prevention of infection in recipients will focus on the drive line exit site until technical advances can achieve a totally implantable device.

Future Directions: From Blood and Guts to Bits and Bytes

Technologic advances are continually being brought into the operating room with increasing use of robotics and teleoperating systems and virtual environment, which is the fusion of robotics and three-dimensional imaging technology. One issue with laparoscopic surgery is control of the camera (laparoscopic lens) while the surgeon operates. There may be problems with second guessing where the surgeon wants the camera lens directed; movement of the camera lens, leading to iatrogenic complications; and the expense of additional personnel. Voice activation of a surgical robotic assistant has permitted single-surgeon thorascopic surgery (14). The surgeon registers voice commands into a voice card, and the thorascope is connected with a robotic arm. In a study of human-assisted versus robotic-assisted surgeries, all procedures were successfully completed with no difference in operating times and no technical mishaps related to the robot.

Teleoperating systems and telesurgery allow the operator to perform surgery from a remote site. A three-dimensional camera is outfitted with tactile, auditory, and proprioceptive feedback. This technology may provide a means to treat patients in hazardous or distant environments where evacuation is not feasible. NASA is planning to send astronauts on a 3-year mission to Mars by 2020 and believes an acute medical crisis is likely during such a voyage. Biomedical space researchers are reviewing the creation of a digitized virtual astronaut, a computerized representation of the entire physiology, updated in real time by input from a comprehensive bank of sensors (Groopman J. Medicine on Mars. New Yorker, February 14, 2000). Any necessary surgery would be performed by the flight surgeon, coached by the virtual mentor and aided by robotics.

In summary, the operating room remains a dynamic environment undergoing rapid change and innovation. The challenge for infection control practitioners is to adopt a facilitative (not passive or resistant) involvement in measurement and data-tracking instruments (e.g., registries, conversion rates, surgical site infection rates) and embrace opportunities for comparison.

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Preventing Surgical Site Infections: A Surgeon's Perspective

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Wound site infections are a major source of postoperative illness, accounting for approximately a quarter of all nosocomial infections. National studies have defined the patients at highest risk for infection in general and in many specific operative procedures. Advances in risk assessment comparison may involve use of the standardized infection ratio, procedure-specific risk factor collection, and logistic regression models. Adherence to recommendations in the 1999 Centers for Disease Control and Prevention guidelines should reduce the incidence of infection in surgical patients.

Postoperative surgical site infections remain a major source of illness and a less frequent cause of death in the surgical patient (1). These infections number approximately 500,000 per year, among an estimated 27 million surgical procedures (2), and account for approximately one quarter of the estimated 2 million nosocomial infections in the United States each year (3). Infections result in longer hospitalization and higher costs.

The incidence of infection varies from surgeon to surgeon, from hospital to hospital, from one surgical procedure to another, and—most importantly—from one patient to another. During the mid1970s, the average hospital stay doubled, and the cost of hospitalization was correspondingly increased when postoperative infection developed after six common operations (4). These costs and the length of hospital stay are undoubtedly lower today for most surgical procedures that are done on an outpatient basis, such as laparoscopic (minimally invasive) operations or those that require only a short postoperative stay. In these cases, most infections are diagnosed and treated in the outpatient clinic or the patient's home. However, major complications such as deep sternal infections continue to have a grave impact, increasing the duration of hospitalization as much as 20-fold and the cost of hospitalization fivefold (5). Any surgical site infection after open heart surgery results in a substantial net loss of reimbursement to the hospital compared with uninfected cases, a factor that should motivate hospitals to minimize the incidence of postoperative infections (6).

Description of Surgical Site Infections

The Centers for Disease Control and Prevention (CDC) term for infections associated with surgical procedures was changed from surgical wound infection to surgical site infection in 1992 (7). These infections are classified into incisional, organ, or other organs and spaces manipulated during an operation; incisional infections are further divided into superficial (skin and subcutaneous tissue) and deep (deep soft tissue-muscle and fascia). Detailed criteria for these definitions have been described (7). These definitions should be followed universally for surveillance, prevention, and control of surgical site infections.

Microbiology of Surgical Site Infections

The pathogens isolated from infections differ, primarily depending on the type of surgical procedure. In clean surgical procedures, in which the gastrointestinal, gynecologic, and respiratory tracts have not been entered, *Staphylococcus aureus* from the exogenous environment or the patient's skin flora is the usual cause of infection. In other categories of surgical procedures, including clean-contaminated, contaminated, and dirty, the polymicrobial aerobic and anaerobic flora closely resembling the normal endogenous microflora of the surgically resected organ are the most frequently isolated pathogens (8).

According to data from the National Nosocomial Infections Surveillance System (NNIS), there has been little change in the incidence and distribution of the pathogens isolated from infections during the last decade (9). However, more of these pathogens show antimicrobial-drug resistance, especially methicillin-resistant *S. aureus* (10). Postoperative infections, including surgical site infections, were caused by multiple organisms in a multicenter outbreak due to contamination of an intravenous anesthetic, propofol (11). In this outbreak, CDC identified 62 patients at seven hospitals who had postoperative infections, primarily of the bloodstream or surgical site, after exposure to propofol. Only exposure to this anesthetic was substantially associated with these postoperative infections. In six of the seven hospitals, the same pathogen was isolated from several infected patients. The infections were due to extrinsic contamination of the propofol by the anesthesia personnel, who frequently carried the pathogens in lesions on their hands or scalp or in their nares. Lapses in aseptic technique and reuse of single-use vials for several patients were important factors in these outbreaks (11,12). This report stresses the importance of conducting a formal epidemiologic investigation when a cluster of infections involves an unusual organism such as *Moraxella osloensis* or *Serratia marcescens*.

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Prevention of Surgical Site Infections

The most critical factors in the prevention of postoperative infections, although difficult to quantify, are the sound judgment and proper technique of the surgeon and surgical team, as well as the general health and disease state of the patient (13-14). Other factors influence the development of postoperative wound infection, especially in clean surgical procedures, for which the infection rate (<3%) is generally low. Infections in these patients may be due solely to airborne exogenous microorganisms (15).

In 1999, CDC's Health Care Infection Control Practices Advisory Committee published revised guidelines for the prevention of infections (Table 1). This guideline delves extensively into the literature concerning perioperative factors associated with postoperative infections (16). The 1999 edition of the guideline has been extensively revised (Table 2).

Prophylactic Antibiotic Use in the Surgical Patient

The use of antibiotic prophylaxis before surgery has evolved greatly in the last 20 years (17). Improvements in the timing of initial administration, the appropriate choice of antibiotic agents, and shorter durations of administration have defined more clearly the value of this technique in reducing postoperative wound infections. Some historical milestones of the last 4 decades shed light on the current situation.

Historical Aspects

Confusing and heated debate concerning the efficacy of prophylactic antibiotics in surgery followed the publication of clinical trials during the 1950s. Errors in study design of these early efforts included nonrandomization, lack of blinding, faulty timing of initial antibiotic administration, prolonged antibiotic use, incorrect choices of antimicrobial agents, and inappropriate choices of control agents.

Experimental studies published during the early 1960s helped clarify many of these problems and resulted in a more scientifically accurate approach to antimicrobial prophylaxis. Most important was the report by Burke (18), which demonstrated the crucial relationship between timing of antibiotic administration and its prophylactic efficacy. His experimental studies showed that to greatly reduce experimental skin infection produced by penicillin-sensitive *S. aureus*, the penicillin had to be in the skin shortly before or at the time of bacterial exposure. This study and others fostered the attitude that to prevent subsequent infection the antibiotic must be in the tissues before or at the time of bacterial contamination. This important change in strategy helped correct the common error of first administering the prophylactic antibiotic in the recovery room.

As early as 1964, Bernard and Cole (19) reported on the successful use of prophylactic antibiotics in a randomized, prospective, placebo-controlled clinical study of abdominal operations on the gastrointestinal tract. The success of antibiotic prophylaxis noted in this early study was clearly due to the authors' appropriate patient selection and wise choice of available agents, as well as the timing of administration. Further advances in understanding of antibiotic prophylaxis in abdominal surgery occurred in the 1970s. During this decade, the qualitative and quantitative nature of the endogenous gastrointestinal flora in health and disease was appropriately defined (20). Many prospective, blinded clinical studies in the 1980s and 1990s prompted

Table 1. Hospital Infection Control Practices Advisory Committee partial recommendations for the prevention of surgical site infection,1999 (16)

Rankings	
Category 1A	Strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiologic studies
Category 1B	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale
Category II	Suggested for implementation and supported by suggestive clinical or epidemiologic studies or theoretical rationale
No recommendation; unresolved issue.	Practices for which insufficient evidence or no consensus regarding efficacy exists
Recommendations—Preoperative—partial and modified	
A. Preparation of the patient	
Category 1A	Treat remote infection before elective operation; postpone surgery until treated; Do not remove hair from operative site unless necessary to facilitate surgery; If hair is removed, do immediately before surgery, preferably with electric clippers
Category 1B	Control serum blood glucose perioperatively; Cessation of tobacco use 30 days before surgery; Do not withhold necessary blood products to prevent SSIs; Shower or bath on night before operative procedure; Wash incision site before performing antiseptic skin preparation with approved agent
Category II	Prepare skin in concentric circles from incision site; Keep preoperative stay in hospital as short as possible
Unresolved	Improve nutritional status; Use of mupirocin in nares; Improve oxygenation of wound space; Taper or discontinue systemic steroid use before elective surgery
B. Antimicrobial prophylaxis	
Category 1A	Select (if indicated) an antimicrobial agent with efficacy against expected pathogen; Intravenous route used to ascertain adequate serum levels during operation and for at most a few hours after incision closed; Before elective colorectal operations, in addition to parenteral agent, mechanically prepare the colon by use of enemas and cathartics. Administer nonabsorbable oral antimicrobial agents in divided doses on the day before the operation
Category 1B	Do not routinely use vancomycin for antimicrobial prophylaxis

SSI = surgical site infections

Table 2. Changes in CDC surgical site infections prevention guidelines, 1999 (16)

1985	1999
Category 1	Category 1A
Category II	Category 1B
Category III	Category II or no recommendation; unresolved
Preoperative hair removal	
Do not remove hair unless it will interfere with the operation Category II	Recommendation unchanged Category 1A
If removed, remove by clipping or use of a depilatory, not by shaving Category II	If removed, preferably remove immediately before the operation with electric clippers Category 1A
Preoperative shower or bath	
Patient should bathe with antimicrobial soap the night before an elective operation Category III	Require patients to shower or bathe with an antiseptic agent at least the night before surgery Category 1B
Preoperative hand and forearm antisepsis	
Perform surgical scrub for at least 5 minutes before first operation of day Category 1	Perform surgical scrub for at least 2-5 minutes with an appropriate antiseptic Category 1B
Between consecutive operations perform surgical scrub 2 to 5 minutes Category II	
After scrub, dry hands with sterile towel, don sterile gown and gloves Category 1	After scrub, keep hands up and away from body; dry hands with sterile towel; don sterile gown and gloves Category 1B
Preoperative patient preparation	
Treat and control all bacterial infections before operation Category 1	Identify and treat all remote infections before elective operation Category 1A
The hospital stay should be as short as possible Category II	Keep hospital stay as short as possible Category II
If patient is malnourished, enteral or parenteral nutrition should be given Category II	No recommendation to use nutritional support solely to prevent surgical site infection Unresolved
Preoperative antimicrobial prophylaxis	
Use for operations with high infection rate or for those with severe or life-threatening consequences if infection occurs Category 1	Administer antimicrobial agent only when indicated and select based on published recommendations for a specific operation and efficacy against most common pathogens Category 1A
Select antimicrobial agents that are safe and effective Category 1	
Start parenteral IV antimicrobial agents shortly before operation and discontinue shortly afterward Category 1	Administer antimicrobial agents by IV timed to ensure bactericidal serum and tissue levels when incision made Category 1A
	Maintain therapeutic levels during operation and, at most, a few hours after closure Category 1A
	Before colorectal elective operations, in addition to IV antimicrobial drugs, mechanically prepare the colon with enemas and cathartic agents; administer nonabsorbable oral antimicrobial agents in individual doses the day before surgery Category 1A
	For cesarean sections in patients at high risk administer IV antimicrobial agent immediately after cord is clamped Category 1A
	Do not routinely use vancomycin for prophylaxis Category 1B

definitive recommendations concerning the proper approaches to antibiotic prophylaxis in surgery (21).

Current Use of Parenteral Antibiotic Agents in Surgical Prophylaxis

The choice of parenteral prophylactic antibiotic agents and the timing and route of administration have become standardized on the basis of well-planned prospective clinical studies (21). It is generally recommended in elective clean surgical procedures using a foreign body and in clean-contaminated procedures that a single dose of cephalosporin, such as cefazolin, be administered intravenously by anesthesia personnel in the operative suite just before incision. Additional doses are generally recommended only when the operation lasts longer than 2 to 3 hours. Other controversial areas include the routine use of antibiotic prophylaxis in clean surgical procedures, such as hernia repair or breast surgery (21,22). This subject has been summarized in a published review (23), and some specific situations will be described.

Antibiotic Prophylaxis before Elective Colon Resection

The human colon and distal small intestine contain an enormous reservoir of facultative and anaerobic bacteria, separated from the rest of the body by the mucous membrane. A reliable method of sterilizing the colonic contents has been a goal of surgeons throughout this century (24). In the past 25 years, clinical trials have demonstrated that to substantially reduce septic complications after elective colon surgery, antibiotics must have activity against both colonic aerobes (e.g., *Escherichia coli*) and anaerobes (e.g., *Bacteroides fragilis*), a finding we reported over 25 years ago (25). Today, approaches to mechanical cleansing differ widely (26). Modern approaches include standard outpatient mechanical cleansing with dietary restriction, cathartics, and enemas for a 2-day period, or whole-gut lavage with an electrolyte solution of 10% mannitol, Fleet's phospho-soda, or polyethylene glycol, done the day before the operation.

Most surgeons use both antibiotics and mechanical cleansing for preoperative preparation before elective colon resection (26). Three regimens of oral agents combine neomycin with erythromycin base, metronidazole, or tetracycline. The most popular regimen in the United States has been the neomycin-erythromycin base preparation, which was introduced in 1972 (27).

In a survey published in 1997, 471 (58%) of 808 board-certified colorectal surgeons described their bowel preparation practices before elective procedures (26). All respondents used mechanical preparation: oral polyethylene glycol solution (70.9% of respondents), oral sodium phosphate solution with or without bisacodyl (28.4%), and accepted methods of dietary restriction, cathartics, and enemas (28.4%). Most (86.5%) surgeons added both oral and parenteral antibiotics to the regimen; 11.5% added only parenteral antibiotics, 1.1% added only oral antibiotics, and 0.9% did not add antibiotics. Oral neomycin and erythromycin or metronidazole were combined with a perioperative parenteral antibiotic by 77.8% of respondents. Most patients started the preparation as outpatients the day before surgery, and parenteral drugs were added to the regimen 1 to 2 hours before the procedure. The use of outpatient bowel preparation is increasing; however, patient selection is critical, and education is needed to reduce the rate of complications.

Antibiotic Prophylaxis for Appendectomy

The pathologic state of the appendix is the most important determinant of postoperative infection (28,29). Wound infection after appendectomy for perforative or gangrenous appendicitis is four to five times higher than for early disease. A prospective study of nonperforated appendicitis, using a logistic regression analysis of risk factors, showed that the risk for postoperative infection is related to lack of perioperative antibiotic prophylaxis and to the determination that the appendix was gangrenous (29). Because the pathologic state of the appendix often cannot be determined before or during operation, a parenteral antibiotic agent is recommended as prophylaxis in all patients.

Regimens with activity against both facultative gram-negative bacilli and anaerobes are more effective than those active only against aerobes (29). The use of antimicrobial agents in perforated appendicitis with evidence of local or general peritonitis or intraabdominal abscess, or both, should be considered therapeutic rather than prophylactic.

Preventive Antibiotics in Penetrating Abdominal Trauma

Hollow-lumen visceral damage with associated escape of endogenous microorganisms is the main risk factor for postoperative infections after exploratory laparotomy for penetrating abdominal trauma. A single dose of parenterally administered antibiotic, given just before abdominal exploration for penetrating abdominal trauma, is associated with low postoperative infection rate in patients with no observed gastrointestinal leakage (30). If gastrointestinal leakage is identified at the time of the operation, continuing the antibiotic agents for 1 to 3 days is usually recommended. It is important to use antibiotic agents with both facultative and anaerobic activity. Leaving the operative wound open, packed with saline-soaked gauze, decreases the incidence of postoperative wound infection in patients at high risk (31).

Preventive Antibiotic Use in Traumatic Chest Injuries

Recently published studies have shown the value of parenteral antibiotic prophylaxis in the prevention of pneumonia or empyema after the placement of a chest tube to correct the hemopneumothorax associated with chest trauma (32,33). In one study, 500 mg of cefazolin was given intravenously every 8 hours for 24 hours (32). In the other study, 1 g of cefonicid was administered every 24 hours until the chest tube was removed, usually before 5 days (33). In both studies patients receiving antibiotics had substantially lower infection rates than those receiving placebos.

Conclusions

Recent improvements in antibiotic prophylaxis, including the timing of initial administration, appropriate choice of antibiotic agents, and shortening the duration of administration, have established the value of this technique in many clinical surgical settings. Future study designs should strongly consider risk factors for individual patients when new antibiotic agents are tested or administration techniques are refined. A concentrated effort should be made in areas of clinical surgery where the value of antibiotic prophylaxis has not been proven. A single-dose systemic regimen of an appropriately chosen cephalosporin given during the immediate preoperative period is safe and the indicated practice.

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Hygiene of the Skin: When Is Clean Too Clean?

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Skin hygiene, particularly of the hands, is a primary mechanism for reducing contact and fecal-oral transmission of infectious agents. Widespread use of antimicrobial products has prompted concern about emergence of resistance to antiseptics and damage to the skin barrier associated with frequent washing. This article reviews evidence for the relationship between skin hygiene and infection, the effects of washing on skin integrity, and recommendations for skin care practices.

For over a century, skin hygiene, particularly of the hands, has been accepted as a primary mechanism to control the spread of infectious agents. Although the causal link between contaminated hands and infectious disease transmission is one of the best-documented phenomena in clinical science, several factors have recently prompted a reassessment of skin hygiene and its effective practice.

In industrialized countries, exposure to potential infectious risks has increased because of changing sociologic patterns (e.g., more frequent consumption of commercially prepared food and expanded child-care services). Environmental sanitation and public health services, despite room for improvement, are generally good. In addition, choices of hygienic skin care products have never been more numerous, and the public has increasing access to health- and product-related information (1). This paper reviews evidence for the relationship between skin hygiene and infection, the effects of washing on skin integrity, and recommendations for skin care practices for the public and health-care professionals.

Does Skin Cleansing Reduce Risk for Infection?

Personal Bathing and Washing

There is a clear temporal relationship between improvement in general levels of cleanliness in society and improved health. Greene (2) used historical and cross-cultural evidence and causal inference to associate personal hygiene with better health. However, the role of personal cleanliness in the control of infectious diseases over the past century is difficult to measure, since other factors have changed at the same time (e.g., improved public services, waste disposal, water supply, commercial food handling, and nutrition) (3).

Studies of personal and domestic hygiene and its relationship to diarrhea in developing countries demonstrate the effectiveness of proper waste disposal, general sanitary conditions, and handwashing (4,5). However, aside from hand cleansing, specific evidence is lacking to link bathing or general skin cleansing with preventing infections. Part of the difficulty in demonstrating a causal association between general bathing or skin care and gastrointestinal infection is that interventions to reduce diarrheal disease have been multifaceted, often including health education, improved waste disposal, decontaminating the water supply, and general improvement in household sanitation as well as personal hygiene (6,7). Risk for diarrheal disease has also been linked to the level of parental education (8). Multiple influences complicate definition of the impact of any single intervention.

In 11 studies reviewed by Keswick et al. (9), use of antimicrobial soaps was associated with substantial reductions in rates of superficial cutaneous infections. Another 15 experimental studies demonstrated a reduction in bacteria on the skin with use of antimicrobial soaps, but none assessed rates of infection as an outcome.

Extensive studies of showering and bathing conducted since the 1960s demonstrated that these activities increase dispersal of skin bacteria into the air and ambient environment (10-12), probably through breaking up and spreading of microcolonies on the skin surface and resultant contamination of surrounding squamous cells. These studies prompted a change in practice among surgical personnel, who are now generally discouraged from showering immediately before entering the operating room. Other investigators have shown that the skin microflora varies between persons but is remarkably consistent for each person over time. Even without bathing for many days, the flora remain qualitatively and quantitatively stable (13-15).

For surgical or other high-risk patients, showering with antiseptic agents has been tested for its effect on postoperative wound infection rates. Such agents, unlike plain soaps, reduce microbial counts on the skin (16-18). In some studies, antiseptic preoperative showers or baths have been associated with reduced postoperative infection rates, but in others, no differences were observed (19-21). Whole-body washing with chlorhexidine-containing detergent has been shown to reduce infections among neonates (22), but concerns about absorption and safety preclude this as a routine practice. Several studies have demonstrated substantial reductions in rates of acquisition of methicillin-resistant *Staphylococcus aureus* in surgical patients bathed with a triclosan-containing product (23,24). Hence, preoperative showering or bathing with an antiseptic may be justifiable in selected patient populations.

Hand Hygiene for the General Public

Much contemporary evidence for a causal link between handwashing and risk for infection in community settings comes from industrialized countries (5,7,25-27). Although

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many of these studies may be limited by confounding by other variables, evidence of an important role for handwashing in preventing infections is among the strongest available for any factor studied. Reviews of studies linking handwashing and reduced risk for infection have been recently published (28,29). The most convincing evidence of the benefits of handwashing for the general public is for prevention of infectious agents found transiently on hands or spread by the fecal-oral route or from the respiratory tract (30). Plain soaps are considered adequate for this purpose.

Several highly publicized, serious outbreaks from commercially prepared foods have raised questions about food safety and the hygienic practices of food handlers and others in the service professions. Despite public awareness, however, handwashing generally does not meet recommended standards—members of the public wash too infrequently and for short periods of time (31).

These factors have led to suggestions that antimicrobial products should be more universally used, and a myriad of antimicrobial soaps and skin care products have become commercially available. While antimicrobial drug-containing products are superior to plain soaps for reducing both transient pathogens and colonizing flora, widespread use of these agents has raised concerns about the emergence of bacterial strains resistant to antiseptic ingredients such as triclosan (32,33). Such resistance has been noted in England and Japan (34), and molecular mechanisms for the development of resistance have been proposed (32,35). Although in some settings exposure to antiseptics has occurred for years without the appearance of resistance, a recent study described mutants of *Escherichia coli* selected for resistance to one disinfectant that were also multiply-antibiotic resistant (35). Some evidence indicates that long-term use of topical antimicrobial agents may alter skin flora (36,37). The question remains whether antimicrobial soaps provide sufficient benefit in reducing transmission of infection without added risk or cost.

Hand Hygiene in Health-Care Settings

Issues regarding hand hygiene practices among health-care professionals have been widely discussed and may be even more complicated than those in the general public. Unless patient care involves invasive procedures or extensive contact with blood and body fluids, current guidelines recommend plain soap for handwashing (38,39); however, infection rates in adult or neonatal intensive care units or surgery may be further reduced when antiseptic products are used (40-42).

Skin Barrier Properties and Effect of Hand Hygiene Practices

The average adult has a skin area of about 1.75 m^2. The superficial part of the skin, the epidermis, has five layers. The stratum corneum, the outermost layer, is composed of flattened dead cells (corneocytes or squames) attached to each other to form a tough, horny layer of keratin mixed with several lipids, which help maintain the hydration, pliability, and barrier effectiveness of the skin. This horny layer has been compared to a wall of bricks (corneocytes) and mortar (lipids) and serves as the primary protective barrier (43). Approximately 15 layers make up the stratum corneum, which is completely replaced every 2 weeks; a new layer is formed approximately daily (44). From healthy skin, approximately 10^7 particles are disseminated into the air each day, and 10% of these skin squames contain viable bacteria (45). The dispersal of organisms is greater in males than in females and varies between persons using the same hygienic regimen by as much as fivefold (46).

Water content, humidity, pH, intracellular lipids, and rates of shedding help retain the protective barrier properties of the skin. When the barrier is compromised (e.g., by hand hygiene practices such as scrubbing), skin dryness, irritation, cracking, and other problems may result. Although the palmar surface of the hand has twice as many cell layers and the cells are >30 times thicker than on the rest of the skin (47), palms are quite permeable to water (48).

Long-term changes in skin pH associated with handwashing may pose a concern since some of the antibacterial characteristics of skin are associated with its normally acidic pH (49). In one report, pH increased 0.6 to 1.8 units after handwashing with plain soap for 1 to 2 min and then gradually declined to baseline levels over a period of 45 min to 2 hr (50). Some soaps can be associated with long-standing changes in skin pH, reduction in fatty acids, and subsequent changes in resident flora such as propionibacter (51).

In an investigation of the effect on skin of repeated use of two washing agents, all skin function tests (stratum corneum capacitative resistance, lipids, transepidermal water loss, pH, laser Doppler flow, and skin reddening) were markedly changed after a single wash, and after 1 week further damage was noted (52). In a study of irritant skin reactions induced by three surfactants, damage lasted for several days; complete skin repair was not achieved for 17 days (53).

Soaps and detergents have been described as the most damaging of all substances routinely applied to skin (43). Anionic and cationic detergents are more harmful than nonionic detergents (54), and increased concentrations of surfactant result in more rapid, severe damage (55). Each time the skin is washed, it undergoes profound changes, most of them transient. However, among persons in occupations such as health care in which frequent handwashing is required, long-term changes in the skin can result in chronic damage, irritant contact dermatitis and eczema, and concomitant changes in flora.

Irritant contact dermatitis, which is associated with frequent handwashing, is an occupational risks for health-care professionals, with a prevalence of 10% to 45% (56-58). The prevalence of damaged skin on the hands of 410 nurses was reported to be 25.9% in one survey, with 85.6% of nurses reported to have problems at some time. Skin damage was correlated with frequency of glove use and handwashing (56). Washing with plain soap may actually increase the potential for microbial transmission because of a 17-fold increase in the dispersal of bacterial colonies from the skin of the hands (59). Skin condition clearly plays a major role in risk for transmission.

Microbiology of Hands of Health-Care Professionals

Damaged skin more often harbors increased numbers of pathogens. Moreover, washing damaged skin is less effective at reducing numbers of bacteria than washing normal skin, and numbers of organisms shed from damaged skin are often higher than from healthy skin (60,61). The microbial flora on the clean hands of nurses (samples taken immediately after handwashing) have been reported in several recent studies (Table). Methicillin resistance among coagulase-negative

Table. Microbial flora colonizing hands of health-care professionals

A. Microbial counts

Year (ref.)	Sample (No. subjects)	Mean $\log_{10}$ CFU
1986 (62)	Staff of bone marrow transplant unit (22)	4. 89
1992 (63)	Pediatric staff, Peru (62)	5.88
1997 (64)	Nurses in acute care unit (40)	5.61

B. Resistance of coagulase-negative staphylococcal flora

Year (ref.)	Sample (No. isolates)	Resistant (%) to methicillin	Resistant (%) to tetracycline
1986 (62)	Staff of bone marrow transplant unit (50)	68.0	23.0
1988 (65)	Oncology, dermatology staff (152)	50.7	30.7
1992 (63)	Pediatric staff, Peru (279)	40.9	45.4
1997 (64)	Acute care nurses (122)	59.0	10.5

staphylococcal flora on hands did not seem to increase during the 1980s to the 1990s, and tetracycline resistance decreased (Table).

When Is Clean Too Clean?

Even with use of antiseptic preparations, which substantially reduce counts of hand flora, no reductions beyond an equilibrium level are attained (66). The numbers of organisms spread from the hands of nurses who washed frequently with an antimicrobial soap actually increased after a period of time; this increase is associated with declining skin health (67). In a recent survey, nurses with damaged hands were twice as likely to be colonized with *S. hominis, S. aureus*, gram-negative bacteria, enterococci, and *Candida* spp. and had a greater number of species colonizing the hands (64).

The trend in both the general public and among health-care professionals toward more frequent washing with detergents, soaps, and antimicrobial ingredients needs careful reassessment in light of the damage done to skin and resultant increased risk for harboring and transmitting infectious agents. More washing and scrubbing are unlikely to be better and may, in fact, be worse. The goal should be to identify skin hygiene practices that provide adequate protection from transmission of infecting agents while minimizing the risk for changing the ecology and health of the skin and increasing resistance in the skin flora.

Recommendations for the General Public

Bathing or showering cleans the skin by mechanical removal of bacteria shed on corneocytes. Bacterial counts are at least as high or higher after bathing or showering with a regular soap than before. Frequent bathing has aesthetic and stress-relieving benefits but serves little microbiologic purpose. Mild, nonantimicrobial soap should suffice for routine bathing. Bathing with an antimicrobial product reduces rates of cutaneous infection and could be beneficial when skin infections are likely or before certain surgical procedures. With those exceptions, available data do not support a recommendation for bathing with antimicrobial products.

No single recommendation for hand hygiene practices in the general population would be adequate. The potential advantage of sustained antimicrobial activity for certain occupations (e.g., food handlers and child-care providers) must be balanced with the theoretical possibility of emergence of resistant strains and perhaps other, as yet unrecognized, safety issues.

An alternative to detergent-based antiseptic products is the use of alcohol hand rinses, which have recently become widely available over the counter. Their advantages include rapid and broad-spectrum activity, excellent microbicidal characteristics, and lack of potential for emergence of resistance. Alcohol-based products could be recommended for use among persons who need immediate protection after touching contaminated surfaces or before and after contact with someone at high risk for infection.

Since hands are a primary mode of fecal-oral and respiratory transmission, specific indications for use of antiseptic hand products by the general public are close physical contact with persons at high risk for infection (e.g., neonates, the very old, or immunosuppressed); close physical contact with infected persons; infection with an organism likely to be transmitted by direct contact (diarrhea, upper respiratory infection, skin infections); or work in a setting in which infectious disease transmission is likely (food preparation, crowded living quarters such as chronic-care residences, prisons, child-care centers, and preschools).

Recommendations for the Health-Care Professional

Detergent-Based Antiseptics or Alcohol

Because of increasingly vulnerable patient populations, the demand for hand hygiene among health-care professionals has never been greater. However, frequent handwashing is not only potentially damaging to skin, it is also time-consuming and expensive (68). Finnish investigators demonstrated that after frequent washing the hands of patient-care providers became damaged and posed greater risk to themselves and patients than if they had washed less often. A mild emulsion cleansing rather than handwashing with liquid soap was associated with a substantial improvement in the skin of nurses' hands (69). Alcohol-based formulations are superior to antiseptic detergents for rapid microbial killing on skin (66,67,70-72) and, with the addition of appropriate moisturizers, are probably milder (67,73,74). Since alcohols are rapid acting, are broad spectrum, and require no washing or drying, damage caused by detergents and mechanical friction from toweling is avoided.

Use of Lotions and Moisturizers

Moisturizing is beneficial for skin health and reducing microbial dispersion from skin, regardless of whether the product used contains an antibacterial ingredient (75-77). Because of differences in the content and formulations of lotions and creams, products vary greatly in their effectiveness (78,79). Lotions used with products containing chlorhexidine gluconate must be carefully selected to avoid neutralization by anionic surfactants (80). The role of emollients and moisturizers in improving skin health and reducing microbial spread is an area for additional research.

To improve the skin condition of health-care professionals and reduce their chances of harboring and shedding microorganisms from the skin, the following measures are

recommended: 1) For damaged skin, mild, nonantimicrobial skin cleansing products may be used to remove dirt and debris. If antimicrobial action is needed (e.g., before invasive procedures or handling of highly susceptible patients) a waterless, alcohol-based product may be used. 2) In clinical areas such as the operating room and neonatal and transplant units, shorter, less traumatic washing regimens may be used instead of lengthy scrub protocols with brushes or other harsh mechanical action. 3) Effective skin emollients or barrier creams may be used in skin-care regimens and procedures for staff (and possibly patients as well). 4) Skin moisturizing products should be carefully assessed for compatibility with any topical antimicrobial products being used and for physiologic effects on the skin (81).

Conclusions

From the public health perspective, more frequent use of current hygiene practices may not necessarily be better (i.e., perhaps sometimes clean is "too clean"), and the same recommendations cannot be applied to all users or situations. Future investigation is likely to improve understanding of the interaction between skin physiology, microbiology, and ecology and the role of the skin in the transmission of infectious diseases.

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Antiseptic Technology: Access, Affordability, and Acceptance

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Factors other than antimicrobial activity of soaps and antiseptic agents used for hand hygiene by health personnel play a role in compliance with recommendations. Hand hygiene products differ considerably in acceptance by hospital personnel. If switching from a nonmedicated soap to an antiseptic agent or increased use of an existing antiseptic agent for hand hygiene prevented a few more infections per year, additional expenditures for antiseptic agents would be offset by cost savings.

Although the antimicrobial activity of preparations used by health-care workers for hand hygiene (soap and water or waterless antiseptic agents) is an important aspect of such preparations (1,2), other factors that influence the frequency of use of hand hygiene products by personnel are important.

Access

The accessibility of sinks or other facilities may be an important factor, since nurses and other health-care personnel are expected to wash their hands frequently. Nurses wash their hands an average of 13 to 30 times each day, with as many as 44 times reported (Table 1) (3-5). In an observational study in an intensive care unit (ICU), nurses needed an average of 62 seconds to walk to a sink, wash and dry their hands, and return to the patient's bed (6). If nurses wash their hands for 10 seconds and 12 nurses work in an ICU, handwashing would require 16 hours of nursing time per shift (assuming 100% compliance with recommended handwashing practices). If nurses obtain an alcohol hand disinfectant from a bedside dispenser and 15 seconds is required for drying, 100% compliance would require 4 hours of nursing time per shift. Making a rapidly effective waterless antiseptic agent accessible at each patient's bedside should make it easier for nurses with heavy workloads to comply with recommended hand hygiene practices.

Few investigators have studied the relationship between access to sinks and handwashing frequency among health-care workers. Preston and colleagues (7) recorded personnel compliance with recommended handwashing in an open ICU with six beds and two sinks. After the ICU was converted into an isolation unit with 16 beds and 15 sinks (a sink for nearly every bed), the crude rate of compliance improved from 16% to 30%.

In an observational study in two ICUs, frequency of handwashing by health-care workers after contact with patients or their environment was recorded (8). In the medical ICU, where the sink:bed ratio was 1:1, personnel complied with recommended handwashing measures 76% of the time. In the surgical ICU, where the sink:bed ratio was 1:4, compliance decreased to 51%, indicating that improved access to handwashing facilities increases handwashing compliance. However, differences in handwashing compliance on medical and surgical services may be related to factors such as the number of opportunities for handwashing and attitudes of personnel toward hand hygiene (9).

Table 1. Frequency of handwashing per shift by health-care workers

Author	Average/shift	Range
Ojajarvi (3)	20-30	11-44
Larson (4)	16-25	<8–25+
Boyce (5)	13-15	5–27

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In a study of the impact of sink location on incidence of nosocomial infections (10), patients whose beds were located next to a sink had a 26% reduction in risk for infection compared with those whose beds were located farther away from a sink. In addition to placing sinks near patient beds whenever possible, hospitals should ensure that medical equipment adjacent to the patients' beds (e.g., ventilators or intravenous pumps) does not obstruct access to sinks. Physical barriers that restrict access to sinks may discourage personnel from washing their hands.

Automated handwashing machines have been tested, usually for improving the quality or the frequency of handwashing (11,12). Health-care personnel used these automated sinks infrequently, and they do not appear to be a useful solution to improving hand hygiene.

Other investigators observed health-care worker compliance with recommended hand hygiene practices in a medical ICU unit during three periods (13). During the baseline period, hands were washed with soap and water. Then, an alcohol-based hand disinfectant was made available, with one alcohol dispenser for every four beds. In the third period, additional dispensers were added so that there was one alcohol dispenser for each bed. During the baseline period, 25% of health-care workers washed their hands when recommended. Hand hygiene compliance improved to 41% when one alcohol dispenser was made available for every four beds and to 48% when a dispenser was placed next to every bed. This study also suggests that better access to hand hygiene facilities results in improved compliance.

Cost

Few data are available regarding the cost of antiseptic agents used for hand hygiene. In 1999, a 450-bed community-teaching hospital spent $22,000 on 2% chlorhexidine-containing

preparations, plain soap, and alcohol hand rinse, for a cost of $0.72 per patient per day (Figure 1). If hand hygiene supplies for clinics and non-patient care areas are included, the total annual budget for soaps and hand disinfectants was $30,000, or approximately $1 per patient per day. Because of different use patterns and varying product prices, annual hand hygiene budgets at other institutions could vary considerably.

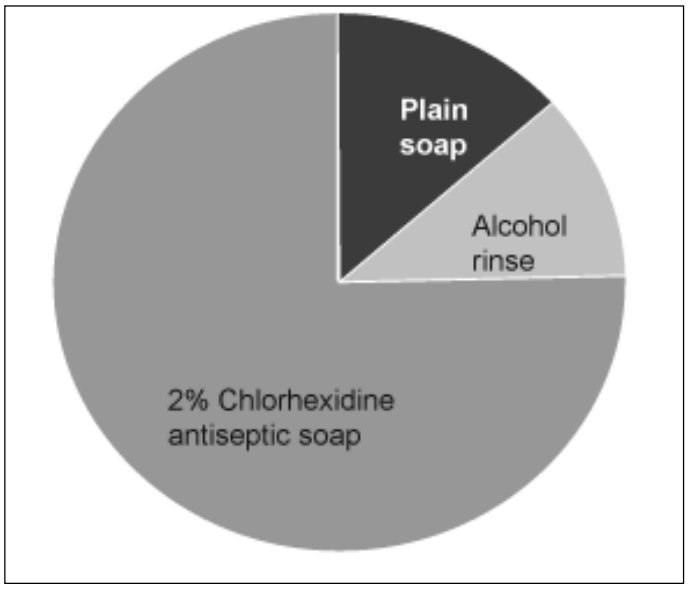

Figure 1. Annual expenditures for hand hygiene products used in patient care areas in a 450-bed community hospital, 1999.

The relative cost per liter was calculated for the products available through the hospital's buying group purchase contract (Table 2). The 2% chlorhexidine gluconate detergent was 1.7 times as expensive as the nonmedicated soap, and the alcohol-based hand gel was twice as expensive. Expenditures for soap or waterless hand disinfectants may be compared with excess hospital costs associated with nosocomial infections (Table 3). The excess hospital expense associated with four or five nosocomial infections of average severity is equal to the entire annual budget for soap and alcohol products used for hand hygiene in inpatient care areas. A single severe surgical site infection, lower respiratory infection, or bloodstream infection may cost the hospital more than the entire annual budget for antiseptic agents used for hand hygiene. If a change from nonmedicated soap to an antiseptic agent or a substantial increase in the use of antiseptic agents resulted in preventing a few additional nosocomial infections per year, the additional costs associated with using antiseptics would be offset by cost savings.

Table 2. Relative cost per liter of hand hygiene products

Product category	Relative cost
Nonmedicated liquid soap	1.0[a]
2% chlorhexidine gluconate detergent	1.7
Alcohol-based hand gel A	2.1
Alcohol hand rinse	
A	1.8
B	1.6
Alcohol foam	
A	4.7
B	4.8

[a]Nonmedicated liquid soap was arbitrarily assigned a relative cost of 1.0.

Table 3. Excess length of stay and hospital costs associated with nosocomial infections

Site of infection	Increased length of stay (days)	Increased cost ($) Average	Increased cost ($) Maximum
Urinary tract	1-4	600-930	8,280
Surgical Site	7-14	2,000-5,040	26,000
Lower respiratory	4-21	5,000-5,800	41,600
Bloodstream	4-24	3,000-40,000	>40,000

Adapted from: Jarvis WR. Selected aspects of the socioeconomic impact of nosocomial infections: morbidity, mortality, cost, and prevention. Infect Control Hosp Epidemiol 1996;17:552-7.

Acceptance

In studies of acceptance of hand hygiene products by health-care personnel, the adverse effects of frequent handwashing on the skin are considered an important issue by hospital personnel, one likely to affect the frequency of use of hand hygiene products (4,14). When hospital personnel rated five soap products for their tendency to cause skin dryness, cracking, or redness (3), the product that caused the greatest cracking and redness of the skin was least preferred by personnel. In a recent study (15), health-care workers subjectively evaluated four 4% chlorhexidine-containing products with respect to fragrance (smell), texture, lather, ease of rinsing, and tendency to cause itching. One of the four products evaluated was rated the worst in terms of smell, texture, and lather, but did not differ from the other preparations in ease of rinsing and tendency to cause itching. A subsequent questionnaire showed that the product with the undesirable smell and texture was the least popular among personnel.

Larson et al. (16) asked personnel to rate the condition of their skin before and after using water, bar soap, or one of three antiseptic preparations (antiseptics 1, 2, and 3). In self-assessments of skin condition, washing with bar soap or antiseptic 3 caused the most skin problems. In objective assessments of skin condition based on measurements of transepidermal water loss, handwashing with bar soap and antiseptic 3 produced the most skin damage. Clearly, not all handwashing preparations are equally acceptable to health-care personnel.

In the United States, health-care workers have believed that use of alcohol-based disinfectants causes excessive skin irritation and dryness. This attitude may be based on prior experience with products such as rubbing alcohol, which contains no emollients, or on outdated approaches to hand disinfection. Self-assessments of skin condition were recorded by volunteers who used an alcohol-based preparation without emollients and the same substance containing emollients (17). After 1 week of use and again after 2 weeks, the alcohol preparation containing emollients was thought to result in less damage to the skin.

In a recent prospective randomized trial (5), 29 nurses working on three hospital wards volunteered to participate. Half the nurses were randomly assigned to wash their hands with a nonmedicated soap (Soft N Sure, Steris, Inc., Mentor,

OH); the other half used an alcohol hand gel (Purell, GoJo Industries, Akron, OH) after patient contacts. Dispensers for the alcohol hand gel were placed outside each patient's room or in the patient's cubicle in the ICU. Nurses in both groups were asked not to use hand lotions or creams during the study period. After 2 weeks, all nurses resumed using standard soap-and-water hand washing and were allowed to use hand lotions or creams; the nurses who initially used soap and water switched to the alcohol hand gel regimen, and vice versa. Skin irritation and dryness were assessed by three methods: self-assessment by participating nurses, visual assessment by a study nurse, and electrical capacitance measurements of the skin on the dorsal surface of the nurses' hands (a measure of epidermal water content). Electrical capacitance measurements showed that nurses had more skin dryness if they washed their hands with soap and water than if they used the alcohol hand gel (Figure 2). Self-assessments by participants and visual assessments by the study nurse also showed that nurses had substantially greater skin irritation and dryness when using the soap-and-water regimen. On a questionnaire assessing attitudes toward the alcohol hand gel, 88% of nurses agreed or strongly agreed that the alcohol gel caused less dryness than soap-and-water handwashing; 92% agreed or strongly agreed that they would be willing to use the alcohol hand gel routinely. This study demonstrated that an alcohol hand gel containing appropriate emollients can achieve a high degree of acceptance by hospital personnel.

However, installing dispensers for alcohol-based hand disinfectants throughout a facility does not necessarily guarantee a high level of use. In a recent study, the number of liters of an alcohol hand disinfectant used per 1,000 patient-days increased substantially after implementation of a hospital-wide, multidisciplinary program to improve hand hygiene practices (18). The findings suggest that continuing educational and motivational efforts may be necessary for wide acceptance and frequent use of alcohol-based disinfectants by health-care workers.

Conclusion

Ease of access to antiseptic agents and level of acceptance of products by personnel can influence compliance with recommended hand hygiene practices. Both these factors, as well as the costs and antimicrobial activity of preparations, should be taken into consideration in the selection of hand hygiene products for health-care workers.

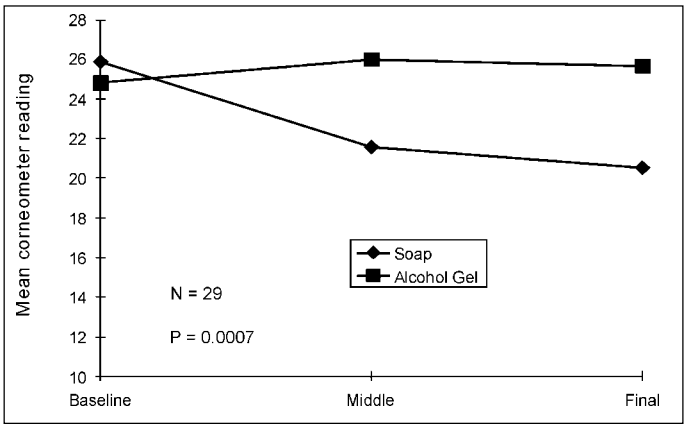

Figure 2. Electrical capacitance of dorsal hand skin surface (5).

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Improving Adherence to Hand Hygiene Practice: A Multidisciplinary Approach

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Hand hygiene prevents cross-infection in hospitals, but health-care workers' adherence to guidelines is poor. Easy, timely access to both hand hygiene and skin protection is necessary for satisfactory hand hygiene behavior. Alcohol-based hand rubs may be better than traditional handwashing as they require less time, act faster, are less irritating, and contribute to sustained improvement in compliance associated with decreased infection rates. This article reviews barriers to appropriate hand hygiene and risk factors for noncompliance and proposes strategies for promoting hand hygiene.

Hand hygiene is the simplest, most effective measure for preventing nosocomial infections (1,2). Despite advances in infection control and hospital epidemiology, Semmelweis' message is not consistently translated into clinical practice (3,4), and health-care workers' adherence to recommended hand hygiene practices is unacceptably low (3,5-10). Average compliance with hand hygiene recommendations varies between hospital wards, among professional categories of health-care workers, and according to working conditions, as well as according to the definitions used in different studies. Compliance is usually estimated as <50% (Table 1).

Promotion of hand hygiene is a major challenge for infection control experts (3,19-21). In-service education, distribution of information leaflets, workshops and lectures, and performance feedback on compliance rates have been associated with transient improvement (3,6,13,22,23). No single intervention has consistently improved compliance with hand hygiene practices (24). This review summarizes factors influencing lack of adherence by health-care personnel to hand hygiene procedures and suggests strategies for improvement.

Table 1. Compliance with hand hygiene in different hospital settings

Year	Setting	Average compliance	Author	Ref.
1981	Open ward	16%	Preston	11
	ICU	30%		
1981	ICUs	41%	Albert	5
	ICUs	28%		
1983	All wards	45%	Larson	12
1987	PICU	30%	Donowitz	13
1990	ICU	32%	Graham	6
1990	ICU	81%	Dubbert	14
1991	SICU	51%	Pettinger	15
1992	NICU/others	29%	Larson	16
1992	ICUs	40%	Doebbeling	7
1992	ICUs	40%	Zimakoff	17
1994	Emergency room	32%	Meengs	18
1999	All wards	48%	Pittet	9
	ICUs	36%		

ICUs = intensive care units; PICU = pediatric ICU; NICU = neonatal ICU.

Definitions

Two major groups of microorganisms are found on the skin: organisms that normally reside on it (resident flora) and contaminants (transient flora) (25). Unless introduced into body tissues by trauma or medical devices such as intravenous catheters, the pathogenic potential of the resident flora is low (26). Transient flora, which are easily removed by handwashing, cause most hospital infections resulting from cross-transmission (27-29).

The term hand hygiene includes several actions intended to decrease colonization with transient flora. This objective can be achieved through handwashing or hand disinfection. Handwashing refers to washing hands with an unmedicated detergent and water or water alone. Its objective is to prevent cross-transmission by removing dirt and loose transient flora (10,30). Hygienic handwash refers to the same procedure when an antiseptic agent is added to the detergent. Hand disinfection refers to use of an antiseptic solution to clean hands, either medicated soap or alcohol. Some experts refer to the action of "degerming" as the use of detergent-based antiseptics or alcohol (21). Hygienic hand rub is rubbing hands with a small quantity (2 mL to 3 mL) of a highly effective, fast-acting antiseptic agent.

Hand Hygiene Agents

If hands are known to be or suspected of being contaminated, transient flora must be eliminated by washing or disinfecting the hands to render them safe for the next patient contact. Plain soap with water can physically remove a certain level of microbes, but antiseptic agents are necessary to kill microorganisms (10,31-33). Hand antiseptic agents are designed to rapidly eliminate most transient flora by their mechanical detergent effect and to exert an additional sustained antimicrobial activity on remaining flora. The multiplication of resident flora may be retarded as well, so that hand disinfection may be useful in situations in which microbiologically clean hands are required for extended periods.

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Rotter showed that hand hygiene with unmedicated soap and water removed some transient flora mechanically; preparations containing antiseptic or antimicrobial agents not only removed flora mechanically but also chemically killed contaminating and colonizing flora, with long-term residual activity (30,34). Alcohol-based preparations have more rapid action than products containing other antiseptics (e.g., chlorhexidine gluconate or povidone iodine) (30,31,35).

Semmelweis observed that normal handwashing did not always prevent the spread of fatal infection (1) and recommended hand disinfection in a solution of chlorinated water before each vaginal examination. Hand disinfection is substantially more efficient than standard handwashing with soap and water or water alone (2,30), particularly when contamination is heavy (14,36-40). Frequent handwashing may result in minimal reduction or even an increase in bacterial yield over baseline counts of clean hands (21,41).

Because alcohols have excellent activity and the most rapid bactericidal action of all antiseptics, they are the preferred agents for hygienic hand rubs, so-called "waterless hand disinfection." In addition, alcohols are more convenient than aqueous solutions for hygienic hand rubs because of their excellent spreading quality and rapid evaporation. At equal concentrations, n-propanol is the most effective alcohol and ethanol the least (30). Alcohol-based hand rubs are well suited for hygienic hand disinfection for the following reasons: optimal antimicrobial spectrum (active against all bacteria and most clinically important viruses, yeasts, and fungi); no wash basin necessary for use and easy availability at bedside; no microbial contamination of health-care workers' clothing; and rapidity of action. After extensive reduction following hand disinfection with an alcohol preparation, it takes the resident skin flora several hours to become completely restored (30). Since alcohol alone has no lasting effect, another compound with antiseptic activity may be added to the disinfection solution to prolong the effect. These antiseptics have recently been extensively reviewed by Rotter (30).

Prevention of bacterial contamination and subsequent infection requires timely hand cleansing. Guidelines have delineated indications for hand cleansing (10,32,42) but without reliance on evidence-based studies of microbiologic contamination acquired during routine patient care. To provide such evidence, we studied the dynamics of bacterial contamination of health-care workers' hands in daily hospital practice (43). Our findings should help identify patient-care situations associated with high contamination levels and improve hand cleansing practices.

Structured observations of patient care were conducted by trained external observers, who took an imprint of the fingertips of the health-care worker's dominant hand to quantify bacterial colony counts at the end of a defined period of patient care (43). Bacterial contamination on ungloved hands increased linearly during patient care (mean 16 CFU per minute, 95% confidence interval [CI] 11-21). Activities independently associated with higher contamination levels were direct patient contact, respiratory care, handling body fluids, and disruption in the sequence of patient care (all $p<0.05$). Contamination levels varied according to hospital location, with the medical rehabilitation ward having the highest levels (>49 CFU, $p = 0.03$). Both the duration and type of patient care influenced hand contamination. Furthermore, simple handwashing before patient care, without hand disinfection, was also associated with higher colony counts (>52 CFU, $p = 0.03$), which suggests that hand antisepsis is better than standard handwashing. These findings suggested that intervention trials should explore the role of systematic hand disinfection as a cornerstone of infection control to reduce cross-transmission in hospitals.

Factors Influencing Noncompliance with Hand Hygiene

Risk factors for noncompliance with hand hygiene have been determined objectively in several observational studies or interventions to improve compliance (3,14,20,24,44-47). Factors influencing reduced compliance, identified in observational studies of hand hygiene behavior, included being a physician or a nursing assistant rather than a nurse; being a nursing assistant rather than a nurse; being male; working in an intensive care unit (ICU); working during weekdays rather than the weekend; wearing gown and gloves; using an automated sink; performing activities with high risk for cross-transmission; and having many opportunities for hand hygiene per hour of patient care.

In the largest hospital-wide survey ever conducted (9), we also identified predictors of noncompliance with hand hygiene during routine patient care. Variables included professional category, hospital ward, time of day or week, and type and intensity of patient care, defined as the number of opportunities for hand hygiene per hour of patient care. In 2,834 observed opportunities for hand hygiene, average compliance was 48%. In multivariate analysis, compliance was highest during weekends and among nurses (odds ratio [OR] 0.6, 95% CI 0.4-0.8). Noncompliance was higher in ICUs than in internal medicine (OR 2.0, CI 1.3-3.1), during procedures with a high risk for bacterial contamination (OR 1.8, CI 1.4-2.4), and when intensity of patient care was high (21 to 40 opportunities [OR 1.3, CI 1.0-1.7], 41 to 60 opportunities [OR 2.1, CI 1.5-2.9], >60 opportunities [OR 2.1, CI9 1.3-3.5]) compared with a reference level of 0 to 20 opportunities. In other words, compliance with handwashing worsened when the demand for hand cleansing was high; on average, compliance decreased by 5% (±2%) per increment of 10 opportunities per hour when the intensity of patient care exceeded 10 opportunities per hour. Similarly, the lowest compliance rate (36%) was found in ICUs, where indications for handwashing were typically more frequent (on average, 20 opportunities per patient per hour). The highest compliance rate (59%) was observed in pediatrics, where the average activity index was low (on average, eight opportunities per patient per hour). This study confirmed modest levels of compliance with hand hygiene in a teaching institution and showed that compliance varied by hospital ward and type of health-care worker, thus suggesting that targeted educational programs may be useful. These results also suggested that full compliance with current guidelines may be unrealistic (9,20,48) and that facilitated access to hand hygiene could help improve compliance.

Perceived Barriers to Hand Hygiene

Several barriers to appropriate hand hygiene have been reported (9,14,24,44-47). Reasons reported by health-care workers for the lack of adherence with recommendations include skin irritation, inaccessible supplies, interference with worker-patient relation, patient needs perceived as priority, wearing gloves, forgetfulness, ignorance of guidelines, insufficient time, high workload and understaffing, and

lack of scientific information demonstrating impact of improved hand hygiene on hospital infection rates.

Risk Factors for Noncompliance

Some of the perceived barriers for the lack of adherence with hand hygiene guidelines have been assessed or even quantified in observational studies (3,14,20,24,44-47). The most frequently reported reasons associated with poor compliance, in addition to those mentioned above, are inconveniently located or insufficient numbers of sinks; low risk for acquiring infection from patients; belief that glove use obviates need for hand hygiene; and ignorance of or disagreement with guidelines and protocols.

Skin irritation by hand hygiene agents is an important barrier to appropriate compliance (49). The superficial skin layers contain water to keep the skin soft and pliable and lipids to prevent dehydration of the corneocytes. Hand cleansing can increase skin pH, reduce lipid content, increase transepidermal water loss, and even increase microbial shedding. Soaps and detergents are damaging when applied to skin on a regular basis, and health-care workers need to be better informed about their effects. Lack of knowledge and education on this topic is a key barrier to motivation. Alcohol-based formulations for hand disinfection (whether isopropyl, ethyl, or n-propanol, in 60% to 90% vol/vol) are less irritating than antiseptic or nonantiseptic detergents. Alcohols with added emollients are at least as well tolerated and efficacious as detergents. Emollients are recommended and may protect against cross-infection by keeping the resident skin flora intact, and hand lotions help protect skin and may reduce microbial shedding (21).

The value of easy access to hand hygiene supplies, whether sink, soap, medicated detergent, or waterless alcohol-based hand rub solution, is self explanatory. Asking busy health-care workers to walk away from the patient bed to reach a wash basin or a hand antisepsis solution invites noncompliance with hand hygiene recommendations (9,48). Engineering controls could facilitate compliance, but hand hygiene behavior should be carefully monitored to identify negative effects of newly introduced devices (50).

Wearing gloves might represent a barrier for compliance with hand hygiene (8,51,52). Failure to remove gloves after patient contact or between dirty and clean body site care for the same patient constitutes noncompliance with hand hygiene recommendations (9). Washing and reusing gloves between patient contact is ineffective, and handwashing or disinfection should be strongly encouraged after glove removal. In a study involving artificial contamination, organisms were cultured from 4% to 100% of the gloves and observed counts were up to 4.7 log on hands after glove removal (53).

Additional barriers to hand hygiene compliance include lack of active participation in promotion at the individual or institutional level, of a role model for hand hygiene, of institutional priority assigned to hand hygiene, of administrative sanctions for noncompliance; and of an institutional climate encouraging safety (14,22,41,54,55). A system change may be necessary for improvement in hand hygiene practices by health-care workers.

Impact of Improved Hand Hygiene

Lack of scientific information on the definitive impact of improved hand hygiene on hospital infection rates has been reported as a possible barrier to adherence with recommendations. Hospital infections have been recognized for more than a century as a critical problem affecting the quality of patient care provided in hospitals. Studies have shown that at least one third of all hospital infections are preventable (56). A substantial proportion of infections results from cross-contamination, and transmission of microorganisms by the hands of health-care workers is recognized as the main route of spread (57). Seven quasi-experimental hospital-based studies of the impact of hand hygiene on the risk of hospital infections were published from 1977 to 1995 (Table 2) (7,22,58,60-63). Despite limitations, most reports showed a temporal relation between improved hand hygiene practices and reduced infection rates.

We recently reported the results of a successful hospital-wide hand hygiene promotion campaign, with emphasis on hand disinfection, which resulted in sustained improvement in compliance associated with a significant reduction in hospital infections and methicilllin-resistant *Staphylococcus aureus* cross-transmission rates over a 4-year period (63). The beneficial effects of hand hygiene promotion on the risk of cross-transmission have also been reported in surveys conducted in schools, day-care centers (64-68), and a community (69-71). Although additional scientific and causal evidence is needed for the impact of improved hand hygiene on infection rates, these results indicate that improvement in behavior reduces the risk of transmission of infectious pathogens.

Improving Adherence with Practices

In 1998, Kretzer and Larson (46) revisited hand hygiene behavioral theories in an attempt to better understand how to target more successful interventions. These researchers

Table 2. Improved adherence with hand hygiene practice compared with hospital infection rates

Year	Authors	Hospital setting	Results	Ref.
1977	Casewell and Philips	Adult ICU	Reduction in HI[a] due to endemic *Klebsiella* spp	58
1982	Maki and Hecht	Adult ICU	Reduction in HI rates	59
1984	Massanari and Heirholzer	Adult ICU	Reduction in NI rates	60
1990	Simmons et al.	Adult ICU	No effect	22
1992	Doebbeling et al.	Adult ICU	Significant difference in rates of HI between two different hand hygiene agents	7
1994	Webster et al.	NICU	Elimination of MRSA	61
1995	Zafar et al.	Newborn nursery	Elimination of MRSA	62
1999	Pittet et al.	Hospital-wide	Significant reduction in HI and MRSA cross-transmission rates	63

[a]HI = hospital infection; ICU = intensive care unit; NICU = neonatal ICU; MRSA = methicillin-resistant *Staphylococcus aureus.*

proposed a hypothetical framework to enhance hand hygiene practices and stressed the importance of considering the complexity of individual and institutional factors in designing behavioral interventions. Behavioral theories and secondary interventions have primarily focused on the individual, which is insufficient to effect sustained change (46,72,73). Interventions aimed at improving compliance with hand hygiene must be based on the various levels of behavior interaction (20,46,74). Thus, the interdependence of individual factors, environmental constraints, and institutional climate should be considered in strategic planning and development of hand hygiene promotion campaigns. Factors associated with noncompliance with recommendations are related not only to the individual worker but also to the group to which he or she belongs and, by extension, to the parent institution. Factors influencing compliance at the group level include lack of education and performance feedback; working in critical care (high workload); downsizing and understaffing; and lack of encouragement or role models from key staff. Factors operating at the institutional level include lack of written guidelines; lack of appropriate hand hygiene agents; lack of skin care promotion and agents; lack of hand hygiene facilities; lack of atmosphere of compliance; and lack of administrative leadership, sanctions, rewards, and support. Interventions to promote hand hygiene in hospitals should take into account variables at all these levels.

The complex dynamic of behavioral change involves a combination of education, motivation, and system change. Various psychosocial parameters influencing hand hygiene behavior include intention, attitude toward the behavior, perceived social norms, perceived behavioral control, perceived risk of infection, habits of hand hygiene practices, perceived model roles, perceived knowledge, and motivation (46). Factors necessary for change include dissatisfaction with the current situation, perception of alternatives, and recognition, both at the individual and institutional level, of the ability and potential to change. While the last factor implies education and motivation, the former two necessitate primarily a system change.

Among reasons reported for poor adherence with hand hygiene recommendations, some that are clearly related to the institution (i.e., the system) include lack of institutional priority for hand hygiene, need for administrative sanctions for noncompliance or rewards for compliance, and lack of an institutional climate that encourages safety. Whereas all three reasons would require a system change in most institutions, the last would also involve management commitment, visible safety programs, an acceptable level of work stress, a tolerant and supportive attitude toward reported problems, and belief in the efficacy of preventive strategies (20,46,73,75).

Strategies for Improvement

Improvement in infection control practices requires questioning basic beliefs, continuous assessment of the stage of behavioral change, interventions with an appropriate process of change, and supporting individual and group creativity (46). Because of the complexity of the process of change, single interventions often fail, and a multimodal, multidisciplinary strategy is necessary.

A framework for change should include parameters to be considered for hand hygiene promotion, together with the level at which each change must be applied: education, motivation, or system (Table 3). Some parameters are based on epidemiologic evidence and others on the authors' and other investigators' experience and review of current knowledge. Some parameters may be unnecessary in certain circumstances and helpful in others. In particular, changing the hand hygiene agent could be beneficial in institutions or hospital wards with a high workload and a high demand for hand hygiene when waterless hand rub is not available (9,61,62,76). However, a change in the recommended hand hygiene agent could be deleterious if introduced during winter, when skin is more easily irritated.

Several parameters that could potentially be associated with successful promotion of hand hygiene would require a system change (Table 3). Enhancing individual and institutional self-efficacy (the judgment of one's capacity to organize and execute actions to reach the objective), obtaining active participation at both levels, and promoting an institutional safety climate represent major challenges that exceed the current perception of the infection control practitioner's role.

More research is needed to determine whether education, individual reinforcement technique, appropriate rewarding, administrative sanction, enhanced self-participation, active involvement of a larger number of organizational leaders,

Table 3. Strategies for successful promotion of hand hygiene in hospitals

Parameter	Tool for change	Selected ref.[a]
Education	E[a] (M, S)	14,23,63,74,76
Routine observation and feedback	S (E, M)	6,14,23,63,74,76
Engineering controls	S	63
Make hand hygiene easy, convenient	S	63,74,77,78
Make available alcohol-based hand rub	S	63
Alcohol-based hand rub available in high-demand situations	S	63,78
Patient education	S (M)	79
Reminders in the workplace	S	52,63
Administrative sanctions, rewards	S	3,20
Change in hand hygiene agent	S (E)	21,80
Promote, facilitate skin care for HCW hands	S (E)	17,21,47,63
Obtain active participation at individual and institutional levels	E, M, S	46,63
Ensure institutional safety climate	S (M)	46,63
Enhance individual and institutional self-efficacy	S (E, M)	46,63
Avoid overcrowding, understaffing, excessive workload	S	9,15,63,81,82
Combination of above strategies	E, M, S	14,23,46,63,74

[a]E = education; M = motivation; S = system; HCW = health-care worker

[b]Only selected references are listed; refer to more extensive reviews (10,30,46) for exhaustive reference lists.

enhanced perception of health threat, self-efficacy, and perceived social pressure (20,46,83,84), or combinations of these factors would improve health-care workers' adherence to recommendations. Ultimately, compliance with hand hygiene could become part of a culture of patient safety in which a set of interdependent elements interact to achieve a shared objective (85).

More readily achievable than major system change, easy and timely access to hand hygiene in a timely fashion and the availability, free of charge, of skin care lotion both appear to be necessary prerequisites for appropriate hand hygiene behavior. In particular, in high-demand situations, such as in critical care units, in high-stress working conditions, and at times of overcrowding or understaffing, having health-care workers use a hand rub with an alcohol-based solution appears as the best method for achieving and maintaining a higher level of compliance with hand hygiene. Alcohol-based hand rub, compared with traditional handwashing with unmedicated soap and water or medicated hand antiseptic agents, may be better because it requires less time (48), acts faster (30), and irritates hands less often (21,30). This method was used in the only program that reported a sustained improvement in hand hygiene compliance associated with decreased infection rates (63).

Finally, strategies to improve compliance with hand hygiene practices should be multimodal and multidisciplinary (Table 3). It is important to note, however, that the proposed framework for such strategies needs further research before implementation.

Future Research

Among key questions regarding the practices of hand hygiene in the health-care setting today, the following need to be addressed in controlled studies: What are the key determinants of hand hygiene behavior and promotion? Should hand disinfection replace conventional handwashing? What are the best hand hygiene agents? Should hand hygiene solution include a long-lasting compound? What are the most suitable skin emollients to include in hand hygiene solution? How can skin irritation and dryness from hand hygiene agents be reduced? How does skin care protection with hand cream affect the microbiologic efficacy of hand hygiene agents? and What are the key components of hand hygiene agent acceptability by health-care workers? Additional research questions include— How can researchers generate more definitive scientific evidence for the impact of improved compliance with hand hygiene on infection rates? What is the acceptable level of compliance with hand hygiene (i.e., What percentage increase in hand hygiene results in a predictable risk reduction in infection rates?) and To what extent should the use of gloves be encouraged or discouraged? Finally, recognizing that individual and institutional factors are interdependent in terms of behavioral changes in health-care settings, what is the best way to obtain top management support for hand hygiene promotion? These questions are addressed to infection control practitioners, laboratory research scientists, and behavioral epidemiologists.

The challenge of hand hygiene promotion could be summarized in one question: How can health-care workers' behavior be changed? Tools for change are known; some have been tested, and others need to be tested. Some may prove irrelevant in the future; others have worked in some institutions and need to be tested in others. Infection control professionals should promote and conduct outstanding research and provide solutions to improve health-care worker adherence with hand hygiene and enhance patient safety.

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"Cloud" Health-Care Workers

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Certain bacteria dispersed by health-care workers can cause hospital infections. Asymptomatic health-care workers colonized rectally, vaginally, or on the skin with group A streptococci have caused outbreaks of surgical site infection by airborne dispersal. Outbreaks have been associated with skin colonization or viral upper respiratory tract infection in a phenomenon of airborne dispersal of *Staphylococcus aureus* called the "cloud" phenomenon. This review summarizes the data supporting the existence of cloud health-care workers.

A variety of infectious agents can be transmitted from health-care workers to patients (1,2). Certain of these agents are transmissible through the air, which means that transmission from health-care workers can occur in spite of standard infection control measures such as handwashing. Thus, airborne transmission increases the likelihood that an outbreak can occur. While it is well known that health-care workers can transmit infections such as tuberculosis, varicella, and influenza by the airborne route, it is less well appreciated that they can also transmit certain bacterial pathogens through the air.

Bacteria transmissible through the air for which no data support transmission by health-care workers include *Clostridium diphtheriae, Haemophilus influenzae, Neisseria meningiditis, Streptococcus pneumoniae*, and *Yersinia pestis*. For all these agents except *S. pneumoniae*, the epidemiologic data supporting airborne transmission are strong enough that the Centers for Disease Control and Prevention recommends that infected patients be placed on droplet precautions (3). However, for all five agents, no episodes are well documented of health-care workers transmitting such infections to other patients by the airborne route, perhaps because workers with such infections may be too sick to work. For three other bacteria, *Bordetella pertussis, Streptococcus pyogenes*, and *Staphylococcus aureus*, strong data support airborne transmission from health-care workers to patients.

Bordetella pertussis

Although most children are vaccinated against *B. pertussis* and the vaccine is quite effective up to age 12, approximately 50% of adults are nonimmune (4). Thus, in a vaccinated population, transmission of pertussis is primarily from adults to either nonimmune children (<1 year of age) or to adults whose immunity has waned. Several well-described hospital outbreaks of pertussis have occurred in which *B. pertussis* was thought to be transmitted to or from health-care workers in a manner suggesting airborne transmission (Table 1) (5-9). Most hospital outbreaks have involved pediatric patients (5,6,8,9), but at least one outbreak has occurred in a nursing home (7). No prolonged carrier state has been identified (10,11), and transmission is most likely associated with active symptoms, particularly coughing (12). The use of air samplers and polymerase chain reaction analysis has shown that *B. pertussis* DNA can be found in the air surrounding patients with *B. pertussis* infection, providing further evidence of airborne spread (13). Terminating *B. pertussis* hospital outbreaks involves removing symptomatic health-care workers from clinical care, isolating symptomatic or exposed patients, and treating symptomatic and exposed health-care workers and patients with antibiotics.

Table 1. Hospital *Bordetella pertussis* outbreaks involving health-care workers and possible airborne transmission

Reference	Health-care workers (no.)	Other adults (no.)	Patient population	Infected patients (no.)
Kurt (5)	5	1	Pediatrics	2
	4	0	Pediatrics	0
Linneman (6)	13	0	Pediatrics	6
Addis (7)	5	0	Nursing Home	4
Christie (8)	87	0	Pediatrics	1
Nouvellon (9)	1	0	Pediatrics	1

Group A *Streptococcus pyogenes* (GAS)

Health-care worker-associated GAS outbreaks attributed to airborne spread are uncommon, associated only with asymptomatic health-care workers, and involving only surgical site infections (14-18). The health-care workers carrying GAS may be present during surgery (e.g., anesthesiologist, operating room nurse) (16,17) or not present at all (e.g., medical attendant, operating room technician) (14,15,18). In five GAS outbreaks associated with health-care workers (Table 2), volumetric or settle plate air cultures showed that the health-care workers dispersed GAS into the air. Sites of GAS colonization identified on the health-care workers include the rectum, vagina, and skin. The mechanism by which GAS becomes airborne is not entirely clear and could include increased activity (14), friction with clothing, or, in the case of an anesthesiologist who was a rectal carrier, flatulence. Such outbreaks may cause substantial illness and even death. Termination of GAS health-care worker-associated outbreaks requires eradicating the carrier state with antibiotics. In some cases eradication has been difficult because the health-care workers' family was also colonized with GAS, which may have led to initial treatment failure.

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Table 2. Hospital group A streptococcal outbreaks suggesting airborne transmission by asymptomatic health-care workers

Reference	Health-care worker	Source of GAS[a,b]	Patient population	Infected patients (no.)
McKee (14,15)	Attendant	Rectum	Gynecologic	11
Schaffner (16)	Anesthesiologist	Rectum	Surgical	20
Berkelman (17)	OR nurse	Vagina	Surgical	10
Mastro (18)	OR technician	Scalp	Surgical	20

[a]GAS air cultures were all positive
[b]GAS = Group A Streptococcus, OR = operating room

Staphyloccoccus aureus

Factors affecting the airborne dispersal of *S. aureus* have been studied more intensively than those of any other organism. In the general population, airborne dispersal of *S. aureus* is uncommon and appears to be quantitatively related to the number of *S. aureus* colonizing the anterior nares (19). Up to 10% of healthy *S. aureus* nasal carriers disperse the organism into the air (20), and females are much less likely to disperse the organism than males (21,22). Such airborne dispersers typically were surrounded by 0.01 to 0.1 CFU/m^3 of *S. aureus* and, rarely, as high as 2.6 CFU/m^3 (21,22). Hare and Thomas demonstrated that when agar plates were held directly under the noses of nasal carriers of *S. aureus*, airborne dispersal was insignificant with nasal breathing, counting, coughing 6 times, or sneezing once (23). Only with snorting did substantial dispersal occur. In contrast, when the same volunteers were moving, large numbers of *S. aureus* were dispersed into the air. This dispersal was attributed to *S. aureus* on the skin and clothing, thought to be liberated into the air by friction and movement. Coughing increases airborne dispersal of organisms other than *S. aureus*, and lack of airborne dispersal of *S. aureus* through coughing is thought to be due to its rare presence in the oropharyngeal cavity. In other studies, talking increased dispersal of organisms other than *S. aureus*, and sneezing dramatically increased the number of bacteria dispersed into the air, including *S. aureus* (24,25). Ehrenkranz demonstrated that oral tetracycline caused the number of *S. aureus* in the nose of a nasal carrier of tetracycline-resistant *S. aureus* to increase by tenfold and concommitantly increased the number of *S. aureus* dispersed into the air (26).

In detailed studies of *S. aureus* transmission in a newborn nursery setting (27,28), Rammelkamp et al. found that newborn infants exposed to nurses who handled colonized infants acquired *S. aureus* 14% of the time if good handwashing was performed and 43% of the time in the absence of good handwashing (presumed direct contact transmission). Infants acquired *S. aureus* 10% of the time when they were exposed to nurses who were not colonized with *S. aureus* and who did not handle infants colonized with *S. aureus* (presumed airborne transmission). Under these controlled circumstances, airborne transmission was about two thirds as likely as contact transmission. The infants infected by presumed airborne transmission were four times more likely to acquire the organism first in their noses than were the infants infected by direct contact (4/16 vs. 3/49; p=0.056). During a 3-year period, Nobel demonstrated that a few patients (8/3,675) were associated with airborne dispersal of *S. aureus* (29). One of eight dispersers identified was associated with an outbreak. While inactive, such patients were associated with air counts of up to 0.3 CFU/m^3 air. The highest number of *S. aureus* in the air was found in association with bedmaking of colonized patients (up to 4.9 CFU/m^3). Elevated airborne dispersal has also been associated with individual patients (30,31). Hare and Cooke found that airborne dispersal was facilitated by eczema, mycosis fungoids, or perineal carriage (31). In a few published outbreaks, health-care workers have been identified who clearly dispersed *S. aureus* into the air (32,33); in one case, dispersal was thought to be due to heavy skin colonization with *S. aureus* (15). In other outbreaks where airborne transmission has been suspected, no air cultures were performed, so the contribution of airborne transmission was not determined (34,35). Thus, although airborne dispersal from both patients and health-care workers occurs, under the circumstances previously studied, it is relatively uncommon.

However, outbreaks associated with such airborne dispersers are frequent (>10%) (29,32). Clearly, if some factor augments the ability of *S. aureus* carriers to produce airborne dispersal, the potential for *S. aureus* outbreaks to occur might be greatly increased. In 1960, the American Journal of Diseases of Children preceded an article with a brief editorial entitled "The Preposterous Cloud Baby" (36). The first sentence of the introduction stated "Once in a blue moon a journal is privileged to publish an article which introduces an important revolutionary concept." In the report that followed, Eichenwald et al. described a group of *S. aureus*-colonized, virally infected newborn infants who had the ability to disperse *S. aureus* from their noses into the air—so-called "cloud babies" (36). These researchers demonstrated by culture and epidemiologic study that a viral upper respiratory infection (e.g., with adenovirus or echo virus) was the essential "cloud factor." Up to 75% of newborn infants who carried *S. aureus* nasally became cloud babies once they acquired a viral upper respiratory infection. Most importantly, these cloud babies were also capable of causing *S. aureus* outbreaks (36). Although these infants had no greater risk for staphylococcal infection, the families of cloud babies had a fourfold higher risk for infection than the families of infants colonized with *S. aureus* that were not cloud babies. In spite of what was believed to be a revolutionary concept, no further observations about cloud babies have been published since Eichenwald's study in 1960.

In 1986 we reported that an *S. aureus* nasal carrier, a nurse, caused outbreaks in two newborn nurseries at different hospitals in association with upper respiratory infections (34). The nurse's strain of *S. aureus* and the outbreak strains were identical by phage typing. Infants' risk for acquiring staphylococcal skin disease was fivefold greater when the nurse had a upper respiratory infection. She was treated with topical bacitracin ointment and hexachlorophene baths to eradicate her *S. aureus* carrier state, and no further outbreaks of staphylococcal skin disease occurred. We postulated then that the probable source of the outbreak might be a cloud adult (4).

In 1996, an outbreak of methicillin-resistant *S. aureus* (MRSA) pneumonia occurred in an intensive care unit (33). Multivariant analysis demonstrated that the only independent risk factors for MRSA pneumonia were intubation and exposure to a single physician, who was nasally colonized with the outbreak strain of MRSA as shown by molecular typing. During the outbreak period, this physician had a

prolonged upper respiratory infection, and an experimental rhinovirus upper respiratory infection caused him to increase airborne dispersal of *S. aureus* 40-fold and become a cloud adult. The use of a mask during this experimental rhinovirus infection caused a 75% reduction in the airborne dispersal of *S. aureus*.

To a hospital epidemiologist, the identification of two cloud adults as the cause of the only two tightly clustered *S. aureus* outbreaks investigated during his career is either a striking coincidence or an indication that the frequency with which airborne transmission plays a role in *S. aureus* outbreaks has been underestimated. Many hospital outbreaks of *S. aureus* infections have been reported that were thought to be due to a single health-care worker (32-35,37-52). A few of these were probably related to heavy skin colonization (32) or sinusitis (35), but in most cases no other risk factor was apparent that could account for these persons' being capable of causing an outbreak. The role of airborne transmission was investigated in only two studies (32,33). In the group without identifiable risk factors, virtually all the health-care workers were nasally colonized with *S. aureus*. Indeed, *S. aureus* nasal colonization in health-care workers is quite common (20% to 90%) (53-56). However, if *S. aureus* nasal colonization was the only factor necessary to cause an outbreak, the high frequency of *S. aureus* nasal colonization in health-care workers should be associated with a high frequency of *S. aureus* outbreaks. Since this is not the case, some other factor(s) must modify the *S. aureus* nasal carrier state to facilitate the outbreak. One such factor is likely a viral upper respiratory infection. Since adults have an average of two viral upper respiratory infections each year (57), cloud adults may be working around patients all year.

We recently investigated the generalizability of the cloud adult phenomenon by giving six persistent nasal carriers of *S. aureus* a rhinovirus infection (58). One of the six volunteers became an unequivocal cloud adult, with a 40-fold increase in *S. aureus* airborne dispersal that could be blocked by a mask. Another volunteer had a similar increase in airborne dispersal, but it could not be prevented by a mask. The six volunteers came from a group of 18 persistent nasal carriers of *S. aureus* identified from 95 volunteers screened for *S. aureus* nasal carriage. These findings suggest that the ability to become a cloud adult could occur with a frequency of up to 6% or more in the general population.

Viral upper respiratory infections facilitate the transmission of other bacterial infections, including the following pathogens that colonize the nose: *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, and *N. meningitidis* (59-62). Thus, cloud adults have the potential to play a role in the transmission of other organisms and might be involved with some of the explosive outbreaks of infection occasionally seen in day-care centers, homeless shelters, the military, and hospitals. Further work is necessary to understand the importance of cloud adults in the transmission of hospital infections.

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Preventing Nosocomial *Mycobacterium tuberculosis* Transmission in International Settings

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Tuberculosis (TB) is a worldwide disease, and nosocomial transmission is known to occur. Authoritative preventive guidelines such as the one developed by the Centers for Disease Control have been published, but the expenses for implementing them can be prohibitive. Each country needs to develop its own protocol to prevent nosocomial transmission of TB. This article describes the key elements of a protocol undertaken for all public hospitals in Hong Kong, where TB is endemic.

Tuberculosis (TB) is an international disease of epidemic proportions. More than 3 million reported cases occur worldwide each year (1), and the actual incidence is estimated to be >10 million cases (2). The World Health Organization (WHO) has published a global strategy for TB control in the community (3) and has called on all nations to develop national TB programs. However, preventing TB in the hospital is just as critical internationally. This report focuses on issues related to preventing nosocomial TB in the international setting.

The High Cost of Prevention

Numerous guidelines for preventing nosocomial TB have been introduced in the industrialized world. One of the most authoritative protocols is the guideline formulated by the Centers for Disease Control and Prevention (CDC) (4). Implementing this guideline, however, can be expensive. Various studies have estimated that the cost of preventing one case of occupational TB in a hospital, using the CDC guideline, could run into millions of U.S. dollars (5,6). This expense is a heavy burden for hospitals and beyond the capability of many developing countries.

The expense is related to the elaborate demands in the CDC guideline, which was developed in 1994 specifically for the United States after a serious resurgence of TB. The urgency of the matter was summarized succinctly in the 1993 document of the U.S. Occupational Safety and Health Administration (OSHA) (7). New TB cases had increased by 18%, reversing an 18-year downward trend. Outbreaks had occurred in many hospitals, and at least five health-care workers had died. Under such a cloud, making impeccable recommendations in spite of high expenses in cost and manpower seemed reasonable.

The situation can be entirely different in other countries, and therefore guidelines should be tailored to meet local needs. This paper discusses the approach needed to formulate a local TB prevention guideline for hospitals, using a guideline for public hospitals developed in Hong Kong. The challenge is to develop a tool that will be effective locally and yet remain consistent with established scientific principles. At least four elements are needed for a successful local program: 1) integrating important principles from existing guidelines; 2) collecting local epidemiologic data; 3) taking into account local capabilities and priorities; and 4) ongoing monitoring for efficacy.

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Integrating Important Principles from Existing Guidelines

The first element of a successful local TB prevention program is to integrate important principles from existing guidelines. Building on the work of others is critical. The CDC guideline is an important source, as is a guideline for health-care facilities formulated by WHO (8).

A useful concept in these guidelines is three levels of control measures, ordered according to their importance and priority for implementation: 1) administrative controls, which are aimed at reducing the TB exposures of health-care workers; 2) engineering controls, which are environmental methods to reduce the concentration of droplet nuclei in the air; and 3) personal respiratory protection for health-care workers who are exposed to TB in patient care (4). The protocol we developed in Hong Kong adopted these three levels as its basic format.

Collecting Local Epidemiologic Data

A second element of a successful local TB prevention protocol is collection of local epidemiologic data. Accurate local data on the incidence of TB can be difficult to obtain. Fortunately, most countries do have case notification data. In cities like Hong Kong, which have effective TB control programs, case reports approximate the true incidence of TB (9).

In Hong Kong, the incidence of TB peaked in 1952, and BCG vaccine was made mandatory at birth. Subsequently, the incidence and crude death rate dropped dramatically (Figure 1). Nevertheless, TB remains endemic in Hong Kong, with an incidence rate of 1/1,000 population for the past decade.

Figure 2 shows the antimicrobial drug-resistance rate for TB strains isolated in the government laboratory in 1998.

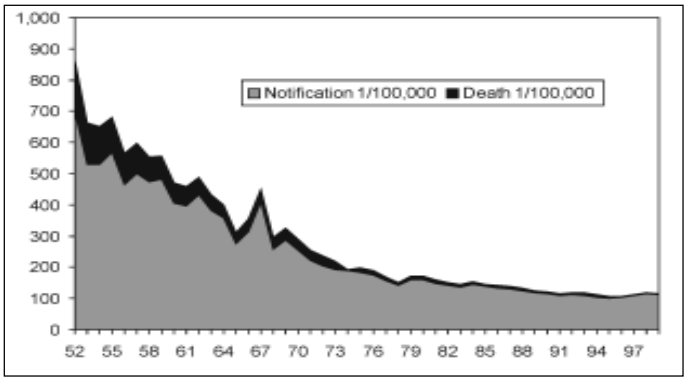

Figure 1. TB notifications and crude death rates, Hong Kong.

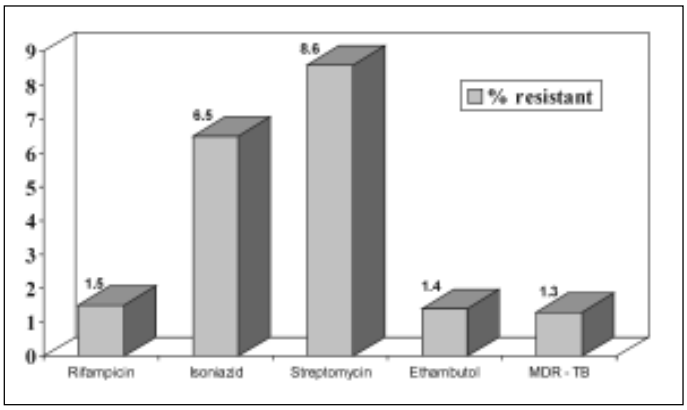

Figure 2. Antimicrobial sensitivity of MDR-TB strains from Government Laboratory, Hong Kong.[a]
[a]N = 1,345 (patient specific).

Multidrug-resistant (MDR)-TB is still relatively low, at 1.3%. One reason may be the effective use of short-course therapy (five drugs), provided free to the public for the past 20 years.

Finally, we collected data from large, acute-care public hospitals that participated in the surveillance network of health-care workers who had nosocomial TB. In Hong Kong, infection control units are in place in most public hospitals, and, with the help of the hospital laboratory, staff clinic, and human resource departments, they regularly identify staff diagnosed with active TB. Data should be especially accurate after 1996, when a new law, the Occupational Safety and Health Ordinance, made reporting of employees with active TB mandatory. There is also a strong personal incentive for reporting because the ordinance stipulates compensation for verified TB cases. The incidence of health-care workers with active TB was found to be consistently below that of the general populace, even when the rates were adjusted for the younger ages of the health-care workers from 1994 (Table). This trend persisted even after the ordinance was introduced, making underreporting unlikely.

Surveys of health-care workers to identify tuberculin skin-test conversions are not conducted in Hong Kong. Such surveys would not be accurate for detecting active infections because BCG is given at birth and repeated if needed in the school health system. Furthermore, if the incidence of active TB in health-care workers is clearly below the general populace and the first prerogative of infection control is preventing active disease (10), the value of surveys that identify only immune responses is questionable.

In summary, TB is still endemic in Hong Kong, but the incidence has been stable for more than a decade. The percentage of MDR-TB cases is small, and the incidence of active TB in health-care workers is lower than in the general population. This low incidence is probably due to a high herd immunity. The mandatory BCG vaccination with repeated challenges from a TB-endemic environment and a robust general health must certainly be contributing factors. Nevertheless, local data indicate that, unlike the United States in 1993, no TB crisis confronts Hong Kong.

Emphasizing Local Capabilities and Priorities

The third element in a successful local TB-prevention program is taking into account local capabilities and priorities. A guideline for preventing TB in the hospital was introduced in 1996 in Queen Mary Hospital, the teaching hospital for the University of Hong Kong. The guideline was then formally endorsed by the authorities as the reference guideline for all public hospitals in the territory.

The underlying assumption was that no crisis situation was at hand in Hong Kong; thus, drastic measures were probably not required. Nevertheless, best possible practice within the allocated resources ought to be promoted. The salient points of this guideline are summarized below.

Administrative Control

Administration control is focused on three sectors of the hospital: patients, contacts, and staff.

Patients

The first strategy is to minimize hospitalization of TB patients. Pulmonary TB patients are generally treated as outpatients in Hong Kong. For those admitted, a 24-hour laboratory service for sputum microscopy is provided. The infection control nurse reviews all TB cases diagnosed by the laboratory (both smears and cultures) and facilitates their

Table. Comparison of tuberculosis in hospital health-care workers (HCWs) and community, Hong Kong

	Year							
	1991	1992	1993	1994	1995	1996	1997	1998
Hospitals (no.)	3	3	4	7	7	7	7	7
Staff (no.)	9,063	9,063	10,844	17,983	19,555	21,228	21,434	21,863
HCWs with TB (no.)	8	6	9	15	9	8	18	11
Incidence in HCWs[a]	88	66	83	83	46	38	84	50
Case reports of TB, Hong Kong	6,283	6,292	6,537	6,319	6,212	6,501	7,072	7,673
Incidence, Hong Kong[a,b]	109	112	110	104/90[b]	101/91[b]	103/87[b]	109/94[b]	115/89[b]

[a]per 100,000.
[b]age-adjusted for HCWs.

discharge or transfer to designated TB hospitals. In Queen Mary Hospital, under such a system, 95% of TB patients are discharged from the hospital within 4 days of a positive microbiology report.

An attempt is made to isolate patients with active disease for 2 weeks, but since facilities are limited, priority is given to those who are strongly (+++) smear positive, AIDS patients, and those suspected of having MDR-TB. If isolation cannot be maintained for 2 weeks, it is maintained for up to 5 days after effective chemotherapy has begun. Even when isolation is not possible, exposure of patients to neonates, young children, and immunocompromised hosts is not permitted for 4 weeks.

Contacts

The admission rates for TB patients in Hong Kong hospitals are rather high and in Queen Mary Hospital, more than 200 inpatients are seen each year. In spite of this, the low incidence of health-care workers with active TB suggests that the risk of active infection in contacts is not overly high. Therefore, draconian measures to investigate contacts are not recommended.

However, when a strongly (+++) smear-positive patient is seen in a high-risk area (with neutropenic patients or neonates), a list of contacts in the same cubicle is generated. Those who have had prolonged contact (>3 weeks) or who have symptoms suggestive of TB are given a chest X ray. All contacts of a strongly smear-positive case who are immunocompromised or children <3 years old are followed up for 3 months.

Chemoprophylaxis is generally not recommended for contacts but may be considered for infants who are exposed. All contacts are counseled to obtain a chest X ray if they develop symptoms suggestive of pulmonary TB that last for 3 weeks.

Staff

The infection control nurse conducts surveillance for active TB in health-care workers. Physical therapists are to avoid chest drainage on patients who are smear positive unless they are connected to a closed suction system. A respirator mask is provided for a health-care worker if intubation is needed for patients who are smear positive.

Some strategies routinely recommended elsewhere were not included in the Hong Kong guideline. An assessment of transmission risk at all sites is not conducted. The admission rate for TB is so high that it seems reasonable to assume that the frequency of exposure is probably high in most departments. This high number of admissions also makes routine education of contacts and staff difficult. The suggestion of triage and special precautions in departments such as accident and emergency and radiology was proposed, but not adopted by the respective departments because they never had nosocomial TB reported nor encountered difficulties with their present arrangements. As stated above, surveys of health-care workers for TST conversion are not done, nor are surveys of chest X rays or symptoms because these are reported to be inaccurate (8).

Engineering Controls

Engineering controls are another major point of our guideline. In hospitals with no central air conditioning, a specially designed isolation room is not provided. In fact, WHO has stated that hospitals ought to "maximize natural ventilation through open windows" (8). Negative-pressure isolation rooms are usually installed in hospitals with central air conditioning. The locations of these isolation rooms, as with the 10 available in Queen Mary Hospital, must be clearly listed in the guideline for the hospital. The number of isolation rooms provided is generally insufficient, and therefore contingency plans with a priority list for isolation are included as recommendations in the guideline.

Other control measures for proven TB cases are included in the guideline. Filters are used on ventilated patients and changed daily. Heat mist exchangers are recommended to avert frequent tubing change. Finally, for patients in the intensive care unit, a closed suction system with disposable suction canisters and tubings is recommended. UV lights and portable HEPA filters are not recommended in Hong Kong.

Respirator Protection

Respirator protection is another feature of our guideline. Special N95 masks are provided only for bronchoscopists and staff with substantial contact (e.g., during intubation) with patients who have active TB and are not on effective chemotherapy. For other patient-care activities, only the surgical mask is recommended. There is no evidence that the N95 is better than the surgical mask in preventing employee skin-test conversion in the United States (11). Routine fit testing and medical screening, as mandated by OSHA in America (7), are not conducted, as even U.S. specialists have questioned their benefit (11).

Ongoing Monitoring for Efficacy

The efficacy of the preventive measures should be monitored. In Hong Kong, this is made possible by the ongoing surveillance program for TB in health-care workers. Our guideline was introduced in 1996. Surveillance data in 1997 and 1998 (Table) should offer an evaluation on its effectiveness.

Conclusions

With the resurgence of TB as a global problem, due attention needs to be given to this disease in the health-care setting. Although authoritative guidelines for preventing nosocomial TB are available, each country needs to develop its own specific protocol because, to be effective, guidelines must address local issues such as disease patterns and resource availability. The Hong Kong experience hopefully can be a model for other hospitals engaged in similar undertakings.

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Epidemiology and Prevention of Pediatric Viral Respiratory Infections in Health-Care Institutions

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Nosocomial viral respiratory infections cause considerable illness and death on pediatric wards. Common causes of these infections include respiratory syncytial virus and influenza. Although primarily a community pathogen, rhinovirus also occasionally results in hospitalization and serious sequelae. This article reviews effective infection control interventions for these three pathogens, as well as ongoing controversies.

Infection control professionals worldwide rely on the Guideline for Isolation Precautions in Hospitals promulgated by the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (1). This widely venerated document has assumed almost ecclesiastical authority. The guidelines have been framed carefully to reflect current evidence and opinion on the modes of transmission of nosocomial pathogens, and it is this rigorous evidence-based process that insures their credibility. However, scrutiny of guidelines addressing the nosocomial spread of viral pathogens reveals the fragile data on which many of the recommendations are based.

Evidence on modes of transmission of viruses tends to be the most fragmentary and unconvincing. When the first Decennial Conference was held, viral diagnostics was in its infancy, and few hospital clinical laboratories were equipped to assist infection control professionals in understanding the epidemiology of nosocomial viral disease. Moreover, our current knowledge about the spread of infection by droplets and droplet nuclei is a relatively recent phenomenon. It was not that long ago that all infections were thought to be spread by miasms, those putrid vapors emanating from decomposing organic matter and environmental filth. William Farr, an excellent epidemiologist and close colleague of Florence Nightingale, firmly believed that the 1849 cholera outbreak in London was caused by miasms rising from the fetid River Thames. Malaria (literally from the Italian root, *mal aria*, or "bad air") and yellow fever were attributed to miasms before their mosquito vectors were discovered near the turn of the century. Indeed, some authorities predicted with confidence that these diseases, which killed thousands of workers who were trying to dig the Panama Canal, would be eradicated as soon as the canal trench was filled with water, sealing over the miasm-generating tropical ooze. Not until mid-century did Wells et al. at Johns Hopkins demonstrate that tiny droplet nuclei could convey infectious microorganisms over long distances from patient to patient (2).

What, then, do we know about the transmission of common, clinically important nosocomial viruses? Studies of three viruses of importance to pediatric hospital epidemiologists (respiratory syncytial virus [RSV], influenza virus, and rhinovirus) illustrate that modes of transmission have been clarified somewhat but that serious gaps in our knowledge persist. Many of these studies should provide inspiration for young hospital epidemiologists and infection control professionals. Almost without exception, they were performed by hard-nosed investigators who had little, if any, external funding—investigators who exploited serendipitous events or devised and conducted original studies on a shoestring.

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RSV

RSV is the most important cause of respiratory infection in young children worldwide, infecting virtually every child in the first few years of life. Immunity is feeble and fleeting, and repeated infections are the rule. One in every 100 or 200 infected infants requires hospitalization, usually for bronchiolitis. Therefore, pediatric hospital wards are flooded with patients with community-acquired RSV every winter, and failure to follow fastidious infection control procedures inevitably leads to nosocomial transmission (3,4). RSV is, in fact, one of the "perennial weeds" on pediatric wards that Caroline Breese Hall discussed at this same conference 20 years ago (5). The consequences of RSV infection can be especially dire for children with underlying conditions such as prematurity, cardiac and pulmonary disease, or immunosuppression (6-9). Nosocomial RSV infection in immunocompromised adults results in prolonged, substantial illness and even death (10). RSV also takes a heavy toll on members of the nursing and medical staff, with attack rates in some studies approaching 50% (5). Bronchiolitis does not develop in health-care providers because, as adults, they have considerably larger airways than infants; however, severe colds and reactive airway disease do develop (11). Because winter is the busiest time of year on pediatric wards, ill staff members seldom take time off to recuperate, thus serving as efficient vectors in the chain of disease transmission.

Since RSV is a respiratory virus, one might be tempted to speculate that it is transmitted primarily by droplet nuclei or droplet contact. However, Hall et al. demonstrated clearly that contact transmission predominates (12). Freshly infected infants, who were producing copious secretions, were placed in a crib in a room reserved for the study. Volunteers were brought into the room and assigned to one of three

groups. "Cuddlers" performed routine care, picked the baby up, and played with the child. "Touchers" had extensive contact with objects in the baby's environment, which had been contaminated heavily with secretions. "Sitters" sat right next to the crib for 3 hours but did not touch anything in the baby's environment. None of the 14 sitters developed RSV infection, but five of the seven cuddlers and four of the 10 touchers became ill.

Infants secrete enormous concentrations of RSV, often more than 10^7/mL of nasal discharge, and the concentration of virus diminishes only slowly over a period of days (13). Moreover, RSV survives well on fomites; for example, virus can be cultured for >5 hours on impervious surfaces such as bed rails (14). Thus, care givers have numerous opportunities to contaminate their hands during routine care, and unless they wash their hands, virus will be transmitted by indirect contact to other infants. Furthermore, symptomatic infection has a high probability of developing in care givers who touch their eyes or nose with contaminated fingers.

Numerous studies have evaluated potential strategies to control nosocomial transmission of RSV. Gowns and masks were studied before the modes of transmission of RSV were understood fully (15,16). These studies, which were underpowered, did not detect a beneficial impact on the rate of cross-infection. Hall's group, recognizing that the eyes are an unprotected portal for inoculation of virus in health-care workers, evaluated especially designed eye-nose goggles that ward staff could wear when caring for infants infected with RSV (17). Although these goggles reduced the rate of infection in care givers and infants to 5% and 6%, respectively, the goggles were not well accepted by the staff and eventually were abandoned.

Studies at Children's Hospital, Boston, provide considerable support for the key role of contact with contaminated secretions in RSV transmission, as well as the value of wearing gowns and gloves when caring for infected patients (18). Surreptitious surveillance of compliance with gown and glove precautions on a general pediatric ward documented adherence in only 38.5% of encounters with ill infants. When open monitoring, education, and feedback of nosocomial infection rates were introduced, compliance reached levels as high as 95% and remained very good even after surreptitious surveillance was reintroduced. The rate of nosocomial RSV infection fell from 6.4 to 3.1 cases per 1,000 patient days. The magnitude of the effect was by far the greatest at the peak of the winter epidemic in the community, when the ward was crowded with infected infants. Thus, simple barrier precautions, including wearing gloves when touching contaminated objects, proved extremely effective in limiting RSV transmission. Of course, it is possible that excellent compliance with handwashing might obviate the need for gloves, as is the case for all nosocomial infections transmitted from patient to patient by contaminated hands. Isaacs et al. (19) found that handwashing and cohorting were effective in reducing the nosocomial infection rate. For RSV, using a hand antisepsis agent that contains detergent or alcohol is critical. Aqueous chlorhexidine without detergent has poor activity against RSV (20).

Some investigators have advocated performing rapid tests for RSV on all symptomatic infants during the annual RSV season, cohorting RSV-positive patients, and placing them on gown and glove precautions. Madge found that this approach was more effective than gowns and gloves or cohorting alone (21), although compliance was not measured. Snydman noted a reduction in nosocomial infection in a newborn nursery when rapid testing was combined with cohorting, visitation restrictions, and gowns, gloves, and masks (22). However, the cost-effectiveness of routinely testing all symptomatic infants for RSV remains to be demonstrated conclusively. Once the virology laboratory has documented that the RSV season has started, a child with bronchiolitis will likely have RSV, and screening only children who have atypical symptoms may be sufficient.

Recently, investigators using polymerase chain reaction (PCR) to detect RSV RNA suggested that RSV might be transmitted over considerable distances by air (23). RNA was found in air samples taken as far as 7 m from the bedside of infected patients for up to day 7 of hospitalization. However, a positive PCR result does not prove that infectious virus is present, and it seems premature to use such data to refute excellent epidemiologic studies by several groups of investigators documenting the primary importance of contact transmission.

Influenza

Influenza is a substantial threat to hospitalized patients despite the availability of a relatively effective vaccine and two classes of drugs (M2 ion channel inhibitors and neuraminidase inhibitors) shown to prevent infection in clinical trials (24). Although influenza is widely viewed as affecting primarily elderly patients and adults with coexisting illnesses or conditions, such as chronic pulmonary and cardiac disease, nosocomial transmission has been well documented in young children (25,26). Perhaps nosocomial disease is less frequently diagnosed in hospitalized children because infants are unable to articulate many of influenza's characteristic symptoms, and influenza often presents simply as an episode of fever in this population.

The proper isolation procedures for hospitalized patients with influenza are controversial. Infection can likely be transmitted by direct and indirect contact, as well as by droplet contact. Airborne spread by droplet nuclei has sparked controversy, since true airborne transmission would best be controlled by isolating patients in rooms with negative air pressure and requiring staff to wear masks on entering the room. Such precautions would be costly and difficult to implement at the height of an influenza outbreak.

What is the evidence for airborne transmission of influenza? The explosive nature of influenza outbreaks supports airborne transmission. Some investigators have even suggested that the rapid intercontinental transmission of influenza can be mediated by transport of aerosolized virus on air currents over hundreds to thousands of kilometers in low-pressure centers with frontal waves (27). However, data substantiating the airborne theory of transmission are relatively sparse. Perhaps the most compelling data come from animal models of influenza. Mice inoculated with influenza virus readily transmitted infection to susceptible animals from which they had been separated by double wire screens (28). The attack rate increased at low relative humidity, as would be expected, since virus suspended in aerosolized droplet nuclei survives much longer at lower humidity. Moreover, transmission occurred more frequently when the ventilation in the chamber housing the mice was poor, as Wells established is typical of diseases spread by the airborne route. In a ferret influenza model, infected ferrets

transmitted influenza to uninfected ferrets separated by a 9-foot duct with two 90° bends (29). Large droplets certainly would not be able to negotiate such curves, whereas droplet nuclei typically can.

A natural experiment in patients at the Veterans Administration Hospital in Livermore, California, can be viewed as the human counterpart of these animal experiments (30). One building housing 150 patients with tuberculosis and chronic pulmonary disease was ventilated by UV light-irradiated air, whereas another part of the hospital housing 250 tuberculosis patients received nonirradiated air. During the 1957-58 influenza season, the attack rate in patients in the irradiated building (as confirmed serologically) was 2%, but the attack rates among patients and staff in the nonirradiated area were 19% and 18%, respectively.

Probably the most dramatic example of airborne spread in humans occurred during an airplane flight from Anchorage to Kodiak, Alaska (31). At an intermediate stop in Homer, Alaska, the plane had mechanical difficulty and remained on the tarmac for several hours with an inoperative ventilation system. A young woman had boarded the flight in Homer and within 15 minutes developed full-blown symptoms of acute influenza. A point-source outbreak of influenza ensued, and 72% of the 54 passengers became ill within 72 hours. The attack rate was highest in passengers who remained on the crippled plane the longest, and the six passengers who deplaned immediately remained well. Although the passengers who stayed on the plane moved about at will, influenza developed in few of those who had close contact with the index patient.

Since available evidence tends to support airborne transmission of influenza, attempting to place infected patients on precautions suitable for protecting susceptible patients and staff from virus-laden droplet nuclei seems prudent. Of course, improved compliance with current recommendations for immunizing health-care workers remains the key to influenza control in the hospital. Most facilities will be severely challenged if they try to isolate all patients with symptoms compatible with influenza.

Rhinovirus

Although nosocomial rhinovirus infection is not as substantial a problem as RSV and influenza on pediatric wards, it can have serious sequelae in premature neonates and children with chronic diseases or immunosuppression (32). For example, in another session at this decennial meeting, Huskins and his colleagues at Children's Hospital, Boston, report an outbreak of rhinovirus infection at a pediatric chronic-care facility that was associated with considerable illness and death. However, there is another reason to discuss the transmission of rhinovirus–namely, that this pathogen demonstrates the difficulty in proving conclusively how respiratory viruses are transmitted.

The common cold is a profound nuisance in everyday life, although seldom a cause of serious illness. The average child can expect to have four to eight episodes per year, and adults three to five infections. Many viruses, such as parainfluenza, RSV, and coronavirus, can produce similar symptoms, but rhinovirus is by far the most frequent etiologic agent. Repeated colds are virtually guaranteed because there are >100 distinct rhinovirus serotypes, and infection with one serotype does not confer substantial immunity against the others.

A prodigious volume of work at the Common Cold Research Unit in Salisbury, England, following World War II established that colds could be produced by inoculating secretions into the nose or eye of volunteers (33). These rather crude experiments were replicated with nasal inoculation of small concentrations of rhinovirus once the specific viral agents that cause the common cold were elucidated (34). Presumably, therefore, persons might acquire rhinovirus by touching their nasal or ocular mucosa with contaminated fingers. A study by Hendley et al. at the University of Virginia demonstrated that health-care workers are not immune to practices that might promote self-inoculation (35). One third of grand-rounds attendees picked their nose, and one in 2.7 rubbed their eyes during a 1-hour lecture. Subsequent work demonstrated that it was difficult to transmit rhinovirus by kissing (36), and that exposure to cold did not increase the likelihood of "catching a cold" (37).

These studies could not answer the central question of whether rhinovirus is transmitted primarily by direct contact, indirect contact, droplet contact, or droplet nuclei. Unfortunately, considerable additional investigation has not resolved the issue completely (38). Essentially, two experimental approaches, both highly contrived, have come to different conclusions. Work by Hendley and Gwaltney at the University of Virginia generally has supported transmission by hand contact and self-inoculation, while experiments by Dick at the University of Wisconsin have favored spread by large droplets, droplet nuclei, or both.

The Virginia group demonstrated that adults with experimental rhinovirus colds readily contaminated their hands and that rhinovirus could be recovered from 43% of plastic tiles they touched with their contaminated fingers (39). Adults with natural rhinovirus colds contaminated their hands in 39% of cases, and virus was found on 6% of objects in their homes (35,40). Virus could survive from a few hours to as long as 4 days on nonporous surfaces, and for at least 2 hours on human skin (35). Volunteers who had contact with contaminated objects or with fingers of persons with rhinovirus colds had a high rate of infection when they intentionally touched their eyes or nose. Infection generally could be prevented by treating contaminated surfaces with disinfectant or applying iodine to fingers (39).

In a labor-intensive, randomized clinical trial, the Virginia group found that treating mothers' fingers with iodine reduced the rate of secondary infection (38). Specifically, as soon as a cold occurred in another member of the family, mothers were instructed to dip their fingers in iodine or placebo when they awoke in the morning, every 3 to 4 hours during the day, and after activities that might wash the iodine from the skin. The investigators counted on the well-established residual activity of iodine to kill virus on contact. Over the 4-year study period, the secondary attack rate for colds in the intervention group was 7%, versus 20% in the control group. In the iodine-treated group, no confirmed rhinovirus infection occurred in susceptible mothers who had been exposed to 11 index cases. In contrast, five infections occurred after 16 exposures in the placebo group, although this difference was not significant.

These studies provide considerable evidence for indirect contact transmission by contaminated fomites and fingers. In other experiments, the Virginia investigators found little support for transmission via large respiratory droplets or droplet nuclei. Exposure of susceptible volunteers to highly

symptomatic volunteers across a small table (droplet contact and droplet nucleus transmission) or a double-wire barrier (droplet nucleus spread) resulted in infections in 1 of 12 and zero of 10 subjects, respectively (39). These rates of transmission were far less than the 11 infections among 15 persons (73%) who self-inoculated their mucous membranes with contaminated fingers.

Meanwhile, the Wisconsin group was developing models to study transmission of rhinovirus colds, building on observations showing high attack rates among men crowded together in a small hut in Antarctica (41). In one such model, symptomatic volunteers were housed with susceptible volunteers in a room approximately 12-by-6-by-3 m (42). The subjects played various board, card, and video games during the study period. Since viral titers in nasal secretions fall as symptoms diminish, volunteers were replaced with highly symptomatic persons as soon as they experienced reduced rhinorrhea or sneezing. The average length of exposure required for transmission was very high, 200 hours of exposure to achieve a 50% attack rate. Based on these results, Dick et al. suggest that exposure times in the Virginia studies were too short to exclude droplet and airborne transmission.

In additional experiments, the Wisconsin group extended these studies by having volunteers play poker for 12 hours while sitting at round tables (43). Three experiments were performed involving 24 symptomatic "donors" and 36 susceptible "recipients." Half of the recipients were fitted with restraints, either arm braces that allowed them to reach their cards but not touch their face, or a plastic shield that left their hands free but did not allow them to reach their eyes or nose. Despite these barriers, the attack rates were 56% and 67%, respectively, strongly favoring transmission by air since self-inoculation was impossible. Moreover, when 12 additional susceptible volunteers were brought to a separate room to play poker with chips and cards that were literally soaked with contaminated secretions from donors, no rhinovirus infections occurred. In addition, little virus was found on the chips and cards. The Wisconsin group suggested that the relatively high attack rates seen in the self-inoculation studies conducted by the Virginia group might be attributable to intensive exposure to fresh wet secretions (e.g., the volunteers literally blew their noses into their hands).

The above studies provide only a glimpse of the extensive literature on the transmission of rhinovirus colds, but controversy still simmers. The prudent person probably will wash his or her hands after shaking hands with someone who has a cold or after touching environmental objects potentially contaminated with relatively fresh secretions. Alcohol-based, waterless antiseptics are ideal for this purpose. Although droplet contact or airborne transmission of rhinovirus infection is possible, prolonged and close exposure is apparently required.

Dr. Goldmann, who is professor of pediatrics at Harvard Medical School, has a research focus on the epidemiology and control of hospital-acquired infections, especially antimicrobial drug-resistant infections in intensive care units. In addition, he studies the epidemiology and prevention of medical errors and adverse events in pediatrics. Dr. Goldmann collaborates with colleagues at the Channing Laboratory in Boston regarding the pathogenesis of staphylococcal foreign body infections and is working to develop imunologic approaches for their prevention.

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HIV Postexposure Prophylaxis in the 21st Century

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The administration of postexposure prophylaxis has become the standard of care for occupational exposures to HIV. We have learned a great deal about the safety and potential efficacy of these agents, as well as the optimal management of health-care workers occupationally exposed to HIV. This article describes the current state of knowledge in this field, identifies substantive questions to be answered, and summarizes basic principles of postexposure management.

Since 1988, institutions have been offering antiretroviral postexposure prophylaxis (PEP) for occupational exposures to HIV (1,2). Although much has been accomplished since 1990, many important questions remain: What are the initiating events in the pathogenesis of occupational HIV infection associated with a percutaneous exposure? What evidence supports the effectiveness of PEP in preventing occupational HIV infection? How can the use of PEP be improved by eliminating overtreatment? How can access to and use of expert consultants be facilitated? How can adherence to PEP medication regimens be improved? What is the relevance of the source patient's prior antiretroviral experience? How should occupational exposures be managed in pregnant health-care workers?

Pathogenesis

The early events in the pathogenesis of occupational HIV infection are incompletely characterized, although the last 10 years have seen substantial developments. Several studies have suggested an important role for the dendritic cell in the early events of infection. In the macaque simian immunodeficiency virus (SIV) model, dendritic cells, which are the first cells infected after intravaginal inoculation (3), can foster extensive viral replication when they interact with susceptible T cells (4). Another important piece of evidence underscoring both the role of the dendritic cell and the potential benefit of antiretroviral PEP comes from the studies of Pope et al., which demonstrated that infection of susceptible T cells by HIV-bearing dendritic cells could be blocked in vitro by the addition of antiretroviral agents to the culture system (4).

The role of host defense against HIV is also incompletely delineated. Ruprecht et al. were among the first to demonstrate efficacy of antiretroviral PEP in an animal system (a mouse model of retroviral infection). These investigators demonstrated that, for PEP to be effective, the mice needed to have intact cellular immunity (5). Clerici et al., who evaluated T cells from eight HIV-exposed but uninfected health-care workers, found that cells from six of the eight produced interleukin-2 when exposed to HIV peptide antigens, whereas cells from only one of nine unexposed controls mounted an interleukin-2 response (6). In follow-up studies from the same laboratories, investigators demonstrated that cytotoxic T-lymphocyte responses to HIV envelope peptides could be detected in 35% of occupationally exposed health-care workers, but in none of 20 health-care workers who had been exposed to blood from patients who did not have HIV infection (7). Administration of antiretroviral PEP to health-care workers who have sustained occupational HIV exposures may blunt this cellular response (8).

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Effectiveness of PEP in Preventing Occupational HIV Infection

The risk for occupational infection with HIV after a parenteral exposure to blood from an HIV-infected patient is approximately 0.3% (9). Because of this low rate of transmission and the difficulty in amassing a sufficient sample size of health-care workers with documented occupational HIV exposure, conducting a clinical trial is virtually impossible (2). During the past 10 years, however, evidence supporting the efficacy of PEP has come from three types of studies: in animal models; in preventing maternal-fetal transmission of HIV in humans; and a worldwide retrospective case-control study.

Animal Studies of PEP

Several recent studies have demonstrated the efficacy of various antiretroviral agents in preventing retroviral infections in animals. Bottiger et al. demonstrated that a 3-day course of the nucleoside analog BEA-005 (2,3'-dideoxy-3'-hydroxymethyl cytidine) prevented either SIV or HIV-2 infection (10). Tsai et al. demonstrated the efficacy of the nucleotide analog phosphonyl-methoxy-propyladenine (PMPA) (Tenofovir, Gilead Sciences, Foster City, CA) in preventing SIV infection in macaques (11). In subsequent studies, duration of PEP treatment influenced the success of chemoprophylaxis in this model; the timing of administration of the dose relative to exposure or infection is also critical. All the macaques treated for 28 days but only half the macaques treated for 10 days and none of those treated for 3 days were protected. Delaying PEP also was found to be detrimental: 100% of macaques that received PEP within 24 hours of intravenous infection with SIV remained uninfected, but 50% of the animals that received the first PEP dose 48 hours after infection and 25% of those that received the first dose 72 hours after infection were protected (12). In a similar study

presented at the 4th Decennial Conference, PMPA PEP was effective after vaginal inoculation of macaques with HIV-2. All animals treated within 36 hours of inoculation were protected, but one of four treated at 72 hours after inoculation became infected (13).

Efficacy in Preventing Maternal-Fetal Transmission of HIV

Progress has been made in the past 10 years in preventing the transmission of HIV from infected mothers to their offspring. In the United States, the incidence of perinatally transmitted HIV infection declined by two thirds from 1992 to 1997 (14). In the groundbreaking AIDS Clinical Treatment Group (ACTG) protocol 076, zidovudine (ZDV) was administered to mothers before birth and during labor and delivery and to the newborns for 6 weeks after birth (15). For mother-offspring pairs in the treatment arm of this study, the risk for vertical transmission of HIV was reduced by 67% (15). Since publication of the ACTG 076 trial, several studies have confirmed and extended these initial results (14,16-30). Wade et al. demonstrated that administration of antiretroviral agents to the newborn within the first 48 hours of life significantly reduced the risk for perinatal HIV transmission (31). Several recent studies have evaluated combinations of antiretroviral agents (23,24), altered dosing schedules (22,28-31), delivery strategies (19,20), or short-term administration of nonnucleoside reverse transcriptase inhibitors (25)—all with similar success (Table). As in the study by Wade and colleagues, in some of these studies only the infant received the agents (22). These studies effectively dispel the early concern that, because of their mode of action, antiretroviral agents (in particular, nucleoside analogs) could not be effective in prophylaxis (2). Further, the studies that show a preventive effect when the drugs are administered only to newborns offer definitive proof that PEP (at least for vertical exposure) can be effective in humans.

Table. Clinical trials assessing the efficacy of antiretroviral agents in preventing maternal-fetal transmission of HIV

Study (ref)	Regimen[a]	Timing[b]	Outcome (%)
Connor (15)	ZDV	A+L+P	8.3 vs 25.5
Shaffer (28)	ZDV	A+L	9.4 vs 18.9
Wiktor (29)	ZDV	A+L	12.2 vs 21.7
Dabis (30)	ZDV	A+L+P	18.0 vs 27.5
Wade (31)	ZDV	A+L+P	6.1 vs 26.6
	ZDV	L+P	10.0 vs 26.6
	ZDV	P (<48 hr)	9.3 vs 26.6
	ZDV	P (>72 hr)	18.4 vs 26.6
Bulterys (22)	ZDV	A+L+P	8.2 vs 15.5
	ZDV	L+P	8.6 vs 15.5
	ZDV	P	8.1 vs 15.5
Saba (23)	ZDV+3TC	A+L+P	52 (reduction)
	ZDV+3TC	L+P	40 (reduction)
	ZDV+3TC	L	no reduction
Blanche (24)	ZDV+3TC	A+L+P	2.6
	ZDV	A+L+P	6.5
Guay (25)	ZDV	L+P	25.1
	NVP	L+P	13.1

[a]ZDV = zidovudine (azidothymidine); 3TC = lamivudine; NVP = nevirapine

[b]A - Prenatal therapy (usually beginning at 36 weeks); L - Therapy during labor and delivery; P - Postpartum treatment of infant.

The Retrospective Case-Control Study

The third piece of evidence supporting the efficacy of antiretroviral PEP comes from the retrospective case-control study of health-care workers who sustained occupational exposures to HIV (32). In this study, cases of occupational infection were matched with controls from the Centers for Disease Control and Prevention (CDC)'s ongoing study of self-reported occupational HIV exposures. This study identified four factors associated with the risk for occupational infection and also found that ZDV PEP was associated with an >80% reduction in infection risk (32). Despite these limitations (33), the study findings are extremely important, as no other data directly address this issue.

Overtreatment and the Use of Expert Consultants

A concern in the prescribing and administration of PEP is that the persons who are asked to prescribe PEP are often not familiar with the drugs. Emergency room staff or occupational medicine personnel may be called on to prescribe drugs for PEP but have limited experience with the drugs and their toxicities and, because these occurrences are rare, often are unfamiliar with what constitutes an exposure. Occupational HIV exposures are crisis situations demanding immediate, decisive action. Indirect evidence that the primary prescribers may not be entirely familiar with the optimal management strategies for PEP comes from the University of California at San Francisco prophylaxis hotline. In 1997, in 58% of the calls to the hotline, staff recommended either stopping or not starting PEP (34). In 1998, 59% of calls were handled similarly (D. Bangsberg, pers. comm.). These problems could at least in part be averted by providing ready access to expert consultants.

The choice of agents for PEP is also a source of confusion and an area in which expert consultants could provide substantial assistance. To err on the conservative side of the issue, providers may assume that more is better. Adding additional agents, however, may mean that the health-care worker is unable to adhere to the regimen. For most exposures, only two agents are necessary (35). For more complicated situations (e.g., a source patient with extensive antiretroviral experience), expert consultation is essential.

Finally, the duration of PEP is somewhat controversial. In some maternal-fetal studies, a short course was effective (e.g., two doses of nevirapine) (25). In certain animal studies, shortened courses were effective (10), but in others, the shortened course was associated with decreased efficacy (12). Providing a regimen to which the exposed health-care worker can adhere is of paramount importance. Without definitive data to demonstrate the safety of shorter courses, the "traditional" 28-day course of PEP is preferable.

Relevance of the Source Patient's Experience with Antiretroviral Agents

An issue that frequently arises in centers treating large numbers of patients with HIV infection is whether the PEP regimen should be altered for exposures to a patient who has extensive experience with antiretroviral agents. Some instances of PEP failure have been associated with genotypic or phenotypic resistance to the agent(s) selected for PEP (35). Instances have been reported in which PEP failure was ascribed at least in part to isolates resistant to one or more of the three drugs in the standard regimen (36). Conversely, especially in the maternal-fetal studies, genotypic resistance

has not precluded a beneficial drug effect (17). For example, in the ACTG-076 study, ZDV therapy was effective despite the fact that HIV isolates from 25% to 30% of the women demonstrated genotypic resistance to ZDV (17). If a source patient has a resistant isolate, expert consultation should be sought with an HIV specialist. Tailoring the PEP regimen to the source patient's antiretroviral experience makes intuitive sense. If the source patient is controlled on therapy (i.e., has a low or undetectable viral burden), working with the expert consultant to select a regimen based on the source patient's drugs is also reasonable.

Tailoring regimens for all health-care workers who have exposures to antiretroviral-experienced patients may lead to the administration of newer, less well-tested, and potentially more toxic agents to the exposed health-care workers, clearly increasing their risk. However, a patient who is breaking through on therapy (i.e., has a high viral titer despite treatment) may not always have resistant isolates. Treatment failures may be due to poor adherence with treatment regimens rather than viral resistance (37,38), and circulating isolates (i.e., wild-type virus) may be nonresistant. In addition, some evidence indicates that resistance disappears rapidly after treatment is stopped (39), so that aggressive selection of PEP agents may not be necessary. Nonetheless, the most recent U.S. Public Health Service guideline for managing health-care workers who have sustained occupational HIV exposures recommends adding an agent from a class of drugs to which the source patient's isolate has not been exposed when resistance is highly suspected or known (35). Based on the new information cited above, such an agent should be added only if resistance is documented.

PEP in Pregnant Health-Care Workers

The administration of antiretroviral PEP to pregnant health-care workers who have sustained an occupational exposure to HIV has long been a matter of controversy. Information about the risks of administering these agents to pregnant women has been extremely limited, but a few basic principles should be applied. First, pregnancy per se should not preclude PEP for an exposed health-care worker. Second, the decision whether PEP should be administered to a pregnant health-care worker should be hers, after she has had the benefit of thorough counseling about risks for infection and adverse drug effects for herself and her fetus. Third, the regimen offered to a pregnant health-care worker should be the one with the best chance of preventing infection. Fourth, pregnant workers electing PEP should be followed scrupulously for signs of adverse events. Recently, concern has been expressed about potential for mitochondrial toxicity in infants born to mothers receiving antiretroviral agents. In the French cooperative study evaluating the administration of antiretroviral agents to prevent maternal-fetal HIV transmission, two infant deaths among children who did not acquire HIV infection were ascribed to progressive neurologic disease (40). After this cohort was screened for elevated lactate levels, six additional cases of potential mitochondrial toxicity were identified (40). Four patients had received ZDV alone, and four had received the ZDV/3TC combination. Three of the additional six cases had neurologic findings including status epilepticus, myopathy, seizures, spastic diplegia, and febrile seizures (40). The U.S. Food and Drug Administration has evaluated postmarketing data from manufacturers of nucleoside analogs and has not identified additional deaths in this dataset. The U.S. Public Health Service has also examined data from CDC surveillance, CDC studies of maternal-fetal transmission, the National Institutes of Health's ACTG Studies, and the large database from the Women and Infants Transmission Study without identifying additional deaths attributable to mitochondrial disease. These data provide some reassurance, but the French findings indicate that additional scrutiny is warranted.

Conclusions

We have made substantial progress in our management of occupational exposures to HIV since the 1990 Decennial Conference. The rationale for offering PEP to health-care workers after documented occupational exposures to HIV now seems much more solid than in 1990. Nonetheless, several important questions remain unanswered: How are the generally encouraging data generated from animal studies and from studies of the efficacy of antiretroviral agents in preventing vertical transmission of HIV in humans relevant to the use of chemoprophylaxis after sexual exposures to HIV? What roles will new agents (e.g., BEA-005 or PMPA) play in postexposure management? Why do patients coinfected with hepatitis C and HIV have such differing prognoses and disease progression?

Several basic principles should be followed in postexposure management of occupational exposures to HIV. First, ensure that treatment is immediately accessible. Second, make certain an exposure has occurred (using expert consultants whenever necessary). Third, if PEP is administered, select a regimen to which the health-care worker can adhere (dependent on the source patient's therapy and viral level). Fourth, learn to anticipate and treat side effects prophylactically. Fifth, monitor the health-care worker closely for adherence with the regimen and for adverse drug effects.

Finally, regardless of the development of successful postexposure management strategies, we need to continue to invest a substantial effort in preventing occupational exposures to bloodborne pathogens. Several institutions have worked aggressively to reduce these exposures, some with great success (41-44). We need to learn from our colleagues' experiences and continue to minimize such occupational exposures.

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Tuberculosis Control in the 21st Century

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In response to tuberculosis (TB) outbreaks in the United States in the late 1980s and early 1990s, U.S. hospitals spent tremendous resources to ensure a safer workplace. A remarkable decrease in nosocomial transmission resulted, along with a decrease in TB cases nationally. Federal standards have been promulgated to ensure a safer work environment for all U.S. workers potentially exposed to TB. However, these measures may prove costly and burdensome and thus may compromise the ability to deliver care.

A consensus that caring for patients with tuberculosis (TB) posed a risk to health-care workers did not emerge until the 1950s and 1960s, when studies established that *Mycobacterium tuberculosis* infection was transmitted by the airborne route (1). However, occupational transmission received little attention until numerous outbreaks of TB and multidrug-resistant tuberculosis (MDRTB) occurred in U.S. and European hospitals in the 1980s and 1990s (2).

More than 20 health-care workers became ill with MDRTB, and at least 10 died (3). Hundreds of health-care workers may be latently infected with MDRTB and thus represent a large repository at risk for future reactivation of disease. Thus, although the MDRTB and drug-sensitive TB outbreaks in the United States and Europe have largely been controlled, the consequences of these outbreaks are still being felt. This article reviews current approaches to TB control in hospitals and prospects for improved control.

General Considerations

Efficient control of nosocomial TB is compromised by the same difficulties complicating community control, including an insensitive, slow method of diagnosing active disease; an insensitive, nonspecific method of diagnosing latent disease; and relatively slow-acting, complicated courses of medical therapy. However, enormous strides in hospital TB control were made during the late 1980s and 1990s by using common sense, trial and error, and published guidelines (4-6). Most U.S. hospitals now have TB control programs adequate to deal with current TB levels. Should another epidemic occur, however, these approaches may prove insufficient, as in the mid-1980s when the AIDS epidemic introduced a new group at high risk for active TB.

Community versus Hospital

At the height of the TB resurgence in the early 1990s, many urban U.S. hospitals reported purified protein derivative (PPD) conversion rates in health-care workers of 3% to 5% (3). A survey of U.S. hospitals conducted by the Centers for Disease Control and Prevention (CDC) found a mean conversion rate of 1.6% (7,8). Most recent studies have demonstrated rates <1% annually. Although some of the elevated conversion rate of the early 1990s resulted from the booster phenomenon, much was due to occupationally acquired infection.

Because the conversion rate is now <1% for most U.S. hospitals, infection control teams can investigate each instance of potential exposure from an infectious source case. Despite thousands of potential exposures, many infection control teams are unable to document tuberculin conversions in exposed staff, suggesting that many PPD conversions are the result of community, rather than occupational, transmission. Supporting this perspective are studies associating zip code or area of residence with PPD conversion, rather than specific hospital occupation or specific exposure (9,10).

In some hospitals occupation is significantly associated with risk for PPD conversion. In studies from New York City (11) and Brazil (A. Kritski, pers. comm.), housekeepers were at particularly high risk, independent of area of residence. The hospitals reporting this finding treated high numbers of patients with TB (>100 per year), increasing risk for nosocomial transmission. In hospitals caring for relatively few cases of TB, however, occupational exposure may indeed be less important than exposure in the home or community.

The Purified Protein Derivative Test

An active surveillance program must rely on the time-honored tuberculin PPD test, which is difficult to place, read, and interpret. In addition, the sensitivity and specificity of the 19th century test are far lower than those of other modern diagnostic tests. Among criticisms of the proposed Occupational Safety and Health Administration (OSHA) standard (10), perhaps the most compelling is the reliance of a $250 million program on the PPD test.

The Booster Phenomenon

The booster phenomenon confounds the interpretation of the PPD test, complicating TB control programs (12). The extent of boosting in healthy populations was demonstrated in several CDC-led studies of serial skin testing in otherwise healthy young health-care workers. A surprising number of conversions were encountered at the third and fourth test, even in those not exposed to TB, which suggests that boosting with the third and fourth serial test may be more common than assumed. The dramatic rise in PPD conversion rates in hospitals with outbreaks may result as much from nonspecific boosting as from true nosocomial transmission and acquisition of *M. tuberculosis.* By the same logic, subsequent decreases in PPD conversion rates may result from the

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exhaustion of the booster phenomenon in a population, rather than true reduction of nosocomial transmission.

The booster phenomenon is now minimized in hospitals because the efforts of TB control leaders have resulted in frequent skin testing. As TB case rates continue to decrease, along with concern about nosocomial transmission, more unboosted health-care workers will enter the workforce, setting the stage for pseudo-outbreaks similar to those in the 1980s and 1990s (13). In worker populations with high rates of BCG vaccination, boosting is more common (3,13,14). The strongest argument for maintaining the current 6- to 12-month skin testing programs is the need to continue to minimize the booster phenomenon, rather than the need for heightened surveillance to detect TB transmission.

Approach to Control

The 1994 CDC guidelines for TB control in hospitals and other health-care facilities (4) have become the basis for all U.S. hospital TB control programs, as well as the proposed OSHA standard (10). TB was controlled in hospitals by implementing numerous control measures within a few months, in addition to improving staff awareness and concern (5,15). Thus, it is impossible to know which intervention is the best or most cost-effective for a hospital with limited resources and a low TB case-rate. That said, the old adage that the undiagnosed case is the one most likely to transmit infection remains useful in establishing priorities for TB control.

The 1994 guidelines divide the implementation strategy into a hierarchy of three approaches. Administrative interventions include those to increase the isolation of persons with suspected cases, development of a hospital-wide TB control plan, and maintenance of an active tuberculin skin-test program for health-care workers. Engineering controls, which focus on how best to handle air, include negative pressure capability in respiratory isolation rooms, placement of UV light fixtures, and installation of HEPA filters.

Personal protective equipment (PPE, masks and respirators) decisions were complicated by the lack of clinically meaningful information to guide decisions. After several years of debate, a relatively cheap and comfortable product, the N-95 particulate respirator, was settled upon and is recommended in the proposed OSHA standard.

Research Needs

In addition to unanswered questions regarding these three interventions, the problems of PPD's insensitivity and nonspecificity and the long treatment courses necessary for cure further complicate hospital TB control. Cost-effective control of TB may depend on improvement in each of these areas.

Whom to Isolate?

Prompt diagnosis of probable TB requires at least one of three elements: a compatible clinical presentation; sputum smear revealing acid-fast bacilli (AFB); or a chest X ray suggesting TB. Each of these three approaches, however, is relatively insensitive and nonspecific.

One reason that TB control failed so dramatically during the early AIDS epidemic was the relative nonspecificity of TB symptoms in this population. Weight loss, low-grade fevers, and inanition were often the only complaints, even in patients with active pulmonary disease. In patients with advanced AIDS, the same symptoms may be seen in cytomegalovirus disease, lymphoma, or disseminated *M. avium-intracellulare*. This experience illustrated the variable clinical appearance of TB, particularly in populations with abnormal immune function.

Infection control decisions regarding maintenance of respiratory isolation have traditionally been based on the AFB sputum smear, which has approximately 50% sensitivity for TB diagnosis. Therefore, half of patients with active pulmonary TB (i.e., smear-negative disease) are removed from isolation. The relative contagiousness of patients with smear-negative pulmonary results is unknown, but indirect evidence suggests they may transmit infection. A classic study by Grzybowski et al. defined the tuberculin status of an entire community, stratified according to exposure to persons with TB (16). Of small children living in a household with an adult with AFB smear-negative disease, 6% were tuberculin reactive, compared with 0.7% of unexposed age-matched controls. In recent report, a longitudinal molecular typing study (17) indicated up to 17% of cases of TB in San Francisco derived from a smear-negative source case. Despite these studies, the three-smear rule-out has served hospitals well with only rare problems. A practical approach might be for clinicians to continue isolation only for patients who have initial AFB-negative sputum smears but compelling clinical symptoms and chest X rays.

The use of genetic-based tests to diagnose TB may improve diagnostic sensitivity (18). However, few such tests are useful in smear-negative cases and so are of little use in routine infection control practice. They are appropriate, however, to further classify persons with AFB smear-positive disease.

The chest radiograph is notoriously insensitive as a TB screening tool. Up to 10% of persons with pulmonary TB may have an initially normal chest X ray (19). Although computed tomography is sensitive in identifying many abnormalities, routine chest tomography in patients with potential pulmonary disease is not practical.

When to Discontinue Isolation?

Discontinuing isolation of patients with known TB often is less important for physicians but of paramount importance to the hospital infection control staff, who need to know when a patient no longer can transmit the tubercle bacillus. Previous work, including studies comparing home versus hospital therapy (20) and comparing outcome according to smear or culture status at discharge (21), is >25 years old and may no longer be pertinent to TB care in the 21st century.

Among time-honored approaches (22), the most common is the practice of considering discharge after 2 weeks of apparently effective therapy. Others wait until the sputum AFB smear converts from positive to negative, which may take 4 to 6 weeks. In areas where drug-resistant TB is common, a more cautious approach might be waiting for at least 2 weeks of smear-negativity or, if MDRTB is documented, for culture negativity.

As important as clinical and smear status are the conditions to which the patient will return. Because TB disproportionately affects poor, homeless, and HIV-infected persons, many TB patients should not return to their previous living conditions until shown to be culture-negative. From an infection control perspective, the question "Where is the patient being discharged to?" is often more pertinent than the question "When can the patient be discharged?"

Engineering Needs

Providing rooms with negative-pressure ventilation was a formidable task for hospitals in the 1990s, and maintaining these rooms is difficult. Warped door frames, shifts in outdoor wind direction, and leaky window seals may interfere with negative-pressure ventilation. Furthermore, no practical consensus has been reached regarding the number of air exchanges per hour needed to protect workers and other patients.

Many experts advocate other engineering controls such as UV light. Innovative studies are ongoing to define optimal aerodynamics and ventilation and establish (or exclude) the role of UV light in TB control. Certainly its inexpensiveness, practicality, and exportability make it the most attractive alternative, should it prove effective.

Personal Protective Equipment

A long public debate regarding optimal masks and respirators was waged in the early 1990s, as cost and comfort had to be weighed against patient and worker safety (23,24). Eventually, a practical solution, the N-95 particulate respirator, was agreed upon and is now used in U.S. hospitals. Many infection control programs lost a degree of credibility and good will in hospitals where clinicians resisted accepting uncomfortable masks. Although compliance was achieved, the consequences of forcing staff to follow an unpopular, unproven regulation should not be minimized. The success of other important infection control functions, such as annual influenza vaccination drives and handwashing initiatives, depends as much on good will as on scientific merit. The effort expended to enforce a single intervention may have affected the success of other programs to control nosocomial infections.

An additional problem relating to PPE is the requirement for annual fit-testing of masks. Many health-care workers have learned to expedite fit-testing by pretending not to taste the saccharine used in fit-test checks. In addition, few hospitals can deal effectively with the small subset of employees who cannot be fit-tested successfully. Most continue in their current jobs, using putatively inadequate masks. Given the diminishing resources available to hospitals, annual fit-testing could be replaced by an annual self-assessment health questionnaire to identify workers who need fit-testing.

The OSHA TB Standard

OSHA determined that the occupational risk for TB warranted a standard to ensure worker protection and, in 1997, issued a working draft (10)—the second time that OSHA has developed regulations to protect against an infectious disease. The first such example was the Bloodborne Pathogens Standard, which has significantly reduced occupationally transmitted hepatitis B nationally. The date for implementation of the TB standard is uncertain.

Many health-care workers in urban hospitals had colleagues who became ill with acute TB infection during the MDRTB outbreaks of the late 1980s and early 1990s. Some have watched colleagues die of this nosocomial disease. Thus, most workers welcome attempts to minimize nosocomial spread of *M. tuberculosis.* Concern has arisen, however, that the OSHA approach, estimated to cost $250 million annually, is not scientifically sound and will not reduce risk beyond the current regulations. The debate about scientific soundness derives from the reliance on the PPD test, which is neither sensitive nor specific, unlike the hepatitis B antibody and surface antigen test on which the bloodborne pathogen standard is based. Furthermore, the death rates used in the cost assumptions appear far in excess of what most centers have seen in the past decade. Finally, the regulations may impose a financial burden on facilities such as homeless shelters and drug treatment centers.

The ultimate goal of the standard, no occupational risk, may not be achievable, even with unlimited resources and a perfect test for latent disease. However, the intention of the OSHA standard (minimizing occupational risk for contracting TB) is worthy and will serve to draw public and employer attention to the larger issue of occupational risk for infectious disease. As additional data emerge, a more practical standard that both protects workers and conserves valuable resources may be developed.

Conclusions

A great deal about hospital TB control was relearned in the 1990s, as hospitals nationwide struggled to contain outbreaks. We are now faced with the realization that we do not know which of the many interventions were effective. Furthermore, 21st century TB control efforts continue to rely on the 19th-century PPD test and the insensitive sputum AFB smear. It is hard to be optimistic about great gains in TB control in the years ahead, beyond the current cautious, but effective "isolate frequently" approach, as long as programs continue to rely on these inadequate diagnostic tests. For at least the next decade, the decidedly low-tech measures of isolating persons with potential disease, wearing masks, and keeping doors closed in rooms that house potential TB patients will remain the cornerstones of TB control in U.S. hospitals.

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Hospital Infection Control in Hematopoietic Stem Cell Transplant Recipients

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Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients contains a section on hospital infection control including evidence-based recommendations regarding ventilation, construction, equipment, plants, play areas and toys, health-care workers, visitors, patient skin and oral care, catheter-related infections, drug-resistant organisms, and specific nosocomial infections. These guidelines are intended to reduce the number and severity of hospital infections in hematopoietic stem cell transplant recipients.

The Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), and the American Society for Blood and Marrow Transplantation (ASBMT) sponsored the Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. This document was drafted in 1997 by a working group of infectious disease and transplant experts,[1] revised extensively from 1997 to 1999, and released for public comment on September 15, 1999, on the CDC website. The final document was published in CDC's Morbidity and Mortality Weekly Report on October 20, 2000, and in the Biology of Blood and Marrow Transplantation in late 2000. The term hematopoietic stem cell transplant recipients (HSCT) is preferable to "bone marrow transplant recipients" because the new term more accurately describes the current state of transplantation, which may involve harvesting donor cells from peripheral blood, umbilical cord blood, or bone marrow (1).

The document is an evidence-based statement of recommended strategies for preventing opportunistic infections in HSCT recipients. The prevention strategies are rated by the strength of the recommendation and the quality of the evidence supporting it. This rating system was developed by IDSA and the U.S. Public Health Service for use in the guidelines for the prevention of opportunistic infections in persons infected with HIV (2). The rating system allows the importance of each recommendation to be assessed. An A rating indicates strong evidence for efficacy and clinical benefit and an intervention that should always be offered; an intervention with a B rating is supported by moderate evidence and generally should be offered; a C rating indicates an optional intervention because evidence is insufficient to support a recommendation or evidence for efficacy might not outweigh adverse effects; a D rating indicates that moderate evidence for lack of efficacy or adverse outcome supports recommending against the intervention; and an E rating indicates strong evidence that an intervention is contraindicated because of lack of efficacy or adverse effects. Three categories are used to rate the quality of evidence supporting each recommendation, with I the highest, indicating evidence from at least one randomized, controlled trial; II indicating evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time-series, or dramatic results from uncontrolled experiments; and III indicating evidence from authorities' opinions based on clinical experience, descriptive studies, or reports of expert committees. This article summarizes the hospital infection control guidelines in the Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients, with ratings in brackets.

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Ventilation

All allogeneic HSCT recipients should be placed in rooms with >12 air exchanges per hour (3,4) and point-of-use, high-efficiency (>99%) particulate air (HEPA) filters capable of removing particles ≥0.3 μm in diameter (4-7) [AIII]. This recommendation is particularly important for facilities undergoing construction and renovation (8). The need for environmental HEPA filtration for autologous HSCT recipients has not been established; however, the use of HEPA-filtered rooms should be considered for autologous HSCT recipients who have prolonged neutropenia, the major risk factor for nosocomial aspergillosis [CIII].

The use of laminar air flow rooms for bone marrow transplant recipients has been controversial. Such rooms contain filtered air that moves in parallel, unidirectional flow; the air enters the room from one wall and exits the room on the opposite wall (3). Although LAF protects patients from infection in aspergillosis outbreaks during hospital construction (9,10), its routine use may not be valuable for all HSCT recipients (11). Since 1983, rooms with laminar air flow have been preferred for allogeneic HSCT recipients with aplastic anemia and human leukocyte antigen-identical sibling donors because the reported death rate of patients in regular rooms was nearly four times higher (12). However, the survival of aplastic anemia HSCT recipients in the late 1990s exceeds that reported in the early 1980s, and no study has yet

[1]Chair: Clare A. Dykewicz: Members: Raleigh A. Bowden, David Emanuel, David Longworth, Philip A. Rowlings, Robert H. Rubin, Kent A. Sepkowitz, Keith Sullivan, and John R. Wingard. CDC members: Robert T. Chen, Brian R. Edlin, Beth Hibbs, Harold W. Jaffe, William R. Jarvis, Jonathan Kaplan, Thomas J. Spira.

determined whether survival of HSCT recipients with aplastic anemia improves when they are treated in rooms with laminar air flow. Therefore, such rooms need not be constructed for every HSCT recipient, and use of available rooms is optional [CII].

Hospital rooms should have directed airflow so that air enters at one side of the room and is exhausted at the opposite side (5) [BIII]. Each hospital room should be well sealed (e.g., around windows and electrical outlets) (5) [BIII]. To provide consistent positive pressure in the HSCT recipient's room, consistent pressure differentials should be maintained between patients' rooms and the hallways or anterooms at >2.5 Pascals (3,4) [BIII]. In general, air pressure in hospital rooms of HSCT recipients should be higher than in adjoining hallways, toilets, and anterooms.

Backup emergency power and redundant systems should be provided to maintain room pressurization and a constant number of air exchanges in HSCT units when the central ventilation system is shut off for maintenance and repair (13) [BIII]. In addition, protocols should be developed to protect HSCT units from bursts of mold spores when air-handling systems are restarted after routine maintenance [BIII].

Construction

Hospital construction and renovation have been associated with increased risk for nosocomial fungal infection, especially aspergillosis, among severely immunocompromised patients (14). Therefore, people responsible for HSCT unit construction or renovation should consult published recommendations for environmental controls (15,16) [AIII]. Planning for construction or renovation should include strategies for intensified aspergillosis-control measures [AIII]. The planning committee should include engineers, architects, housekeeping staff, infection control personnel, the director of the HSCT unit, administration representatives, and safety officers [BIII].

Isolation

HSCT units should follow published guidelines for hospital isolation practices, including CDC guidelines for the prevention of nosocomial infections (17,18) [AIII]. However, the efficacy of specific isolation and barrier precautions in preventing nosocomial infections in HSCT recipients has not been evaluated. HSCT recipients should be placed in private rooms [BIII]. When indicated, HSCT recipients should also be placed on airborne, droplet, or contact precautions in addition to standard precautions (17) [AIII]. Careful observation of isolation precautions is important to prevent transmission of infectious agents among HSCT recipients, health-care workers, and visitors.

Hand Hygiene

Hand hygiene is the single most effective procedure for preventing nosocomial infection (17). Everyone, especially health-care workers, should wash hands before entering and after leaving rooms of HSCT recipients and candidates undergoing conditioning therapy (chemotherapy and radiation) (17,19) or before and after any direct contact with patients, regardless of whether hands were soiled [AI]. HSCT recipients should be encouraged to practice good hand hygiene (e.g., washing hands before eating, after using the toilet, before and after touching a wound) [BIII]. Hands should be washed with antimicrobial soap and water [AIII]; hygienic hand rubs are also an acceptable means of maintaining hand hygiene (20,21). Health-care workers wearing gloves should put them on in the patient's room after handwashing and then discard them in the same patient's room before washing hands again on exiting the room. Gloves should always be changed between patients or before touching a clean area if the gloves become soiled (e.g., change gloves after touching the perineum and before touching a clean area) [AIII]. Appropriate gloves should be used by all persons handling potentially contaminated biological materials [AII].

Equipment

HSCT units should monitor opened and unopened wound-dressing supplies such as adhesive bandages (22) and surgical and elastic adhesive tape (23) to detect mold contamination and prevent cutaneous transmission to patients [BII]. All bandages and wound dressings should be discarded that are out of date, have damaged packaging, or are visually contaminated by construction debris, moisture. [BIII].

Plants

Exposure to plants and flowers has not been conclusively shown to cause fungal infections in HSCT recipients. However, most experts strongly recommend that plants and dried or fresh flowers not be allowed in the hospital rooms of HSCT recipients or candidates undergoing conditioning therapy because *Aspergillus* spp. have been isolated from the soil of potted ornamental plants (e.g., cacti), the surface of dried flower arrangements, and fresh flowers (5,7,24) [BIII].

Play Areas and Toys

Play areas for pediatric HSCT recipients and candidates undergoing conditioning therapy should be cleaned and disinfected weekly and as needed [BIII]. Only toys, games, and videos that can be kept clean and disinfected should be allowed in the HSCT unit [BIII]. HSCT units and clinics should follow published recommendations for washing and disinfecting toys (25) [BIII].

Health-Care Workers

Each hospital or HSCT center should prepare a written comprehensive policy on the immunization of hospital personnel that meets current recommendations of CDC, the Advisory Committee on Immunization Practices, and the Healthcare Infection Control Practices Advisory Committee (26) [BIII]. Immunizations are needed to prevent transmission of vaccine-preventable diseases to HSCT recipients and candidates undergoing conditioning therapy. In general, health-care workers should be immune to measles, mumps, rubella, and especially varicella and influenza.

Visitors

Hospitals should have written policies for screening HSCT unit visitors, especially children, for potentially infectious conditions. Such screening should be performed by clinically trained health-care personnel [BII]. Visitors who have communicable infectious diseases such as upper respiratory infection or flulike illness, recent exposure to communicable diseases, an active shingles rash (whether covered or not), a *Varicella zoster*-like rash within 6 weeks of receiving a chickenpox vaccine, or a history of receiving an oral polio vaccine within the previous 3 to 6 weeks should not

be allowed to enter the HSCT unit or have direct contact with HSCT recipients or candidates undergoing conditioning therapy [AII].

Patient Skin Care

Skin care during neutropenia should include daily inspection of sites likely to be portals of infection, such as the perineum and intravascular access sites [BIII]. HSCT recipients and candidates undergoing conditioning therapy should maintain good perineal hygiene to minimize loss of skin integrity and risk for infection [BIII]. To facilitate this, HSCT units should develop special protocols for patient perineal care. To prevent vaginal or cervical irritation and abrasions, menstruating immunosuppressed HSCT recipients should not use tampons [DIII]. (Immunosuppressed HSCT recipients are defined as being <24 months post-HSCT, on immunosuppressive therapy, or having graft-versus-host disease.) The use of rectal thermometers, enemas, suppositories, and rectal exams are contraindicated for HSCT recipients because of the risk for skin or mucosal breakdown [DIII].

Oral and Dental Care

Establishing optimal periodontal health before HSCT is one of the most important steps patients can take to avoid oral infections, and maintaining good oral hygiene after the transplant can minimize the severity and facilitate healing of mucositis, especially before engraftment [BIII]. All HSCT candidates should receive a dental evaluation and relevant treatment before conditioning therapy begins (27) [AIII]. Likely sources of dental infection should be rigorously eliminated [AIII].

HSCT recipients with mucositis and HSCT candidates undergoing conditioning therapy should maintain good oral hygiene by rinsing the mouth four to six times a day with sterile water, normal saline, or sodium bicarbonate solutions (27) [AIII]. HSCT recipients and candidates should brush their teeth at least twice a day with a soft regular toothbrush (27) [BIII]. Patients who cannot tolerate these brushings may use ultra-soft toothbrushes or sponge or foam toothettes (Sage Products, Crystal Lake, IL) [CIII], but these products are less effective in removing dental debris (17). Toothpaste is optional, depending on patient tolerance (27) [CIII]. HSCT recipients and candidates undergoing conditioning therapy who are skilled at dental flossing should floss daily if this can be done without trauma [BIII].

Prevention of Bacterial Infections Related to Intravascular Catheters

HSCT units are advised to implement published guidelines for preventing infections related to the use of intravascular devices (28) [AIII]. HSCT units should avoid tap-water contact with the central venous catheter site [BIII]. To prevent bloodstream infections associated with the use of needleless intravenous-access devices, HSCT recipients should cover and protect the catheter tip or end cap during bathing or showering to protect it from tap-water contamination, change the device in accordance with manufacturers' recommendations, and have a care giver perform IV infusions whenever possible (29) [BII].

Drug-Resistant Organisms

Avoiding the misuse of antibiotics will decrease the emergence of drug-resistant strains of bacteria. Therefore, HSCT units should routinely review patterns of use for antibiotics and should prudently prescribe all antibiotics, especially vancomycin, to prevent the emergence of multidrug-resistant organisms. Medical and ancillary staff members responsible for monitoring antimicrobial use patterns should routinely review vancomycin use (30) [AIII]. Vancomycin and all other antibiotics, especially third-generation cephalosporins and antianaerobic agents such as metronidazole, must be used judiciously (30) [AII].

Specific Nosocomial Infections

Nosocomial pathogens are potential threats to all patients; however, if infected, HSCT recipients are at risk for more severe disease. Nosocomial pathogens of concern include *Legionella* spp., methicillin-resistant *Staphylococcus aureus*, *Streptococcus viridans*, and *Mycobacterium tuberculosis*, and community respiratory viruses such as influenza, respiratory syncytial virus, adenovirus, and parainfluenza virus.

Legionellosis

Clinicians should always consider infection with *Legionella* spp. in the differential diagnosis of pneumonia in HSCT recipients. Because HSCT recipients are at much higher risk for disease and death from legionellosis (31), periodic routine culturing for legionellae in water samples from the transplant units' potable water supply may be part of an overall prevention strategy in such units [CIII]. However, the optimal methods (frequency, number of sites) for environmental surveillance cultures in transplant units have not been determined, and the cost-effectiveness of this strategy has not been evaluated. Because HSCT recipients are at high risk for legionellosis and a safe concentration of legionellae organisms in potable water has not been determined, the goal, if environmental surveillance is undertaken, should be to maintain water systems with no detectable organisms [AIII]. Clinicians must maintain a high index of suspicion for legionellosis in transplant patients with nosocomial pneumonia even when environmental surveillance cultures do not yield legionellae [AIII].

Community Respiratory Virus Infections

Clinicians should institute appropriate precautions and infection control measures to prevent nosocomial pneumonia in hospitalized HSCT recipients and candidates undergoing conditioning therapy, especially during community or nosocomial respiratory virus outbreaks (5) [AIII]. Even when there is no nosocomial or community outbreak of respiratory virus infections, which are emerging infections in HSCT recipients, everyone who enters an HSCT unit, including visitors and health-care workers, should be screened daily for symptoms of upper respiratory infection [BIII]. Some experts recommend that health-care workers who work in HSCT units should provide daily verification (e.g., sign-in sheets) that they are symptom free before being allowed to care for patients. To minimize the risk for transmission, health-care workers and visitors with upper respiratory symptoms should be restricted from contact with HSCT recipients and candidates undergoing conditioning therapy [AIII]. All health-care workers with upper respiratory infection symptoms should be restricted from patient contact and reassigned to nonpatient care duties until their symptoms resolve [BIII]. Visitors with such symptoms should be asked to defer their visit to the HSCT unit until their symptoms resolve [BIII].

Viral shedding among HSCT recipients with community respiratory virus infection has been documented to last up to 4 months for influenza (32), 2 years for adenovirus (33), and 22 days for respiratory syncytial virus (34); however, viral shedding has been reported to last up to 112 days in a child with severe combined immunodeficiency (35). Therefore, to prevent nosocomial transmission, HSCT units should factor such possible prolonged viral shedding into policy decisions about duration of precautions for infected HSCT recipients or candidates undergoing conditioning therapy [CIII].

Mycobacterium tuberculosis

HSCT candidates should be screened for tuberculosis (TB) by a careful medical history and chart review to ascertain any history of TB exposure [AIII] because latent TB infection is more likely to progress to active disease among persons who are immunocompromised (36). HSCT units should also consider administering a tuberculin skin test (TST) by the Mantoux method with 5 tuberculin units of purified protein derivative (PPD) [CIII]; however, the TST may not be reliable in immunocompromised patients. Patients with a recent positive TST result or a history of a positive TST result and no prior preventive therapy should be given a chest X ray and evaluated for active TB (36) [AI]. Because immunocompromised patients have a decreased ability to mount a delayed hypersensitivity response, a positive TST result for them is defined as ≥5 mm of induration (36) rather than ≥10 mm [CIII]. Since immunosuppressive therapy decreases the sensitivity of the TST, HSCT providers should not rely solely on the TST to determine presence of latent TB infection and need for preventive therapy [DIII]. Instead, a full 9-month course of isoniazid preventive therapy should be given to immunocompromised HSCT recipients or candidates who have had close contact with someone with active, infectious (i.e., sputum-smear positive) pulmonary or laryngeal TB, regardless of the HSCT recipient's or candidate's TST status (36) [BIII]. Routine anergy screening results may not be reliable for HSCT recipients and candidates undergoing conditioning therapy, and therefore such screening is not recommended [DIII]. HSCT should not be canceled or delayed because of a positive TST result [DIII].

Infection Control Surveillance

HSCT units should not perform routine fungal or bacterial cultures of asymptomatic HSCT recipients (37) [DII]. In the absence of epidemiologic clusters of infections, HSCT units should not perform routine periodic bacterial surveillance cultures of the HSCT unit environment or of equipment or devices used for respiratory therapy, pulmonary-function testing, or delivery of inhalation anesthesia (5) [DIII]. Some experts suggest that hospitals routinely sample air, ceiling tiles, ventilation ducts, and filters to test for molds, especially when construction or renovation occurs near or around the rooms of immunocompromised patients (24,37) or when clinical surveillance demonstrates a possible increase in mold (e.g., aspergillosis) cases [CIII]. In the absence of a nosocomial fungal outbreak, HSCT units need not perform routine fungal cultures of devices and dust in the rooms of HSCT recipients and candidates undergoing conditioning therapy [DIII]. HSCT units should routinely monitor the number of aspergillosis cases occurring in HSCT recipients, especially during hospital construction or renovation [BIII]. A twofold or greater increase in the attack rate of aspergillosis during any 6-month period indicates that the HSCT unit environment should be evaluated for breaks in infection control techniques and procedures and that the ventilation system should be carefully investigated (21) [BIII].

Careful adherence to the recommendations in these Guidelines for the Prevention of Opportunistic Infections in Hematopoietic Stem Cell Transplant Recipients may decrease the rate of hospital infections among HSCT recipients.

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Emerging Health Care-Associated Infections in the Geriatric Population

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The increasing number of persons >65 years of age form a special population at risk for nosocomial and other health care-associated infections. The vulnerability of this age group is related to impaired host defenses such as diminished cell-mediated immunity. Lifestyle considerations, e.g., travel and living arrangements, and residence in nursing homes, can further complicate the clinical picture. The magnitude and diversity of health care-associated infections in the aging population are generating new arenas for prevention and control efforts.

The term geriatric refers to the aging human population, and geriatrics refers to the medical field that deals with clinical problems specific to old age and the aging. Neither these definitions nor the medical literature specifies a precise age range to delineate this group. Cutoffs of 50, 60, 65, and 70 years, none entirely satisfactory, have been used to identify the elderly (1,2). These differing cutoffs reflect the limitations of using chronologic age as a marker for senescence, often viewed as a fundamental characteristic of the group. Regardless, human populations continue to age at an impressive rate. In 1900, only 1% of the earth's population—15 million persons—was >65 years of age (3). By 1992, 6% of the global population, or 342 million persons, were in this category. By the year 2050, these figures will have risen to 20% and 2.5 billion, respectively.

From the standpoint of health care, the geriatric population is diverse. Most Americans 65 to 84 years of age enjoy sufficient health for full function (3). Nevertheless, many persons in this group and even more in the ≥85 age group constitute a definable population at increased risk for nosocomial and other health care-associated infections. The 1.5 to 1.8 million residents of nursing homes in the United States epitomize this group at risk (4). Although their experiences frequently dominate discussions about health care-associated infections in the elderly, the problem is much broader. This article focuses on three categories of risk factors—impaired host defenses, lifestyle considerations, and living arrangements—and provides specific examples of emerging health care-associated infections.

Factors Related to Impaired Host Defenses

The elderly have defective host defenses that compromise their ability to ward off infectious agents; factors influencing immunocompetence include immune senescence, changes in nonadaptive immunity, chronic diseases, medications, malnutrition, and functional impairments. T-lymphocyte production and proliferation decline with age, resulting in decreased cell-mediated immunity and decreased antibody production to new antigens (3-5). Thinning skin, enlarged prostate, diminished cough reflex, and other anatomic or physiologic accompaniments of aging are changes in nonadaptive immunity that render the elderly more vulnerable to infection. Chronic diseases—cancer, atherosclerosis, diabetes mellitus, dementia—predispose to certain types of infection. Medications such as sedatives, narcotics, anticholinergics, and gastric acid suppressants may further suppress innate defenses. Malnutrition, which reduces cell-mediated immunity, is common in nursing home residents (4) and may be more common in the geriatric community at large than is generally realized (6). Finally, functional impairments (e.g., immobility, incontinence, dysphagia) can complicate aging and enhance susceptibility to infection. These impairments may necessitate the use of urinary catheters, feeding tubes, and other invasive devices that magnify susceptibility.

Alone or in combination, these defects in host defense(s) place geriatric populations in the forefront of nosocomial infection statistics. Data from the National Nosocomial Infections Surveillance system for the period 1986-1990 indicated that persons 65 years of age accounted for 54% of all nosocomial infections (7). Similarly, Gross and colleagues observed a decade-specific risk for nosocomial infection of 10 per 1,000 discharges from birth through the fifth decade. However, this risk steadily rose from the fifth decade onward, exceeding 100 infections per 1,000 discharges in patients ≥70 years of age (8). Finally, Saviteer and coworkers, who reported a similar increase in nosocomial infections after the fifth decade (9), calculated daily nosocomial infection rates of 0.43% and 0.63% for persons aged ≤60 years and ≥60 years, respectively. The higher infection rates in the elderly were not attributable to increased lengths of stay.

Geriatric patients, like transplant recipients, may be compared to "sentinel chickens"—the first to be affected by new or emerging infections in hospitals and other health-care environments that care for adult patients. For example, the mean age of affected patients in a nosocomial outbreak of gastroenteritis caused by a small round-structured virus was 65 years (10).

The problem of tuberculosis (TB) deserves particular mention in the context of waning cell-mediated immunity. The elderly have not only this risk factor but also higher frequencies of latent infection, stemming from exposures during an era when TB was more prevalent. TB is the most

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commonly reported notifiable disease in persons ≥65 years of age (3). In 1995, 23% of reported cases in the United States occurred in this age group. Elderly persons living in the community have twofold increased rates of active disease. As a health care-associated infection in this age group, TB comes to the fore in hospital and nursing home outbreaks (11). Elderly persons living in long-term care facilities have fourfold increased rates of active TB. The combination of decreased cell-mediated immunity and high prevalence of latent infection suggests that TB will continue to reemerge in geriatric populations.

Decreased cell-mediated immunity may also predispose geriatric patients to nosocomial cryptosporidiosis. A microbiologic review for a 325-bed hospital in Rhode Island identified 36 patients with cryptosporidiosis (12); 13 of these patients were in the 63- to 93-year age group (mean 77 years). In seven of these older patients, nosocomial acquisition was suspected. In addition, outbreaks of this disease have occurred in elderly nursing home residents (13). Thus, cryptosporidium may be an emerging health care-associated infection in the aged.

Factors Related to Lifestyle Considerations

The lifestyles of the elderly may entail additional risk factors for both acquiring and transmitting health care-associated infections. In western countries retired persons use their increased leisure time to travel, including domestic trips to visit family, cruises or tours to foreign countries, or volunteer work in developing countries, which put elderly travelers at risk for infections. In addition, recreational activities such as golfing, spelunking, hunting, and gardening may bring the elderly into contact with unusual pathogens. Volunteer work, visiting ill friends in the hospital, and other patterns of socialization also expose the geriatric population to infections that may be transmitted or acquired in the health care setting.

Several factors specifically related to health care deserve attention in this regard. The first concerns outpatient visits. The elderly spend increased amounts of time visiting their physicians, potentially exposing themselves to various contagious diseases in the health-care environment. They also make frequent use of food services and providers of prepared foods, which carry some risk for transmitting foodborne diseases. These infections may then enter the health-care system and lead to secondary cases. Adult day-care centers and home care services, which have proliferated under medical auspices in recent years, provide additional avenues for geriatric populations to acquire health care-associated infections.

The impact of these lifestyle factors on nosocomial and other health care-associated infections has not been well documented. Several observations provide examples of the potential influence of these factors. A recent report from Taipei described a nosocomial outbreak of malaria resulting from contamination of a computed tomography injection device with blood from a returning traveler (14). Likewise, a 1998 outbreak of influenza in Alaska and the Yukon Territories, where 60,000 to 70,000 tourists visit each summer, further delineated the potential role of travel (15). Prospective surveillance in 1998 identified 2,199 cases of acute respiratory illnesses in 12 hospitals and clinics in Alaska and the Yukon Territory. Among these illnesses, 35% of cases in tourists and tourism workers met criteria for influenzalike illness and 3.2% for pneumonia. Median ages were 60 years for all persons with acute respiratory illnesses and 72 years for all persons with pneumonia. Fifty of the persons with pneumonia required hospitalization.

The role of lifestyle factors related to health care has received little attention, but one recent publication illustrates the potential problem. A 4-year study of acute respiratory illnesses in three senior day-care centers documented the annual occurrence of viral respiratory infections in 16 to 43 elderly participants and 6 to 23 staff (16). Identified pathogens included influenza A, influenza B, respiratory syncytial virus, coronavirus, parainfluenza virus, and rhinovirus. Of special importance, an educational campaign stressing the importance of handwashing combined with use of a portable virucidal foam product cut the infection rate by 50% during the fourth year. This article describes a new setting for health care-associated infections and confirms that traditional approaches to prevention still apply.

Factors Related to Living Arrangements

The spectrum of living arrangements for geriatric populations ranges from private residences in the community to skilled nursing homes. Between these extremes are retirement homes, assisted living facilities, foster and group homes, chronic disease hospitals, and other arrangements that provide for the needs of persons with sustained self-care deficits (4). Little is known about the role that these arrangements play in the overall scope of health care-associated infections. However, during the last 15 years several studies have examined the problem of health care-associated infections in skilled-nursing homes (2,4).

Nursing homes are residential facilities for persons who require nursing care and related medical or psychosocial services (4). Approximately 90% of nursing home residents fall into the geriatric age range. As a group, nursing home residents exhibit virtually all the risk factors for infections associated with the geriatric population. As a consequence, infections occur commonly in this setting, and emerging health care-associated infections are no exception. Three types of endemic infections occur regularly in all these facilities: urinary tract infections, lower respiratory tract infections—principally pneumonia, and various skin and soft tissue infections (4) (Table). In the United States, the overall rates for nursing home-acquired infection are 3 to 7 infections per 1,000 resident day, or 1.6 to 3.8 million infections per year (4).

Occasionally, new etiologic agents crop up as causes of these endemic infections. For example, in a 2-year serologic study of selected pathogens causing respiratory tract infections and febrile episodes in two Canadian long-term care facilities, Orr and colleagues identified a positive serologic response to *Chlamydia pneumoniae* in 9.4% of 224

Table. Endemic infection rates in long-term care facilities (4), United States, 1978–1989

Category of infection	Rate (no. of infections/ 1,000 resident care days)
All infections	1.8 to 13.5
Urinary tract infections	0.1 to 3.5
Respiratory tract infections	0.3 to 4.7
Skin and soft tissue infections	0.1 to 2.1

febrile episodes (17). These positive responses were associated with 12% of respiratory infections, including 5 of 30 pneumonias and 6.5% of infections of unknown origin. These data suggest that *C. pneumoniae* may be an emerging health care-associated infection in this setting.

Outbreaks also account for a proportion of the health care-associated infections observed in nursing homes (2,4). Respiratory infections and gastroenteritis occur most frequently. Although no national data on frequency of occurrence are available, published reports suggest that outbreaks are not uncommon. During 1970 to 1984, outbreak reports constituted approximately one-third of publications on infections in long-term care facilities (18). From 1975 to 1987, the Centers for Disease Control and Prevention (CDC) received reports from 26 states about 115 foodborne outbreaks in nursing homes (19). Of the 106 outbreaks investigated by CDC's Hospital Infections Program during the last decade, 6% occurred in long-term care facilities (20).

Emerging pathogens account for some of the outbreaks in nursing homes. During the last decade, *Streptococcus pyogenes*—the "flesh-eating" bacterium—was identified in nursing homes (21). More recently, a foodborne outbreak of gastroenteritis caused by both *Salmonella heidelberg* and *Campylobacter jejuni* was reported (22). Loeb and colleagues recently described an outbreak of respiratory illness caused by *L. sainthelensi* in two Canadian nursing homes (23). These and other reports emphasize the vulnerability of frail, elderly residents who share common sources of air, food, water, and health care in nursing homes.

Health care-associated infections caused by antimicrobial drug-resistant bacteria have caused both endemic infections and outbreaks in nursing homes in the United States. The frequent movement of patients between hospitals and nursing homes undoubtedly facilitates the transfer of resistant microbes (24). During the last 2 decades, gram-negative uropathogens with multidrug resistance and methicillin-resistant *S. aureus* have received the most attention (25). Gram-negative enteric bacilli have recently become resistant to fluoroquinolones and extended-spectrum cephalosporins (26). In addition, vancomycin-resistant enterococci and penicillin-resistant pneumococci have been identified in long-term care facilities (27-29). The appearance of the latter organism, which is seldom regarded as a nosocomial pathogen, again underscores the unique situation of this health-care setting. Because of the frequent interchange of patients between hospitals and nursing homes, infections caused by antimicrobial drug-resistant bacteria will continue to emerge in geriatric populations.

Recognition of such threats has prompted new interest in the prevention and control of infections associated with long-term care facilities. Recent guidelines have addressed requirements for infection control programs, as well as influenza, antimicrobial use, and antimicrobial resistant pathogens (25,30-32). Although reports from the 1980s described numerous deficiencies in infection control practices in nursing homes, recent reports have been more encouraging (4,33,34). A survey of 136 long-term care facilities in New England indicated that 98% had persons dedicated to infection control activities for a median of 8 hours per week (33). Nevertheless, protection of the vulnerable elderly residents in nursing homes merits additional attention, and changes in nursing home licensure and certification requirements may be needed at both state and national levels (35). Surveillance activity in less conventional care settings is a necessary first step in evaluating potential hazards.

Conclusions

The vulnerable geriatric population plays a leading role in the scope of nosocomial and health care-associated infections. As the world's population ages, its role is likely to increase. As health care continues to move beyond hospital walls, the spectrum of health care-associated infections in the elderly will continue to expand, reflecting their multiple risk factors for infectious diseases. Infection control practitioners and hospital epidemiologists are well advised to follow and study the aging population in the evolving health-care system. Undoubtedly, they will find new opportunities to prevent health care-associated infections. In addition, they may be able to develop strategies to prevent the diverse contagions of the elderly from entering hospitals.

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Emerging Waterborne Infections in Health-Care Settings

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Water is used in vast quantities in health-care premises. Many aquatic microorganisms can survive and flourish in water with minimal nutrients and can be transferred to vulnerable hospital patients in direct (e.g., inhalation, ingestion, surface absorption) and indirect ways (e.g., by instruments and utensils). Many outbreaks of infection or pseudoinfection occur through lack of prevention measures and ignorance of the source and transmission of opportunistic pathogens.

Wholesome (clear, palatable, and safe) drinking water is fundamental to public health. More than 95% of the population of the United Kingdom have a public supply of piped drinking water, almost all chlorinated and some fluorinated. The bacteriologic quality of drinking water has been maintained in accordance with well-established guidelines (1). In the United Kingdom, water providers have been required by law since 1847 to supply wholesome drinking water. However, it is only in the most recent legislation, the Water Act 1989 and its accompanying Water Supply (Water Quality) Regulations (2), that a definition of "wholesome" appears (3). Directives are one of the means by which European Community legislation is applied to member states. Two of these, the Surface Water Directive and the Sampling Directive, concern the use of surface water as a source of drinking water; a third, the Drinking Water Directive (4,5), is intended to ensure a wholesome water supply for drinking and for food and drink manufacture.

Public Water Companies

Public water companies have considerable expertise and resources to ensure that their supply systems are designed, operated, and monitored to comply with the minimum requirements of the law. U.K. legislation regards *Escherichia coli* as synonymous with fecal coliforms and does not give precise numerical values for colony counts. Baseline colony counts should be established for each supply system, and increases should be investigated. Most waterborne disease is related to fecal pollution of water sources; therefore, microbiologic testing of water needs to identify indicators of fecal pollution such as coliforms and *E. coli,* although the use of enterococci and *Clostridium perfringens* as surrogate markers is increasing. Coliforms must not be detected in 95% of samples when >50 samples are taken from the same sampling point during a 1-year period. Detecting *E. coli* in any one sample constitutes an infringement of the regulation. Recent U.K. legislation requires continuous monitoring of at-risk water treatment works for cryptosporidial oocysts (6). Supplying water containing >100 cryptosporidial oocysts per 100 L is a criminal offense; at least 1,000 L of water need to be filtered each 24 hours.

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Private Water Supplies

Private water supplies may be used solely for domestic purposes (category 1) or on a larger scale to supply nursing homes, hospitals, and houses (category 2). Approximately 1% of the U.K. population obtains water from a well, borehole, or spring, which may not be treated. The quality of water from private supplies must comply with the requirements given in the Private Water Supplies Regulations 1991 (7). Category 1 supplies are further divided into classes A-F, depending on the amount of water and number of people supplied. Monitoring private supplies is problematic since water quality can change with the weather and smaller supplies are monitored infrequently (8).

Outbreaks of cryptosporidiosis traced to tap water from the main supply are uncommon but may affect large numbers of people and cause public alarm. A recent report highlights a new problem of *Cryptosporidium parvum* contamination of filtered borehole water causing confirmed cases in 345 persons (9). Borehole supplies have been traditionally regarded as relatively pure sources of water, so this outbreak has implications for future monitoring and treatment of drinking water extracted from boreholes.

Water Storage and Distribution

Water should be stored safely in large, protected reservoirs and treated at the source, often by coarse filtration. Water should be distributed in a purpose-designed system, under pressure in a chlorinated form (e.g., 0.5 ppm free residual chlorine). Storage tanks should be protected from extraneous contamination, including by birds and vermin, and should be free from bacteria, particularly *E. coli.* Distribution systems should be controlled and free of "dead legs" (conduits that are capped off or rarely used) and spurs; joints and leaks should be repaired by qualified plumbers using defined materials. Uncontrolled water supplies are readily contaminated with coliform bacteria, environmental mycobacteria, *Legionella* spp., and filamentous fungi.

Water as a Reservoir of Hospital Pathogens

While >40 *Legionella* spp. are known, most outbreaks of Legionnaires' disease are caused by *Legionella pneumophila* serotypes 1 and 6; 600 to 1,300 cases are reported each year in

the United States, although these figures may represent underreporting (10). Legionellae are naturally distributed in aquatic environments, growing best at temperatures of 25°C to 42°C. Colonization is enhanced by water stagnation and sediment buildup as a result of alterations in the plumbing of the complex distribution systems often found in hospital hot-water systems. Cooling towers are often implicated in hospital and community outbreaks. Wet cooling towers (if used) and cooling water systems should be regularly maintained, cleaned, and disinfected. Cooling towers readily generate fine water droplets, as they operate by spraying water onto a packing material through which there is a countercurrent flow of air. How systems become seeded with *Legionella* is unclear, but these organisms can colonize certain types of water fittings, pipework, and materials. In practice, *Legionella* is found in many recirculating and hot-water systems with no associated clinical infection; in fact, the number of organisms that cause infection has not been determined reliably and varies with host susceptibility and species of *Legionella*. For these reasons, routine water sampling for *Legionella* is not advocated, but sampling may sometimes be appropriate to check the efficiency of the water treatment regimen.

Water systems should be designed to minimize colonization and multiplication of bacteria. Water should not be allowed to stagnate and should be circulated at temperatures below 20°C or above 60°C. Storage tanks and calorifiers should be regularly inspected, cleaned, and disinfected. In reported cases of Legionnaires' disease in which hot-water systems were implicated, contaminated water droplets were most commonly disseminated by showers and by taps with spray heads (faucet aerators). System design is all important in preventing buildup of *Legionella*; actions that lessen the risk for clinical cases include removing dead legs, avoiding washers and gaskets made of natural rubber (nutrient source), replacing heavily scaled faucets and showerheads, and avoiding shock absorbers and pipe materials not made of copper or plastic. Conditions that affect the proliferation of legionellae include sludge, scale, rust, algae, and organic particulates thought to provide nutrients for growth. Infection can be minimized by good engineering practices supplemented by heat, disinfectants, and biocides (11).

Clinical Disease

A confirmed case of Legionnaires' disease is defined as clinical or radiologic evidence of pneumonia and a microbiologic diagnosis by culture of *L. pneumophila* from respiratory specimens, or a fourfold rise in serum antibody levels against *L. pneumophila* serogroups (often serogroups 1 and 6). Testing for *L. pneumophila* antigen in urine, which is rapid and convenient, is becoming the most common diagnostic method. Clinical cases have also occurred because of the inhalation of water droplets containing the blue-white fluorescent group of legionellae, e.g., *L. gormanii* and *L. bozemanii*. Care must be taken with the indirect immunofluorescent antibody test to absorb any cross-reactions from *Campylobacter*. Immunocompromised patients, e.g., transplant or dialysis patients or those on cytotoxic therapy, are at higher risk for infection with *Legionella*.

Legionellosis: Control by Disinfection

Ideally, hospital water systems should be free of legionellae, but it is exceptional for a water supply to be entirely free of aquatic organisms. Provided that water is derived from the public mains and its quality is preserved in the storage and distribution system by correct design, installation, and maintenance, it can be regarded as being microbiologically acceptable for use without further treatment. However, if the appropriate detection systems are in place to culture and detect nonculturable organisms, it is likely that legionellae will be found in distribution systems (12). Marrie et al. demonstrated that a water system may be contaminated without clinical consequence (13), although risk should be assessed. If regular prospective surveillance and environmental cultures are undertaken and low levels ($<10^2$ per L) of legionellae are found, no action is necessary; counts of 10^2 to 10^3 on successive samples warrant a review of control procedures.

Heat

If storing water at 60°C is not practical or acceptable or the calorifier is not in use for 1 week or more, raising the temperature of the calorifier water to 70°C to 75°C for 1 hour will kill legionellae. However, this technique may not be effective if the temperature of water at the bottom of the calorifier does not reach 70°C.

Chlorination

Hot-water systems can be disinfected by chlorinating the water in the header tank (20 ppm to 50 ppm, superchlorination), allowing the water to flow to all parts of the system, and then allowing it to stand for at least 4 hours while not in use. The system should then be completely and thoroughly flushed before use. Cooling towers and cooling water systems can be chlorinated with 5 ppm for several hours before flushing. Water in a cleaned system can then be dosed to give a circulating level of free residual chlorine of approximately 1 ppm, although this may increase corrosion.

Biocides

Some biocides are effective against legionellae if used in sufficient concentrations for a sufficient time. Alternating high-level biocide treatment with chlorination and shock-dosing the water system are likely to be more effective than continuous low-level dosing with a single biocide. Strategies for preventing Legionnaires' disease (14) and guides to minimizing the risk are available (15).

Other Disinfection Methods

Copper-silver ionization can be used to control legionellae in hospital hot-water recirculating systems (16). This method electrically generates copper and silver ions, which bind to the bacterial cell wall, causing cell-wall disruption and lysis. Other methods for disinfecting drinking water include ozonation, chlorine dioxide, and irradiation by UV light.

Legionella spp. and Free-Living Protozoa

Legionellae thrive in stagnant water at ambient temperatures and may survive chlorination by residing in sludge and scale or inside certain protozoa, e.g., *Acanthamoeba*, *Hartmannella*, and *Tetrahymena* spp. While legionellae and

most protozoan trophozoites are inactivated by 1 ppm to 2 ppm of free residual chlorine, some protozoan cysts can resist 50 ppm chlorine; intracellular legionellae may be more resistant than the planktonic forms (17).

Rinse Water as a Source of Hospital Pathogens

Automatic washer-disinfector systems are widely used for decontaminating flexible fiberoptic endoscopes. These expensive scopes may be cleaned and decontaminated manually in individual diagnostic units or in centralized endoscopy-decontamination units. The main water supply may contain environmental microorganisms, such as mycobacteria, legionellae, and aerobic gram-negative bacilli, which may recontaminate the endoscope during rinsing. Pseudoepidemics of *L. pneumophila* serogroup 6 associated with contaminated bronchoscopes have been reported (18), as has the transmission of highly drug-resistant *Mycobacterium tuberculosis* caused by inadequate cleaning and disinfection of a bronchoscope (19). Hospital water supplies can readily become contaminated with environmental mycobacteria, e.g., *M. xenopi, M. abscessus, M. fortuitum*, and *M. chelonae*; if decontamination units do not have filters (0.2 µm) fitted to the water supply, rinse water may become contaminated. Water filters need to be fitted and maintained, but even this filtration system does not guarantee bacteria-free water (20). Environmental mycobacteria such as *M. chelonae* can resist temperatures of 45°C and some disinfectants such as 2% alkaline glutaraldehyde. Washer-disinfectors should be installed and maintained according to manufacturer's recommendations. Management policies should emphasize regular cleaning and maintenance (21). Use of contaminated or hard water should be avoided to lessen formation of biofilm and buildup of lime scale. Use of poor-quality water also should be avoided, and the supply to the washer-disinfector should be pretreated with heat and filtration and other processes such as UV irradiation and reverse osmosis. Additional chlorination of the water also should be considered, as should a final endoscope rinse with sterile water (22).

Immersion in Water

Hydrotherapy Pools: Preventing Infection

The physical structure of hydrotherapy pools, their high water and air temperatures, and intermittently intensive use by diverse groups of patients and staff produce potentially hazardous conditions (23). Hydrotherapy has become popular, and many district hospitals have installed suitable pools. Each pool should be a self-contained part of the hospital physiotherapy facilities with a senior physiotherapist responsible for overall daily management. The pool should be designed to allow water to circulate through a filter and for the addition of a suitable disinfectant (often hypochlorite) in appropriate amounts with a mechanism for adjusting the pH (appropriate range 7.2 to 7.8). Pools should be cleaned regularly, have some water replaced weekly, and be emptied annually. Additional measures should be implemented if users release unformed stool into the pool, and strict adherence to the rules of cleanliness and hygiene both in and out of the pool should be enforced. Physiotherapists, microbiologists, and engineers should have effective working relationships. Management programs should be established, and careful records should be kept. Despite careful control of water quality, users will suffer from pool-related skin, ear, chest, and gastrointestinal infections from time to time. Numerous microorganisms have been implicated in these infections, including *Pseudomonas aeruginosa*, *Legionella* spp., adenoviruses, and enteroviruses. Legionnaires' disease has been associated with whirlpool spas, where agitation and aeration of the water enable bacteria to be inhaled (24). (The terms spa pool, spa bath, whirlpool, and hot tub are sometimes used interchangeably [25]). More recently, a cluster of gastrointestinal illnesses, including one case of hemolytic uremic syndrome and one culture-confirmed *E. coli* O157:H7 infection, was attributed to a poorly maintained swimming pool (26). Frequently, immersion of hospitalized patients contaminates the tub environment, including the tub water, drains, agitators, floors, and walls.

Water Births: Minimizing Infection

Water births, pioneered in the 1960s, are increasingly being used. The perceived infection problem is that the birthing-pool water becomes contaminated with amniotic fluid, blood, and fecal material, all of which contain large quantities of maternal bacteria and viruses. Risks include bloodborne viruses, e.g., hepatitis B and C, HIV-1, and HIV-2, and fecal-orally transmitted viruses, e.g., the enteroviruses and adenoviruses (27). Many of these concerns may be unfounded, and calls for maternal testing for HIV have not been supported. A more reasonable approach is to ensure that infection control policies for water births include instructions for pool maintenance and decontamination, use of universal precautions, and use of personal protective equipment for staff (28). Postnatal surveillance of mothers and babies should be conducted to define infection rates.

Washing or Rinsing in Water

Burns Units: Part of Irrigation Therapy

Kolmos et al. reported five patients with extensive deep burns in whom *P. aeruginosa* serogroup 0-7 septicemia developed shortly after hospital admission (29). Routine microbiologic monitoring of such patients is not required, provided the water quality is secured and the irrigation tubing is decontaminated between uses.

Bathing Infants: Basic Hygiene and Appearance

At birth, infants are often diffusely covered in vernix, amniotic fluid, and blood. Even though bathing them to remove unsightly body fluids is very tempting, total body immersion for preterm babies is not recommended. The skin of a newborn is ideal for absorbing unwanted microorganisms. In a report by Verweij et al., contaminated water was used to wash preterm infants, leading to the colonization of four infants and death of a fifth from *Stenotrophomonas maltophilia* (30). The outbreak was controlled by reenforcing hand disinfection, limiting use of tap water for handwashing, and using sterile water to wash the preterm babies. For cosmetic reasons, washing can be restricted initially to the head and neck.

Miscellaneous Waterborne Outbreaks

Water baths used to warm up dialysis fluids (31), fresh-frozen plasma, and albumin (32) have been implicated as the

source of infection by *Acinetobacter calcoaceticus* var *anitratum* and *P. aeruginosa*. Molecular methods such as pulsed-field gel electrophoresis or random amplification of polymorphic DNA can confirm the relatedness of some of these complex aerobic gram-negative bacilli. Removing the contaminated water baths ends the outbreaks.

Holy water is a potential source of cross-infection with various coliform bacteria, including *A. baumanii* and *Aeromonas hydrophila* (33). Patients with widespread burns and other debilitating skin lesions are at risk. Sterile holy water is one solution to this concern.

A number of pseudooutbreaks have been reported that implicate contaminated ice machines. Coliforms and environmental mycobacteria such as *M. gordonae* are frequently found in the water source (34). Pseudoinfection by *M. gordonae* and others can be prevented by adequate machine maintenance.

An outbreak of group A hemolytic streptococcal puerperal sepsis was traced to the communal use of bidets (35). Decontamination of the water spray nozzle and drain was necessary to control the outbreak. Routine cleaning might have prevented its occurrence.

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Biofilms and Device-Associated Infections

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Microorganisms commonly attach to living and nonliving surfaces, including those of indwelling medical devices, and form biofilms made up of extracellular polymers. In this state, microorganisms are highly resistant to antimicrobial treatment and are tenaciously bound to the surface. To better understand and control biofilms on indwelling medical devices, researchers should develop reliable sampling and measurement techniques, investigate the role of biofilms in antimicrobial drug resistance, and establish the link between biofilm contamination and patient infection.

Microbial biofilms develop when microorganisms irreversibly adhere to a submerged surface and produce extracellular polymers that facilitate adhesion and provide a structural matrix. This surface may be inert, nonliving material or living tissue. Biofilm-associated microorganisms behave differently from planktonic (freely suspended) organisms with respect to growth rates and ability to resist antimicrobial treatments and therefore pose a public health problem. This article describes the microbial biofilms that develop on or within indwelling medical devices (e.g., contact lenses, central venous catheters and needleless connectors, endotracheal tubes, intrauterine devices, mechanical heart valves, pacemakers, peritoneal dialysis catheters, prosthetic joints, tympanostomy tubes, urinary catheters, and voice prostheses).

Characteristics of Biofilms on Indwelling Medical Devices

Biofilms on indwelling medical devices may be composed of gram-positive or gram-negative bacteria or yeasts. Bacteria commonly isolated from these devices include the gram-positive *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis*, and *Streptococcus* viridans*;* and the gram-negative *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa*. These organisms may originate from the skin of patients or health-care workers, tap water to which entry ports are exposed, or other sources in the environment. Biofilms may be composed of a single species or multiple species, depending on the device and its duration of use in the patient. Urinary catheter biofilms may initially be composed of single species, but longer exposures inevitably lead to multispecies biofilms (1). A distinguishing characteristic of biofilms is the presence of extracellular polymeric substances, primarily polysaccharides, surrounding and encasing the cells. These polysaccharides, which have been visualized by scanning electron microscopy (Figure 1), appear either as thin strands connecting the cells to the surface and one another or as sheets of amorphous material on a surface. Most biofilm volume is actually composed of this extracellular polymeric substance rather than cells, a fact that has been confirmed by ruthenium red staining and transmission electron microscopy (2). This biofilm matrix may act as a filter, entrapping minerals (1) or host-produced serum components (3). Biofilms are both tenacious and highly resistant to antimicrobial treatment; Anwar et al. (4) showed that treatment with levels of tobramycin far in excess of the MIC reduced biofilm cell counts for *P. aeruginosa* by approximately 2 logs, while the same dosage provided a >8-log decrease in planktonic cells of this organism.

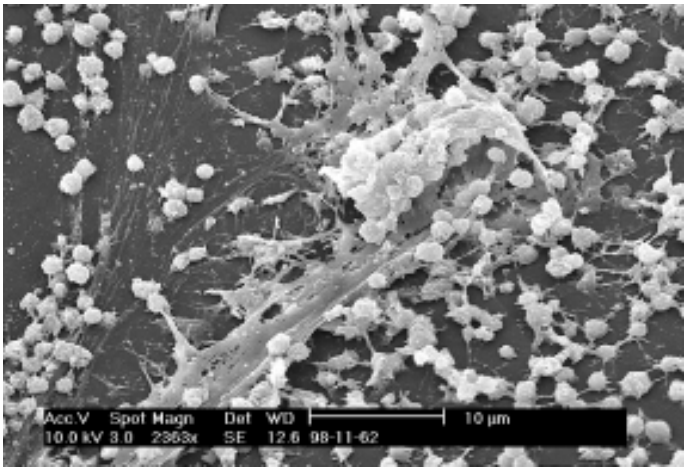

Figure 1. Scanning electron micrograph of a *Staphylococcus* biofilm on the inner surface of a needleless connector.
Photograph by Janice Carr, Centers for Disease Control and Prevention, Atlanta, GA USA.

Factors Influencing Rate and Extent of Biofilm Formation

When an indwelling medical device is contaminated with microorganisms, several variables determine whether a biofilm develops. First the microorganisms must adhere to the exposed surfaces of the device long enough to become irreversibly attached. The rate of cell attachment depends on the number and types of cells in the liquid to which the device is exposed, the flow rate of liquid through the device, and the physicochemical characteristics of the surface. Components in the liquid may alter the surface properties and also affect rate of attachment. Once these cells irreversibly attach and

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produce extracellular polysaccharides to develop a biofilm, rate of growth is influenced by flow rate, nutrient composition of the medium, antimicrobial-drug concentration, and ambient temperature. These factors can be illustrated by examining what is known about biofilms on three types of indwelling medical devices: central venous catheters, mechanical heart valves, and urinary (Foley) catheters.

Central Venous Catheter Biofilms

Scanning and transmission electron microscopy has shown that virtually all indwelling central venous catheters are colonized by microorganisms embedded in a biofilm matrix (5). The organisms most commonly isolated from catheter biofilms are *Staphylococcus epidermidis, S. aureus, Candida albicans, P. aeruginosa, K. pneumoniae,* and *Enterococcus faecalis* (6,7).

These organisms originate from patient's skin microflora, exogenous microflora from health-care personnel, or contaminated infusates. They gain access to the catheter by migration externally from the skin along the exterior catheter surface or internally from the catheter hub or port (8). Colonization of these devices can occur rapidly (within 24 hours) and may be a function of host-produced conditioning films (platelets, plasma, and tissue proteins) (8). Raad et al. (9) found that biofilm formation on central venous catheters was universal, but the extent and location of biofilm formation depended on the duration of catheterization: short-term (<10 days) catheters had greater biofilm formation on the external surface; long-term catheters (30 days) had more biofilm formation on the catheter inner lumen. The nature of the fluid administered through central venous catheters may affect microbial growth: gram-positive organisms (*S. epidermidis, S. aureus)* did not grow well in intravenous fluids, whereas the gram-negative aquatic organisms (e.g., *P. aeruginosa, Klebsiella* spp*., Enterobacter* spp*., Serratia* spp*.,* and *Pantoea* sp*.)* sustained growth (10-14). Because many of these solutions have limited nutrients, bacterial growth rarely produces turbidity, meaning that numbers are $<10^7$ organisms per milliliter. The number of organisms on the catheter tip is related to occurrence of bloodstream infection in the patient (7,15-17), supporting the concept of a critical level of biofilm development above which substantial cell detachment and embolism occur.

Several studies have examined the effect of various types of antimicrobial treatment in controlling biofilm formation on these devices. Freeman and Gould (18) found that addition of sodium metabisulfite to the dextrose-heparin flush of the left atrial catheter eliminated microbial colonization of these catheters. Darouiche et al. (19) found that catheters impregnated with minocycline and rifampin were less likely to be colonized than those impregnated with chlorhexidine and silver sulfadiazine. In a study by Kamal et al. (20), catheters coated with a cationic surfactant (tridodecylmethylammonium chloride), which was in turn used to bond cephalosporin to the surface, were less likely to become contaminated and develop biofilms than were untreated catheters. Flowers et al. (21) found that an attachable subcutaneous cuff containing silver ions inserted after local application of polyantibiotic ointment conferred a protective effect on catheters, resulting in lower rates of contamination. Maki (8) suggested several ways to control biofilms on central venous catheters, including using aseptic technique during implantation, using topical antibiotics, minimizing the duration of catheterization, using an in-line filter for intravenous fluids, creating a mechanical barrier to prevent influx of organisms by attaching the catheter to a surgically implanted cuff, coating the inner lumen of the catheter with an antimicrobial agent, and removing the contaminated device.

Mechanical Heart Valve Biofilms

Microorganisms may attach and develop biofilms on components of mechanical heart valves and surrounding tissues of the heart, leading to a condition known as prosthetic valve endocarditis. The primary organisms responsible for this condition are *S. epidermidis, S. aureus, Streptococcus* spp*.,* gram-negative bacilli, diphtheroids, enterococci, and *Candida* spp. These organisms may originate from the skin, other indwelling devices such as central venous catheters, or dental work (3). The identity of the causative microorganism is related to its source: whether the contaminating organism originated at the time of surgery (early endocarditis, usually caused by *S. epidermidis*), from an invasive procedure such as dental work (*Streptococcus spp.),* or from an indwelling device (a variety of organisms). Implantation of the mechanical heart valve causes tissue damage, and circulating platelets and fibrin tend to accumulate where the valve has been attached. Microorganisms also have a greater tendency to colonize these locations (3). The resulting biofilms more commonly develop on the tissue surrounding the prosthesis or the sewing cuff fabric used to attach the device to the tissue (22,23) than on the valve itself (24). Antimicrobial agents are usually administered during valve replacement and whenever the patient has dental work to prevent initial attachment by killing all microorganisms introduced into the bloodstream. As with biofilms on other indwelling devices, relatively few patients can be cured of a biofilm infection by antibiotic therapy alone (25). Illingworth et al. (22) found that a silver-coated sewing cuff on a St. Jude mechanical heart valve (St. Jude Medical Inc., St. Paul, MN) implanted into a guinea pig artificially infected with *S. epidermidis* produced less inflammation than did uncoated fabric. Although the number of attached organisms was not determined, the authors concluded that the degree of inflammation was proportional to the number of viable organisms. Carrel et al. (23) also found this approach was effective in in vitro studies with different organisms.

Urinary Catheter Biofilms

Urinary catheters are tubular latex or silicone devices, which when inserted may readily acquire biofilms on the inner or outer surfaces. The organisms commonly contaminating these devices and developing biofilms are *S. epidermidis, Enterococcus faecalis, E. coli, Proteus mirabilis, P. aeruginosa, K. pneumoniae,* and other gram-negative organisms (1). The longer the urinary catheter remains in place, the greater the tendency of these organisms to develop biofilms and result in urinary tract infections. For example, 10% to 50% of patients undergoing short-term urinary catheterization (7 days) but virtually all patients undergoing long-term catheterization (>28 days) become infected (1). Brisset et al. (26) found that adhesion to catheter materials was dependent on the hydrophobicity of both the organisms and the surfaces; catheters displaying both hydrophobic and hydrophilic regions allowed colonization of the widest variety of organisms. Divalent cations (calcium and magnesium) and

increase in urinary pH and ionic strength all resulted in an increase in bacterial attachment. Tunney et al. (27) stated that no single material is more effective in preventing colonization, including silicone, polyurethane, composite biomaterials, or hydrogel-coated materials. Certain component organisms of these biofilms produce urease, which hydrolyzes the urea in the patient's urine to ammonium hydroxide. The elevated pH that results at the biofilm-urine interface results in precipitation of minerals such as struvite and hydroxyapatite. These mineral-containing biofilms form encrustations that may completely block the inner lumen of the catheter (27). Bacteria may ascend the inner lumen into the patient's bladder in 1 to 3 days (28); this rate may be influenced by the presence of swarming organisms such as *Proteus* spp. (D. Stickler, pers. comm.). Several strategies have been attempted to control urinary catheter biofilms: antimicrobial ointments and lubricants, bladder instillation or irrigation, antimicrobial agents in collection bags, impregnation of the catheter with antimicrobial agents such as silver oxide, or use of systemic antibiotics (29). Most such strategies have been ineffective, although silver-impregnated catheters delayed onset of bacteriuria for up to 4 days. In a rabbit model, biofilms on Foley catheter surfaces were highly resistant to high levels of amdinocillin, a beta-lactam antibiotic (30). However, Stickler et al. (31) found that treatment of a patient with a polymicrobial biofilm-infected catheter with ciprofloxacin allowed the catheter to clear and provide uninterrupted drainage for 10 weeks. Morris et al. (32) found that time to blockage of catheters in a laboratory model system was shortest for hydrogel- or silver-coated latex catheters and longest for an Eschmann Folatex S All Silicone catheter (Portex Ltd., Hythe, Kent, England). Biofilms of several gram-negative organisms were reduced by exposure to mandelic acid plus lactic acid (33). In a study in which ciprofloxacin-containing liposomes were coated onto a hydrogel-containing Foley catheter and exposed in a rabbit model, the time to development of bacteriuria was double that with untreated catheters, although infection ultimately occurred in the rabbits with treated catheters (34).

Directions for Future Research

To better understand and control biofilms on indwelling medical devices, research must progress in several key areas. More reliable techniques for collecting and measuring biofilms should be developed. For central venous catheters, the reference method for quantification of biofilms on catheter tips is the roll-plate technique, in which the tip of the catheter is removed and rolled over the surface of a nonselective medium. Quantification of the biofilm depends on the number of organisms recovered by contact with the agar surface. Biofilm-associated cells on the inner lumen of the device are not detected with this method, which has low diagnostic sensitivity and low predictive value for catheter-related bacteremia (7). In addition, this method cannot detect more than 1,000 colony-forming units (CFU) per tip. A method that used sonication plus vortexing as a means of quantifying biofilms on catheter tips showed that a level of 10^4 CFU per tip is predictive of catheter-related septicemia. Although this method is an improvement over the semi-quantitative roll-plate technique, the recovery efficiency of the method needs to be determined (i.e., the percentage of cells that are not recovered and quantified). Zufferey et al. (35) described a method for rapidly detecting biofilm cells on catheters by direct staining of the catheter with acridine orange. Although they found good agreement with culture techniques and noted that this technique provided more rapid results, they did not quantify cells; instead, they recorded a simple positive or negative result. Techniques that allow counting of biofilm cells directly on the catheter surface would be an improvement over established methods.

Model systems should be developed and used to study biofilm processes on various indwelling medical devices. These systems should closely simulate the in vivo or in situ conditions for each device, while at the same time providing reproducible, accurate results. To investigate biofilm formation on needleless connectors, Donlan et al. (14) used a biofilm disk reactor system (Figure 2) that incorporated a medium (intravenous fluid), a material (teflon coupons or needleless connectors), an organism (*Enterobacter cloacae*), and a flow rate (1 mL/min) that closely simulated conditions of use for these devices. Results were both reproducible and precise, and the system was capable of developing a steady state biofilm (Figure 3). This system design could be used to investigate and compare various biofilm control treatments, device design modifications, or different media formulations. By performing a similar experiment in an animal model system, biofilm processes in vivo could be predicted.

Another area of great importance from a public health perspective is the role of biofilms in antimicrobial-drug resistance. Bacteria within biofilms are intrinsically more

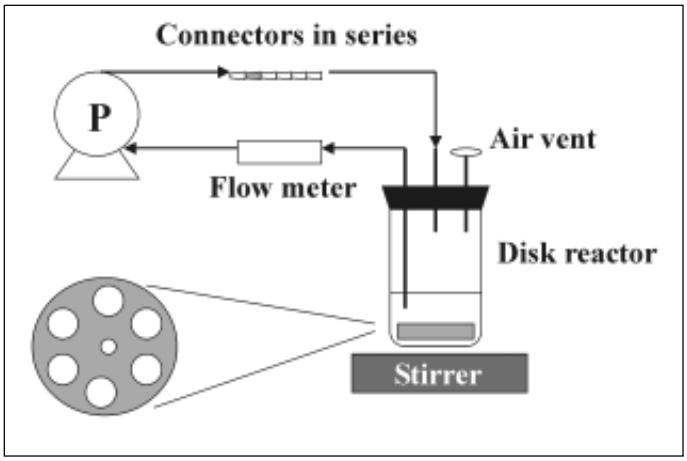

Figure 2. Biofilm disk reactor system.

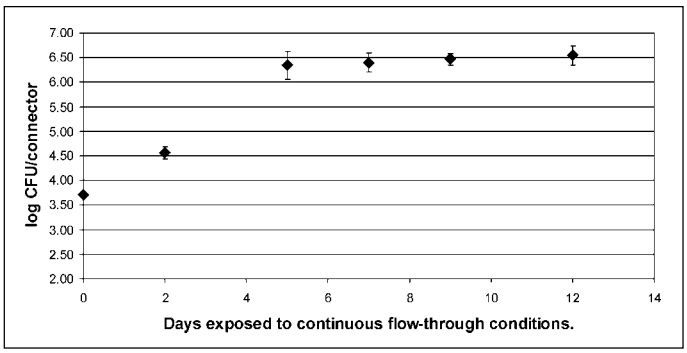

Figure 3. *Enterobacter cloacae* biofilm formation on needleless connectors.

resistant to antimicrobial agents than planktonic cells because of the diminished rates of mass transport of antimicrobial molecules to the biofilm associated cells (36) or because biofilm cells differ physiologically from planktonic cells (37). Antimicrobial concentrations sufficient to inactivate planktonic organisms are generally inadequate to inactivate biofilm organisms, especially those deep within the biofilm, potentially selecting for resistant subpopulations. This selection may have implications for treatments that use controlled release of antimicrobial agents to prevent biofilm growth on indwelling devices. Bacteria can transfer extachromosomal genetic elements within biofilms; Roberts et al. (38) demonstrated transfer of a conjugative transposon in a model oral biofilm. Hausner and Wuertz (39) demonstrated conjugation in a lab-grown biofilm with rates one to three orders of magnitude higher than those obtained by classic plating techniques. Resistance-plasmids could also be transferred within biofilms on indwelling medical devices.

The link between biofilm contamination of an indwelling device and patient infection is often unclear. Raad et al. (9) noted that biofilm formation was universal on vascular catheters collected from patients, yet observed that this universal colonization rarely resulted in bloodstream infection. A better understanding of the factors that control cell detachment may help answer the questions: Is there a critical biofilm density threshold above which detachment occurs? What is the role of the exopolymers in this process? Davies et al. (40) demonstrated the role of acyl homoserine lactones (HSL) in biofilms of *P. aeruginosa* and showed that HSL-knockouts were deficient in biofilm architecture and much more readily detached than wild-type organisms. Stickler et al. (41) detected these quorum-sensing molecules in biofilms on urethral catheters. A greater understanding of cell-to-cell communication within biofilms may lead to better predictability of biofilm processes such as detachment, as well as more effective control strategies.

Conclusions

Microbial biofilms may pose a public health problem for persons requiring indwelling medical devices. The microorganisms in biofilms are difficult or impossible to treat with antimicrobial agents; detachment from the device may result in infection. Although medical devices may differ widely in design and use characteristics, specific factors determine susceptibility of a device to microbial contamination and biofilm formation. For example, duration of use, number and type of organisms to which the device is exposed, flow rate and composition of the medium in or on the device, device material construction, and conditioning films on the device all may influence biofilm formation. More effective biofilm control strategies should result as researchers develop more reliable techniques for measuring biofilms and better model systems for evaluating control strategies. A clearer picture of the importance of biofilms in public health should also result as the role of biofilms in antimicrobial-drug resistance is investigated and the link is established between biofilm contamination and patient infection.

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Applying Economic Principles to Health Care

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Applying economic thinking to an understanding of resource use in patient care is challenging given the complexities of delivering health care in a hospital. Health-care markets lack the characteristics needed to determine a "market" price that reflects the economic value of resources used. However, resource allocation in a hospital can be analyzed by using production theory to determine efficient resource use. The information provided by hospital epidemiologists is critical to understanding health-care production processes used by a hospital and developing economic incentives to promote antibiotic effectiveness and infection control.

The application of basic textbook principles to understanding economic behavior in the health-care industry is not a straightforward exercise because of the complex nature of health care as a service or product. Health care is not an item that is pulled off a store shelf, placed in a shopping cart, and paid for at the cash register. The desired result cannot be guaranteed and depends on various factors, many of which are beyond the control of the health-care provider. Economic analysis is based on the fundamental notion of efficient use of available resources. Two basic points are 1) economics is about resource allocation, and 2) efficiency in resource use (getting the most from available resources) in health care can be understood by identifying production functions representing health-care services.

Economics is a behavioral science that begins with two propositions about human behavior. First, human behavior is purposeful or goal directed, implying that persons act to promote their own interests. Second, human desires and demands are unlimited; however, resources are limited and cannot meet unlimited demands. Thus, the basic problem addressed by economics is how to allocate limited resources among unlimited demands. Within this context, the concept of cost in economics is based on opportunity costs rather than financial costs. Opportunity cost is the value of a resource when it is employed in its next best use. Costs are not expressed as expenses paid (or financial accounting) but as the value of lost output if resources were employed in an alternative productive process.

With the focus on resource allocation, one of the main concerns in designing a social mechanism to allocate society's resources is efficiency—getting the greatest output from productive inputs (a problem for suppliers). Another concern is product choice—determining what goods and services should be produced (meeting consumer demands). Finally, there is concern about product distribution (who gets the products produced).

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The Gold Standard of Resource Allocation Mechanisms

Understanding the social conditions that affect resource allocation is at the heart of economic thinking. Economics has what can be referred to as a "gold standard" of resource allocation mechanisms—the perfectly competitive market, which has the following characteristics (1): 1) many buyers and sellers with no single economic agent influencing the exchange of goods among market participants; 2) a homogeneous or standardized product (i.e., goods that individual producers cannot alter or differentiate to collect a higher price); 3) no barriers to movement of firms into or out of the market; 4) perfect information about market conditions that is available to all market participants; and 5) a fully defined system of property rights in which ownership of all products and productive resources is assigned.

This mechanism allows producers and consumers to freely interact; and from this interaction, consumer preferences about the product are revealed (Figure 1, demand curve), as well as the quantity producers are willing to supply at various prices (Figure 1, supply curve). The demand curve shows that consumers will purchase greater quantities of a good as price decreases, while the supply curve shows that

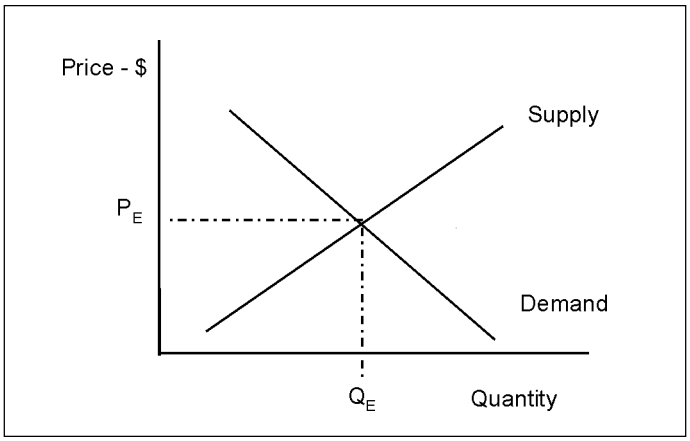

Figure 1. Supply and demand curves.

producers will produce greater quantities of a good as product price increases. As market participants interact, an equilibrium price level will emerge so that the quantity demanded at price P_E by consumers is equal to the quantity that producers will supply at price P_E. P_E becomes the market price because at no other price level does the quantity demanded by consumers match the quantity provided by suppliers. Prices greater than this level will result in excess supply; prices below this level result in excess demand.

Prices in a perfectly competitive market act as a feedback mechanism to market participants. Prices simultaneously reflect the value of the product to consumers and provide a signal to suppliers whether to change the amount of product they should produce relative to changes in consumer demand. The market for antibiotic drugs provides an example of how prices communicate preferences in the market place. There is debate regarding the extent to which prices for antibiotic drugs encourage the development and production of new agents to counter antibiotic resistance. An economist would assess this issue by examining the market price for antibiotics to determine whether prices are communicating to producers that new drugs are needed to meet future demands. If prices are not providing the appropriate "feedback," an economist would identify the characteristics in the market (e.g., number of producers, barriers to market entry or exit) responsible for the distortion in the price signal to market suppliers.

The power of the perfectly competitive market is that the perspectives of consumers, producers, and society as a whole converge. This market structure provides incentives for individual economic agents to act ultimately in the best interest of society (e.g., produce the greatest possible output from limited resources). Producers must be efficient and get the most output from the resources used. Inefficient producers will be unable to make a profit in the long run and will be forced to leave the market. Across the various markets, consumer demands are met (product choice), producers supply the most output possible (therefore maximizing profits), and society gets the most output from the scarce resources available.

Other types of resource allocation mechanisms are associated with markets with different characteristics, such as monopolies (single seller, e.g., power utilities) or oligopolies (a few sellers, e.g., automobile industry). However, these markets have shortcomings in terms of promoting the greatest output from society's resources and achieving the level of efficiency that could be obtained by the perfect market.

Resource Allocation in Health Care

Examination of resource allocation in the health-care industry is complicated because the market characteristics differ from those in a perfectly competitive market. The market for health-care services is considered an imperfect market because—1) Health care is a heterogeneous product, as the patient can experience a range of outcomes; 2) Patients who are insured have third-party payers covering their direct medical expenses; and 3) A "market price" is lacking, i.e., no feedback mechanism exists that reflects the value of the resources used in health care.

While the perspectives of consumers, producers, and society converge in a perfectly competitive market, hospital patient costs in the health-care market are different for patients (consumers), health-care providers (suppliers), insurance companies (third-party payers), and society. The economic impacts of pain and suffering are of concern to the patient and society, but may not be relevant to a purely economic analysis of costs from the perspective of health-care providers or third-party payers (2).

Regardless of perspective, economic thinking provides one common goal: efficiency, or getting the most from available resources. A hospital administrator, for example, is faced with the challenge of organizing resources to meet the organization's goals. The relationship between the range of productive inputs utilized and outputs produced can be characterized by a production function, which shows the maximum amount of product that can be obtained from any specific combination of resources (or inputs) used in producing a product (or output). By identifying the relationship between output and inputs, one can find the combination of inputs and output that maximizes economic return.

The classic production function from economic theory follows a standard curve (Figure 2) that demonstrates the relation between one input and one output (3). This curve involves a variable input as opposed to a fixed input. Changes in the quantity of variable inputs will cause variation in the quantity of output produced (e.g., varying application of a fertilizer to a crop). Fixed inputs are those that must be in place before production can begin and do not vary with output levels (e.g., buildings). This curve embodies the notion of diminishing marginal returns. As one increases an input, a point is reached at which the additional output produced by adding another unit of input begins to get smaller and smaller, ultimately leading to a decline in the total output produced. The fixed input becomes overextended by the expanded production. For example, adding too much fertilizer to a crop can compromise soil quality and lead to a decline in output.

This is a technical relationship that does not yet include dollars. If the organizational goal is to maximize output, a producer would employ I_B units of input to produce O_B units of output. This approach would make sense if inputs were free. However, inputs are usually not free. This is where an economist steps in. At some point before the maximum, the value of the additional output created by an additional unit of input is less than the cost of this additional input (e.g., spending $10 in

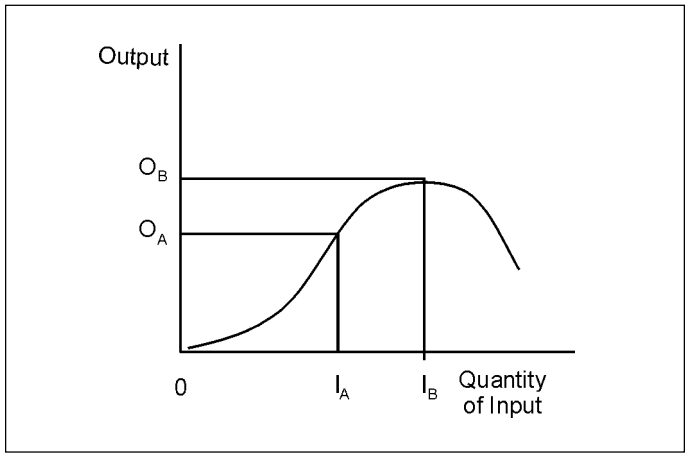

Figure 2. Standard curve of production function, demonstrating the relation between one input and one output.

additional input costs may yield only $8 in additional output value). The decision rule is to produce only as long as the value of additional output is just equal to the cost of the additional input.[1] For this figure, the region where it is "economic" to produce is somewhere between input quantities I_A and I_B. The information needed to identify these productive relationships in a hospital must come from hospital epidemiologists as well as from hospital accountants. Epidemiology, being the principal measurement tool for population health status, provides measures of health-care outcomes (outputs). Measures of resource use (inputs) in a hospital should be based on hospital purchasing and cost accounting records (as opposed to hospital patient charges that do not accurately reflect actual resource use).

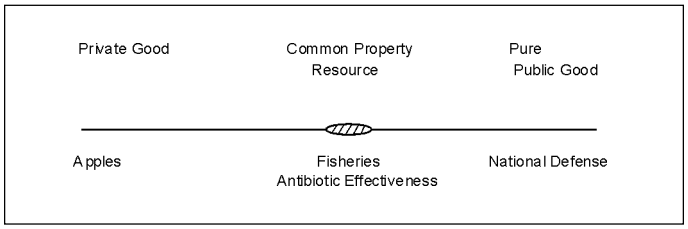

Figure 3. Continuum illustrating the degree to which an economic good has characteristics that make it a private or public good.

Resource Use for Preserving Antibiotic Effectiveness

The framework for identifying efficient resource use can be applied to the production of health care in a hospital. Two major concerns of hospital epidemiologists are the effectiveness of antibiotic drugs and the incidence of health care-associated infections. Policy makers in health care are concerned about antibiotic resistance and how to maximize the effectiveness of existing antibiotic drugs. A production function quantifies the flow of resources that can be used to promote this effectiveness. Understanding the production function will help identify the trade-offs a clinician must make between the patient's health, the antibiotic treatment to prescribe, and the impact of this treatment on the rate of resistance. However, two production processes are affected by the decision to use antibiotics: promoting an individual patient's health and maintaining antibiotic effectiveness in the treatment of future patients.

The economic analysis in this instance is similar in complexity to the analysis of environmental problems such as air and water quality (4). Like clean air and clean water, antibiotic effectiveness is an economic good that is difficult to allocate efficiently using our gold standard allocation mechanism because it has some characteristics of a public good. Public goods represent a class of economic goods because by their nature they are nonrivaled and nonexclusive in consumption. The classic example of a public good often used by economists is national defense. It is unrivaled in consumption because, once provided, one person's consumption of defense does not affect another person's consumption. It is nonexclusive in consumption because, once provided, there is no practical way to exclude or prevent consumption of defense by those who choose not to pay for providing it. Because of these product characteristics, public goods will not work in our ideal resource allocation mechanism because there is no practical way to reveal a demand curve for a public good. Public goods are usually provided by a governmental agency (thus the name public good) or by some type of collective organization.

A continuum (Figure 3) can be used to describe the degree to which a particular economic good possesses characteristics that make it a private or public good. Antibiotic effectiveness falls between these two classes: it is exclusive in that only medical professionals (at least in the developed world) can administer the drug, but it is not purely nonrivaled because consumption of antibiotics by one person can affect future consumption by others.

This leads to an externality: the use of a resource or product by one person can affect others without their permission. The decision to provide antibiotic treatment to one patient can affect the future efficacy and quality of the drug to other consumers (5). Resource allocation of antibiotic effectiveness is analogous to the management of fisheries: a fisherman, acting to maximize personal profits, can overfish and diminish the future stock (or quantity) of fish for all other fishermen of the same fish stock.

A fishery, like antibiotic effectiveness, is a common property resource. A common property resource, using fisheries as an example, is usually managed by some collective organization to restrict the quantity of fish harvested and monitor the health of the fishery to sustain a viable fish population in future years. Economists help design resource allocation mechanisms for common property resources that provide incentives (regulations, taxes, or subsidies) for individual agents to act in the interest of the whole collective. These incentives act like prices in that they provide the "feedback" about the values of the resources being used. To design a resource allocation mechanism for antibiotic effectiveness will necessitate much more information about the epidemiology and microbiology of biologic resistance and the trade-offs clinicians face in treatment decisions.

Resource Allocation in Infection Control

The production function presented here is a simple relationship involving a single variable input. However, most production processes involve many variables, and determining the shape of a multidimensional production function can be a complicated statistical problem. However, understanding the technical relationship between health-care inputs (e.g., provider time, resources actually used for infection control) and outputs (i.e., patient health outcomes), and learning where resources are being over-employed (wth no real gains in output) are crucial in determining efficiency and therefore savings in production costs. Hospital infection control is an input to all the productive services a hospital provides (e.g., pediatric care, general surgery, trauma, cancer). Changes in infection control may influence health outcomes throughout the hospital, in ways that may not be obvious.

[1] A complicating factor omitted from the discussion is time. In a longer view of time, all fixed inputs are considered variable and can be redeployed to some other productive process. Therefore, fixed costs must be covered in the long run. Since fixed costs are "sunk" costs (spent before production even begins), it makes sense to keep operating for short time periods (as opposed to shutting down all production) if variable costs are covered.

Conclusions

Efficiency in resource use (getting the most out of limited resources) is a goal that every health-care organization can accept, regardless of one's perspective (e.g., that of society, insurers, hospital administrators, or patients). Economic analysis is fundamentally about resource use and can serve an important role in health-care decision-making. Applying economic thinking to health care presents challenges to researchers and will require new approaches to analysis. Measuring the productive process in hospital care is complicated by the fact that the patient is both an input and an output in the process (i.e., the patient's health is a function of factors determined outside the hospital, such as lifestyle and genetics). Precise and accurate information from hospital epidemiology is critical to understanding the resources needed, and thus the economic impact, of caring for hospitalized patients.

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Economic Impact of Antimicrobial Resistance

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One reason antimicrobial-drug resistance is of concern is its economic impact on physicians, patients, health-care administrators, pharmaceutical producers, and the public. Measurement of cost and economic impact of programs to minimize antimicrobial-drug resistance is imprecise and incomplete. Studies to describe and evaluate the problem will have to employ new methods and be of large scale to produce information that is broadly applicable.

One reason antimicrobial-drug resistance has recently become a concern is its economic impact. The Institute of Medicine estimates the annual cost of infections caused by antibiotic-resistant bacteria to be U.S.$4 to $5 million (1). However, methods for measuring economic impact of resistance are in their infancy, and the studies leave many questions unanswered (2). In this review, I examine perspectives from which economic impact of resistance is important, assess available data about economic methods used for evaluating economic effect, and suggest issues important for these assessments, as well as approaches for further study.

Economic Impact: Differing Viewpoints

Several viewpoints toward antimicrobial-drug resistance and its impact include those of physicians, patients, health-care businesses, the drug industry, and the public (Table 1).

Table 1. Perspectives of economic impact of antimicrobial-drug resistance[a]

	Focus	Outcome	Time	Motivation	Approach
Physician	Individual	Health	Short	Professionalism	Treatment
Patient	Individual	Health	Short	Health	Treatment
Provider	Care group	Lower cost	Short	Profit	Cost containment
Industry	Clients	Sales	Short, long	Profit	New drugs, viable old drugs
Public	Population	Health	Long	Social good	Lower chance of resistance

[a]Cordell RL, Solomon SL, Scott RD, McGowan JE Jr, unpub. data.

Physicians

The view most considered in day-to-day medical care is that of the practicing physician. Physicians focus on individual patients and are motivated by professionalism that demands they seek the absence of disease, most often in persons who are ill when they visit a physician. Thus, the main economic problems that resistance presents for physicians are related to ineffective treatment (e.g., consequences arising from patient death, disease). From this treatment perspective, a production model of the type presented by Scott (3) would relate the existence of multiple antimicrobial agents to likely effectiveness in curing a given patient's infection. To clinicians treating individual patients, availability of more antimicrobial agents than needed would be of little or no concern. However, clinicians would be alarmed by absence of effective agents (the "postantibiotic era" cited frequently since Cohen's publication of that title [4] in 1992). From this viewpoint, the economic impact of diminishing effectiveness of a given drug or group of drugs depends on the availability of other drugs.

Patients

Patients with infections are likely to have a view similar to that of the physician (Table 1), except that their motivation for participating in the treatment process is their own well-being. Economic impact is also measured in terms of consequences arising from illness and death, specifically the added cost of treatment of a resistant organism, since patients pay retail prices for drugs and services. Such charges are assumed directly when patients pay their own bills or absorbed indirectly when added costs of multiple drugs and services result in increasing premiums for patients who have health-care coverage.

Health-Care Businesses

Today, health-care system financial resources in the United States are less frequently controlled by doctors and nurses and more often by administrators, financial managers, third-party payers, and politicians. These people see reduced illness and death as a reasonable goal, but also seek objective evidence that this goal is achieved with fiscal efficiency (i.e., by the least expenditure of increasingly scarce financial resources [5]). Antimicrobial drugs represent a way to provide cost-effective care to patients who are part of a defined population being served. The economic cost of antimicrobial-drug resistance for health-care businesses is in the measures they must take to preserve the effectiveness of antimicrobial agents in the care group. These measures may include costs for a series of different drugs and services, as well as for personnel time, supplies, space, and equipment for institutional programs to deal with antimicrobial-drug resistance (e.g., pharmacy and therapeutics committees,

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antimicrobial-drug use review, practice guidelines). The benefit is decreased costs associated with care of patients infected with resistant organisms. Antimicrobial-drug resistance in other settings is of interest to the health business professional only as it affects or has the potential to affect the population receiving the health-care organization's services. From this perspective, health-care organizations may be the easiest setting in which to measure the economic impact of antimicrobial-drug resistance. Here, the analysis is limited to specific antimicrobial drugs, and the impact on care for a specific group of patients can be measured in terms of costs to the specific business. In addition, the costs of measures to preserve effective treatment can also be assessed in relation to other costs.

Drug Industry

The focus for pharmaceutical firms and other groups providing products for treatment and prevention of infectious diseases (e.g., antimicrobial agents, products to stimulate host defenses, vaccines) is similar to that of the health-care business. This group is also motivated by profit and focuses on potential clients; however, the clients of interest are the potential users of their products--direct (patients) and indirect (health-care systems, governments, and the like)--rather than enrolled subscribers to a health plan. Product sales are the desired outcome, and a short-term view of sales is part of their outlook. However, industry must also take a longer view of the subject and consider the impact of resistance as potential for introduction and sale of new products, necessitating a two-pronged approach. On the one hand, firms wish to maintain the life of their current antimicrobial products, a goal threatened by new patterns of antimicrobial-drug resistance. On the other hand, resistance may make obsolete a competitor's product, opening up the field for a product that may have been less marketable because it cost more or was less safe or effective. In addition, resistance to drugs may produce a niche for a new antimicrobial agent.

Public ("Societal View")

A final view to be considered is that of public health or the public good. This societal perspective, fueled by the goal of social good, encompasses entire populations, whether of towns, cities, countries, and even the entire world. As the goal here is to maximize health for the whole population, the time frame is usually long term. Since antimicrobial drugs enhance both prevention and treatment of infections, society considers them a valuable resource. As resistance diminishes this resource, a societal goal would be to minimize resistance and therefore the forces that produce resistance.

In the jargon of economics, antimicrobial agents are a scarce resource, that is, one in which consumption (current use) decreases its effectiveness (future value) (6). Any use of antimicrobial agents enhances the likelihood of resistance. From a societal viewpoint, then, appropriate use of antimicrobial drugs for treatment and prevention of infection would lead to an appropriate or acceptable decrease in the value of antimicrobial effectiveness. Conversely, overuse or misuse of antimicrobial drugs would create an inappropriate decrease in these resources. When treating one person leads to decreased effectiveness in treating the next person receiving the drug, society is affected adversely. This impact is often ignored because the short-term outcome and cost of drugs (for example, for perioperative prophylaxis) can be measured readily, and the detrimental effect on long-term usefulness is unquantified for most situations (7).

Whose Perspective?

The economic costs and benefits of programs to preserve antimicrobial effectiveness must be interpreted in the context of these differing points of view. In any single study, it is essential to keep the same perspective, whichever it may be. Analyses that mix the different points of view in assessment tend to confuse rather than clarify the problem and its extent. For example, the business viewpoint might value loss of effectiveness of a cheap antimicrobial agent as important when it leads to use of a more expensive agent for patient care. In contrast, the medical viewpoint might find loss of effectiveness of the cheaper drug of little consequence as long as other effective drugs are available.

Similarly, the value of antimicrobial effectiveness might differ from an economic viewpoint rather than the medical one. For example, from a public health perspective, the use of antimicrobial agents to promote growth in animals would be evaluated by comparing the relative benefit to food production against the potential for decreasing the effectiveness of prevention and treatment of infections in humans. In contrast, the physician's perspective would evaluate the use of antimicrobial agents in animals in terms of its impact on the effectiveness of specific medical therapeutic agents.

A third example of varying perspectives is the use of measures to control the physician's choice of antimicrobial agents. This step may make great sense to hospital or other health-care administrators when it is likely to produce more efficient use of resources. Yet the control measures might be seen as having no value by clinicians who are willing to use any and all resources to cure their patients.

Assessing the Economic Impact of Resistance

Net economic impact of resistance can be viewed as the attributable cost of treatment of an infection due to a resistant isolate ("treatment cost") minus the cost of preventing such infections ("prevention cost"). Cost analysis should include consideration of all resources affected by illness or intervention (8). Economic impact of antimicrobial-drug resistance includes a wide range of factors important to various viewpoints (Table 2). The difference in this situation is the added cost for each element associated with infection with a resistant organism compared with the cost for the same element if associated with infection caused by a susceptible microbe (Table 2).

Costs for laboratory tests, radiologic studies, bronchoscopies, or other diagnostic procedures are part of diagnostic costs and primarily of concern to the health-care institution when these costs cannot be passed on to the patient or an insurer. The same is true of costs for purchase and administration of antimicrobial drugs and other therapeutic agents. Patients experience both direct costs of health care and indirect costs (e.g., loss of productivity resulting in reduction in income). Other types of indirect costs of antimicrobial-drug resistance are costs to the drug industry resulting from diminishing marketability of their drugs and costs to businesses for loss of workers' productive time. All these factors are part of the economic impact of resistance.

Studies of the economic impact of resistance have not included measurement of most of these variables. They have

Table 2. Elements of the economic impact of antimicrobial-drug resistance, by perspective affected

Element	Measurement[a]	Perspective affected
Death	[Costs associated withtreatment failure (R)] - [Costs associated with treatment failure (S)]	Physician, patient, HCB
Illness	[Costs associated with pain, suffering, inconvenience (R)] - [Costs associated with pain, suffering, inconvenience (S)]	Physician, patient
Care cost	[Charges for care (R)] - [Charges for care (S)]	Patient
Care time	[Time devoted to care (R)] - [Time devoted to care (S)]	Physician, HCB
	[Length of process (R)] - [Length of process (S)][b]	Patient, society
Diagnosis costs	[Costs for diagnosis (R)] - [Costs for diagnosis (S)]	HCB
Treatment costs	[Costs for drugs (additional drugs and treatments, more expensive drugs (R)] - [Costs for drugs (S)]	HCB
Diminished marketability	[Market for drug use (R)] - [Market for drug use (S)]	Drug industry
New markets	[Market for new drug (S)] - [New market for new drug (R)] (replace current market leader; replace inexpensive drug with more expensive drug; provide new product)	Drug industry
Impact on non-treated	[Increased resistance (R)] - [Increased resistance (S)]	Society

[a]R = extent in patients infected with resistant organism; S = extent in patients infected with susceptible organism; HCB = health-care business.
[b]Costs associated with lack of routine functions during infection, including loss of work, quality of life for patient (includes both inpatient and outpatient components); for society, reduction of useful function in workforce.

usually focused on hospital charges and length of stay, features that are objective and relatively easy to collect compared with other aspects of impact. Recent studies of impact have also included estimates of increased hospital or other institutional stay, incremental specific treatments, and additional diagnostic tests needed for a patient infected with a resistant organism compared with a patient infected with a strain of the same organism that is drug susceptible (Table 3) (9-23). Attempts have also been made to measure death and illness associated with resistant infections. Although these are objective indicators of economic impact, until recently it was impractical to obtain this information on the small patient groups studied at individual hospitals or other single health-care settings. In addition, few studies have been published on the impact of antimicrobial-drug resistance outside health-care locations. Further attention is needed to the community setting, where much of antimicrobial treatment is given and received (24).

Generalizations from single-center studies are hindered by differences in local practices. For example, some centers experience delays in transferring patients with positive cultures for vancomycin-resistant enterococci or methicillin-resistant *Staphylococcus aureus* (MRSA) from acute-care centers to long-term care facilities (25). Estimates of incremental increase in length of hospital stay for these institutions might differ from those where such problems do not exist. Thus, multicenter studies would be needed to obtain data that could be used to generalize about regional or national estimates of impact.

Determining the economic impact of antimicrobial-drug resistance to a given drug may have several facets (26). The relative benefit of being able to use a given drug in comparison with alternatives when this drug is not available must be assessed. Thus, to decide the worth of an antimicrobial drug, several elements must be considered. The incremental cost of treating the patient with alternative agents must be assessed, often by studies in which costs for care of patients infected with isolates resistant to a commonly used agent

Table 3. Examples of studies of economic impact of resistance published in 1999-2000

Year	First author (ref.)	Study methods	Features measured
2000	Soriano (9)	Case-control, cohort	Death, length of hospital stay
2000	Roghmann (10)	Cohort	Mortality rates at 7 & 30 days, length of hospital stay, direct health-care costs
2000	Vanhems (11)	Cohort	Death
2000	Simor (12)	Comparison of cases with arbitrary criteria	Incremental length of hospital stay
2000	Harthug (13)	Case-control	Death
2000	Bhavnani (14)	Case-control	Death
2000	Feikin (15)	Cohort	Death
2000	Garbutt (16)	Retrospective cohort	Death
1999	Carmeli (17)	Cohort	Death, length of hospital stay, hospital charges
1999	Rubin (18)	Modeling, assumption and extrapolation from case reports	Death, direct medical costs
1999	Weingarten (19)	Case-control	Use of ventilators, length of hospital stay, duration and number of antimicrobial agents, hospital and pharmacy charges
1999	Gonzalez (20)	Cohort	Death
1999	Abramson (21)	Case-control	Length of hospital stay, attributable median total cost

(drug X) are compared with costs for care of patients with isolates that are susceptible to drug X. A potential problem with this type of comparison is that a uniform reference group is not readily available. For example, a study may compare costs for care of patients with susceptible isolates treated with drug X to costs for patients infected with isolates resistant to drug X who are then treated with one or more alternative drugs (e.g., Y,Z), when choice of drug is left to the patient's physician. However, other factors (such as altered renal function or a patient's inability to take oral medications) leading to use of drugs Y or Z to treat patients infected with resistant organisms may also have led to treatment with one of these drugs in patients infected with susceptible organisms. Thus, costs must be evaluated carefully to compare these two groups of patients and account for other factors affecting therapy. Study design may also influence the measured impact of resistance (27,28).

Current Situation

For these and other reasons, measurement of the economic impact of resistance is imprecise and incomplete. Neither methods for direct measurement nor appropriate surrogate variables have been found for some important features. Methods used have primarily focused on case-control strategies, which have limitations (27).

Further work needed on this aspect of the question includes defining optimal methods of measurement, including more aspects of economic impact, and disclosing the perspective from which the assessment is being made. Measurement of impact of resistance on patients through cost-utility analysis may be helpful as well (29).

Measuring Benefit of Programs to Minimize Resistance

Steps to Minimize Antimicrobial-Drug Resistance and Its Economic Impact

Several strategies and approaches have attempted to deal with resistance (Table 4) (30,31). The term "control" seems inappropriate because true control of antimicrobial-resistant organisms and their effects seems biologically and historically impossible. However, statements from professional societies, independent review groups, and governmental agencies stress several measures to minimize the detrimental effects of resistance (32-35). These include professional educational programs, enhanced microbiologic surveillance, enhanced surveillance of patients, implementation of infection control procedures, development of vaccines against resistant organisms, and prudent use of antimicrobial agents for treatment and prophylaxis. These measures can be evaluated in terms of their success in reducing antimicrobial-drug resistance and its associated costs (36). However, costs associated with each of the strategies must also be included in the calculation of overall economic impact (26). These costs are more or less important, depending on the perspective from which the analysis is being conducted. The few analyses of this type conducted to date focus on costs of infection control (37).

Developing New Antimicrobial Drugs and Other Therapeutic Agents

The most obvious way to combat resistance is to develop new antimicrobial agents (38). Several new combinations or classes of antimicrobial agents now may prove valuable to combat infections caused by resistant bacteria (39,40). Nonantimicrobial means to combat resistant organisms (e.g., development of vaccines) will also assume more importance (41,42).

Economic impact here is primarily a concern for the pharmaceutical industry and consists of the net difference between costs associated with developing new agents and the profit from sale of the agents when they are marketed.

Surveillance for Antimicrobial-Drug Resistance

Surveillance is vital to determining measures needed to control antimicrobial-drug resistance (43). New, rapid laboratory methods are becoming available to facilitate this important effort. Surveillance methods produce expenses in use of diagnostic testing (e.g., microbiologic cultures), and they require additional time for infection control and laboratory personnel, as well as patient care staff, to interact with infection control personnel and implement surveillance programs.

Implementing Infection Control Measures

Approximately 30% to 40% of resistant infections arise from cross-infection via hands of hospital personnel, 20% to

Table 4. Elements of the economic impact of measures to deal with antimicrobial drug resistance, by perspective affected

Element	Measurement[a]	Perspective affected directly
Develop new antimicrobial agents	[Costs associated with drug development] - [Profit resulting from new drug's use]	Drug industry, HCB, patient, society
Conduct surveillance	[Cost of surveillance for infected and colonized patients (R)] - [Cost of surveillance for infected and colonized patients (S)]	HCB
Implement isolation	[Costs associated with barrier isolation (R)] - [Costs associated with barrier isolation (S)]	HCW, visitor, patient, HCB
Adapt lab procedures	[Costs associated with testing (R)] - [Costs associated with testing (S)]	HCB, patient, society
Educate about resistance	[Costs associated with educational programs (staff, patients) (R)] - [Costs associated with educational programs (staff, patients) (S)]	HCW, patient, visitor, HCB
Improve drug administration	[Costs for programs to improve drug administration (R)] - [Costs for programs to improve drug administration (S)]	HCW, HCB
Improve drug choice	[Costs for programs to improve drug choice (R)] - [Costs for programs to improve drug choice (S)]	Prescribers, HCB

[a]R = extent in patients infected with resistant organism; S = extent in patients infected with susceptible organism; HCB = health-care business; HCW = health-care workers.

25% from the selective antimicrobial pressure, 20% to 25% from introduction of new pathogens, and 20% from other or unknown pathways (44). Costs for control of cross-infection include those for masks, gowns, gloves, antiseptics, and other equipment needed for proper isolation precautions; increased personnel time needed to implement isolation procedures; and effort involved in teaching procedures to health-care personnel.

Adapting Laboratory Methods for Detecting New Types of Antimicrobial-Drug Resistance

Emerging antimicrobial-drug resistance affects the ability of the clinical microbiology laboratory to detect and report resistance. Several new resistance mechanisms in gram-positive and gram-negative bacterial organisms are difficult to detect with usual laboratory methods. To counter these problems, the National Committee for Clinical Laboratory Standards (Villanova, Pennsylvania) and other groups have developed new testing methods, as well as guidelines and standards for testing resistant organisms (45). Costs associated with these efforts are usually borne by the health-care system, whether or not the tests are performed in-house. Patients and society ultimately bear these costs, depending on the mechanism by which the health-care system is paid.

Educational Programs

Physicians, students, residents, nurses, pharmacists, infection control and quality assurance personnel, administrative staff, and others are frequently part of the health-care team. Making sure that awareness of the problem of antimicrobial-drug resistance and how to deal with it are part of the educational program or in-service education offerings is a key part of obtaining support to minimize resistance. Costs here result from the time needed to prepare and deliver educational presentations and for attendees to participate; these costs are primarily borne by the health-care system.

Optimizing Antimicrobial Agent Administration

The way that antimicrobial agents are prescribed is a major risk determinant for resistance (46). Programs to monitor and improve procedures for proper dosing, interval of administration, duration of treatment, and monitoring for adverse effects have been undertaken and recently updated (47,48).

The economic impact relates to the time and efforts of prescribers, pharmacists, drug delivery personnel, and administrative staff who provide direct care to patients and set policy in pharmacy and therapeutics committees. Thus, health-care institutions are primarily affected by these attempts to minimize antimicrobial-drug resistance. The combination of measures must be individualized to the particular organism-antimicrobial pair, health-care institution, and specific care setting, for at least two reasons (47). First, the reservoir for important resistant organisms varies dramatically. For some, like MRSA, the reservoir is now in persons in some communities as well as in health-care facilities (49). For others, such as gram-negative bacilli containing extended-spectrum beta-lactamase enzymes, acute-care hospitals (especially intensive care units) and nursing homes are the main reservoir (50). Second, the modes by which different organisms are spread differ. MRSA seems closely linked to person-to-person spread, whereas gram-negative nonfermenting bacilli are often spread through contaminated liquids and respiratory therapy devices. Thus, assessment of economic impact of measures to minimize resistance depends on the specific measures that must be introduced in a given institution or setting.

Influencing Drug Choice

Recent interest has focused on improving antimicrobial-drug use by controlling the choice of antimicrobial agents by individual prescribers. Some reported efforts attempt to limit use of inappropriate agents by removing specific drugs from the list of available agents in the formulary or restricting them to certain specialists (51,52). Practice guidelines are a means of achieving uniformity of antimicrobial-drug use that have been applied to many areas in addition to that of infectious diseases. Project ICARE (Intensive Care Antimicrobial Drug Resistance Epidemiology) is a cooperative project of the National Nosocomial Infections System of the Centers for Disease Control and Prevention and the Rollins School of Public Health of Emory University. A 1998 survey of 47 hospitals participating in Project ICARE showed that clinical practice guidelines were reported frequently (70% of hospitals) among measures to improve prescribing practices (53). Guidelines are particularly useful in reducing costs of therapy and total costs of prescription, while maintaining quality of care (54). The question is whether these efforts can reduce prevalence of antimicrobial-drug resistance; major successes have been noted in recent studies, both in the community and hospital (54).

Status of Methods and Results

Measurement of the economic impact of strategies to minimize resistance is imprecise and incomplete (55). Some information is available about the impact of these measures on drug cost and length of hospital stay, number of diagnostic tests, and number of therapeutic drugs used. Further work needed includes designation or identification of optimal methods for measurement, inclusion of more aspects of economic impact, and carefully defining the perspective from which the assessment is being made.

Conclusions

Determining the true economic impact of antimicrobial-drug resistance is a challenge because so many variables and perspectives are involved. Better methods are needed to assess the practical implications for those from all perspectives, whether prescriber, patient, health-care business, pharmaceutical company, or the public. Because studies completed to date have been hampered by their small size and lack of uniformity, validity of the information provided is unclear and extrapolating the studies to regional or national or international levels is questionable.

Population-based studies of the true impact of resistance would require large multicenter study groups and would be valuable to help address the different perspectives. Relevant studies will require sufficient size to describe baseline antimicrobial-drug resistance, deal with limits of random variation, and control for variables. Multicenter study groups will likely have to be assembled to provide enough observations, as well as sufficient resources. Only when this is done can there be adequate exploration of the true magnitude of the economic impact of antimicrobial-drug resistance.

The economic impact of antimicrobial-drug resistance deserves more attention from government and professional

societies. Neither the summary of the Report by the American Society for Microbiology Task Force on Antibiotic Resistance nor the National Coalition on Antibiotic Resistance mentions this as an important area for study or as a concern for health care (32,56). A draft public health action plan to combat antimicrobial-drug resistance published by the federal Interagency Task Force on Antimicrobial Drug Resistance notes that costs of treating resistant infections place a substantial burden on society and mentions the impact of in-hospital cost of six common kinds of resistant bacteria (57).

As the U.S. health-care system has evolved into a business in the past decade, administrators concerned with cost and benefit have become important decision makers. Thus, economic arguments are needed to convince health-system administrators that antimicrobial-drug resistance is a serious issue. The same considerations apply in other countries as well (58). Lack of attention means that funding to solve the problems is unlikely to be found. A change in perception and action is needed to give this important issue of the economic impact of antimicrobial-drug resistance the priority it deserves.

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Cost-Effective Infection Control Success Story: A Case Presentation

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In a surgical intensive care unit, the 1996-1997 incidence of central catheter-associated bloodstream infections exceeded that of hospitals participating in the National Nosocomial Infections Surveillance System. Interventions were implemented, and a cost-benefit analysis was done that led to hiring a vascular catheter care nurse. Subsequent outcome data demonstrated a substantial reduction in central catheter-associated bloodstream infections.

Most hospital-acquired bloodstream infections are associated with use of an intravascular device, specifically central venous catheters. Catheter-associated bloodstream infections occur more often in intensive care unit (ICU) patients than in ward patients. The attributable mortality rate for bloodstream infections in surgical ICUs has been estimated to be 35% (1). ICU-acquired bloodstream infections account for an estimated $40,000 increase in costs per survivor and an estimated $6,000 increase in hospital costs (2).

In 1997, the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance System reported 0.4 to 9.2 bloodstream infections per 1,000 central-line days in patients in surgical ICUs. A mean of 5.1 and a median of 3.6 infections per 1,000 patient days was reported. Coagulase-negative staphylococcus was found to be the predominant microorganism responsible. In 1997, despite conventional infection prevention and control strategies, we identified a mean of 8.8 and a median of 8.9 catheter-associated bloodstream infections per 1,000 patient days in patients in a surgical ICU at Texas Medical Center. The predominant microorganism responsible for these catheter-associated bloodstream infections was coagulase-negative staphylococcus, which has been associated with a lower risk of death than other hospital-acquired bloodstream pathogens.

The Study

The Methodist Hospital, a tertiary-care facility in the Texas Medical Center with 900 beds, is affiliated with Baylor College of Medicine. The increased incidence of catheter-associated bloodstream infections was identified in a 32-bed surgical ICU. Prospective surveillance for device-related infection is performed in the surgical ICU by an experienced nurse epidemiologist. All positive cultures are reported to infection control by the microbiology laboratory. CDC's definition for catheter-associated bloodstream infection is used (3).

In response to the increased rate of infections, three working groups were formed to develop strategies for catheter selection, insertion, care, and maintenance; and clinical practice guidelines. Products and practices used in the ICU were reviewed, and a literature search was performed to identify best practices associated with insertion, care, and maintenance of central venous catheters, which formed the basis for the clinical practice guidelines. The Design, Measure, Assess, Improve model described by the Joint Commission on Accreditation of Healthcare Organizations was used to guide the plan of action (Figure).

The following recommendations were adopted by the Infection Prevention and Control Committee: use an antibiotic-coated catheter for patients expected to have the device in place for >7 days; disseminate the clinical practice guideline to surgeons, anesthesiologists, house staff, and nursing staff; dispense maximum barrier precaution supplies (i.e., gown, mask, gloves, and fenestrated drape with insertion tray); and hire a vascular catheter-care nurse for the surgical ICU. The nurse's responsibilities would include educating the house staff and nursing staff on the clinical practice guideline; observing practices associated with insertion, care, and maintenance of the central venous catheter system on all three shifts; collecting and analyzing outcome data related to bloodstream infections; and providing status reports to the nursing staff, medical staff, and the Infection Prevention and Control Committee.

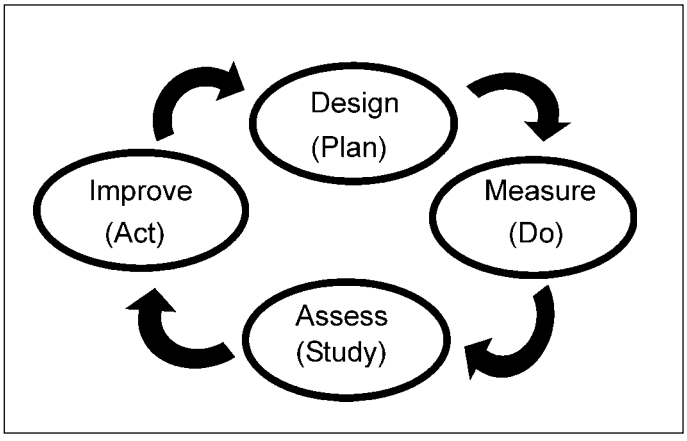

Figure. Performance improvement model described by the Joint Commission on Accreditation of Healthcare Organizations.

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Cost Analysis

A cost-benefit analysis was presented to the hospital administration to justify hiring the nurse, at a projected salary of $50,000. A cost of $6,000 per catheter-associated bloodstream infections was used. We proposed that adding the nurse to the staff would prevent at least one bloodstream infection per month, or 12 infections annually. This cost-benefit analysis approach was effective in securing approval for the position. A registered nurse with 15 years of surgical ICU experience at Methodist Hospital was hired in March 1999.

In January 2000, 9 months after joining the infection control team, the nurse reported that 18 fewer bloodstream infections occurred in 1999 than in 1998, for an estimated savings of $108,000, with no change noted in surgical ICU patient days. The 1999 mean bloodstream infection rate was 6.6 per 1,000 central-line days; the median was 6.7 per 1,000 central-line days (Table).

Table. Catheter-associated bloodstream infections per 1,000 central-line days, surgical ICU, Texas

Year	Mean	Median
1977	8.8	8.9
1998	7.3	7.4
1999	6.6	6.7

Conclusions

The pathogenesis of catheter-associated bloodstream infections is multifactorial. A multidisciplinary approach is necessary to develop and enforce corrective measures. Efforts to prevent bloodstream infections in the surgical ICU patient population are cost-effective from both the patient and hospital standpoint. We were able to effectively present a cost-benefit analysis to secure approval for a unique infection prevention and control position.

In a cost-benefit analysis, the outcome is presented in monetary terms (4). Another decision analysis tool, cost-effectiveness analysis, incorporates both the cost and the effect of the intervention. Cost-effectiveness analysis measures the net cost of providing a service as well as the outcome obtained. The outcomes are reported in a single unit of measurement, e.g., years of life saved, number of lives saved, or number of cases of a specific disease prevented (4,5). The advantage of cost-effectiveness analysis is that it considers the possibility of improved outcomes in exchange for the use of more resources. A cost-effectiveness analysis is planned to further justify the resource allocation of an ICU nurse to the position of vascular catheter-care nurse.

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Feeding Back Surveillance Data To Prevent Hospital-Acquired Infections

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We describe the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance system. Elements of the system critical for successful reduction of nosocomial infection rates include voluntary participation and confidentiality; standard definitions and protocols; identification of populations at high risk; site-specific, risk-adjusted infection rates comparable across institutions; adequate numbers of trained infection control professionals; dissemination of data to health-care providers; and a link between monitored rates and prevention efforts.

According to a 1996 Institute of Medicine (IOM) report, preventable "adverse health events," a category defined as injuries such as medical errors (a failure of planned actions) and hospital-acquired infections caused by medical interventions, are responsible for 44,000 to 98,000 deaths per year at a cost of $17-$29 billion (1). The IOM report recommended immediate and strong mandatory reporting of medical errors and voluntary reporting of other adverse health events, suggesting that monitoring leads to reduction. A hallmark of monitoring any adverse health event is reporting the information back to those who need to know. We examine the value of feeding back information on hospital-acquired infections to reduce and prevent them.

Hospital-Acquired Infections Surveillance Systems as a Model to Monitor and Prevent Other Adverse Health Events

Hospital-acquired infections affect approximately 2 million persons each year (2). Such infections have been monitored in the United States since the 1970s, and the monitoring is often a model for monitoring other adverse health events (3). Principles used in the surveillance of hospital-acquired infections are strikingly similar to those used in the continuous quality improvement process in manufacturing (4). Both systems emphasize changes at the system rather than individual level. Deming described two types of errors in manufacturing: special causes and usual causes. Special causes of error comprise only 5% to 10% of all errors; usual causes constitute the remainder. Similarly, only 5% to 10% of hospital-acquired infections occur in recognized outbreaks (4,5).

Surveillance Systems for Hospital-Acquired Infections

Surveillance is defined as "the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know" (6). The scientific value of surveillance as part of a hospital infection-control program was demonstrated most strongly in the landmark Study of the Efficacy of Nosocomial Infection Control (SENIC) (2). In that study, highly trained data collectors evaluated more than 338,000 patient records from a probability sample of U.S. hospitals to calculate infection rates. The hospitals' control programs were also evaluated. SENIC found that hospitals with the lowest nosocomial infection rates had strong surveillance and prevention programs. Other studies have suggested that surveillance also has a strong scientific basis. For example, the collection, calculation, and dissemination of surgeon-specific, surgical site infection (SSI) rates to surgeons were found to reduce SSI rates in all published studies (3,6-9).

During the last two decades, hospitals have established internal systematic monitoring of hospital-acquired infection rates. Monitoring with benchmarks external to those of a single hospital's surveillance system has also been suggested (10). A single hospital may use its own definitions, methods, and monitoring protocols. Developing a monitoring system with external benchmarks requires considerable additional effort.

To be successful, a multicenter monitoring system must satisfy three requirements: it must have a very clear purpose; it must use standard definitions, data fields, and protocols (including of cohorts or groups to be monitored and periods of data collection); and it must identify an aggregating inst itution to standardize definitions and protocols, receive the data, assess them for quality, standardize the approach to risk-adjusting the benchmarks, and interpret and disseminate the data.

The NNIS System

The Centers for Disease Control and Prevention (CDC's) National Nosocomial Infections Surveillance (NNIS) system has been serving as an aggregating institution for 30 years. The NNIS system is a voluntary, hospital-based reporting

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system established to monitor hospital-acquired infections and guide the prevention efforts of infection control practitioners. In 1999, 285 hospitals in 42 states participated in the NNIS system (11). All NNIS hospitals have ≥100 beds and, on average, are larger than other U.S. hospitals (median bed size: 360 versus 210); however, NNIS hospitals have a geographic distribution similar to all other U.S. hospitals. The NNIS system establishes a national risk-adjusted benchmark for nosocomial infection rates and invasive device-use ratios (12,13) by using uniform case definitions and data-collection methods and computerized data entry and analysis. To promote the latter, CDC provides infection control practitioners with 28 hours of training and sponsors a biennial conference.

Patients in intensive-care units (ICUs) are at high risk for nosocomial infections and since 1987 have been monitored in the NNIS system by site-specific, risk-adjusted infection rates according to ICU type (12). The risk-adjusted benchmark infection rates and device-use ratios are published annually for use by both NNIS and non-NNIS hospitals (12). (Internet address for NNIS SemiAnnual Report: http://www.cdc.gov/ncidod/hip/surveill/NNIS.htm).

Data Quality

For an aggregating institution to assess the quality of data, meaningful surveillance definitions of adverse health events must be available. These definitions do not define clinical illness; rather, they are used for credible, consistent application across institutions. There is always a balance between the resources expended to find these cases and the value within the institution of using the collected data and comparing them to the external benchmarks. There is no single source of information that allows an infection control practitioner to accurately identify hospital-acquired infections. CDC definitions of nosocomial infections include clinical and laboratory information that requires training, counseling, and updating—tasks that are largely the responsibility of the aggregating institution. Several studies have examined attempts at shortcuts around the training and counseling components; all studies suggest that medical record abstractors perform very poorly compared with infection control practitioners in case-finding for nosocomial infections (9). Hospital-acquired infection case ascertainment is time-consuming, and the process is becoming more difficult with earlier discharge of patients and lack of agreement on methods of postdischarge surveillance (14,15). Progress in this area has been slow, and more efficient methods of case ascertainment are needed. Sands et al. have proposed using exposure to antimicrobial drugs as a sensitive method for finding cases of SSI in the postdischarge outpatient setting (16). Although this method is efficient, many institutions are unable to acquire antimicrobial-drug use data for outpatients who have recently undergone hospital surgical procedures. Finally, despite current difficulties, a recent study in NNIS hospitals suggests accurate case finding can be achieved (Table 1).

Table 1. Estimates of accuracy of prospectively reported infections in nine NNIS Hospitals[a]

Infection site	Predictive value positive (%)	Sensitivity (%)	Specificity (%)
Bloodstream	87	85	98.3
Pneumonia	89	68	97.8
Surgical site	72	67	97.7
Urinary tract	92	59	98.7
Other	80	30	98.6

[a]Adapted from Emori TG, et al. Infect Control Hosp Epidemiol (17).

Measuring Infection Rates: Endemic- or Epidemic-Disease Rates?

Surveillance measures the endemic-disease rate of nosocomial infection. Less than 10% of all nosocomial infections occur in recognized outbreaks (5). If an outbreak occurs in a hospital, it is often because one prevention strategy failed for a short period. The endemic-disease rate provides hospitals with knowledge of the ongoing infection risks of hospitalized patients when no recognized outbreaks are occurring. This rate represents 90% to 95% of all hospital-acquired infections (5). Thus, ongoing surveillance measures the endemic-disease rate. Unlike outbreaks, rates established by ongoing surveillance usually require that many problems be addressed to lower a high rate of infection.

Measuring Success in a Surveillance System

From 1990 through 1999, we examined risk-adjusted, hospital-acquired infection rates used by participating NNIS hospitals (18). We found that decreases in risk-adjusted infection rates occurred at all three body sites (respiratory tract, urinary tract, and bloodstream) monitored in ICUs (18). Substantial decreases in bloodstream infection rates occurred in medical (44%), surgical (31%), and pediatric (32%) ICUs (Figure). Decreases also occurred in other ICU types (Table 2)

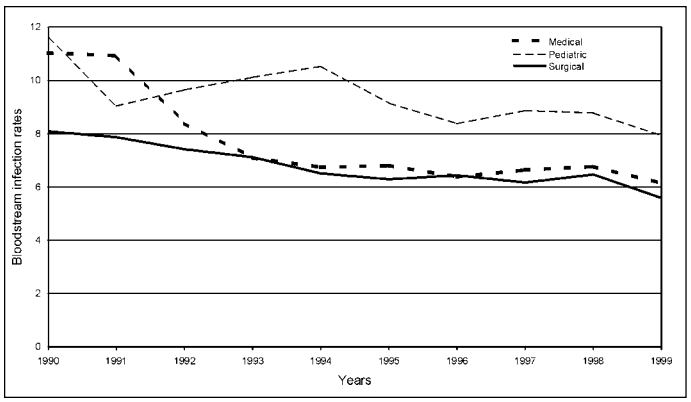

Figure. Trends in bloodstream infection rates by type of intensive care unit, National Nosocomial Infections Surveillance system, 1990-1999. Bloodstream infection rate is number of central line-associated primary bloodstream infections per 1,000 central line-days.

Table 2. Decrease in hospital-acquired infection rates, NNIS, 1990–1999

Type of ICU	Bloodstream infection rate[a] (%)	Ventilator-associated pneumonia rate (%)	Urinary tract infection rate[b] (%)
Coronary	43	42	40
Medical	44	56	46
Surgical	31	38	30
Pediatric	32	26	59

[a]Central line associated.
[b]Catheter associated.

and in infection rates at other sites (18). The reasons for these decreases are unknown, but several explanations are possible. First, the improvements seen in NNIS hospitals also reflect other national efforts to prevent infections (e.g., new research findings, prevention guidelines). Second, the U.S. health-care system has shifted away from hospital-based care. Some of the observed rate reductions could be attributable to this shift. However, a portion of these observed decreases likely represented true decreases in hospital-acquired infection rates in NNIS hospitals. Disseminating risk-adjusted, reliable infection rates within NNIS hospitals to infection control practitioners, patient care givers, and administrators was an essential part of NNIS efforts during the 1990s. By all reports, patient-care personnel began to perceive value in the data, relied on them for decisions, and altered their behavior in ways that may have reduced the incidence of nosocomial infections in NNIS hospitals. By changing the behavior of patient care givers, the NNIS approach to surveillance of nosocomial infections may have actually improved the quality of patient care. This report (18) demonstrated the value of the NNIS system as a model for preventing hospital-acquired infections (18).

Critical Elements of a Surveillance System for Hospital-Acquired Infections

The NNIS elements critical for successful reductions in infection rates included 1) voluntary participation and confidentiality; 2) standard definitions and protocols; 3) defined populations at high risk (e.g., intensive care, surgical patients); 4) site-specific, risk-adjusted infection rates comparable across institutions; 5) adequate numbers of trained infection control practitioners; 6) dissemination of data to health-care providers; and 7) a link between monitored rates and prevention efforts, where patient-care personnel relied on the data to alter their behavior in ways that may have reduced the incidence of nosocomial infections (17).

Challenges for the NNIS System's Future

Despite NNIS' success, many challenges remain. The IOM report recommends mandatory reporting of medical errors (1). Others have advocated public availability of such information. But achieving accurate data may be difficult if mandatory reporting and public availability of these data are required in all circumstances. These requirements heighten the need to assess the accuracy of self-reported data from institutions, a process that is difficult and expensive. The demand for publicly available data is particularly troubling. The NNIS Evaluation Study has suggested that, while data on nosocomial infections are generally accurately reported, sensitivity (underreporting of infections) was a more serious problem than other measures of accuracy such as predictive value positive or specificity (17). When the added pressure of publicly available data is added to a process that already has a tendency to miss cases of nosocomial infection, the possibility of serious underreporting of infections becomes cause for concern. Validating data is essential if data from performance measurement systems are to be credible.

All segments of the health-care community may not want or need the same data or the same level of detail in the data. Take the example of a consumer purchasing an automobile. The consumer rightly anticipates that the car will have a braking system that is safe and fully operational and thus would find the rate of errors for brake installation from the manufacturer of limited interest. This rate of error would be of vital interest to the manufacturer, however. Similarly, it is doubtful that regulators, payers, the public, or the health-care institution all want the same information with the same level of detail.

The medical marketplace is very dynamic. Surveillance must also be dynamic to keep pace with the changing environment. Improved methods of case ascertainment, especially with regard to postdischarge and outpatient surveillance, will be needed as more health care is provided outside the hospital. Improvement in measures of intrinsic and extrinsic patient risk factors will also be needed for improved risk adjustment. As computerization and integration of health care continue, these improvements will be possible. However, sound epidemiologic principles used by knowledgeable workers must guide use of the new technologies. A key to NNIS's success is infection control practitioners who use monitoring data to implement prevention activities. Any new system for preventing adverse health events will need to develop a cadre of professionals at the health-care facility to design and implement the prevention programs to promote patient safety and health-care quality (19).

Demonstrating the value of surveillance data to both the hospital's patient-care personnel and administration is essential. However, patient-care personnel must perceive value in the data; if they do, they will rely on the data for decisions and alter their behavior in ways that should reduce the incidence of nosocomial infections. By changing the behavior of care givers, surveillance of nosocomial infections or other adverse health events can improve the quality of patient care. However, SENIC suggested that only approximately one third of nosocomial infections are preventable (2). Better measures of adverse health events, including of nosocomial infections that are truly preventable, will make this monitoring more efficient and useful (20). Prevention measures will help move nosocomial infections from adverse health events to what the IOM described as medical errors (1). Solving the problem of medical errors still has its challenges.

Better understanding of the inner workings of the health-care delivery system to determine the root cause of errors is needed. Additionally, consistently good performers in a system where interhospital comparison of rates has been performed can identify the best practices. We are only beginning to understand the multiple prevention efforts of these high performers and how they differ from those of other institutions.

Despite the difficulties and challenges, application of epidemiologic principles can lead to success. A surveillance system to monitor hospital-acquired infections requires standardization, targeted monitoring, risk adjustment, trained professionals, and a link between the disseminated data and prevention efforts. A system such as the NNIS system with all these critical elements can be successful in preventing infections.

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Promoting Quality Through Measurement of Performance and Response: Prevention Success Stories

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Successful efforts to prevent health-care acquired infections occur daily in U.S. hospitals. However, few of these "success stories" are presented in the medical literature or discussed at professional meetings. Key components of successful prevention efforts include multidisciplinary teams, appropriate educational interventions, and data dissemination to clinical staff.

In the past two decades in the United States, demands from patients, insurance companies, managed-care organizations, employers, providers, and policy makers for improved health care have increased dramatically (1). An essential component of quality improvement efforts is performance measurement, the quantification of processes and outcomes by using one or more dimensions of performance (2). Such data can be used for accountability, research, or improvement (3). An important part of the improvement perspective is sharing success stories or "best practices." We describe key improvement concepts of performance measurement from individual hospitals and selected hospitals in the National Nosocomial Infections Surveillance (NNIS) system.

Success Stories from Individual Hospitals

Improving Central-Line Care in Neonates

In 1995, the neonatal intensive care unit (ICU) at Allegheny General Hospital in Pittsburgh, Pennsylvania, underwent substantial expansion. Subsequently, the ICU experienced a 40% increase in very low birth weight (<1,000 g) babies, which resulted in increased overall use of central lines (4). Although the rate of bloodstream infections remained stable during 1995 and 1996, the total number of such infections increased. Concerned neonatal ICU staff formed a multidisciplinary team to develop interventions to prevent them. The team focused on improving procedures for central-line dressings. At the time, central-line sites were covered with gauze and a transparent dressing. The dressing was routinely changed three times each week, which required central-line manipulation. Less frequent changes were not performed because nurses could not see the central-line site, except during dressing changes. The team recommended discontinuing use of gauze over the central-line insertion site but continuing use of the transparent dressings. The team also developed standard protocols for inserting and caring for central lines. Inservice education was provided to nurses and house staff on central-line management. As a result, both the total number and rate of central-line associated bloodstream infections significantly declined in 1997 (Figure 1).

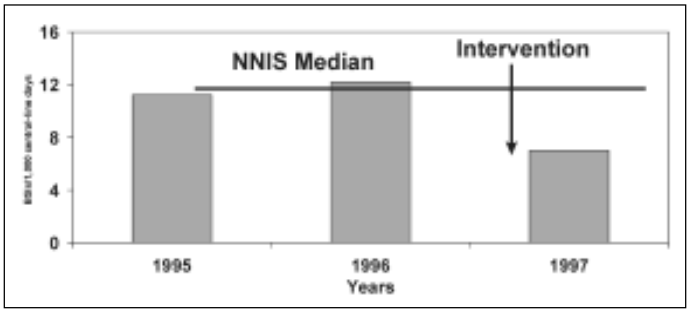

Figure 1. Rates of bloodstream infections (BSIs) associated with central lines in neonatal ICU, Allegheny General Hospital.

Reducing Use of Urinary Catheters

The Hospital of St. Raphael in New Haven, Connecticut, reported joining NNIS in 1992 (5). Infection control professionals performed infection surveillance in the surgical, medical, and coronary ICUs. During 1992 and 1993, the catheter-associated urinary tract infection rate in all three ICUs was well above median rates for NNIS hospitals. After reviewing urinary tract infections and use of urinary catheters in ICUs, infection control staff identified prolonged use of urinary catheters (mean = 21 days) as the chief risk factor for infection. Although educational sessions to reemphasize existing prevention guidelines for catheter care were conducted with nursing staff, no changes in infection rate were observed. In 1995, a multidisciplinary team was formed to address the system of care for patients with urinary catheters. The team included medical directors, patient-care managers, clinical nurse specialists, physicians, microbiologists, and infection control and quality assurance staff. The team developed a guideline for using urinary catheters, a protocol for removing catheters without a physician's order,

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and a protocol requiring urinalyses when urine cultures were ordered. The protocol for removing a catheter required approval by the Connecticut Division of Healthcare Regulation, the hospital medical board, and the hospital's critical care and infection control committees. Nurses, house staff, and attending physicians were extensively educated about the new protocol. Compliance was high for both the physicians' urinalysis protocol (93%) and the nurses' catheter removal protocol (88%). After these protocols were implemented, urinary tract infection rates in all three ICUs decreased and the length of urinary catheter use was shortened.

Ward-Specific Dissemination of Data

In the Veterans Affairs (VA) Medical Center in Pittsburgh, Pennsylvania, general medical-surgical, non-ICU patients were perceived by clinical staff to have high rates of urinary tract infection. Although there was no national benchmark for comparison, infection control staff used NNIS definitions and data collection methods to calculate ward-specific rates. The major intervention was to disseminate these ward-specific rates to nursing staff. No other changes to policies or protocols were made, and no new products were introduced during this period. After ward-specific feedback was begun, the rate of infections underwent a dramatic and sustained reduction (50%), which saved an estimated $400,000 per year. The authors felt that dissemination of ward-specific rates of urinary tract infection stimulated nurses to improve compliance with prevention guidelines (Figure 2) (6).

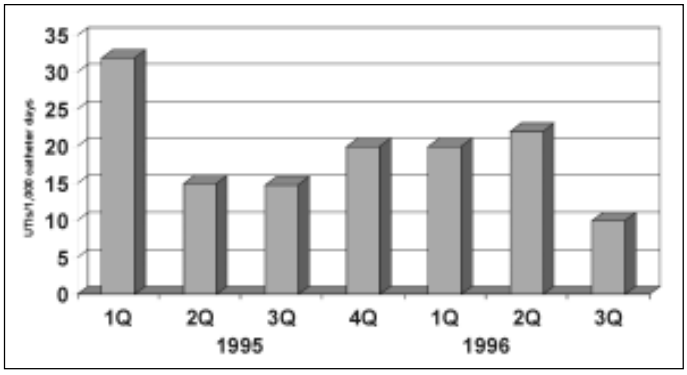

Figure 2. Rates of urinary tract infections (UTIs) in general medical/surgical patients, Pittsburgh VA Medical Center.

Synthesis of Individual Success Stories

Several key improvement concepts are illustrated by these success stories. Improvements should be determined by local health-care facility needs and involve staff. Comparison to national benchmarks is important for building credibility among clinical staff and allowing facilities to focus attention and resources but does not preclude improvement efforts when external benchmarks are not available or infection rates are relatively low. Since initial improvement efforts may not always succeed, commitment to improvement is vital. Finally, disseminating data back to clinical staff is a simple yet powerful tool for improvement.

Success Stories from Selected Hospitals in NNIS

Background and Method

NNIS is the oldest and largest surveillance system for hospital-acquired infections. An important reason for its success has been feedback of data to participating institutions (7). To better understand how surveillance data were used and how institutions worked to reduce infections, NNIS program staff conducted a telephone survey of infection control professionals at NNIS hospitals that had reported reductions in infection rates in ICUs. Specific questions included how their interventions were developed, what types of activities occurred, and how feedback was performed.

Results

Infection control professionals at 15 (94%) of 16 hospitals responded to the survey. Reductions were reported for ventilator-associated pneumonia (7/15), bloodstream infections (5/15), and urinary tract infections (3/15). While the specific interventions varied at each hospital, the three features common to all 15 institutions were 1) use of multidisciplinary teams, 2) tailored educational interventions directed to clinical staff, and 3) feedback to clinical staff of facility infection rates.

Multidisciplinary Teams

The primary function of multidisciplinary teams was to build consensus that a problem existed, disseminate information about the infection and any planned interventions to their colleagues, and assist infection control professionals with investigations and prevention. All teams included infection control professionals. Almost all (14/15) teams had physician representation, including a hospital epidemiologist, infectious disease and critical care specialists, and where appropriate other subspecialists (e.g., urologist, pulmonologist). Nursing professionals were present on all teams (15/15) and included critical care nurses and administrative nurses. Most teams (13/15) also included other professionals, such as respiratory therapists, pharmacists, microbiologists, and dieticians.

Education

Once a particular intervention was identified, educational sessions were used to introduce it and provide training. These educational activities included training for nurses and other ICU staff, multidisciplinary ICU rounds, self-paced educational modules, and for physicians, grand rounds and teaching lectures. In all 15 hospitals, the target audience for interventions included nurses, especially those who were providing direct patient care in the ICU. Less often the interventions included activities directed at physicians (4/15) or respiratory therapists (2/15). Infection control professionals organized and delivered most educational material.

Data Dissemination

After interventions were reduced, all hospitals disseminated data to their staff on the impact of the interventions on nosocomial infection rates. Data included comparison of hospital infection rates to NNIS benchmarks, intrahospital rates over time, and compliance with interventions. Respondents thought that feedback was most effective when

directed at ICU staff and least effective when provided to medical and nursing staff hospitalwide. Data dissemination usually occurred through reports to the ICU staff and infection control committee. Several hospitals (5/15) reported that posting infection rates and protocol compliance as charts or posters in ICU was especially effective.

Cycle for Success

The reports in this article represent a small yet important collection of efforts directed at preventing infection. While the specific interventions varied, the process in each hospital was strikingly similar. The cycle for success started, for most facilities, with comparisons to external benchmarks. Multidisciplinary teams with diverse representation were formed and identified the "whys" and "whats" for the infections of interest. Such teams also helped formulate the interventions. Education, usually through training sessions with clinical staff, was crucial in introducing change. Feedback of comparative data to staff provided motivation and reinforcement. Comparison to external benchmarks also allowed staff to gauge their success as compared with other institutions. Finally, collaboration across organizational boundaries was a critical element of success (8). These reports effectively demonstrate how collaboration among physicians, nurses, and other professionals was the driving force for these improvement efforts.

As noted by Berwick, reports of performance improvement are desperately needed to guide quality improvement efforts (9). Real-time and real-life improvement reports can provide insights into how health-care quality can be improved. This report is an example of how both individual and aggregate results can inform the improvement process. The Institute of Healthcare Improvement's Breakthrough Series is another example of how improvement success stories are shared with a broader audience (10). However, much important learning for improvement also occurs in community hospitals, ambulatory care centers, long-term care facilities, or physician's offices. Too often, these experiences are not shared. Efforts to increase "harvesting knowledge from improvement" in these settings are needed (9). These efforts should include more success stories, outline epidemiologic approaches to understanding and describing best practices, and increase the use of analysis of root causes.

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Clinical Microbiology in Developing Countries

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We review the problem of limited microbiology resources in developing countries. We then demonstrate the feasibility of a cohort-based approach to integrate microbiology, epidemiology, and clinical medicine to survey emerging infections in these countries.

Microbiology Resources in Developing Countries

In industrialized countries, it is the best of times for the microbiologic diagnosis and treatment of infections. In some developing countries, progress is also apparent. Ministries of health are building hospital intensive care units (ICUs), with sophisticated medical devices, procedures, and interventions. Increasing numbers of infants and adults are being admitted to, and benefiting from, these units. More patients with conditions such as chronic renal failure or hematologic disorders are being treated in specialized units. The Internet has made physicians generally more knowledgeable than before.

Nevertheless, it is the worst of times for hospitals in other developing countries, where infectious diseases remain the leading cause of death (1). Many sentinel hospitals have less than basic microbiology laboratory facilities; there is no end in sight to the HIV epidemic, and the prevalence rate of tuberculosis (TB) is increasing in parallel with it; hospital infections, especially surgical site infections, have become important causes of illness and death in certain hospitals in sub-Saharan Africa (unpublished data); and invasive medical devices and procedures are increasingly being introduced into ICUs and operating theaters without the necessary infection control procedures. In some developing countries, some institutions have all the needed microbiologic resources, while others have none; some hospital laboratories have instruments and reagents yet have no technical staff to use them; others may be able to amplify genomes yet cannot report the results of a simple Gram stain in a timely manner. For all these reasons, the causes of many infections among inpatients in Africa, Southeast Asia, the Indian subcontinent, and parts of the Americas remain largely unknown or uncharacterized.

In sub-Saharan Africa and Southeast Asia, antimicrobial-drug resistance is being increasingly recognized in pathogens that commonly cause infections in health-care settings, rendering available antimicrobial agents ineffective and further shortening the list of already scarce effective agents (2). Thus, to diagnose and treat infections appropriately and to fully characterize emerging infections in developing countries, enhanced clinical microbiology services are a priority. The clinical microbiology laboratory in developing countries should be patient directed and guided by clinical reality and not by high technology or outside interests.

Two other factors have had a marked effect on the role of clinical microbiology in developing countries, the HIV and TB epidemics. Most (95% of the global total) people with HIV infection live in the developing world (3,4). In almost 6 million of the 34 million adults and children with HIV or AIDS, HIV infection was diagnosed during 1999 (4); 3.8 million cases occurred in sub-Saharan Africa and 1.3 million in South and Southeast Asia. Of the approximately 40 million TB cases globally, 73% are projected to have occurred in Southeast Asia and sub-Saharan Africa (5). TB, which accounts for almost one third of the AIDS deaths worldwide, and other opportunistic bacterial, fungal, and protozoal infections are leading causes of death among HIV-infected patients (3-5). Thus, HIV infection, TB, and HIV-related opportunistic infections have overwhelmed existing resources in hospital microbiology laboratories in most developing nations.

At the Centers for Disease Control and Prevention (CDC), a main objective of the strategy for preventing and controlling emerging infectious diseases in developing countries is establishing more effective international surveillance networks (6). In the industrialized world, infection control relies on results from individual patient-directed diagnostic microbiology laboratory tests. However, basic clinical microbiology has not been recognized as a priority by donor or governmental agencies in industrialized countries or by the developing countries themselves. The problem often has been compounded by lack of trained laboratory personnel or prohibitive costs associated with maintaining a laboratory. Where resources are available, they may be used inappropriately (e.g., nonessential stool, urine, or sputum cultures; antimicrobial susceptibility testing of microorganisms without quality assurance; or complete laboratory characterization and antimicrobial susceptibility testing of bacterial isolates that are not clinically relevant).

Prohibitive costs and doubtful cost-effectiveness of specific tests are commonly cited as reasons for the unavailability of microbiology tests. The first steps in achieving cost-effective use of resources include assessing whether or not a test has sufficient diagnostic value to be used and establishing criteria to limit processing to those organisms most likely to be clinically relevant (7). The concept of clinical value encompasses several issues (8): Why was the test requested? Will the result help or alter patient management? Would a simpler test do? Will the use of a test

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increase knowledge? Can we do without it? Is the test of public health or clinical importance? For example, hospitals in developing countries still routinely obtain and process anaerobic blood cultures, despite that a positive anaerobic blood culture often reflects an underlying anaerobic infection (e.g., intraabdominal sepsis or female genital tract infection) that already is clinically apparent or discernible (9,10). The counter argument is that while such data may reflect reality for a microbiology issue in industrialized nations, they may not be applicable for developing settings—all the more reason for important questions about diagnostic clinical microbiology in developing countries to be addressed through evidence-based clinical studies.

The importance of integrating epidemiology and microbiology is exemplified by studies that ascertained the usefulness of expensive HIV confirmation tests in developing countries. In industrialized countries, confirmation of HIV serologic tests with the Western blot molecular technique is standard practice. In developing countries, the Western blot often is not used because of its complexity and high cost. A study conducted in Thailand with epidemiologic, clinical, and microbiologic components has shown that the use of two enzyme-linked immunosorbent assays (ELISAs) to confirm the presence of HIV antibodies produces results comparable with those of the Western blot (11). This approach to confirming HIV status was used effectively in Tanzania (12), Thailand (13), and Malawi (14). Thus, in a country with a high prevalence rate of HIV infection, limited financial resources, and inadequate laboratory infrastructure, Western blot analysis for confirmation of HIV infection is neither mandatory nor necessary.

Medical services in industrialized nations rely on results from individual, patient-directed, diagnostic microbiology laboratory tests ordered by clinicians. This system appears effective for industrialized settings and is generally sustainable. Not surprisingly, diagnostic microbiology services in some developing countries have been modeled on these practices in industrialized countries. However, such routine laboratory testing may be impossible in developing settings because of lack of microbiology services, or, where these services are available, tests may be unreliable if performed improperly or without adequate quality control. Further, the tests may well be inappropriate, irrelevant, or redundant. For example, antimicrobial susceptibility testing without quality controls may lead to invalid or distorted data that give rise to bias and inaccuracy in reports being used for clinical and public health decision making.

Hospital Cohort-Based Studies

During the past few years, the Hospital Infections Program at CDC and the Clinical Microbiology Laboratory at Duke University Medical Center participated in hospital cohort-based microbiologic surveys. These surveys are conducted with a cohort of patients who meet simple, objective entry criteria or case definitions (e.g., fever, diarrhea, cellulitis, or specific syndromes). Detailed clinical and epidemiologic data are collected for later analyses, and cultures with a high positive predictive value for infection (e.g., blood, cerebrospinal fluid, other sterile sites, or stool for enteric pathogens) are obtained. The emphasis is on performing quality-controlled laboratory testing for a finite period rather than long-term, routine diagnostic testing. These surveys have been conducted in selected hospitals or laboratories that provide a natural gathering point to sample patients meeting these entry criteria. A cohort-based study acting as a surveillance "probe" for a finite period may be more effective than individual patient-directed laboratory testing in providing useful clinical and public health information, in determining the true incidence and prevalence rates of emerging pathogens and antimicrobial-drug resistance, and in yielding clinical predictors for various infections in defined patient cohorts. In addition, cohort-based studies provide the opportunity to establish diagnostic capability in basic clinical microbiology in sentinel hospitals or laboratories and promote surveillance activities in regions where critical public health infrastructure has been neglected.

Cohort Studies of Bloodstream Infection

To test this approach to clinical microbiology, CDC and Duke conducted cohort-based studies of bloodstream infections among inpatients in sub-Saharan Africa and Southeast Asia (12-15). Fever was chosen as the initial case definition because it may be attributed to HIV infection, diarrhea, pneumonia, TB, or, in sub-Saharan Africa, malaria. Blood cultures were obtained because of their high positive predictive value for presence of bloodstream infections in febrile patients.

In Thailand about half of consecutive febrile adults admitted to a sentinel teaching hospital for infectious diseases had bloodstream infections (13); in a similar patient cohort in a Malawi teaching hospital, approximately one quarter of patients had a bloodstream infection (14). In both countries, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, and *Salmonella* spp. were the predominant causes of bloodstream infections in these patients. Data from these studies also included clinical predictors for bloodstream infections and antimicrobial susceptibility profiles of clinically important isolates (including *M. tuberculosis* isolates). Both the predictors and susceptibility profiles were potentially useful for developing algorithms for empiric treatment of febrile inpatients and for helping clinicians decide which patients would most benefit from limited blood culture services, where these were available. Through cohort-based studies in Malawi during the dry and wet seasons, we demonstrated seasonal variation in bloodstream infection: *S. pneumoniae* and *M. tuberculosis* were the predominant bloodstream pathogens during the dry season, whereas *Salmonella* spp. were the predominant bacteria isolated during the wet season (16). We also documented that malaria was overdiagnosed in both the wet and dry seasons in Malawi and that empiric therapeutic decisions had to reflect these realities (16).

Cohort-based studies in Thailand and Malawi demonstrated the occurrence of occult mycobacteremia (15): 42% of patients with *M. tuberculosis* bloodstream infections had neither symptoms nor signs of pulmonary TB. These results highlighted the importance of maintaining a low threshold of suspicion for active TB; the need for strengthening each hospital's microbiology capabilities to examine and report on sputum smears for acid-fast bacilli; and the potential for intrahospital TB transmission from seemingly noninfectious patients.

The public health implications of the cohort-based approach are enormous. Conducting similar studies in other countries would improve microbiology services by encouraging appropriate use of limited resources in sentinel hospital

laboratories and focusing on clinically relevant problems (e.g., bloodstream infections, meningitis, pneumonia, febrile diarrhea, and surgical wounds). Moreover, laboratory personnel would benefit from training to conduct quality-controlled tests, such as antimicrobial-drug susceptibility testing. Prevalence rates of common infections, HIV infection, or resistance of common hospital pathogens to available antimicrobial agents would be available for clinical and public health decision making. Updated lists of probable diagnoses, clinical predictors for specific infections, and development of clinical algorithms and antimicrobial-drug susceptibility profiles based on these objective data would enhance patient care through rational diagnosis and prescribing policies.

Although it may not be economically feasible to obtain cultures for all patients who might benefit from microbiologic tests in developing countries, cohort-based studies could be applied to establish the causes and clinical predictors for these infections and thereby facilitate directed rather than blind empiric therapy.

Hospital laboratories in developing countries need to establish screening and rejection criteria for specimens submitted for culture. Laboratory directors need to address certain questions: Will the results alter patient management? What is the public health importance? What is the relative yield of a Gram-stained smear versus a complete culture?

Data from cohort-based studies in one region or country are not suitable for direct extrapolation to other regions or countries. Rather, regional, season-specific surveillance studies can be tools for optimizing patient care where routine laboratory testing is not available. The task remains to define the role of new and emerging pathogens in various patient populations at hospitals in developing countries.

The Role of Sentinel Hospitals

During the past 5 years, our cohort-based approach to collaborative global endeavors in health-care epidemiology has included identifying sentinel hospitals and then enhancing their clinical microbiology laboratory capacity by infection control assessments and interventions. In developing countries, where limited resources and infrastructure may preclude comprehensive medical, surgical, and laboratory services for every region or province, centralization of available resources in a few selected centers is one way of optimizing resources. This paradigm is evident in many countries in Southeast Asia, Africa, Latin America, and the Caribbean, where a few institutions have evolved into sentinel centers of paramount importance for providing such services.

Sentinel hospitals tend to be large institutions (usually >500 beds) that are the main teaching centers for medicine, surgery, nursing, and laboratory science; they commonly house specialized ICUs, surgery, hemodialysis, or invasive medical procedures; they have problems with hospital infections and antimicrobial-drug resistance; they are associated with microbiology laboratories that are often reference centers with the ability and capacity to conduct various microbiologic tests using scrupulous, quality-controlled methods; and they usually are government affiliated and have very close links with the respective ministry of health. The last attribute is important since governmental agencies from industrialized countries (e.g., World Health Organization [WHO], United States Agency for International Development, and the Department for International Development) generally prefer to maintain collaborative endeavors with sentinel centers for reasons including adequate infrastructure, trained personnel, and access to the ministry of health.

A high priority for future global consortiums of epidemiology and biomedical research centers will be to initiate or build upon existing systems in sentinel hospitals in developing countries for the international monitoring and reporting of antimicrobial susceptibility data. Two systems that offer a foundation of international linkages are CDC's International Nosocomial Surveillance Program for Emerging Antimicrobial Resistance and the WHO Antimicrobial Resistance Monitoring Program. The international and national objectives of these programs depend on conducting proper, quality-controlled, antimicrobial susceptibility testing and promoting the use of resistance data to guide antimicrobial therapy. These results, when integrated with clinical and epidemiologic data on opportunistic and hospital infections, may lead to substantial improvement in patient outcomes.

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New Technology for Detecting Multidrug-Resistant Pathogens in the Clinical Microbiology Laboratory

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Northwestern Memorial Hospital instituted in-house molecular typing to rapidly assess microbial clonality and integrated this typing into an infection control program. We compared data on nosocomial infections collected during 24 months before and 60 months after implementing the new program. During the intervention period, infections per 1,000 patient-days fell 13% (p=0.002) and the percentage of hospitalized patients with nosocomial infections decreased 23% (p=0.000006). In our hospital, the percentage of patients with nosocomial infections is 43% below the U.S. rate. Our typing laboratory costs approximately $400,000 per year, a savings of $5.00 for each dollar spent.

The nosocomial infection rate in U.S. hospitals in the early 1980s was 5.7% (1). Two million Americans acquire a nosocomial infection each year (2), at a rate of 5 per 100 admissions (5%). These infections cost $4.5 billion annually, and 88,000 patients die from them each year; 70% of infections are due to organisms resistant to at least one antimicrobial agent. Although 1.8 million fewer patients were admitted to U.S. hospitals in 1995 than in 1975 (35.9 million vs. 37.7 million) and the average length of stay was lower (5.3 days in 1995 vs. 7.9 days in 1975), the national nosocomial rate was increasing. In 1975, there were 7.18 nosocomial infections per 1,000 patient days compared to 9.77 in 1995, an increase of 36% (2).

Major nosocomial pathogens increasingly resistant to antimicrobial drugs include *Escherichia coli, Staphylococcus aureus,* coagulase-negative staphylococci, *Enterococcus* species, and *Pseudomonas aeruginosa* (3-4). Infections from methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE), and aminoglycoside-resistant *Pseudomonas* spp. are becoming common (5-6).

The clinical laboratory has several critical roles in controlling hospital-acquired infections: accurately identifying nosocomial pathogens, detecting unexpected antimicrobial-drug resistance, and epidemiologic typing (7). Most new rapid tests are not yet helpful for infection control purposes, and automated systems for bacterial identification and susceptibility testing are not as reliable as desired for detecting organisms with emerging drug resistance (7). However, the laboratory can make key contributions through epidemiologic typing, particularly by collaborating with the infection control team during outbreak investigations (8). Molecular techniques for establishing the presence or absence of clonality can be very effective in tracking the spread of infections caused by genetically related pathogens (9-14).

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We formed a permanent, integrated infection control and prevention program that fully incorporates infection control, infectious disease, pharmacy, and clinical microbiology personnel into a single working group to minimize hospital infections (15). We discuss our overall experience with such a program, which has been in place at Northwestern Memorial Hospital for more than 5 years. Our hospital, located in Chicago, is a 700-bed, university-affiliated medical center with more than 39,000 annual discharges, 56,000 emergency cases, and 260,000 annual outpatient visits. We initially postulated that our integrated infection control program could be medically and economically successful in minimizing the incidence of hospital-acquired infections. The laboratory's role was enhanced by introducing a molecular typing section within the Division of Clinical Microbiology; this section rapidly and systematically determines clonality and reports results immediately to the infection control practitioners so that they can quickly take appropriate action (3). We describe our experience with such a program after the first 60 months of its existence and compare its effect with the 24 months immediately before this expanded effort.

Methods

Nosocomial Infections

Nosocomial infections are detected by ongoing surveillance in intensive care units (ICUs), special-care nurseries, and post-surgery units. Standard infection definitions are used (16). The data we report represent the total number of nosocomial infections per 1,000 patient days, and the number of patients with nosocomial infections per 100 patient discharges (percentage of patients with nosocomial infection). Methods for data collection include review of microbiology reports and patients' medical records, direct observation of medical and nursing practice, active surveillance of rectal cultures of patients in nursing units for high-risk patients, and evaluation of suspected nosocomial infections reported by health-care providers. Three full-time infection control professionals collect the infection data. Interpretation,

assessment, and planning of any intervention(s) are performed under the direction of the medical director of the hospital's infection control and prevention department.

Two interventions were made simultaneously to enhance the overall program: a molecular typing laboratory and a weekly planning meeting. The meeting included representatives from infection control, diagnostic medical microbiology (molecular epidemiology), pharmacy, and infectious diseases.

Observation Periods

The preintervention assessment for this evaluation began on September 1, 1992, the start of our 1993 fiscal year (FY). Data were collected and assessed by quarters for 2 years, through the fourth quarter, FY94 (June through August 1994). Initiating the weekly meetings and establishing the molecular typing laboratory occurred during the fourth quarter FY94; the laboratory was fully operational in the first quarter FY95. The intervention time was the first quarter FY95 through the fourth quarter FY99 (September 1994 through August 1999), the period when the enhanced program was in effect.

Organization of the Integrated Program

At the beginning of the intervention period, weekly meetings were initiated to review the ongoing short- and long-term trends in nosocomial infections within the center as well as activities of the infection control professionals and microbiology laboratory personnel; any needed changes were determined. The organizational structure for selecting microbes for typing was shared by the medical directors of infection control and clinical microbiology (12). During the study period, all VRE recovered from clinical and surveillance cultures were routinely genomically typed so that data were current within 2 weeks of an isolate's recovery. Periodic routine typing for surveillance of fluoroquinolone-resistant *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacter cloacae*, and *Clostridium difficile* was also done. Additional organisms for typing were selected by this working group through surveillance of microbiology culture reports discussed at the weekly meeting. The clinical microbiology laboratory referred organisms to the molecular typing section for analysis whenever requested to do so by this group.

Microbial Typing

Fingerprinting is done by extracting genomic DNA according to the technique of Pitcher et al., using the guanidium thiocyanate/EDTA/Sarkosyl (GES) reagent (17). Genomic DNA is digested with various enzymes according to the manufacturer's recommendation (GIBCO BRL, Gaithersburg, MD). Enzymes are selected based on published reports as well as ongoing experience within the typing section. When needed, two enzymes are used for typing to ensure the presence or absence of clonality. DNA fragments are separated into patterns by running them through an agarose gel with constant field electrophoresis. Usual run times are 16 to 24 hours, and the resultant gels are then stained with a nucleic acid bonding fluorescent agent, SYBR Green I (Molecular Probes; Eugene, OR), and visualized with UV illumination. Gels are imaged with a photo documentation system, Gel Print 2000i (Biophotonics; Ann Arbor, MI). The gels are photographed so that the molecular weight marker extends 6 cm to 7 cm in the image (the portion of the gel used for analysis [18]). Similarities between the new and reference types are scored by visual comparison of each 1-mm segment of the top 60 mm of the DNA band pattern. A similarity index is calculated from the number of identical 1-mm segments expressed as a percentage of the total number of 1-mm segments measured. More than six differences in the 1-mm segments constitute a similarity index of <90% and call for designation of a new type. Types are designated by letters, and a distinct band pattern within a type (similarity index >90%, but <100%) is designated by subscript Arabic numbers, indicating a subtype (e.g., A_0, A_1, A_2). Subsequent organisms of the same genus and species are then compared with each main type or subtype to determine clonality. Organisms within the same type are considered related to each other for epidemiologic linkage.

Analysis of Cost Data

The hospital management engineering database was used to determine the total cost of inpatient care. Patient mix data were then used to determine the mean weighted cost per day for hospitalization within our center. The information used for cost calculations in this report is from 1999. The mean number of annual discharges was approximately 33,000 in 1995 to 39,000 in 1999, with an average of 36,444. We used the U.S. weighted mean of 4 days as the excess length of stay for a nosocomial infection in determining cost per patient (3). All other numbers in our calculations came directly from Northwestern Memorial Hospital data.

The resources needed for operating the molecular typing section were based on the cost of equipment, remodeling, reagent and other supplies, salaries and benefits for three technologists, plus all the institutional assessments (e.g., full-cost basis) required to operate a hospital laboratory. The nosocomial infection data in the two periods were analyzed by the Student *t* test (two-tailed distribution).

Results

The initial impetus to develop our more integrated approach to infection control was VRE's emergence as a serious nosocomial problem. Use of molecular typing in an ongoing analysis of vancomycin-resistant *Enterococcus faecium*, the most important species in this epidemic, revealed that our persisting problem had evolved into a pattern of numerous "mini" patient-to-patient outbreaks of distinct clones rather than the spread of a single persisting strain (19). By assessing the VRE problem, we found that genomic typing could readily separate possible episodes of nosocomial infection spread into groupings of those that were likely, possibly, and unlikely due to patient-to-patient transmission (20). We could best use the typing capability to determine the probability of high microbial clonality (more than 90% of outbreak strains clonal), indicating patient-to-patient transmission; the probability of moderate clonality, suggestive of a nosocomial outbreak (35% to 75% clonality); or the probability of clonality with little evidence of horizontal spread (<20% clonality). Using this information, we determined what intervention was likely to control an apparent outbreak (20).

With a fully operational in-house typing facility, we were also able to use this resource to manage other nosocomial infections. During the last 2 years of this study, 25 possible microbial outbreaks were investigated by the typing laboratory, including VRE, fluoroquinolone-resistant

P. aeruginosa, MRSA, *E. cloacae*, and *C. difficile*. A description of a few investigated episodes illustrates how we use the typing information.

Classic Spread of Nosocomial Infection

Nineteen isolates of vancomycin-resistant *E. faecalis* from 16 patients were detected in the microbiology laboratory in a 2-month period; isolates from 14 were from one of two clones (88%), indicating a high probability of nosocomial spread (14). Reviewing the origin of the culture requisitions in the microbiology laboratory did not indicate a possibility of close contact. However, an in-depth investigation found a direct connection between 11 of the 14 patients (14). Reinforcing infection control practices aborted the outbreak.

Moderate Likelihood of Spread of Nosocomial Infections

During a 1-month period, invasive infections caused by five isolates each of *Klebsiella pneumoniae*, *S. epidermidis*, and *S. hemolyticus* were detected in a special-care unit. DNA typing indicated 40% to 60% clonality for each of the bacterial species. This clustering was investigated, and patients with genetically identical organisms occupied adjacent beds. Erecting a barrier on the unit, along with educating medical staff, halted the spread of these infections (15).

Outbreaks not Caused by Patient-to-Patient Spread

Suspected outbreaks consisting of four isolates of *K. pneumoniae* and 64 strains of *Serratia marcescens* were investigated in the ICUs of two hospitals. Both investigations showed 21% clonality, indicating unlikely patient-to-patient spread. Investigation suggested suboptimal handling of ventilator equipment, and both outbreaks were stopped by retraining of personnel using this equipment (12,15).

Pseudooutbreaks

Possible outbreaks occurred in the special-care nursery units of two hospitals, each of which had its own molecular typing section. One possible outbreak consisted of seven *S. aureus* strains, and the other of four isolates of gram-negative bacilli. Both sets of isolates were immediately typed and no (20%) clonality existed. No interventions were instituted, and the apparent outbreaks were determined to be normal variation in infections (15,21). Because of the rapid typing, one hospital avoided culture-based surveillance investigation of staff by the state department of health, and the other avoided closing the unit for a 30-day full disinfection and cleaning (done in previous suspected outbreaks).

Impact of Program Enhancements on Nosocomial Infections and Health-Care Cost

After molecular typing was added to our hospital infection control program, nosocomial infections decreased, as measured by the infection rate per 1,000 patient days (Figure 1) and the proportion of patients with infections (Figure 2). The mean nosocomial infection rate fell from 6.49/1,000 patient days (standard deviation [SD] = ±0.66) in FY93-FY94 to 5.60/1,000 patient days (SD = ±0.74) in FY95-FY99 ($p = 0.002$). The percentage of patients with nosocomial infection dropped 23%, decreasing from 3.34% (SD = ±0.26) in the two preintervention years to 2.56% (SD = ±0.30) during the 5 years of our expanded program ($p = 0.000006$). The weighted cost of care per day in our hospital for FY95 was $1,650, and for FY99 it was $1,907. This increase was primarily due to steadily increasing severity of illness, largely from an increased volume of patients in our solid organ and bone marrow transplantation programs. The mean number of patients with nosocomial infections decreased by 283 per year, a reduction of more than 1,100 inpatient days. The costs

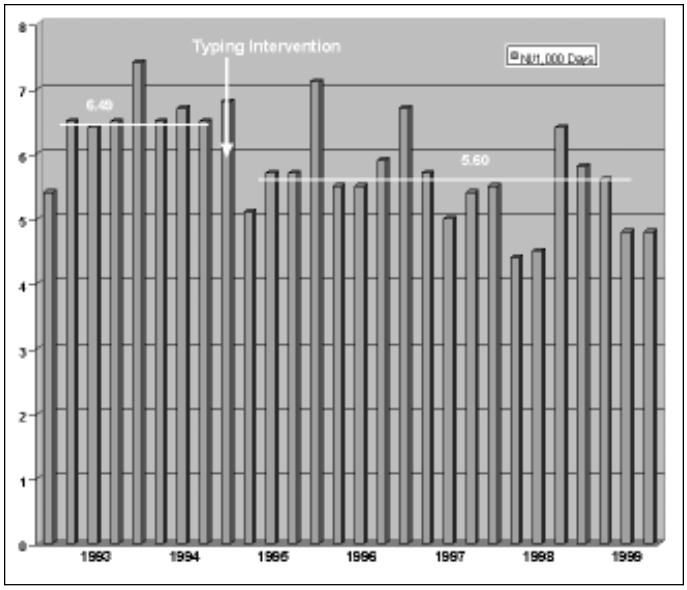

Figure 1. Impact of the availability of a molecular typing facility on overall nosocomial infections/1,000 patient days at Northwestern Memorial Hospital. The mean rate during FY93 to FY94 was 6.49, designated by a heavy horizontal bar. Throughout FY95 through FY99, the mean nosocomial infection rate was 5.60/1,000 patient days, represented by the second (lower) heavy horizontal bar.

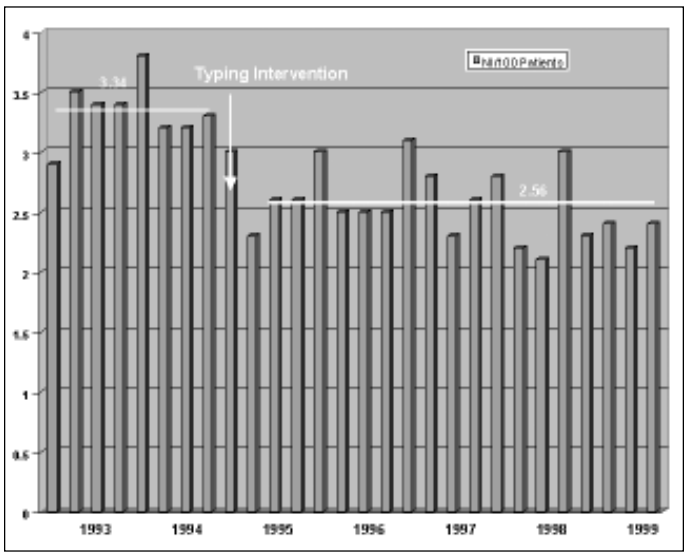

Figure 2. Impact of a molecular typing facility on percentage of patients with nosocomial infections at Northwestern Memorial Hospital. The mean rate during FY93 and FY94 was 3.34%, designated by a heavy horizontal bar. Throughout FY95 through FY99 the mean rate was 2.56%, represented by the second (lower) heavy horizontal bar.

avoided by using this calculation averaged more than $2,150,000/year, based on 1999 dollars.

The cost of this more integrated program was modest. Representatives from infection control, infectious diseases, pharmacy, and clinical microbiology now meet together for 45 minutes each week to assess health-care associated infection problems and determine what needs to be done. For microbiology, the equipment and remodeling cost for opening the typing laboratory totaled $180,050. By the fifth year, costs in the laboratory section were stable. The cost for the laboratory, including three medical technologists, is $400,000 yearly. Virtually all these costs are borne by the hospital.

Discussion

While we agree that new ways to assess infection control outcomes are needed (22), we chose two accepted measures and focused on our own hospital data that remained consistently assessed throughout the study. One measure was the nosocomial infection rate using 1,000 patient days as the denominator. This rate compensated for any reduced length of stay and increased number of admissions during the observation period. During this period, the mean hospital length of stay dropped from 6.1 to 4.1 days, admissions increased from 31,000 to 39,000, total hospital days decreased from 190,000 to slightly more than 164,000, and overall severity of illness increased. The mean hospital-acquired infection rate during the preintervention period was 6.49/1,000 patient days. In the first 2 years after the intervention, it had fallen to 5.79/1,000 patient days, and the overall 5-year intervention rate was 5.60/1,000 days, indicating the ability to maintain improved control of health-care associated infections over the long term. By contrast, the national average nosocomial infection rate per 1,000 patient days rose from 7.18 to 9.77 between 1975 and 1995, despite patient length of stay's falling from 7.9 to 5.3 days, and admissions declining from 37.7 million to 35.9 million (2). Our own rate has remained flat since our intervention period began, even though an increase (because our patients are more severely ill) might have been anticipated. This further suggests a continued positive outcome of the new integrated approach to our overall infection control program.

Our intrahospital comparison shows that before the enhanced approach was introduced, nosocomial infection developed in 3.3% of patients. In the 60 months after the practice change, health-care associated infections developed in 2.6% of admitted patients. More than 1,400 fewer patients acquired infections during this time, averting more than 50 expected deaths (23). Even with endemic vancomycin-resistant *E. faecium*, most of our outbreaks involve three or fewer patients (19).

While it is difficult to extrapolate beyond one's own medical center for an interhospital comparison (24), when our outcome is compared to what would be expected from the national average nosocomial infection rate of 4.4% to 5% of admitted patients in 1994 (23-25), and 1995 (2), the sustained rate reduction to <2.6% each year suggests that a predicted nosocomial infection was prevented in at least 2,600 patients during these 5 years at Northwestern Memorial Hospital as compared to the average 700-bed U.S. hospital.

Any of several molecular typing systems may be appropriate for determining microbial clonality, including restriction of genomic DNA with conventional electrophoresis (REA analysis), pulsed-field gel electrophoresis (PFGE), and rRNA gene probing (ribotyping). All methods are highly reproducible and have been applied to outbreaks. REA and PFGE have been shown equally effective for typing of VRE and *C. difficile* (20,26).

Typing of strains and assessment of clonality is usually available within 1 week of determining that an outbreak may exist and isolating suspected microbes. We have accomplished typing in as little as 48 hours. Identifying strains as clonal implies patient-to-patient spread and calls for enhanced infection control (barrier) precautions. Lack of clonality suggests other reasons for the apparent outbreak, such as antimicrobial-agent use pressure, failure of appropriate nursing-care practices, or simply random variation in the number of infections. Early knowledge of whether microbial clonality is present or absent focuses the scope of an investigation and facilitates appropriate intervention.

Even preventing asymptomatic colonization in health-care institutions is important since subsequent infection by virulent pathogens can have serious consequences (27). Our experience suggests that molecular typing technology can be very useful even when applied to a single medical center if it is part of a comprehensive infection control program.

Additional opportunities for use of molecular testing in detecting nosocomial multidrug-resistant pathogens will present themselves. Stosor et al. have demonstrated the capacity for rapid, sensitive detection of VRE contained in rectal swabs from colonized patients (28). These researchers reported that the cost of rapid detection using the polymerase chain reaction (PCR) was equal to one day of glove isolation, and that the PCR could be completed in a single 8-hour workday. As gene chip technology moves into clinical use, detecting a large number of resistance determinants soon after a patient is admitted to the hospital should be possible.

A microbiology laboratory fully equipped to cooperate in the management of nosocomial infections will also have the necessary infrastructure to act as a sentinel to detect new antimicrobial agent resistance, detect foodborne outbreaks of infection, and recognize and isolate pathogen(s) responsible for a bioterrorist attack. However, building such an infrastructure is not inexpensive and likely will not be undertaken by most hospitals when reimbursement for laboratory testing is declining. A system of incentives for hospitals to equip hospital-based microbiology laboratories with the needed tools is required. We suggest an approach that offers medical centers annual $300,000 to $500,000 federal grants to start a program of enhanced, comprehensive health-care infection control and prevention as described in this report. These grants could be administered through a federal program such as the Agency for Health-Care Research and Quality or the Centers for Disease Control and Prevention, and monitored by current laboratory credential agencies such as the College of American Pathologists or the Joint Commission on Accreditation of Health-Care Organizations. Rules for participation should be developed by professional societies with expertise in infection control and prevention. While such a grant program would cost up to $2 billion each year if all U.S. hospitals participated, the projected reduction in cost of treating nosocomial infections could reach over five times that amount. Monitoring compliance and outcome should be part of the annual grant renewal process. Such an approach is consistent with a recently released report delineating the federal response to

reducing medical errors (29). Our data strongly suggest such an investment will not only reduce illness and death but also avert the high costs of treating avoidable infections.

Nearly 15 years ago, Haley et al. estimated that a 30% reduction in nosocomial infection would result in $300,000 of actual savings for each 250 beds in a single institution (30). The data from our 700-bed medical center substantiate their estimate, and the annual cost reduction of approximately $2 million is comparable to the $825,000 they estimated for our size institution, based on the mid-1980s dollars and health-care costs. Several years ago Lupski suggested the potential power of molecular epidemiology in assessing hospital outbreaks of nosocomial infection (31). He indicated that to gain acceptance, molecular methods need to be easy to perform; provide rapid, reliable information; give additional data not otherwise readily obtainable; and be cost-effective. Our experience has been that a highly integrated infection control program including a molecular typing section fulfills these criteria. The program currently in place, incorporating microbial genetic typing, is within the recently recommended infrastructure guidelines for essential activities of infection control and epidemiology in hospitals (32). Broadening such an approach for managing nosocomial infections to most U.S. hospitals is technically possible, medically useful, and economically justified.

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Molecular Approaches to Diagnosing and Managing Infectious Diseases: Practicality and Costs

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As molecular techniques for identifying and detecting microorganisms in the clinical microbiology laboratory have become routine, questions about the cost of these techniques and their contribution to patient care need to be addressed. Molecular diagnosis is most appropriate for infectious agents that are difficult to detect, identify, or test for susceptibility in a timely fashion with conventional methods.

The tools of molecular biology have proven readily adaptable for use in the clinical diagnostic laboratory and promise to be extremely useful in diagnosis, therapy, and epidemiologic investigations and infection control (1,2). Although technical issues such as ease of performance, reproducibility, sensitivity, and specificity of molecular tests are important, cost and potential contribution to patient care are also of concern (3). Molecular methods may be an improvement over conventional microbiologic testing in many ways. Currently, their most practical and useful application is in detecting and identifying infectious agents for which routine growth-based culture and microscopy methods may not be adequate (4-7).

Nucleic acid-based tests used in diagnosing infectious diseases use standard methods for isolating nucleic acids from organisms and clinical material and restriction endonuclease enzymes, gel electrophoresis, and nucleic acid hybridization techniques to analyze DNA or RNA (6). Because the target DNA or RNA may be present in very small amounts in clinical specimens, various signal amplification and target amplification techniques have been used to detect infectious agents in clinical diagnostic laboratories (5,6). Although mainly a research tool, nucleic acid sequence analysis coupled with target amplification is clinically useful and helps detect and identify previously uncultivatable organisms and characterize antimicrobial resistance gene mutations, thus aiding both diagnosis and treatment of infectious diseases (5,8,9). Automation and high-density oligonucleotide probe arrays (DNA chips) also hold great promise for characterizing microbial pathogens (6).

Although most clinicians and microbiologists enthusiastically welcome the new molecular tests for diagnosing infectious disease, the high cost of these tests is of concern (3). Despite the probability that improved patient outcome and reduced cost of antimicrobial agents and length of hospital stay will outweigh the increased laboratory costs incurred through the use of molecular testing, such savings are difficult to document (3,10,11). Much of the justification for expenditures on molecular testing is speculative (11); however, the cost of equipment, reagents, and trained personnel is real and substantial, and reimbursement issues are problematic (3,11). Given these concerns, a facility's need for molecular diagnostic testing for infectious diseases should be examined critically by the affected clinical and laboratory services. In many instances, careful overseeing of test ordering and prudent use of a reference laboratory may be the most viable options.

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Practical Applications of Molecular Methods in the Clinical Microbiology Laboratory

Commercial kits for the molecular detection and identification of infectious pathogens have provided a degree of standardization and ease of use that has facilitated the introduction of molecular diagnostics into the clinical microbiology laboratory (Table 1). The use of nucleic acid probes for identifying cultured organisms and for direct detection of organisms in clinical material was the first exposure that most laboratories had to commercially available molecular tests. Although these probe tests are still widely used, amplification-based methods are increasingly employed for diagnosis, identification and quantitation of pathogens, and characterization of antimicrobial-drug resistance genes. Commercial amplification kits are available for some pathogens (Table 1), but some clinically important pathogens require investigator-designed or "home-brew" methods (Table 2). In addition, molecular strain typing, or genotyping, has proven useful in guiding therapeutic decisions for certain viral pathogens and for epidemiologic investigation and infection control (2,12).

Detection and Identification of Pathogens Without Target Amplification

Commercial kits containing non-isotopically labeled nucleic acid probes are available for direct detection of pathogens in clinical material and identification of organisms after isolation in culture (Table 1). Use of solution-phase hybridization has allowed tests to be performed singly or in batches in a familiar microwell format.

Although direct detection of organisms in clinical specimens by nucleic acid probes is rapid and simple, it suffers from lack of sensitivity. Most direct probe detection assays require at least 10^4 copies of nucleic acid per microliter for reliable detection, a requirement rarely met in clinical

Table 1. FDA-approved molecular diagnostic tests for infectious disease[a]

Test	Method	Company[b]
Chlamydia trachomatis detection	PCR[c]	Roche
	LCR	Abbott
	TMA	Gen-Probe
	Hybrid capture	Digene
Neisseria gonorrhoeae detection	LCR	Abbott
	Hybrid capture	Digene
C. trachomatis/ *N. gonorrhoeae* screening/detection	Hybridization	Gen-Probe
	SDR	Becton-Dickinson
Mycobacterium tuberculosis detection	PCR	Roche
	TMA	Gen-Probe
HPV screening	Hybrid capture	Digene
CMV	Hybrid capture	Digene
	NASBA	Organon Teknika
Group A strep detection	Hybridization	Gen-Probe
HIV quantitation	PCR	Roche
Gardnerella, Trichomonas vaginalis, and *Candida*	Hybridization	Becton-Dickinson
Culture confirmation for bacteria and fungi	Hybridization	Gen-Probe

LCR = ligase chain reaction; TMA = transcription-mediated amplification; SDR = strand displacement reaction; NASBA = nucleic acid strand-based amplification.
[a]The table contains examples of commercially available methods and is not intended to be all-inclusive. Websites of the principle manufacturers are a useful source of the most up-to-date information.
[b]Companies: Digene, Silver Spring, MD; Chiron, Emeryville, CA; Roche, Branchburg, NJ; Organon Teknika, Durham, NC; Murex/ Abbott, Abbott Park, IL; Gen-Probe, San Diego, CA; Abbott, Abbott Park, IL; Becton-Dickinson, Cockeysville, MD.
[c]PCR = polymerase chain reaction.

Table 2. Noncommercial nucleic acid-based tests for clinically important viral and bacterial pathogens[a]

Organism	Specimen type	Clinical indication
Epstein-Barr virus (EBV)	Cerebrospinal fluid (CSF)	EBV lymphoproliferative disorder
Herpes simplex virus (HSV) types 1 and 2	CSF	Encephalitis
	Vitreous humor	
Varicella-zoster virus virus (VZV)	Various tissues	VZV reactivation
JCV	CSF	Progressive multifocal leukoencephalopathy
Enterovirus	CSF	Aseptic meningitis
Parvovirus B19	Amniotic fluid	Hydrops fetalis
	Serum	Anemia
Adenovirus	Urine	Immunocompromised patients, transplant recipients
	Tissues	
	Blood	
Ehrlichia	Blood	Human granulocytic and monocytic ehrlichiosis
Bordetella pertussis	Nasopharyngeal aspirate	Whooping cough
Legionella pneumophila	Respiratory	Atypical pneumonia
Chlamydia pneumoniae	Respiratory	Atypical pneumonia
Mycoplasma pneumoniae	Respiratory	Atypical pneumonia
Helicobacter pylori	Gastric fluid	Peptic ulcer disease
	Stool	

[a]All tests use polymerase chain reaction. The list is not all-inclusive.

samples without some form of amplification. Amplification of the detection signal after probe hybridization improves sensitivity to as low as 500 gene copies per microliter and provides quantitative capabilities. This approach has been used extensively for quantitative assays of viral load (HIV, hepatitis B virus [HBV] and hepatitis C virus [HCV]) (Table 1) but does not match the analytical sensitivity of target amplification-based methods, such as polymerase chain reaction (PCR), for detecting organisms.

The commercial probe systems that use solution-phase hybridization and chemiluminescence for direct detection of infectious agents in clinical material include the PACE2 products of Gen-Probe and the hybrid capture assay systems of Digene and Murex (Table 1). These systems are user friendly, have a long shelf life, and are adaptable to small or large numbers of specimens. The PACE2 products are designed for direct detection of both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in a single specimen (one specimen, two separate probes). The hybrid capture systems detect human papillomavirus (HPV) in cervical scrapings, herpes simplex virus (HSV) in vesicle material, and cytomegalovirus (CMV) in blood and other fluids. All these tests have demonstrated sensitivity exceeding that of culture or immunologic methods for detecting the respective pathogens but are less sensitive than PCR or other target amplification-based methods.

The signal amplification-based probe methods for detection and quantitation of viruses (HBV, HCV, HIV) are presented in an enzyme immunoassay-like format and include branched chain DNA probes (Chiron) and QB replicase (Gene-Trak) methods (Table 1). These methods are not as sensitive as target amplification-based methods for detection of viruses; however, the quantitative results have proven useful for determining viral load and prognosis and for monitoring response to therapy (13).

Probe hybridization is useful for identifying slow-growing organisms after isolation in culture using either liquid or solid media. Identification of mycobacteria and other slow-growing organisms such as the dimorphic fungi (*Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis*) has certainly been facilitated by commercially available probes. All commercial probes for identifying organisms are produced by Gen-Probe and use acridinium ester-labeled probes directed at species-specific rRNA sequences (Table 1). Gen-Probe products are available for the culture identification of *Mycobacterium tuberculosis, M. avium-intracellulare* complex, *M. gordonae, M. kansasii, Cryptococcus neoformans*, the dimorphic fungi (listed above), *N. gonorrhoeae, Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae, Enterococcus* spp., *S. agalactiae*, and *Listeria monocytogenes*. The sensitivity and specificity of these probes are excellent, and they provide species identification within one working day. Because most of the bacteria listed, plus *C. neoformans*, can be easily and efficiently identified by conventional methods within 1 to 2 days, many of these probes have not been widely used. The mycobacterial probes, on the other hand, are accepted as mainstays for the identification of *M. tuberculosis* and related species (7).

Nucleic Acid Amplification

Nucleic acid amplification provides the ability to selectively amplify specific targets present in low concentrations to detectable levels; thus, amplification-based methods offer superior performance, in terms of sensitivity, over the direct (non-amplified) probe-based tests. PCR (Roche Molecular Systems, Branchburg, NJ) was the first such technique to be developed and because of its flexibility and ease of performance remains the most widely used molecular diagnostic technique in both research and clinical laboratories. Several different amplification-based strategies have been developed and are available commercially (Table 1). Commercial amplification-based molecular diagnostic systems for infectious diseases have focused largely on systems for detecting *N. gonorrhoeae*, *C. trachomatis*, *M. tuberculosis*, and specific viral infections (HBV, HCV, HIV, CMV, and enterovirus) (Table 1). Given the adaptability of PCR, numerous additional infectious pathogens have been detected by investigator-developed or home-brew PCR assays (5) (Table 2). In many instances, such tests provide important and clinically relevant information that would otherwise be unavailable since commercial interests have been slow to expand the line of products available to clinical laboratories. In addition to qualitative detection of viruses, quantitation of viral load in clinical specimens is now recognized to be of great importance for the diagnosis, prognosis, and therapeutic monitoring for HCV, HIV, HBV, and CMV (13). Both PCR and nucleic acid strand-based amplification systems are available for quantitation of one or more viruses (Table 1).

The adaptation of amplification-based test methods to commercially available kits has served to optimize user acceptability, prevent contamination, standardize reagents and testing conditions, and make automation a possibility. It is not clear to what extent the levels of detection achievable by the different amplification strategies differ. None of the newer methods provides a level of sensitivity greater than that of PCR. In choosing a molecular diagnostic system, one should consider the range of tests available, suitability of the method to workflow, and cost (6). Choosing one amplification-based method that provides testing capabilities for several pathogens is certainly practical.

Amplification-based methods are also valuable for identifying cultured and uncultivatable organisms (5). Amplification reactions may be designed to rapidly identify an acid-fast organism as *M. tuberculosis* or may amplify a genus-specific or "universal" target, which then is characterized by using restriction endonuclease digestion, hybridization with multiple probes, or sequence determination to provide species or even subspecies delineation (4,5,14). Although identification was initially applied to slow-growing mycobacteria, it has applications for other pathogens that are difficult or impossible to identify with conventional methods.

Detecting Antimicrobial-Drug Resistance

Molecular methods can rapidly detect antimicrobial-drug resistance in clinical settings and have substantially contributed to our understanding of the spread and genetics of resistance (9). Conventional broth- and agar-based antimicrobial susceptibility testing methods provide a phenotypic profile of the response of a given microbe to an array of agents. Although useful for selecting potentially useful therapeutic agents, conventional methods are slow and fraught with problems. The most common failing is in the detection of methicillin resistance in staphylococci, which may be expressed in a very heterogeneous fashion, making phenotypic characterization of resistance difficult (9,15). Currently, molecular detection of the resistance gene, *mec A*, is the standard against which phenotypic methods for detection of methicillin resistance are judged (9,15,16).

Molecular methods may be used to detect specific antimicrobial-drug resistance genes (resistance genotyping) in many organisms (Table 3) (8,9). Detection of specific point mutations associated with resistance to antiviral agents is also increasingly important (17,18). Screening for mutations in an amplified product may be facilitated by the use of high-density probe arrays (Gene chips) (6).

Despite its many potential advantages, genotyping will not likely replace phenotypic methods for detecting antimicrobial-drug resistance in the clinical laboratory in the near future. Molecular methods for resistance detection may be applied directly to the clinical specimen, providing simultaneous detection and identification of the pathogen plus resistance characterization (9). Likewise, they are useful in detecting resistance in viruses, slow-growing or nonviable organisms, or organisms with resistance mechanisms that are not reliably detected by phenotypic methods (9,19). However, because of their high specificity, molecular methods will not detect newly emerging resistance mechanisms and are unlikely to be useful in detecting resistance genes in species where the gene has not been observed previously (19). Furthermore, the presence of a resistance gene does not mean that the gene will be expressed, and the absence of a known resistance gene does not exclude the possibility of resistance from another mechanism. Phenotypic antimicrobial susceptibility testing methods allow laboratories to test many organisms and detect newly emerging as well as established resistance patterns.

Molecular Epidemiology

Laboratory characterization of microbial pathogens as biologically or genetically related is frequently useful in investigations (12,20,21). Several different epidemiologic typing methods have been applied in studies of microbial pathogens (Table 4). The phenotypic methods have occasionally been useful in describing the epidemiology of infectious diseases; however, they are too variable, slow, and labor-intensive to be of much use in most epidemiologic investigations. Newer DNA-based typing methods have eliminated most of these limitations and are now the preferred techniques for epidemiologic typing. The most widely used molecular typing methods include plasmid profiling, restriction endonuclease analysis of plasmid and genomic DNA, Southern hybridization analysis using specific DNA probes, and chromosomal DNA profiling using either pulsed-field gel electrophoresis (PFGE) or PCR-based methods (12,20). All these methods use electric fields to separate DNA fragments, whole chromosomes, or plasmids into unique patterns or fingerprints that are visualized by staining with ethidium bromide or by nucleic acid probe hybridization (Figure 1). Molecular typing is performed to determine whether different isolates give the same or different results for one or more tests. Epidemiologically related isolates share the same DNA profile or fingerprint, whereas sporadic or epidemiologically unrelated isolates have distinctly different patterns (Figure). If isolates from different patients share the same fingerprint, they probably

Table 3. Molecular methods for detecting antimicrobial resistance[a]

Organism(s)	Antimicrobial agent(s)	Gene	Detection method
Staphylococci	Methicillin Oxacillin	*mec A*[b]	Standard DNA probe Branched chain DNA probe PCR
Enterococci	Vancomycin	*van A, B, C, D*[c]	Standard DNA probe PCR
Enterobacteriaceae *Haemophilus influenzae* *Neisseria gonorrhoeae*	Beta-lactams	bla_{TEM} and bla_{SHV}[d]	Standard probe PCR and RFLP PCR and sequencing
Enterobacteriaceae and gram-positive cocci	Quinolones	Point mutations in *gyr A, gyr B, par C* and *par E*	PCR and sequencing
Mycobacterium tuberculosis[e]	Rifampin	Point mutations in *rpo* B	PCR and SSCP PCR and sequencing
	Isoniazid	Point mutations in *kat G, inh A,* and *ahp C*	PCR and SSCP
	Ethambutol	Point mutations in *emb B*	PCR and sequencing
	Streptomycin	Point mutations in *rps L* and *rrs*	PCR and RFLP
Herpes viruses[f]	Acyclovir and related drugs	Mutations or deletions in the TK gene	PCR and sequencing
	Foscarnet	Point mutations in DNA polymerase gene	PCR and sequencing
HIV[g]	Nucleoside reverse transcriptase inhibitors	Point mutations in RT gene	PCR and sequencing PCR and LIPA
	Protease inhibitors	Point mutations in PROT gene	PCR and sequencing

[a]Adapted from Pfaller (2).
[b]*mecA* encodes for the altered penicillin binding protein PBP2a'; phenotypic methods may require 48 hours incubation or more to detect resistance and are less than 100% sensitive. Detection of *mecA* has potential for clinical application in specific circumstances.
[c]Vancomycin resistance in enterococci may be related to one of four distinct resistance genotypes of which *vanA* and *vanB* are most important. Genotypic detection of resistance is useful in validation of phenotypic methods.
[d]The genetic basis of resistance to beta-lactam antibiotics is extremely complex. The bla_{TEM} and bla_{SHV} genes are the two most common sets of plasmid encoded beta-lactamases. The presence of either a bla_{TEM} or bla_{SHV} gene implies ampicillin resistance. Variants of the bla_{TEM} and bla_{SHV} genes (extended spectrum beta-lactamases) may also encode for resistance to a range of third-generation cephalosporins and to monobactams.
[e]*M. tuberculosis* is very slow growing. Four weeks or more may be required to obtain phenotypic susceptibility test results. Detection of resistance genes in *M. tuberculosis* has potential for clinical application in the short term.
[f]There are no phenotypic methods sufficiently practical for routine clinical detection of resistance to antiviral agents. Genotypic methods represent a practical method for routine detection of antiviral resistance.
[g]Abbreviations not defined in text: RFLP, restriction fragment length polymorphism; SSCP, single-stranded conformational polymorphism; LIPA, line probe assay; TK, thymidine kinase; RT, reverse transcriptase; PROT, protease.

Table 4. Genotypic methods for epidemiologic typing of microorganisms[a,b]

Method	Examples	Comments
Plasmid analysis	Staphylococci Enterobacteriaceae	Plasmids may be digested with restriction endonucleases Only useful when organisms carry plasmids
Restriction endonuclease analysis of chromosomal DNA with conventional electrophoresis	Enterococci *Staphylococcus aureus* *Clostridium difficile* *Candida* spp.	Large number of bands Difficult to interpret Not amenable to computer analysis
PFGE	Enterobacteriaceae Staphylococci Enterococci *Candida* spp.	Fewer bands Amenable to computer analysis Very broad application
Genome restriction fragment length polymorphism analysis: ribotyping, insertion sequence probe fingerprinting	Enterobacteriaceae Staphylococci *Pseudomonas aeruginosa* *Mycobacterium tuberculosis* *Candida* spp.	Fewer bands Computer analysis Sequence-based profiles Automated
PCR-based methods: repetitive elements PCR spacer typing, selective amplification of genome restriction fragments, multilocus allelic sequence-based typing	Enterobacteriaceae *Acinetobacter* spp. Staphylococci *M. tuberculosis* HCV	Crude extracts and small amounts of DNA may suffice
Library probe genotypic hybridization schemes: multilocus probe dot-blot patterns, high-density oligonucleotide patterns	*Burkholderia cepacia* *S. aureus* *M. tuberculosis*	Unambiguous yes-no result Less discrimination than other methods Couple with DNA chip technology

[a]The table contains examples of available methods and applications and is not intended to be all-inclusive.
[b]Adapted from Pfaller (2).

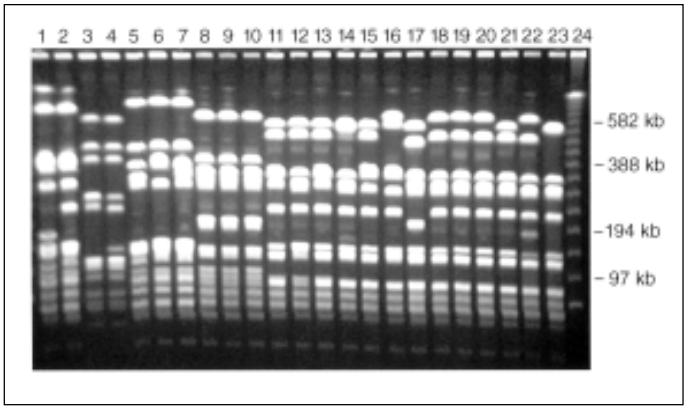

Figure. Pulsed-field gel electrophoresis (PFGE) profiles of *Staphylococcus aureus* isolates digested with Sma 1. A variety of PFGE profiles are demonstrated in these 23 isolates.

originated from the same clone and were transmitted from patient to patient by a common source or mechanism.

Molecular typing methods have allowed investigators to study the relationship between colonizing and infecting isolates in individual patients, distinguish contaminating from infecting strains, document nosocomial transmission in hospitalized patients, evaluate reinfection versus relapse in patients being treated for an infection, and follow the spread of antimicrobial-drug resistant strains within and between hospitals over time (12). Most available DNA-based typing methods may be used in studying nosocomial infections when applied in the context of a careful epidemiologic investigation (12,21). In contrast, even the most powerful and sophisticated typing method, if used indiscriminately in the absence of sound epidemiologic data, may provide conflicting and confusing information.

Financial Considerations

Molecular testing for infectious diseases includes testing for the host's predisposition to disease, screening for infected or colonized persons, diagnosis of clinically important infections, and monitoring the course of infection or the spread of a specific pathogen in a given population. It is often assumed that in addition to improved patient care, major financial benefits may accrue from molecular testing because the tests reduce the use of less sensitive and specific tests, unnecessary diagnostic procedures and therapies, and nosocomial infections (11). However, the inherent costs of molecular testing methods, coupled with variable and inadequate reimbursement by third-party payers and managed-care organizations, have limited the introduction of these tests into the clinical diagnostic laboratory.

Not all molecular diagnostic tests are extremely expensive. Direct costs vary widely, depending on the test's complexity and sophistication. Inexpensive molecular tests are generally kit based and use methods that require little instrumentation or technologist experience. DNA probe methods that detect *C. trachomatis* or *N. gonorrhoeae* are examples of low-cost molecular tests. The more complex molecular tests, such as resistance genotyping, often have high labor costs because they require experienced, well-trained technologists. Although the more sophisticated tests may require expensive equipment (e.g., DNA sequencer) and reagents, advances in automation and the production of less-expensive reagents promise to decrease these costs as well as technician time. Major obstacles to establishing a molecular diagnostics laboratory that are often not considered until late in the process are required licenses, existing and pending patents, test selection, and billing and reimbursement (22).

Reimbursement issues are a major source of confusion, frustration, and inconsistency. Reimbursement by third-party payers is confounded by lack of Food and Drug Administration (FDA) approval and Current Procedural Terminology (CPT) codes for many molecular tests. In general, molecular tests for infectious diseases have been more readily accepted for reimbursement; however, reimbursement is often on a case-by-case basis and may be slow and cumbersome. FDA approval of a test improves the likelihood that it will be reimbursed but does not ensure that the amount reimbursed will equal the cost of performing the test.

Perhaps more than other laboratory tests, molecular tests may be negatively affected by fee-for-service managed-care contracts and across-the-board discounting of laboratory test fees. Such measures often result in reimbursement that is lower than the cost of providing the test. Although molecular tests may be considered a means of promoting patient wellness, the financial benefits of patient wellness are not easily realized in the short term (11). Health maintenance organizations (HMOs) and managed-care organizations often appear to be operating on shorter time frames, and their administrators may not be interested in the long-term impact of diagnostic testing strategies.

Molecular screening programs for infectious diseases are developed to detect symptomatic and asymptomatic disease in individuals and groups. Persons at high risk, such as immunocompromised patients or those attending family planning or obstetrical clinics, are screened for CMV and *Chlamydia*, respectively. Likewise, all blood donors are screened for bloodborne pathogens. The financial outcome of such testing is unknown. The cost must be balanced against the benefits of earlier diagnosis and treatment and societal issues such as disease epidemiology and population management.

One of the most highly touted benefits of molecular testing for infectious diseases is the promise of earlier detection of certain pathogens. The rapid detection of *M. tuberculosis* directly in clinical specimens by PCR or other amplification-based methods is quite likely to be cost-effective in the management of tuberculosis (7). Other examples of infectious disease that are amenable to molecular diagnosis and for which management can be improved by this technology include HSV encephalitis, *Helicobacter pylori* infection, and neuroborreliosis caused by *Borrelia burgdorferi*. For HSV encephalitis, detection of HSV in cerebrospinal fluid (CSF) can direct specific therapy and eliminate other tests including brain biopsy. Likewise, detection of *H. pylori* in gastric fluid can direct therapy and obviate the need for endoscopy and biopsy. PCR detection of *B. burgdorferi* in CSF is helpful in differentiating neuroborreliosis from other chronic neurologic conditions and chronic fatigue syndrome.

As discussed earlier, molecular tests may be used to predict disease response to specific antimicrobial therapy. Detection of specific resistance genes (*mec A, van A*) or point mutations resulting in resistance has proven efficacious in managing disease. Molecular-based viral load testing has

become standard practice for patients with chronic hepatitis and AIDS. Viral load testing and genotyping of HCV are useful in determining the use of expensive therapy such as interferon and can be used to justify decisions on extent and duration of therapy. With AIDS, viral load determinations plus resistance genotyping have been used to select among the various protease inhibitor drugs available for treatment, improving patient response and decreasing incidence of opportunistic infections.

Pharmacogenomics is the use of molecular-based tests to predict the response to specific therapies and to monitor the response of the disease to the agents administered. The best examples of pharmacogenomics in infectious diseases are the use of viral load and resistance genotyping to select and monitor antiviral therapy of AIDS and chronic hepatitis (17,18). This application improves disease outcome; shortens length of hospital stay; reduces adverse events and toxicity; and facilitates cost-effective therapy by avoiding unnecessary expensive drugs, optimizing doses and timing, and eliminating ineffective drugs.

Molecular strain typing of microorganisms is now well recognized as an essential component of a comprehensive infection control program that also involves the infection control department, the infectious disease division, and pharmacy (10, 21). Molecular techniques for establishing presence or absence of clonality are effective in tracking the spread of nosocomial infections and streamlining the activities of the infection control program (21,23). A comprehensive infection control program uses active surveillance by both infection control practitioners and the clinical microbiology laboratory to identify clusters of infections with a common microbial phenotype (same species and antimicrobial susceptibility profile). The isolates are then characterized in the laboratory by using one of a number of molecular typing methods (Table 4) to confirm or refute clonality. Based on available epidemiologic and molecular data, the hospital epidemiologist then develops an intervention strategy. Molecular typing can shorten or prevent an epidemic (23) and reduce the number and cost of nosocomial infections (Table 5) (10). Hacek et al. (10) analyzed the medical and economic benefits of an infection control program that included routine determination of microbial clonality and found that nosocomial infections were significantly decreased and more than $4 million was saved over a 2-year period (Table 5).

The true financial impact of molecular testing will only be realized when testing procedures are integrated into total disease assessment. More expensive testing procedures may be justified if they reduce the use of less sensitive and less specific tests and eliminate unnecessary diagnostic procedures and ineffective therapies.

Table 5. Reduction in number and cost of nosocomial infections through collaborative efforts of infection control, clinical microbiology, and molecular typing laboratories[a]

Time	Nosocomial infection rate (%)[b]	Reduction in total infections (no.)		Reduction in cost (million $)	
		94 vs. 95	94 vs. 96	94 vs. 95	94 vs. 96
FY 1993	3.3				
FY 1994	3.4				
FY 1995	2.6	301		1.8	
FY 1996	2.6		344		2.6

[a]Adapted from Hacek et al. (10).
[b]Percentage of patients with nosocomial infections.

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Building Communication Networks: International Network for the Study and Prevention of Emerging Antimicrobial Resistance

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The global nature of antimicrobial resistance and the failure to control the emergence of resistant organisms demand the implementation of a global surveillance program involving both developed and developing countries. Because of the urgent need for infection control interventions and for rapid distribution of information about emerging organisms, we initiated the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR). Its main objectives are to serve as an early warning system for emerging antimicrobial-drug resistant pathogens, to facilitate rapid distribution of information about emerging multidrug-resistant pathogens to hospitals and public health authorities worldwide, and to serve as a model for the development and implementation of infection control interventions.

The emergence of resistance to antimicrobial agents is becoming a major public health problem worldwide, especially in hospital-acquired infections. Infectious diseases experts are particularly concerned because organisms resistant to available antimicrobial drugs have been isolated in hospitals worldwide. The extent of antimicrobial-drug resistance in developing countries, where inappropriate antimicrobial usage may be more common, is unknown (1-6). The emergence and spread of these multidrug-resistant pathogens demonstrate that the medical community (including laboratories) may have difficulty isolating and identifying these organisms and that infection control interventions are either not implemented, ineffective, or implemented so late that the organism(s) has become endemic; in these circumstances, infection control strategies are not effective, and transmission continues (7,8).

The emergence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vividly demonstrates this failure in infection control. MRSA emerged in Europe nearly 35 years ago concomitantly with the introduction of methicillin; subsequently, during the mid-1980s, epidemic strains spread in hospitals throughout the world. In many hospitals, few, if any, infection control precautions were implemented until recently, by which time these strains had become endemic, with infection rates approaching one per 100 admissions (9-12). The large reservoir of MRSA-colonized or -infected patients at these hospitals complicates infection control interventions.

Epidemiologic studies on antimicrobial resistance have alerted the medical and public health communities about the importance of emergence of antimicrobial resistance. However, most data on antimicrobial-resistant pathogens were collected as part of studies sponsored by the pharmaceutical industry, and most of the studies were methodologically flawed; thus, the data were not useful for generalizations about antimicrobial resistance in hospitals. In addition, in many countries, a close interrelationship does not exist between the laboratory identifying multidrug-resistant pathogens and the infection control personnel responsible for the prevention and control of transmission of such isolates. Furthermore, many laboratory-based surveillance systems are designed for making patient treatment decisions; the data are not organized in a way that can be used to design and implement control and prevention interventions.

With the development of the Emerging Infections Plan at the Centers for Disease Control and Prevention (CDC) and the endorsement and adaptation of this plan by the World Health Organization (WHO), the emergence of antimicrobial resistance has become a public health priority (13,14). Public health authorities in the United States and Europe realize that the emergence of antimicrobial-drug resistance is a global problem; no country is spared, and resistant organisms emerging in one country are likely to spread to other countries. With increasing travel and patient movement throughout the world, the situation exists for transmission of multidrug-resistant pathogens from one country or continent to another (15-19).

Because of the urgent need for infection control interventions to prevent further emergence of antimicrobial drug-resistant strains and for a rapid distribution of information about emerging organisms, we initiated the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR). The main objectives of INSPEAR are to serve as an early warning system for emerging resistant pathogens, to facilitate rapid distribution of information about emerging multidrug-resistant pathogens to hospitals and public health authorities

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worldwide, and to serve as a model for the development and implementation of infection control interventions to prevent the emergence or transmission of antimicrobial drug-resistant pathogens in health-care facilities. Another important function of INSPEAR is to assist microbiologists and infection control personnel in hospitals and countries that lack the expertise needed to conduct microbiologic or epidemiologic studies.

Background

INSPEAR was begun as a collaborative effort between the Hospital Infections Program (CDC) and microbiologists and hospital epidemiologists in the United States and Europe. It is now a consortium of clinical microbiologists, hospital epidemiologists, infectious diseases specialists; experts in the fields of antimicrobial resistance, hospital epidemiology, and computer sciences; public health agencies; and national reference laboratories. One hundred sixty health-care facilities in 40 countries have joined INSPEAR, with 50% of participants in Western Europe and 29% in Eastern Europe.

Recent Activities

Since its initiation in 1998, INSPEAR has conducted several activities essential to the implementation of the early warning system, such as the assessment of the way INSPEAR centers diagnose, conduct surveillance, and control infections caused by multidrug-resistant pathogens, as well as proficiency testing to ensure quality testing in laboratories participating in the program.

An assessment of MRSA infections, performed in 90 centers, was designed to assess the methods used by bacteriology laboratories to identify *S. aureus,* to determine the susceptibility of *S. aureus* to antimicrobial drugs, and to assess the surveillance and infection control programs in INSPEAR centers. This study revealed many deficiencies: Isolation of vancomycin- and teicoplanin-resistant *S. aureus* was reported by three centers but was not confirmed, and public health authorities were not alerted. Of the laboratories surveyed, 11% used oxacillin disks with antimicrobial content different from that recommended by the National Committee for Clinical Laboratory Standards or the Comité de L'Antibiogramme de la Société Française de Microbiologie; 20% did not have an internal quality control program; 36% did not participate in external quality control programs; and 14% did not determine MRSA susceptibility to vancomycin. Of the health-care facilities surveyed, 77% reported surveillance activities; however, only 36.5% determined the incidence rate per admission, and only 23% determined the rate per patient-days; 40% of the facilities did not have an MRSA control program; and 54% did not monitor or control the use of antimicrobial drugs. These data clearly demonstrate the urgent need to strengthen the laboratory and epidemiologic capacities of INSPEAR centers.

A proficiency testing study was performed to investigate the ability of INSPEAR centers to detect clinically important resistance phenotypes, to assist centers in establishing reliable methods to detect particular resistances, to validate data from hospital laboratories participating in INSPEAR, and to ensure consistent quality testing in INSPEAR clinical laboratories. Five strains were sent to the 116 participating laboratories: MRSA, hyper-beta-lactamase producing strain of *S. aureus*, glycopeptide-intermediate *Staphylococcus epidermidis*, and *van A* and *van B Enterococcus faecalis.* Seventy-six laboratories responded. Most laboratories did well with both *S. aureus* challenges; however, 60 (79%) had difficulty detecting reduced susceptibility to glycopeptides in staphylococci. All laboratories testing *van A E. faecalis* identified it correctly as vancomycin resistant, but the results for *van B E. faecalis* varied. Thirty-nine (52%) of 75 laboratories reported susceptible results for vancomycin, but 19% misidentified *van B E. faecalis* as vancomycin resistant. An assessment is being conducted to determine if participants have modified their testing methods based on the results of the proficiency testing and CDC recommendations.

Early Warning System

Another reason antimicrobial resistance is uncontrolled is that clinical microbiology laboratories and the medical community often are not aware of emerging resistance and therefore are not prepared. Preparedness implies that potentially emerging events be known, that laboratorians have the capacity to detect emerging resistance and screen rapidly for colonization, that risk factors for emergence be assessed, and that health-care facilities have access to microbiologic and epidemiologic assistance and have the capacities for efficient isolation precautions (e.g., private rooms with handwashing facilities, availability of gloves). Therefore, to coordinate the timely international scientific and public health response to emerging antimicrobial resistance, we designed an early warning system to monitor, analyze, control, and prevent important events in the emergence of antimicrobial resistance at both the global and regional or local levels. Overall, this early warning system should trigger early epidemiologic and microbiologic interventions to assess risk factors for emerging antimicrobial resistance, leading to more effective control.

Global Sentinel Events

The need to be aware of global sentinel events is leading to an important function of the program: the periodic publication of what INSPEAR members determine by consensus to be important types of antimicrobial resistance heretofore undescribed or of great public health importance (Table 1). Criteria used to arrive at this list included the overall ease of use of the list by most clinical and reference

Table 1. Early warning system: global sentinel events

Microorganism	Resistance
Streptococcus spp.	Penicillinase, gentamicin, glycopeptides, fluoroquinolones
S. pneumoniae	Vancomycin, third-generation cephalosporins, new fluoroquinolones (gemifloxacine, grepafloxacin, levofloxacin, trovafloxacin)
Staphylococcus spp.	Glycopeptides (high level)
Enterobacteriaceae	Carbapenemase
Neisseria meningitidis	Penicillinase, chloramphenicol, cephalosporins, fluoroquinolones
Acinetobacter baumannii	Carbapenemase
Salmonella typhi	Third-generation cephalosporins, fluoroquinolones
Haemophilus influenzae	Cephalosporins
Brucella spp.	Tetracycline, rifampin, streptomycin
Clostridium difficile	Glycopeptides
Clostridium perfringens	Penicillinase

laboratories and the actual and potential public health impact of resistance events based on factors such as pathogen virulence, frequency of infection caused by the pathogen, and absence of other licensed antimicrobial agents for treating infections caused by the pathogen. This list of events will be updated regularly and will be published and disseminated to national and international surveillance systems.

Local and Regional Sentinel Events

Local and regional sentinel events consist of the first observation of a clinically important form of resistance in a particular locality or region. Such resistant phenotypes may already be well described from other localities or regions of the world (Table 2). The new regional emergence of resistance in an INSPEAR facility may warrant a coordinated response from local or international INSPEAR members to prevent the resistant strains from becoming endemic.

Table 2. Early warning system: local and regional sentinel events

Microorganism	Resistance
Staphylococcus aureus	Methicillin, intermediate susceptibility to glycopeptides
Enterococcus spp.	Vancomycin
Enterobacteriaceae	Extended-spectrum beta-lactamase-mediated resistance, carbapenems, fluoroquinolones
Acinetobacter baumannii	Carbapenem
Any bacteria	All antimicrobials available at the regional and local settings

Functioning of the Early Warning System

The early warning system should function according to subsidiarity, defined as the principle that a central authority should have a subsidiary function, performing only tasks that cannot be performed effectively at a more immediate or local level. When an emerging event is suspected at an INSPEAR center, the national or regional coordinator should be alerted and microbiologic confirmation performed at the local, national, or regional level when possible, or with additional INSPEAR resources (Figure). Once an event is confirmed, the INSPEAR coordinator will be informed and the public health authorities, WHO, and the INSPEAR centers will be notified.

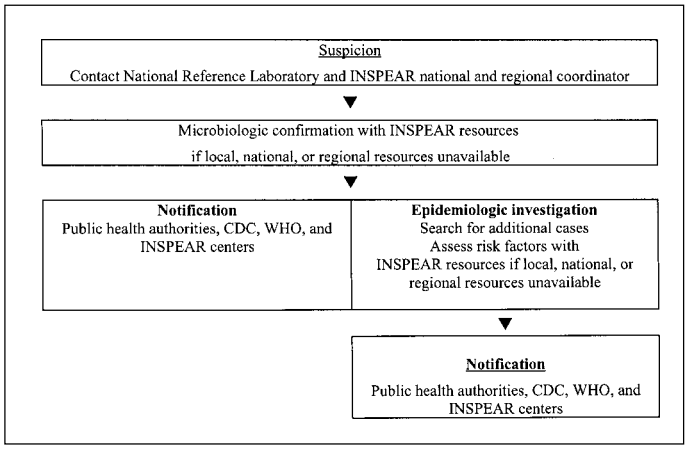

Figure. Functioning of the early warning system.

At the same time, an epidemiologic investigation will search for additional cases and assess risk factors through cohort or case-control studies, and surveillance will be implemented. As with microbiologic support, epidemiologic investigation will be performed at the local, national, or regional level if possible; if necessary, INSPEAR resources will be provided. In addition, public health authorities, WHO, and INSPEAR centers will be notified so that measures may be immediately implemented if such an event occurs elsewhere.

Responses to Emerging Resistance

INSPEAR response may include immediate, specific responses, such as microbiologic support (e.g., confirmation of resistance, studying the mechanism of resistance, molecular typing to determine clonality) or on-site epidemiologic and infection control support (e.g., assistance with outbreak investigation, intervention studies, control measures) (Table 3). The level of response will be determined by local need, importance of the problem, and capacity of INSPEAR members to respond. In addition, the INSPEAR response to emerging resistance will include coordination of longer term studies to improve the methods for detection and control of resistance. Finally, the INSPEAR response will include the education and training of personnel at INSPEAR hospitals.

Table 3. INSPEAR resources

Microbiology	Epidemiology
Bacterial identification	Surveillance system
Antimicrobial Resistance, testing, and characterization of mechanisms	Study design and conduct
Typing	Outbreak investigation
Quality control programs	Infection prevention interventions
Proficiency testing	Statistical analysis
Training	Statistical training

Conclusions

INSPEAR is the first international program dedicated to the control of antimicrobial resistance that combines microbiologic and epidemiologic expertise provided by national reference laboratories and public health agencies. This program should facilitate control of novel antimicrobial-resistant pathogens at the time of their emergence and increase the likelihood of controlling and preventing those pathogens before they become endemic. However, as the results of our MRSA survey and proficiency testing indicate, the microbiologic and epidemiologic capacities of health-care facilities worldwide will need to be strengthened if our goal of detection and control of multidrug-resistant pathogens is to be achieved.

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Molecular Epidemiology of Methicillin-Resistant *Staphylococcus aureus*

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Subtyping methicillin-resistant *Staphylococcus aureus* (MRSA) isolates and tracking nosocomial infections have evolved from phenotypic to genotypic approaches; most laboratories now depend on pulsed-field gel electrophoresis (PFGE). We discuss the limitations of current image-based genotyping methods, including PFGE, and the advantages (including ease of entering data into a database) of using DNA sequence analysis to control MRSA infections in health-care facilities.

Staphylococcus aureus is a major nosocomial pathogen that causes a range of diseases, including endocarditis, osteomyelitis, pneumonia, toxic-shock syndrome, food poisoning, carbuncles, and boils. In the early 1950s, acquisition and spread of beta-lactamase-producing plasmids thwarted the effectiveness of penicillin for treating *S. aureus* infections. In 1959, methicillin, a synthetic penicillin, was introduced. However, by 1960, methicillin-resistant *S. aureus* strains were identified, the direct result of *S. aureus* acquiring the *mecA* gene, which encodes for an altered penicillin-binding protein gene (PBP2a) (1).

By the early 1960s, European hospitals were reporting outbreaks of MRSA infections, and subsequently MRSA clones spread to health-care institutions around the world (2). In the United States, MRSA is responsible for approximately 25% of nosocomial infections, and reports of community-acquired MRSA infections are increasing (3). The multidrug-resistant phenotype of MRSA strains and their intrinsic beta-lactam resistance make them difficult and costly to treat (4,5). In some medical institutions in New York City, MRSA accounts for approximately 29% of nosocomial infections and 50% of associated deaths (5). Controlling MRSA remains a primary focus of most hospital infection control programs (6).

Bacterial strain typing, or subspeciation, has become an important clinical tool to investigate suspected outbreaks and to evaluate nosocomial transmission. Numerous typing methods focus on discriminating MRSA isolates. We discuss the limitations of current image-based genotyping methods and the advantages of using DNA sequence analysis to control MRSA infections in health-care settings.

Genotyping Aims

Bacterial strain typing distinguishes epidemiologically related or clonal isolates from unrelated isolates. Epidemiologically related isolates are viewed as descendants from a common precursor cell; thus, their genomic "fingerprints" will be indistinguishable but recognizably different from unrelated or random isolates from the same species (7). Outbreak investigations of *S. aureus* and other nosocomial pathogens are viewed as short-term events or cases of local epidemiology, and in these settings most genotyping methods are able to distinguish clonal spread from unrelated isolates.

Understanding genetic relatedness becomes more challenging when the strain study population is larger, separated further in time, and recovered from a larger geographic area. The long-term or global epidemiologic question is whether the strains causing disease in one geographic area are related to those causing disease in other regions. A combination of genotyping methods has been used to study global *S. aureus* transmission (8,9).

In addition to tracking outbreaks, genotyping is used to distinguish between contaminating and infecting isolates and between separate episodes of infection and relapse of disease (10). Genotyping is also able to link certain *S. aureus* clonal types and disease syndromes, such as in cases of food poisoning and toxic-shock syndrome. The present challenge is to continue to build bacterial databases linking genetic markers and clinical presentations so that important correlates of disease can be identified.

Typing *Staphylococcus aureus*

Numerous techniques are available to differentiate *S. aureus*, and specifically MRSA, isolates. Historically, isolates were distinguished by phenotypic methods, including antibiotic susceptibility testing and bacteriophage typing. Both methods have limitations, as genetically unrelated isolates commonly have the same antibiogram, and many *S. aureus* isolates are nontypeable by phage typing (7).

With the advent of molecular biology, strain typing focused on DNA-based methods. Initial techniques compared restriction endonuclease patterns of chromosomal or plasmid DNA. The second generation of genotyping methods included Southern blot hybridization using gene-specific probes, ribotyping, polymerase chain reaction (PCR)-based approaches, and pulsed-field gel electrophoresis (PFGE) (10,11). These methods require subjective interpretation and comparison of patterns and fingerprint images. The ability to digitize and store images and to compare patterns by using matching software programs has enhanced these methods. However, they still remain difficult to standardize between laboratories, and the image-based information is difficult to

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organize for rapid search and retrieval by computer. In addition, image-based methods do not provide biological criteria to evaluate the relatedness between different strains (12).

Binary typing is a more objective genotyping method that compares the presence or absence of 12 different targets in the *S. aureus* genome. The binary coding system for each probe creates a numerical type amenable to relational databases (13). However, binary typing fails to provide information on genetic relatedness between strain types. This method is also technically subjective, as it requires interpretation of a positive hybridization signal from background.

DNA Sequence Analysis

DNA sequence analysis is an objective genotyping method; the genetic code (A-T-C-G) is highly portable and easily stored and analyzed in a relational database. Recent advances in DNA sequencing technology, including rapid, affordable, high-throughput systems, have made it possible for sequencing to be considered as a viable typing method.

Sequencing the same DNA targets from disparate isolates and then cataloging mutation patterns constitute an approach termed comparative sequencing. Two different strategies have been used to provide genotyping data: multilocus sequence typing (MLST), which compares sequence variation in numerous housekeeping gene targets, and single-locus sequence typing, which compares sequence variation of a single target.

MLST has been developed for *Neisseria gonorrhoeae*, *Streptococcus pneumoniae,* and *S. aureus,* based on the classic multilocus enzyme electrophoresis (MLEE) method used to study the genetic variability of a species. Sequence analysis of five to seven housekeeping genes provides a database from which to infer relationships in somewhat distantly related isolates that have had substantial time to diversify (14,15).

The MLST approach is too labor-intensive, time-consuming, and costly to use in a clinical setting. More than 2,500 bp must be compared for each isolate. In addition, for certain recent subpopulations, such as MRSA, genetic variability in the housekeeping targets will likely be limited and discrimination will be restricted. However, a single-locus target, if discriminating, provides an inexpensive, rapid, objective, and portable genotyping method to subspeciate bacteria. Using a single target depends on finding a region for sequencing that is sufficiently polymorphic to provide useful strain resolution. Loci with short sequence repeat (SSR) regions may have suitable variability for discriminating outbreaks (16). Two *S. aureus* genes conserved within the species, protein A (*spa*) and coagulase (*coa*), have variable SSR regions constructed from closely related 24- and 81-bp tandem repeat units, respectively. In both genes, the in-frame SSR units are degenerative, variable in number, and variable in the order in which repeat units are organized. The genetic alterations in SSR regions include both point mutations and intragenic recombination that arise by slipped-strand mispairing during chromosomal replication and that result in a high degree of polymorphism (17,18).

Frenay et al. (19) compared the SSR region in the protein A gene in a collection of MRSA isolates studied by classical bacteriophage typing and showed that *spa*-typing clustered isolates previously grouped to phage type III-29. However, van Belkum et al. questioned whether the repeat region was too hypervariable and thus not a sound target for epidemiologic studies (20).

Validation of *spa*-Typing

The *spa*-type database of the Public Health Research Institute Tuberculosis Center includes >950 clinical *S. aureus* isolates; most (~80%) are methicillin resistant. DNA sequence analysis identified 37 unique, 24-bp SSR types; one type was 1 codon longer. The number and organization of the repeat types define the *S. aureus spa* type; to date, 186 *spa* types have been identified and catalogued in a relational database.

To further evaluate the clinical and epidemiologic validity of the protein A repeat region as a genotyping tool, we analyzed two historic collections previously characterized by multiple genetic methods. The Centers for Disease Control and Prevention's (CDC) collection of 59 staphylococci included 58 *S. aureus* isolates, 37 of them methicillin resistant; 29 isolates had been previously grouped into four identifiable clusters based on sound epidemiologic links. These isolates have been repeatedly studied with an array of techniques (e.g., phage typing, antibiograms, PFGE, ribotyping; Table 1). In the CDC collection, 22 SSR regions and 13 different *spa* types were identified. s*pa*-typing correctly classified 27 of the 29 outbreak cultures and incorrectly grouped four isolates to these clusters. Overall, s*pa*-typing produced results better than the mean score of 25 correct classifications and 5 misclassifications (18). These results support the findings of Frenay et al. (19) that *spa*-typing has the stability to correctly group epidemiologically related strains.

The second collection we analyzed consisted of 261 MRSA isolates from 12 New York City hospitals historically catalogued by Southern blot hybridization using *mecA* and Tn*554* and by PFGE. Together, these two methods identified 39 genotypes, which were further categorized into 96 PFGE subtypes. Five major MRSA clonal types were identified, and the predominant *mecA*:Tn*554*:PFGE genotype (I:A:A) was found at each of the 12 hospitals. Of the 261 MRSA isolates, 107 were typed as I:A:A. Twenty-two similar PFGE patterns were grouped to the "A" type (12). We named this genotype pattern, which has been routinely identified as the predominant MRSA clone in the United States, the "North American" MRSA clone (unpub. data). *spa*-typing correctly identified the five major MRSA clonal groups and also

Table 1. Comparison of typing methods used to discriminate *Staphylococcus aureus* strains

Method	Total no. of types	No. classified	No. misclassified
Phage typing	18	25	4
Antibiogram	21	26	6
Biotype	23	17	2
Plasmids	20	23	0
*Hin*dIII ribotyping	16	27	7
ClaI ribotyping	9	29	7
IS typing	9	16	3
RFLP typing	17	28	3
coa-PCR	7	28	8
PFGE	25	28	7
FIGE[a]	25	27	3
Immunoblotting	23	28	6
MLEE	21	26	4
Range	7-25	16-28	0-8
Average	18	25	5
spa-typing	16	27	4

[a]FIGE = field-inversion gel electrophoresis.

categorized 98 of the 107 I:A:A MRSA isolates as *spa* type 2; the remaining 9 isolates were distributed in five different *spa* types, which were grouped by repeat composition and repeat organization (Table 2).

To test the genetic validity of *spa*-typing, we sequenced the SSR region of the coagulase gene. The slower "clock-speed" of the larger coagulase repeat region provided an independent genetic target to compare evolutionary relatedness with the results provided by *spa*-typing. Sequence analysis revealed a common *coa* type among seven of the nine *spa* types (Table 2), providing additional, independent evidence of genetic relatedness of the I:A:A MRSA isolates.

The PFGE fingerprint patterns in the North American MRSA clonal types listed in Table 2 were determined (Figure). The isolates with *spa* types 14, 25, and 28 (lanes 5, 9, and 6, respectively) were grouped to the North American clonal type on the basis of *spa* composition and organization and *coa* type. However, these isolates were initially distinguished by different *mecA*:Tn*554* genotypes and more diverse PFGE patterns.

Conclusions

The finding that *spa*-typing could genotype the *S. aureus* isolates from two different collections in congruence with established procedures disproves the belief that this repeat region is too unstable for epidemiologic studies. While *spa*-typing does not have the resolving power of PFGE subtyping, it is fast, easy to use and interpret, and compatible for building relational databases. Most importantly, DNA sequence analysis of the protein A repeat region provides an unambiguous, portable dataset that simplifies information sharing between laboratories and facilitates creating a large-scale database for studying global and local epidemiology.

The MLST database of *S. aureus* should establish a sound genetic framework to describe the species (14). These data are portable and can be easily linked to a *spa* and *coa* database, a process that takes advantage of the objective nature of sequence information. The *spa*-short repeat region and its variation in both composition and organization have established a library of distinguishable patterns that allows isolates to be easily and accurately genotyped. These groupings are supported by other image-based genotyping methods and sequencing secondary targets such as the coagulase short sequence repeats (17).

Although still limited in number, isolates that have been genotyped on the basis of *mecA*:Tn*554*:PFGE fingerprint

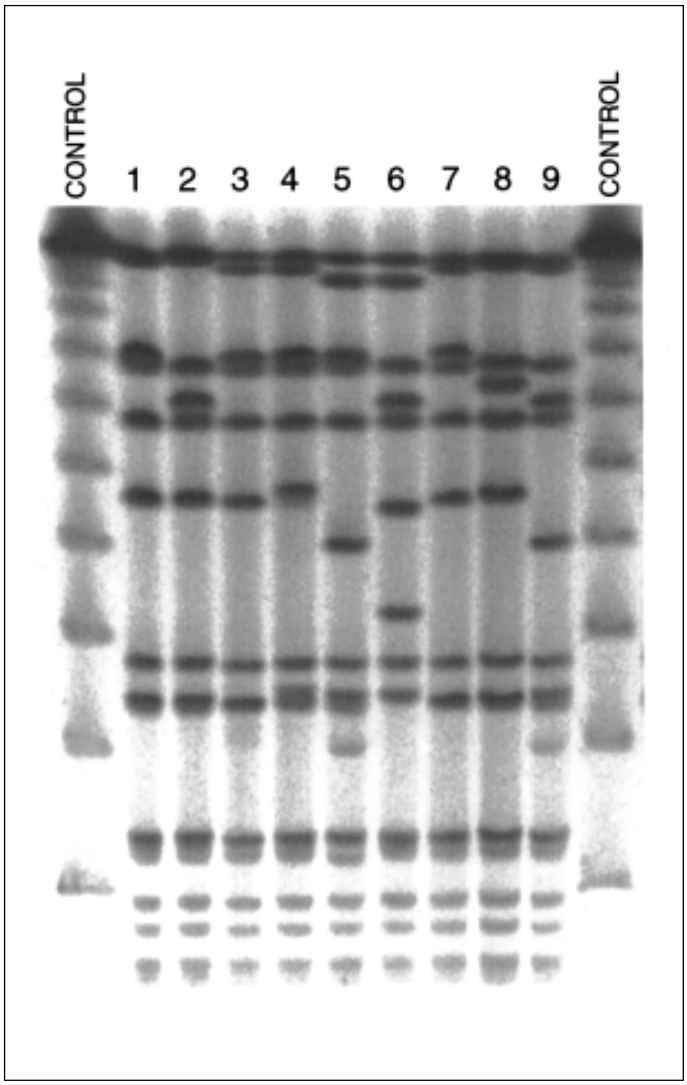

Figure. *Sma*I-pulsed-field gel electrophoresis of nine *Staphylococcus aureus* strains representative of the most prevalent MRSA clonal type in North America.

Table 2. Genotype of the "North American" MRSA clone

Isolates (no. = 107)	mecA	Tn*554*	PFGE	*spa* type	*spa*-type repeats	*coa*-type repeats
98	I	A	A	*spa* type 2	T-J-M-B-M-D-M-G-M-K	A-B-C-D-E-F
2	I	A	A	*spa* type 24	T-J-M-E-M-D-M-G-M-K	
1	I	A	A	*spa* type 23	T-J-M-B-M-D-M-G-K	A-B-C-D-E-F
2	I	A	A	*spa* type 29	T-J-M-B-M-D-M-G-G-M-K	A-B-C-D-E-F
1	I	A	A	*spa* type 60	T-J-M-A-M-G-M-K	
3	I	A	A	*spa* type 26	T-J-M-B-M-G-M-K	A-B-C-D-E-F
New isolates	mecA		PFGE			
1	II	NH	A'	*spa* type 14	T-J-M-B-M-D-M-G-M-K-K	A-B-C-D-E-F
1	II	NH	A'	*spa* type 25	T-J-M-D-M-G-M-K	A-B-C-D-E-F
1	III	NH	A'	*spa* type 28	T-K-J-M-B-M-D-M-G-M-K-K	A-B-C-D-E-F

patterns and *spa*- and coa-typing provide a rich database to study the recent spread of *S. aureus* and MRSA clones. These data provide sound evidence that *Sma*I-PFGE patterns change at a faster clock-speed than do the protein A SSRs and that the coagulase repeats change at a slower clock-speed than the shorter protein A repeats.

In short, sequence typing permits the widespread use of a proactive approach to investigate suspected outbreaks of MRSA.

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Increasing Resistance to Vancomycin and Other Glycopeptides in *Staphylococcus aureus*

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Strains of *Staphylococcus aureus* with reduced susceptibility to glycopeptides have been reported from Japan, the United States, Europe, and the Far East. Although isolates with homogeneous resistance to vancomycin (MICs = 8 µg/mL) continue to be rare, there are increasing reports of strains showing heteroresistance, often with vancomycin MICs in the 1-4 µg/mL range. Most isolates with reduced susceptibility to vancomycin appear to have developed from preexisting methicillin-resistant *S. aureus* infections. Many of the isolates with reduced susceptibility to glycopeptides have been associated with therapeutic failures with vancomycin. Although nosocomial spread of the vancomycin-intermediate *S. aureus* (VISA) strains has not been observed in U.S. hospitals, spread of VISA strains has apparently occurred in Japan. Broth microdilution tests held a full 24 hours are optimal for detecting resistance in the laboratory; however, methods for detecting heteroresistant strains are still in flux. Disk-diffusion tests, including the Stokes method, do not detect VISA strains. The Centers for Disease Control and Prevention and other groups have issued recommendations regarding appropriate infection control procedures for patients infected with these strains.

Staphylococcus aureus continues to be a major cause of community-acquired and health-care related infections in the United States and around the world (1,2). Approximately 20% of community-acquired and nosocomial bacteremias in the United States are caused by *S. aureus* (3-5). The emergence of high levels of penicillin resistance followed by the development and spread of strains resistant to the semisynthetic penicillins (methicillin, nafcillin, and oxacillin), macrolides, tetracyclines, and aminoglycosides has made therapy of staphylococcal disease a global challenge (1,6,7). In the 1980s, because of widespread occurrence of methicillin-resistant *S. aureus* (MRSA), empiric therapy for staphylococcal infections (particularly nosocomial sepsis) was changed to vancomycin in many health-care institutions (8-12). Vancomycin use in the United States also increased during this period because of the growing numbers of infections with *Clostridium difficile* and coagulase-negative staphylococci in health-care facilities (8,9). Thus, the early 1990s saw a discernible increase in vancomycin use. As a consequence, selective pressure was established that eventually led to the emergence of strains of *S. aureus* and other species of staphylococci with decreased susceptibility to vancomycin and other glycopeptides.

In 1997, the first strain of *S. aureus* with reduced susceptibility to vancomycin and teicoplanin was reported from Japan (13). Shortly thereafter, two additional cases from the United States were reported (14). While vancomycin therapy appeared to have failed in the patients infected with these organisms, debate was considerable about whether such strains should be designated as resistant to glycopeptides, since the levels of vancomycin required to inhibit the growth of the strains remained low (vancomycin MIC = 8 µg/mL). Three years later, the debate continues. At the heart of the discussion are conflicting definitions of resistance and resistance breakpoints, a handful of nonstandardized laboratory methods, and a very small sample size of strains collected from the far corners of the world upon which to draw conclusions (15-17). We address this question of reduced susceptibility versus resistance.

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Reduced Susceptibility Versus Resistance—Definitions and Interpretive Criteria

The National Committee for Clinical Laboratory Standards (NCCLS) defines staphylococci requiring concentrations of vancomycin of ≤4 µg/mL for growth inhibition as susceptible, those requiring 8 µg/mL to 16 µg/mL for inhibition as intermediate, and those requiring concentrations of ≥ 32 µg/mL as resistant (18). Similarly, for teicoplanin (a drug not approved for use in the United States), staphylococci requiring inhibitory concentrations of ≤8 µg/mL are designated as susceptible, those requiring 16 µg/mL for inhibition as intermediate, and those requiring concentrations of ≥ 32 µg/mL as resistant. Thus, the acronyms VISA (vancomycin-intermediate *S. aureus*) and GISA (glycopeptide-intermediate *S. aureus*) come directly from the interpretive criteria published by NCCLS. While GISA is technically a more accurate description of the strains isolated to date, since most are classified as intermediate to both vancomycin and teicoplanin, the term glycopeptide may not be recognized by many clinicians. Thus, the term VISA, which emphasizes a change in vancomycin MICs similar to vancomycin-resistant enterococci (VRE), may be a more effective way of communicating to clinicians the changes

occurring in the susceptibility of staphylococci to vancomycin. Although NCCLS has also defined disk-diffusion criteria for interpretation of vancomycin results for staphylococci (19), this method is not sufficiently sensitive to detect decreased susceptibility to vancomycin in staphylococci and should not be used for routine testing of staphylococci (19,20).

In the United States, the term vancomycin-resistant *S. aureus* (VRSA) is reserved for *S. aureus* strains for which the vancomycin or teicoplanin MICs are ≥ 32 µg/mL, as is also true in France, where the Comité de l'Antibiogramme de la Société Française Microbiologie has published breakpoints similar to those of NCCLS (21). However, using the interpretive criteria of the British Society for Antimicrobial Chemotherapy, strains for which the vancomycin MICs are ≥ 8 µg/mL would be reported as VRSA (22). Interpretive criteria for vancomycin from these three organizations are shown (Table 1).

Table 1. Examples of vancomycin interpretive criteria used internationally

	Interpretive criteria for vancomycin (µg/mL)		
Organization[a]	Susceptible	Intermediate	Resistant
NCCLS	≤4	8-16	≥32
CA-SFM	≤4	8-16	≥32
BSAC	≤4	------	≥8

[a]NCCLS, National Committee for Clinical Laboratory Standards; CA-SFM, Comité de l'Antibiogramme de la Société Française Microbiologie; BSAC, British Society for Antimicrobial Chemotherapy.

The term VRSA also has been used by Japanese investigators to denote strains of *S. aureus* that grow on a brain heart infusion screening (BHI) agar plate containing 4 µg/mL of vancomycin within 24 hours, provided that the vancomycin broth microdilution MIC is at least 8 µg/mL (23). Those strains that produce colonies on vancomycin-containing BHI agar with vancomycin MICS of ≤ 4 µg/mL are termed heteroresistant VRSA or hetero-VRSA. By population analysis, subpopulations can be detected in hetero-VRSA strains, often representing only 1 in 100,000 daughter cells, for which the vancomycin MICs are 8 µg/mL. Such strains were first reported from Japan in 1996 (13). The prototype strain is *S. aureus* Mu3, for which the vancomycin MIC range (by standard broth microdilution testing) is 1 µg/mL to 2 µg/mL. Often the vancomycin MICs reported for hetero-VRSA isolates in the literature are those obtained from colonies preselected on vancomycin-containing media and are not those of the original isolate. As Howe et al. point out, this process may, in fact, be selecting for resistance in vitro rather than screening for it (24). Whether the isolation of such hetero-VRSA strains from patients explains the apparent failure of vancomycin therapy remains controversial. While some of the isolates, such as those from Hong Kong (25), have been associated with therapeutic failures with vancomycin, many hetero-VRSA strains (or hetero-VISA strains, as they are also known) were detected through retrospective laboratory screening of MRSA isolates, and the clinical significance of the isolates is unknown (26-28).

Epidemiology of VRSA and VISA Strains

Strains of VISA (vancomycin MIC = 8 µg/mL) have been reported from Japan (13), the United States (29-31), France (32), United Kingdom (24), and Germany (26). Most of these isolates appear to have developed from preexisting MRSA infections. Hetero-VRSA strains have been reported from Spain (33), Scotland (34), Hong Kong (25), Germany (26,28), and Greece, among other countries (27). Most of these isolates were detected during retrospective testing surveys using BHI agar containing 4 µg/mL of vancomycin. For example, a hetero-VRSA isolate from Egypt, first isolated in 1981, was not identified until 1998 during a retrospective review of MRSA strains by Bierbaum et al. (26).

Evidence from the few affected U.S. patients investigated to date suggests that infections caused by VISA, for which the vancomycin MICs are 8 µg/mL, are refractory to vancomycin therapy (29). The Centers for Disease Control and Prevention (CDC) has received reports of several other infections caused by *S. aureus* for which the vancomycin MICs were 4 µg/mL, which suggests that some of these patients did not improve on appropriate vancomycin therapy. Data from rabbit endocarditis models presented by Climo et al. (35) also suggest that vancomycin monotherapy is not adequate for VISA strains. However, the combination of oxacillin and vancomycin is synergistic both in vitro and in vivo in the endocarditis model (35). Similar data on the synergy of beta-lactams and vancomycin for VISA strains were reported by Sieradzki et al. (36). However, the accumulated experience from humans and animals is too small for firm conclusions regarding a loss in the effectiveness of vancomycin for such infections, particularly those caused by strains of *S. aureus* that are heteroresistant to glycopeptides. Our inability to differentiate in the laboratory between vancomycin-susceptible *S. aureus* strains (i.e., those for which the vancomycin MICs are ≤ 2 µg/mL) that have vancomycin-resistant subpopulations versus those vancomycin-susceptible strains that do not have such subpopulations hinders our efforts to clarify the effectiveness of vancomycin for staphylococcal infections.

Mechanisms of Reduced Susceptibility to Vancomycin

The mechanisms by which *S. aureus* isolates become more resistant to vancomycin are poorly understood. However, many of the clinical and laboratory-derived strains with decreased susceptibility to vancomycin share unique features. For example, most VISA strains for which the vancomycin MICs are 8 µg/mL show longer doubling times, decreased lysostaphin susceptibilities, and reduced autolytic activity (37,38). Studies conducted at CDC with Mu50 and the Michigan and the New Jersey VISA strains used changes in redox potential over time as an indicator of bacterial growth measured by using a Cytosensor Microphysiometer System (Molecular Devices Corporation, Sunnyvale, CA). These studies showed dramatically longer doubling times for the VISA strains (Figure 1, three curves on right) compared with the methicillin- and vancomycin-susceptible control strain *S. aureus* ATCC 25923 and two MRSA control strains obtained from CDC (3 curves on left side of Figure 1). However, several authors have noted that the vancomycin MICs for VISA strains are not stable and decrease over time in the absence of selective pressure (35,37,38).

Hanaki et al. reported that hetero-VRSA produced three- to five-fold greater quantities of penicillin-binding proteins 2 and 2' and increased quantities of cell-wall precursors, which presumably trap vancomycin extracellularly (39). In addition, amidation of glutamine residues in cell-wall muropeptides has been reported, which presumably reduces the cross-linking

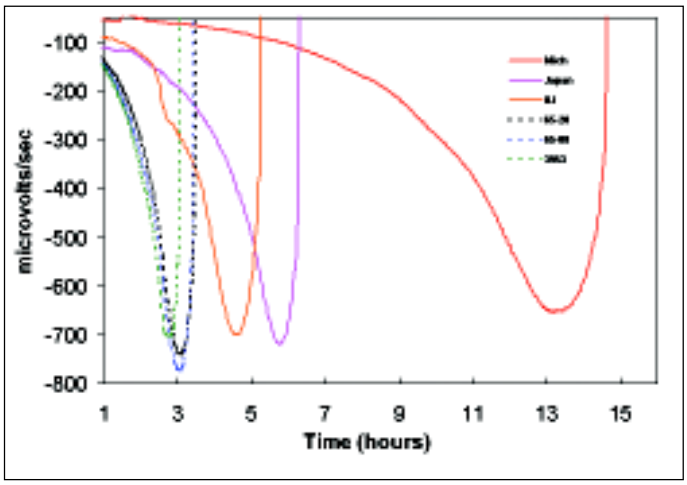

Figure 1. Growth curves of *Staphylococcus aureus* strains measured by changes in redox potential on a cytosensor. Starting from the far right of the graph are the Michigan strain, the Japanese strain Mu50, the New Jersey strain, and three vancomycin-susceptible control strains.

within the cell walls, thereby also reducing the number of intracellular vancomycin target molecules (40). Geisel et al. reported similar biochemical changes in seven MRSA isolates with reduced susceptibility to vancomycin (hetero-VISA) isolated from patients from three hospitals in Düsseldorf, Germany (28). Two of the patients had received vancomycin before the hetero-VISA strains were isolated. All seven isolates, obtained in 1998, had identical pulsed-field gel electrophoresis profiles identical to that of the northern Germany epidemic strain. Whether heteroresistance is a characteristic of all the progeny of this clone is unknown.

Laboratory Detection of VISA

Most VISA isolates initially appear mixed, demonstrating two distinct colony types; however, both colony types yield identical antimicrobial susceptibility test results (Figure 2). Decreased susceptibility to vancomycin (i.e., an MIC of vancomycin of 8 µg/mL) was detected in the *S. aureus* isolates from Michigan and New Jersey by broth microdilution when incubated for 24 hours at 35°C (20). On the other hand, the isolate from New York often demonstrated a vancomycin MIC of 4 µg/mL by broth microdilution but an MIC of 6 µg/mL by Etest methods. Thus, a single MIC test method may not be accurate enough to detect all VISA strains. CDC has adopted three criteria to identify VISA strains (Table 2), broth microdilution vancomycin MICs of 8-16 µg/mL, Etest (AB Biodisk, Piscataway, NJ) vancomycin MICs of ≥6 µg/mL, and growth on commercial BHI agar screen plates containing 6 µg/mL of vancomycin within 24 hours.

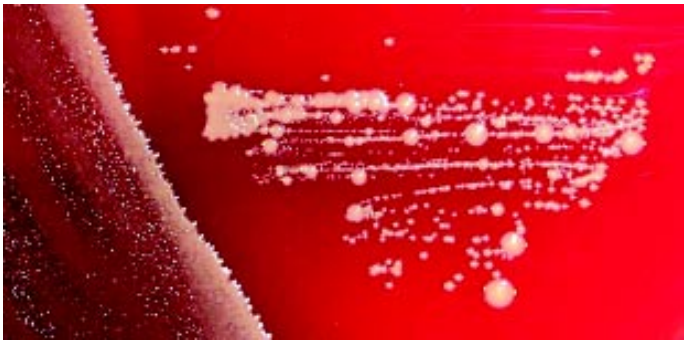

Figure 2. A blood agar plate incubated for 24h at 35°C in which the multiple colonial morphologies of the Michigan VISA strain can be observed. The large cream colored colonies and smaller gray colonies demonstrated the same antibiogram (vancomycin MIC= 8 ug/ml) and pulsed field gel electrophoresis profiles.

VISA isolates are not reliably distinguished from vancomycin-susceptible isolates by the rapid automated methods, such as MicroScan (Dade MicroScan, West Sacramento, CA) rapid panels (20). NCCLS disk-diffusion method and the Stokes method are not accurate predictors of reduced vancomycin susceptibility in staphylococci (20,41). Recent changes in Vitek (Biomérieux, Hazelwood, MO) software (version 7.01) may have improved VISA detection (CDC, unpub. obs.).

The clinical significance of heteroresistance is an issue of considerable controversy regarding the emergence of decreased susceptibility of staphylococci to vancomycin. Staphylococcal isolates with vancomycin MICs of 1 µg/mL to 4 µg/mL can be heterogeneous, that is, only small subpopulations of the isolates will grow in the presence of vancomycin concentrations of 8 µg/mL to 16 µg/mL, often 1 daughter cell in 10^5 CFU. Identifying isolates with subpopulations demonstrating heterogeneous resistance to vancomycin is difficult. CDC has chosen to use an inoculum of 10^6 CFU/mL on BHI containing 6 µg/mL of vancomycin for screening. All the isolates for which the vancomycin MICs are 8 µg/mL grow on these screening plates. Mu3, the hetero-VRSA strain from Japan, does not grow on this medium (20). Hiramatsu et al. (23) suggest using an inoculum of 10^8 CFU/mL on BHI agar containing 4 µg/mL of vancomycin and cell-wall precursors (called Mu3 supplement) to screen for hetero-VRSA. Others have used this approach, omitting the

Table 2. Key techniques for recognizing glycopeptide-intermediate *Staphylococcus aureus* strains[a]

Technique	Results	Comment
Broth microdilution[b]	Vancomycin MIC = 8-16 µg/mL in Mueller-Hinton broth	Hold test for full 24 hours
Brain heart infusion agar containing 6 µg/mL of vancomycin obtained from a commercial source[c]	Growth in 24 hours	One or more colonies is a positive result; use *S. aureus* ATCC 25923 as negative control, and *Enterococcus faecalis* ATCC51299 as positive control
Etest	Vancomycin MIC ≥6 µg/mL on Mueller-Hinton agar	Hold test for full 24 hours

[a]All three criteria must be met before an organism is defined as a glycopeptide-intermediate *S. aureus*.
[b]CDC uses inhouse-prepared MIC plates; however, any full dilution range broth microdilution plates, such as MicroScan conventional panels or PASCO frozen MIC panels, if incubated at 35°C for a full 24 hours, can be used.
[c]See reference 34 for explanation.

supplements (26). Bierbaum et al. reported that 23 of 25 isolates showing growth on BHI agar containing 4 µg/ml of vancomycin were classified as susceptible by NCCLS criteria (vancomycin MICs ≤ 4 µg/mL) even after growth on agar containing 4 µg/mL vancomycin. For the remaining two isolates, the vancomycin MICs were 8 µg/mL; however, the inoculum for the test was taken from vancomycin-containing agar. In our experience (42), growth of a variety of *S. aureus* isolates on screening plates with concentrations of 4 µg/mL of vancomycin is not unusual, but rarely do such strains have elevated vancomycin MICs. Thus, the clinical significance of such isolates remains unclear. Until further clinical data are available to assess the significance of heteroresistance, routine screening of *S. aureus* isolates for vancomycin-heteroresistant subpopulations is not warranted in the United States. Such screening may be undertaken as part of research protocols, but results generated using screening agars with low concentrations of vancomycin, the Etest method with a high inoculum (10^8 CFU/mL) on BHI agar with prolonged incubation, or vancomycin high-salt agar should not be reported as VRSA on a patient's medical record.

Surveillance for VISA

A recent survey of laboratories participating in CDC's Emerging Infections Program indicated that many are not using methods that can detect VISA strains (43). Yet, it is crucial that laboratories develop an algorithm for identifying VISA in their institutions if our understanding of how to treat these infections is to improve. Screening all isolates of *S. aureus* is neither cost-effective nor prudent at this time, given the low prevalence of such strains. Rather, focusing screening efforts on MRSA isolates is likely to be more successful since most VISA and hetero-VRSA isolates to date have been MRSA. With regard to surveillance of patient populations, hemodialysis and chronic ambulatory peritoneal dialysis patients are known to be at high risk for developing MRSA infections since they frequently are carriers of MRSA (44) and often receive long-term glycopeptide therapy. Such patients may be monitored for emerging VISA infections as should other patients who are predisposed to MRSA infections and receive vancomycin.

Infection Control Issues

The most prudent approach to curtailing the spread of VISA infections is still a matter of opinion. CDC has issued interim guidelines to aid hospitals in establishing programs for control of staphylococci with reduced susceptibility to vancomycin (45), and CDC's Hospital Infection Control Practices Advisory Committee has published guidelines for prudent vancomycin use (46). Others have suggested alternative approaches (47). The transfer of VISA strains beyond the source patient has not been documented in the United States, perhaps because the patients reported in Michigan and New Jersey were already in isolation because of pre-existing MRSA or vancomycin-resistant enterococcal infections (29). Identification of a VISA infection in a health-care setting should prompt a careful epidemiologic investigation. Since MRSA are known to be highly transmissible in health-care settings, it is reasonable to assume that VISA isolates would be no less transmissible given the opportunity.

Alternative Therapies

The antibiograms of U.S., German, and French VISA isolates (Table 3) show that isolates remained susceptible to at least some common antimicrobial agents, such as trimethoprim-sulfamethoxazole, as well as to newer agents, such as linezolid and quinupristin-dalfopristin (20). However, the possibility that newer VISA isolates will be resistant to all common drugs in addition to glycopeptides has to be considered. Several of the patients with VISA isolates from Japan and the United States responded to alternate therapies that included arbikacin and ampicillin-sulbactam, gentamicin, and trimethoprim-sulfamethoxazole. Whether the next VISA isolate will have a more resistant antibiogram is a matter of considerable speculation.

Table 3. Resistance patterns of staphylococcal study isolates to commonly tested antimicrobial agents[a]

Isolate (source)	Resistant or intermediate[b]	Susceptible
Staphylococcus aureus (Michigan)	Cd, Cip, E, Gm, Ox, P	C, L, Q-D, Rif, SXT, T
S. aureus (New Jersey)	Cd, Cip, E, Ox, P, Rif	C, Gm, L, Q-D, SXT, T
S. aureus (New York)	Cip, E, Ox, P, Rif	C, Cd, Gm, L, Q-D, SXT, T
S. aureus (Illinois)	C(I), Cd, Cip, E, Ox, P, Rif	L, Q-D, SXT, T
S. aureus (Germany)	Ak, Cd, Cip, E, Gm, Ox, P, Te	Fu, Ne
S. aureus (France, LIM-2)	C, Cd, Cip, E, Ox, P, Rif, Te	C, L, Q-D, SXT

[a]As determined using the broth microdilution reference method.
[b]Abbreviations: C: chloramphenicol; Cd: clindamycin; Cip: ciprofloxacin; E: erythromycin; Fu, fusidic acid; Gm: gentamicin; L: linezolid; Ne: netilmycin; Ox: oxacillin; P: penicillin; Q-D, quinupristin-dalfopristin; Rif: rifampin; SXT: trimethoprim/sulfamethoxazole; T: tetracycline. (I): intermediate. Based on data presented in references 20, 26, 32, and unpublished observations from CDC.

Future Trends

To date, staphylococci harboring the vancomycin resistance genes from enterococci have not been isolated from clinical samples, although some investigators have specifically looked for them (20,38,48). However, isolates of staphylococci appear to have achieved clinically relevant levels of resistance that lead to treatment failures even without the vancomycin resistance genes from enterococci. While CDC recommends that enhanced infection control efforts be initiated for *S. aureus* isolates for which the vancomycin MICs are 8 µg/mL (45), the need for such precautions for strains with MICs of 4 µg/mL is under debate. Such strains of staphylococci, including species other than *S. aureus* (49,50), will continue to emerge, particularly in patients who receive long-term vancomycin therapy. Thus, efforts to contain VISA infections before they become truly resistant to all available antimicrobial agents should be an infection control priority.

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Controversies about Extended-Spectrum and AmpC Beta-Lactamases

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Many clinical laboratories have problems detecting extended-spectrum beta-lactamases (ESBLs) and plasmid-mediated AmpC beta-lactamases. Confusion exists about the importance of these resistance mechanisms, optimal test methods, and appropriate reporting conventions. Failure to detect these enzymes has contributed to their uncontrolled spread and sometimes to therapeutic failures. Although National Committee for Clinical Laboratory Standards recommendations exist for detecting ESBL-producing isolates of *Escherichia coli* and *Klebsiella* spp., no recommendations exist for detecting ESBLs in other organisms or for detecting plasmid-mediated AmpC beta-lactamases in any organisms. Clinical laboratories need to have adequate funding, equipment, and expertise to provide a rapid and clinically relevant antibiotic testing service in centers where these resistance mechanisms are encountered.

Extended-spectrum beta-lactamases (ESBLs) were first reported in 1983 (1), and plasmid-mediated AmpC beta-lactamases were reported in 1988 (2). Typically, ESBLs are mutant, plasmid-mediated beta-lactamases derived from older, broad-spectrum beta-lactamases (e.g., TEM-1, TEM-2, SHV-1), which have an extended substrate profile that permits hydrolysis of all cephalosporins, penicillins, and aztreonam. These enzymes are most commonly produced by *Klebsiella* spp. and *Escherichia coli* but may also occur in other gram-negative bacteria, including *Enterobacter, Salmonella, Proteus,* and *Citrobacter* spp., *Morganella morganii*, *Serratia marcescens*, *Shigella dysenteriae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *Capnocytophaga ochracea* (3-9). Plasmid-mediated AmpC beta-lactamases have arisen through the transfer of chromosomal genes for the inducible AmpC beta-lactamase onto plasmids. This transfer has resulted in plasmid-mediated AmpC beta-lactamases in isolates of *E. coli, Klebsiella pneumoniae, Salmonella* spp., *Citrobacter freundii, Enterobacter aerogenes,* and *Proteus mirabilis* (10-12). To date, all plasmid-mediated AmpC beta-lactamases have similar substrate profiles to the parental enzymes from which they appear to be derived. With one exception (13), plasmid-mediated AmpCs differ from chromosomal AmpCs in being uninducible. Both ESBLs and plasmid-mediated AmpC beta-lactamases are typically associated with broad multidrug resistance (usually a consequence of genes for other antibiotic resistance mechanisms residing on the same plasmids as the ESBL and AmpC genes). A serious challenge facing clinical laboratories is that clinically relevant ESBL-mediated resistance is not always detectable in routine susceptibility tests.

Many clinical laboratories (as well as the wider medical community) are not fully aware of the importance of ESBLs and plasmid-mediated AmpCs and how to detect them; laboratories may also lack the resources to curb the spread of these resistance mechanisms (14-16). This lack of understanding or resources is responsible for a continuing failure to respond appropriately to prevent the rapid worldwide dissemination of pathogens possessing these beta-lactamases. The consequence has been avoidable therapeutic failures (sometimes fatal) in patients who received inappropriate antibiotics (17-22) and outbreaks of multidrug-resistant, gram-negative pathogens that required expensive control efforts (23).

I describe gaps in the capabilities of clinical laboratories to accurately detect and report ESBLs and plasmid-mediated AmpC beta-lactamases; discuss some of the technical difficulties involved in designing tests to detect ESBLs in organisms other than *E. coli* and *Klebsiella* spp.; correlate laboratory problems with the recent emphasis on medical cost-cutting at a time when bacterial pathogens are increasing in complexity; and propose a way to improve laboratory performance to meet the challenge of antibiotic resistance.

Laboratory Testing for ESBLs and Plasmid-Mediated AmpC beta-Lactamases

The National Committee for Clinical Laboratory Standards (NCCLS) has issued recommendations for ESBL screening and confirmation for isolates of *E. coli* and *Klebsiella* spp., and reporting confirmed organisms (24). Compliance varies widely. Many laboratories have difficulty detecting ESBL- or AmpC-mediated resistance and may be unaware of the relevant NCCLS reporting guidelines (14). No NCCLS recommendations exist for ESBL detection and reporting for other organisms or for detecting plasmid-mediated AmpC beta-lactamases.

In the United States, many laboratories await NCCLS recommendations before attempting to detect new resistance mechanisms. Thus, many clinical laboratories attempt to detect ESBLs only in *E. coli* and *Klebsiella* spp. Some researchers suggest that this is the correct approach and that even discussion of such issues is unwarranted because it causes confusion. However, other organisms possessing these resistance mechanisms do cause infections, making this stance unacceptable. Moreover, the laboratory is an early warning system, alerting us to new resistance mechanisms in

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patients. An early warning system that allows time lags of 12 or more years before new types of resistant organisms are detected is untenable. Twelve years is not an early warning, and laboratories that operate in this manner cannot meet their responsibility.

NCCLS and the Emergence of New Pathogens

Can the current deficiencies be rectified? Two issues affect laboratories: the role of NCCLS and the speed with which new types of pathogens are emerging. NCCLS's task of creating laboratory test recommendations is difficult and often underappreciated. The committee has responsibilities in the areas of regulation, standardization, and safety. It is not NCCLS's role to be at the cutting edge of research, nor would it be appropriate for it, or other similar bodies, to be overly hasty and make decisions based on inadequate data. It can take years to gather data about a new, relatively uncommon, resistance mechanism. Time is also needed for analysis and debate. Properly done, the process cannot be rushed. The problem is that bacteria are evolving or adapting faster than this process.

Today, many bacterial pathogens are more complex than a decade or two ago. Thus, previously reliable susceptibility tests may no longer be dependable. For example, there are not only new resistance mechanisms, such as ESBLs, but also isolates that produce multiple beta-lactamases. Such organisms were not encountered often, if at all, when the current NCCLS susceptibility test criteria were prepared. For example, before the 1990s, *K. pneumoniae* isolates typically produced a single beta-lactamase, SHV-1, or occasionally two beta-lactamases (25-27). Today, *K. pneumoniae* isolates that produce three to six beta-lactamases are commonplace in some centers (28-34). Such changes necessitate new or modified tests to provide accurate and clinically relevant susceptibility reports. But instead of laboratory testing methods being upgraded during the last decade, the emphasis has been on cost-cutting and downsizing. Laboratories are under pressure to use cheaper, abbreviated tests or merely to maintain the technical status quo of a decade or more ago. In centers where the newer, more complex pathogens occur, reliance on the older tests leaves patients and institutions at risk.

A More Responsive Approach

One approach to overcoming such problems would be to ensure that each laboratory has a staff member with the time, interest, and expertise to provide leadership in antibiotic testing and resistance. This person would read relevant publications, network with other laboratories, and evaluate potentially useful tests to detect new forms of resistance in the vulnerable interim period before new NCCLS-recommended tests become available. The person with this responsibility should work closely with reference laboratories, such as those of the Centers for Disease Control and Prevention or other sites with expertise. This would help to ensure that, whenever a new resistance mechanism is suspected, it would be properly checked, and the reference laboratory could provide feedback about whether the finding was "real."

Unresolved Issues

The gaps in current laboratory knowledge and testing have generated several unresolved issues. One is whether positive, but unconfirmed, ESBL screens should be routinely reported. This is a consequence of the NCCLS two-step approach to ESBL detection. The first step is a screening for reduced susceptibility to any of the recommended screening agents (cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, or aztreonam). Confirmatory testing, initiated only after a positive screening result, is based on tests with combinations of screening agents and the beta-lactamase inhibitor clavulanate. This testing indirectly detects hydrolysis of a screening agent by an ESBL by demonstrating potentiation of the activity of a screening agent in the presence of the beta-lactamase inhibitor. Confirmatory testing may require up to one extra day to detect ESBLs. If the laboratory reports a positive ESBL screening result to the physician and the isolate subsequently proves to be ESBL negative, the report could lead to unnecessary use of a carbapenem. Alternatively, if the laboratory withholds the positive screening result and the isolate is subsequently confirmed as ESBL positive, appropriate therapy may have been delayed for a day. Clearly, a reporting rule cannot cover all situations. Rather, the need to report a positive screening result should be determined on a case-by-case basis using common sense and experience as guides, taking into account the patient's status, infection control considerations, and the likelihood of a positive confirmatory test (based on prior experience with isolates from the same patient population). Using a reliable, rapid confirmatory test could minimize the time required for the second-step test and lessen this reporting dilemma. Another solution would be including ESBL confirmation testing in the routine susceptibility test.

Another issue is which NCCLS screening agent should be tested. Generally, the most reliable screening agent is the most sensitive. Cefpodoxime is the most sensitive ESBL screening agent for *K. pneumoniae* and *E. coli*, but a poor screening agent for *K. oxytoca* (35). The superior sensitivity of this agent can be accompanied by poor specificity in tests with some ESBL-negative *E. coli* isolates. This is another problem arising from the two-step approach to detecting ESBLs, which could be avoided by including a confirmatory test (ideally cefpodoxime plus clavulanate for *K. pneumoniae* and *E. coli* isolates) in the routine susceptibility test (17,36).

How best to detect ESBLs in organisms other than *Klebsiella* spp. *or E. coli* has not received much attention. The inhibitor-based confirmatory test approach is the most promising detection method (37). However, with isolates of some species, clavulanate is an unreliable agent for this test. The inhibitor-based approach is most reliable for isolates that do not coproduce an inhibitor-resistant beta-lactamase, such as AmpC. High-level expression of AmpC may prevent recognition of an ESBL. This problem is more common in tests with species or strains that produce a chromosomally encoded inducible AmpC beta-lactamase (e.g., *Enterobacter, Serratia*, *Providencia*, *Aeromonas* spp., *M. morganii*, *C. freundii*, *Hafnia alvei*, and *P. aeruginosa*). With these organisms, clavulanate may act as an inducer of high-level AmpC production and increase the resistance of the isolate to other screening drugs, producing a false-negative result in the ESBL detection test (Table 1). Tazobactam and sulbactam are much less likely to induce AmpC beta-lactamases and are therefore preferable inhibitors for ESBL detection tests with these organisms (37). Another possible solution is to include cefepime as an ESBL screening agent (38). High-level AmpC expression has minimal effect on the activity of cefepime, making this drug a more reliable detection agent for ESBLs in the presence of an AmpC beta-lactamase.

Table 1. Example of false-negative, clavulanate-based test for detecting extended-spectrum beta-lactamases with an isolate producing an inducible AmpC beta-lactamase[a]

Isolate	Test agent	MIC (µg/mL)
SHV-2-producing *Enterobacter cloacae*	Ceftazidime alone	2
	Ceftazidime + 4 µg/mL clavulanate	16

[a]Source: Thomson KS, Moland ES, Sanders CC (40).

A further concern with ESBL-producing organisms other than *Klebsiella* and *E. coli* is reporting their antibiotic susceptibilities. In Table 2, the beta-lactam MICs of an SHV-3-producing *C. freundii* isolate are within the NCCLS susceptible range of ≤8 µg/mL. If the isolate were *Klebsiella* or *E. coli*, the NCCLS reporting rule would apply, and the isolate would be reported as resistant to all penicillins, cephalosporins, and aztreonam. However, there is no ESBL reporting rule for other organisms; therefore, this organism would be reported as susceptible to cefotaxime, ceftazidime, aztreonam, and cefepime. This is inconsistent. Not only does this *C. freundii* isolate produce an ESBL, it also produces a chromosomal AmpC beta-lactamase that can hydrolyze the cephalosporins and aztreonam. It therefore seems wrong to report this organism as susceptible to these agents. Moreover, when the organism was tested at a 100-fold higher-than-standard inoculum, a dramatic inoculum effect occurred, with large increases in the MICs of these agents, analogous to the inoculum effect that occurs with ESBL-producing *Klebsiella* spp. and *E. coli* (Creighton University, unpub. data). This finding adds support for reporting all ESBL-producing isolates, not just *Klebsiella* spp. and *E. coli*, as resistant to all penicillins, cephalosporins, and aztreonam.

Detecting and reporting isolates producing plasmid-mediated AmpC beta-lactamases are more difficult issues than those associated with ESBLs. Detection is technically difficult in organisms that also produce a chromosomal AmpC, since proving that an AmpC is plasmid mediated, and not the usual chromosomal enzyme, is necessary. This determination is beyond the capabilities of most clinical laboratories. However, *Klebsiella* spp. do not possess a chromosomal AmpC. This makes them convenient indicator organisms to screen when attempting to detect plasmid-mediated AmpCs. Phenotypic tests for AmpC detection are not well defined. Screening tests could be based on decreased susceptibility to cephamycins. AmpC beta-lactamases are resistant to all marketed beta-lactamase inhibitors. Therefore, negative ESBL confirmatory tests based on these inhibitors may provide indirect evidence of AmpC production, or reduced outer membrane permeability. A positive three-dimensional test result with cefoxitin demonstrates hydrolysis of cefoxitin and differentiates between AmpC production and reduced outer membrane permeability (39). If an investigational AmpC beta-lactamase inhibitor were made available for diagnostic testing, it could be used in combination with a suitable cephem to confirm AmpC production.

Susceptibility reporting may prove controversial for isolates producing plasmid-mediated AmpC beta-lactamases. Isolates that produce these enzymes can be susceptible in vitro to cephalosporins and aztreonam (Table 3). If these agents are used therapeutically for infections with such organisms, determining if they pose a treatment failure risk for patients is a priority.

Table 2. Standard and high-inoculum microdilution MICs in tests with SHV-3-producing *Citrobacter freundii* (MICs in µg/mL)[a]

Inoculum (CFU/mL)	Cefotaxime	Ceftazidime	Aztreonam	Cefepime
5×10^5	2	1	0.5	0.5
5×10^7	256	32	32	>128

[a]Creighton University, unpub. data.

Table 3. MICs associated with plasmid-mediated AmpC production in *Klebsiella pneumoniae* (MICs in µg/mL)[a]

Enzyme	Cefotaxime	Ceftazidime	Aztreonam
FOX-1	4	8	0.5
CMY-1	128	4	32

[a]Creighton University, unpub. data.

Conclusions

Since clinical laboratories are first to encounter bacteria with new forms of antibiotic resistance, they need appropriate tools to recognize these bacteria, including trained staff with sufficient time and equipment to follow up important observations. Because bacterial pathogens are constantly changing, training must be an ongoing process. As we have learned from ESBLs, the methods and training that were previously adequate may no longer suffice against the newer types of pathogens. If laboratories continue to lag years behind new bacterial developments, new pathogens will spread, resulting in increasing problems and costs for patients and institutions.

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Emerging Mechanisms of Fluoroquinolone Resistance

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Broad use of fluoroquinolones has been followed by emergence of resistance, which has been due mainly to chromosomal mutations in genes encoding the subunits of the drugs' target enzymes, DNA gyrase and topoisomerase IV, and in genes that affect the expression of diffusion channels in the outer membrane and multidrug-resistance efflux systems. Resistance emerged first in species in which single mutations were sufficient to cause clinically important levels of resistance (e.g., *Staphylococcus aureus* and *Pseudomonas aeruginosa*). Subsequently, however, resistance has emerged in bacteria such as *Campylobacter jejuni*, *Escherichia coli*, and *Neisseria gonorrhoeae*, in which multiple mutations are required to generate clinically important resistance. In these circumstances, the additional epidemiologic factors of drug use in animals and human-to-human spread appear to have contributed. Resistance in *Streptococcus pneumoniae*, which is currently low, will require close monitoring as fluoroquinolones are used more extensively for treating respiratory tract infections.

The fluoroquinolone class of antimicrobial agents has had broad acceptance in hospitalized and community patients, and usage appears to be increasing (1,2). Although some members of the class (temafloxacin, grepafloxacin, and trovafloxacin) have been withdrawn or restricted because of adverse events, new members continue to be developed and approved (gatifloxacin and moxifloxacin). The last six released fluoroquinolones are for treating patients with respiratory tract infections, the single most common group of infections (3). This fact, plus the convenience of fluoroquinolones (once or twice a day oral dosing), suggests that use will increase (1).

As we approach the halfway point of the second decade of fluoroquinolone use, resistance has already emerged in some species of bacteria and some clinical settings. We examine the mechanisms of fluoroquinolone resistance and discuss epidemiologic factors that may have contributed to the prevalence of antibiotic resistance in clinical settings.

Mechanism of Fluoroquinolone Action

Fluoroquinolones (and earlier quinolones) are novel among antimicrobial agents in clinical use because they directly inhibit DNA synthesis. Inhibition appears to occur by interaction of the drug with complexes composed of DNA and either of the two target enzymes, DNA gyrase and topoisomerase IV. These enzymes are structurally related to each other, both being tetrameric with pairs of two different subunits. The GyrA and GyrB subunits of DNA gyrase are respectively homologous with the ParC and ParE subunits of topoisomerase IV. Both enzymes are type 2 topoisomerases, which act by breaking both strands of a segment of DNA, passing another segment through the break, and then resealing the break. For DNA gyrase, this topoisomerization reaction results in introduction (or removal) of DNA supercoils, thus affecting the negative supercoiling of DNA necessary to initiate DNA replication and remove positive supercoils that accumulate before an advancing replication fork. For topoisomerase IV, the topoisomerization reaction results in separation of the interlocking of daughter DNA strands that develop during replication; this facilitates the segregation of daughter DNA molecules into daughter cells. In both cases, fluoroquinolones appear to trap the enzyme on DNA during the topoisomerization reaction, forming a physical barrier to the movement of the replication fork (4), RNA polymerase (5), and DNA helicase (6). The collision of the replication fork with these trapped complexes triggers other poorly defined events within the cell that ultimately result in cell death.

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Mechanisms of Fluoroquinolone Resistance

In all species studied, mechanisms of fluoroquinolone resistance include one or two of the three main mechanistic categories, alterations in the drug target, and alterations in the permeation of the drug to reach its target. No specific quinolone-modifying or -degrading enzymes have been found as a mechanism of bacterial resistance to fluoroquinolones, although some fungi can degrade quinolones by metabolic pathways (7).

Alterations in Target Enzymes

Most extensively studied have been alterations in target enzymes, which are generally localized to specific domains of each subunit type. These alterations arise from spontaneous mutations in the genes encoding the enzyme subunits and thus can exist in small numbers (1 in 10^6 to 1 in 10^9 cells) in large bacterial populations. With GyrA and ParC subunits of resistant bacteria, amino acid changes are generally localized to a region of the enzyme in the amino terminus that contains the active site, a tyrosine that is covalently linked to the broken DNA strand during enzyme action. Resistance-causing amino acid changes are also clustered in three

dimensions, based on the structure of a fragment of GyrA that has been solved by x-ray crystallography, suggesting that this region constitutes part of a quinolone-binding site on the enzyme (8). One of the common resistance mutations in GyrA, which causes a change from serine at position 83 to tryptophan, causes reduced binding of norfloxacin to the gyrase-DNA complex (9).

For the GyrB and ParE subunits of resistant bacteria, amino acid changes, when present (mutations in these subunits are much less common than those in GyrA or ParC), are usually localized to the mid-portion of the subunit in a domain involved in interactions with their complementary subunits (GyrA and ParC, respectively). The original crystal structure of yeast topoisomerase II, which is related to DNA gyrase and topoisomerase IV, had suggested that this resistance-determining domain was not in proximity to the resistance-determining domains of GyrA and ParC (10); however, structures of other enzyme conformations suggested that the resistance-determining regions of both types of subunits might be in proximity during certain parts of the enzyme catalytic cycle, perhaps defining an enzyme conformation to which quinolones bind (11). No crystal structures in which a quinolone is bound to the enzyme-DNA complex have been solved; thus, contact points between drug, enzyme, and DNA have not been directly determined. Also unknown is how different amino acid changes effect resistance.

Differences in Fluoroquinolone Targets and Resistance

The interaction of a fluoroquinolone with the complexes of either DNA gyrase or topoisomerase IV with DNA may block DNA synthesis and result in cell death (12). The antibacterial potency of a quinolone is defined in part by its potency against the two enzyme targets; the more sensitive of the two enzymes within a cell is the primary target. Many fluoroquinolones have differing potencies against DNA gyrase and topoisomerase IV. A general pattern for most quinolones has emerged: DNA gyrase is the primary drug target in gram-negative bacteria, and topoisomerase IV is the primary target in gram-positive bacteria. These differences correlate with relative drug sensitivities in several cases, the more sensitive of the two enzymes being the primary target defined by genetic tests (13-15). The first step in mutational resistance in the drug target usually occurs by an amino acid change in the primary enzyme target, with a rise in MIC of the cell predicted to be determined by the effect of the mutation itself or by the level of intrinsic sensitivity of the secondary drug target (whichever is lower). Higher levels of resistance may then occur by second mutational steps, in which amino acid changes are selected in the secondary target enzyme. Further mutations result in additional amino acid changes in either enzyme, depending on which was least resistant in the cell under selection. On mechanistic grounds, this pattern of stepwise mutations in alternating target enzymes implies that both high intrinsic potency against the primary target and the similarity of potency against both targets will affect the likelihood of selection of first-step resistant mutants. Thus, fluoroquinolones with a high therapeutic index (defined as the concentration of drug at the site of infection divided by the MIC of the drug for the target bacterium), in which drug concentration exceeds the MIC of a first-step mutant, are unlikely to select spontaneous first-step mutants present in the infecting bacterial population; such mutants are inhibited or killed by these concentrations. Furthermore, the greater the extent to which a fluoroquinolone has similar (and ultimately equal) potency against both enzyme targets, the lower the MIC increment for a first-step drug target mutant. Thus, for drugs with low increments in resistance for first-step mutants because of similar activities against both target enzymes, the extent to which drug concentrations can exceed the MIC of first-step mutants may be enhanced. These principles would predict that selection of fluoroquinolone resistance could occur readily with ciprofloxacin against species such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, organisms in which single mutations cause MICs of ciprofloxacin that approach or exceed achievable serum concentrations. This prediction has been borne out by surveillance data (16).

Alterations in Drug Permeation

To reach their targets in the cell cytoplasm, fluoroquinolones must cross the cytoplasmic membrane and, in gram-negative bacteria, the outer membrane as well. Fluoroquinolones are sufficiently small and have charge characteristics that allow them to cross the outer membrane through porin proteins, which form general diffusion channels; they also appear to cross the cytoplasmic membrane by diffusion (17). Resistance to fluoroquinolones in gram-negative bacteria is associated with reductions in porins and reduced bacterial accumulation of drug, but measurements of diffusion rates suggest that porin reductions alone are generally not sufficient to account for resistance (18).

More recently, resistance caused by reduced accumulation has been shown to require the presence and enhanced expression of endogenous efflux systems that actively pump drug from the cytoplasm. In gram-negative bacteria, these systems typically have three components: the efflux pump located in the cytoplasmic membrane, an outer membrane protein, and a membrane fusion protein thought to link the two. Drug is actively extruded from the cytoplasm or cytoplasmic membrane across the periplasm and outer membrane to the cell exterior; the energy for this process is derived from the proton gradient across the membranes. Pumps of this type also exist in gram-positive bacteria, and increased amounts of these pumps have been associated with low levels of fluoroquinolone resistance. These efflux systems are typically capable of causing resistance to compounds of diverse structural types and thus are referred to as multidrug resistance (MDR) pumps. They appear to be present in many if not all bacteria. The natural substrates for these systems are generally unknown, but current models envision a general role in removing toxic compounds from the cytoplasm or cytoplasmic membrane (19). Although fluoroquinolones are synthetic antimicrobial agents, a number of them are substrates for a range of efflux systems. Among pathogenic bacteria, *Escherichia coli*, *P. aeruginosa*, *S. aureus*, and *Streptococcus pneumoniae* have been most extensively studied for efflux systems causing fluoroquinolone resistance (Table). In most cases, expression of the components of the efflux system is regulated, and resistance occurs by chromosomal mutation that causes coordinated increased expression of pump components. The conditions under which there is physiologically increased expression of these systems are largely unknown. In *P. aeruginosa,* four such efflux systems have been identified, each differing by which

Table. Components of multidrug transport systems in selected bacterial pathogens

Species	Efflux components: Pump	Membrane fusion protein	Outer membrane protein	Regulatory gene or mutation
Gram-negative bacteria				
Pseudomonas aeruginosa	MexB	MexA	OprM	*mexR*
	MexD	MexC	OprJ	*nfxB*
	MexF	MexE	OprN	*mexT*
	MexY	MexX	OprM	*mexZ*
Escherichia coli	AcrB	AcrA	TolC	*acrR*, *marA*, *robA*, *soxS*
Gram-positive bacteria				
Staphylococcus aureus	NorA	--	--	*flqB* promoter mutation, *arlRS*
Streptococcus pneumoniae	PmrA	--	--	?

fluoroquinolones are preferred substrates (20). It appears likely that most bacteria will have multiple MDR efflux systems.

The structural features of a fluoroquinolone that determine whether it is affected by an efflux system are not fully defined but correlate with hydrophilicity in the NorA pump of *S. aureus* (21). The risk for acquisition of resistance may be reduced for quinolones that are poor substrates for efflux pumps, since overexpression of such pumps would be unlikely to be effective as a resistance mechanism. Inhibition of pump function by other compounds is also under investigation as a means of reducing the frequency of resistance selections (22) and enhancing intrinsic activity of fluoroquinolones and other drugs that are also pump substrates.

Other Mechanisms of Resistance

The dominant mechanisms of fluoroquinolone resistance identified are 1) chromosomal mutations causing reduced affinity of DNA gyrase and topoisomerase IV for fluoroquinolones and 2) overexpression of endogenous MDR pumps. One report, however, has documented plasmid-mediated fluoroquinolone resistance in clinical isolates of *Klebsiella pneumoniae*, transferable to *E. coli* in the laboratory (23). Neither the mechanism of this transferable resistance nor the prevalence of fluoroquinolone-resistance plasmids in clinical settings is known.

Clinical Occurrence of Fluoroquinolone Resistance

Fluoroquinolone resistance emerged shortly after these drugs were introduced; two species were particularly affected, *S. aureus* and *P. aeruginosa*. Ciprofloxacin and ofloxacin were the most extensively used fluoroquinolones during this early period. The emergence of resistance was predicted on molecular grounds because, in these species, single mutations, which raise the MIC of ciprofloxacin of these organisms 4- to 16-fold, produce a level of resistance at or above peak drug concentrations achievable in serum, providing an opportunity for spontaneous first-step mutants to survive and emerge when a patient is exposed to fluoroquinolones. In the case of *S. aureus* and coagulase-negative staphylococci, methicillin-resistant strains developed fluoroquinolone resistance more rapidly than methicillin-susceptible strains (1,24). This difference is in part explained by nosocomial transmission in some settings and by the potential for coselection with several antimicrobial agents (because of the common multidrug resistance phenotype of methicillin-resistant strains [25]). Case-control studies have identified fluoroquinolone use as a risk factor for resistance.

Fluoroquinolone resistance has also increased substantially in some settings in species in which multiple mutational events are required for resistance to occur (e.g., *Campylobacter jejuni* [26], *E. coli* [27], and *Neisseria gonorrhoeae* [28]). Emergence in these species would not have been predicted on molecular grounds, suggesting that other epidemiologic factors may have come into play. For *C. jejuni*, resistance emerged in parallel in animal and human populations (29) shortly after fluoroquinolones were introduced for use in humans and other quinolones were introduced in food animal production, particularly poultry, in parts of Europe. In the United States, where use of quinolones in food animals was introduced later, demonstrating a link between resistant *C. jejuni* strains from poultry and food products and those causing human disease was possible (26). Thus, for a known zoonotic pathogen such as *C. jejuni*, resistance was augmented by selection pressures in an animal reservoir of campylobacters.

Fluoroquinolone resistance in *E. coli* has emerged in Europe, particularly in patients with urinary tract infections (30) and neutropenic cancer patients with bacteremia that developed during fluoroquinolone prophylaxis (31). Fecal carriage of resistant *E. coli*, however, appears to be common in both healthy adults and children in Spain (27). Carriage of resistant strains by children, a group in which fluoroquinolones are rarely used, and by adults without prior quinolone exposures (30) suggests acquisition of resistant strains by the population at large. This occurrence (in the context of documented high rates of fluoroquinolone resistance in *E. coli* isolated from poultry in Spain [32] and, by analogy, to what has been documented with campylobacters) suggests that acquisition of resistant strains from food sources may have resulted in substantial colonization of the human population with resistant *E. coli*, creating a reservoir of resistant organisms. Fluoroquinolone use in humans, which has also been shown to be a risk factor for having a resistant strain, may operate in this context to select either already fully resistant or intermediately resistant strains, accounting for the high levels of resistance and multiple mutations reported in resistant strains causing infections in humans. Whether similar problems with fluoroquinolone-resistant *E. coli* will emerge in the United States is not known, but the situation is being monitored.

Humans are the sole reservoir for infections with *N. gonorrhoeae*. In the United States, fluoroquinolone resistance in this organism has resulted largely from clonal outbreaks caused by human-to-human spread (33). Thus, for all three organisms in which fluoroquinolone resistance has become problematic despite a requirement for multiple mutations, other epidemiologic factors (of transmission and ongoing selection in reservoir populations of organisms) appear to be at work.

Newer fluoroquinolones are now incorporated into guidelines for treatment of patients with lower respiratory

tract infections because of rising resistance to beta-lactams and other agents in *S. pneumoniae*, the most commonly identified bacterial pathogen in patients with community-acquired pneumonia (34). Only recently has fluoroquinolone resistance begun to emerge in this organism, albeit at low levels (2). In some cases, fluoroquinolone-resistant strains, like those resistant to beta-lactams, have emerged because of clonal spread (35). Because the newest fluoroquinolones are for treating patients with respiratory tract infections, increasing selection pressure for resistance is possible. This concern is especially great for drugs developed for use in children, who are a major reservoir of *S. pneumoniae* (36). Monitoring will be necessary, as will studies to indicate whether the improved therapeutic index for some fluoroquinolones can be translated into a lower risk of selection of resistant strains, either spontaneous or clonal, in the clinical setting.

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Engineering Out the Risk for Infection with Urinary Catheters

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Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection. Each year, more than 1 million patients in U.S. acute-care hospitals and extended-care facilities acquire such an infection; the risk with short-term catheterization is 5% per day. CAUTI is the second most common cause of nosocomial bloodstream infection, and studies suggest that patients with CAUTI have an increased institutional death rate, unrelated to the development of urosepsis. Novel urinary catheters impregnated with nitrofurazone or minocycline and rifampin or coated with a silver alloy-hydrogel exhibit antiinfective surface activity that significantly reduces the risk of CAUTI for short-term catheterizations not exceeding 2-3 weeks.

Each year, urinary catheters are inserted in more than 5 million patients in acute-care hospitals and extended-care facilities. Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection in hospitals and nursing homes, comprising >40% of all institutionally acquired infections (1-4). Nosocomial bacteriuria or candiduria develops in up to 25% of patients requiring a urinary catheter for ≥ 7 days, with a daily risk of 5% (5-7). CAUTI is the second most common cause of nosocomial bloodstream infection (8-10), and studies by Platt et al. (11) and Kunin et al. (12) suggest that nosocomial CAUTIs are associated with substantially increased institutional death rates, unrelated to the occurrence of urosepsis. Although most CAUTIs are asymptomatic (13), rarely extend hospitalization, and add only $500 to $1,000 to the direct costs of acute-care hospitalization (14), asymptomatic infections commonly precipitate unnecessary antimicrobial-drug therapy. CAUTIs comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens (5-10,15), the most important of which are multidrug-resistant Enterobacteriacae other than *Escherichia coli*, such as *Klebsiella, Enterobacter, Proteus,* and *Citrobacter*; *Pseudomonas aeruginosa*; enterococci and staphylococci; and *Candida* spp. (Table 1).

Table 1. Microbial pathogens causing nosocomial catheter-associated urinary tract infections in U.S. acute-care hospitals, 1990-92 (15)

Pathogens	Hospitalwide (% of total)	Intensive care units (% of total)
Escherichia coli	26	18
Enterococci	16	13
Pseudomonas aeruginosa	12	11
Klebsiella and *Enterobacter* spp.	12	13
Candida spp.	9	25

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Pathogenesis

Excluding rare hematogenously derived pyelonephritis, caused almost exclusively by *Staphylococcus aureus*, most microorganisms causing endemic CAUTI derive from the patient's own colonic and perineal flora or from the hands of health-care personnel during catheter insertion or manipulation of the collection system. Organisms gain access in one of two ways (Figure 1). Extraluminal contamination may occur early, by direct inoculation when the catheter is inserted, or later, by organisms ascending from the perineum by capillary action in the thin mucous film contiguous to the external catheter surface. Intraluminal contamination occurs by reflux of microorganisms gaining access to the catheter lumen from failure of closed drainage or contamination of urine in the collection bag.

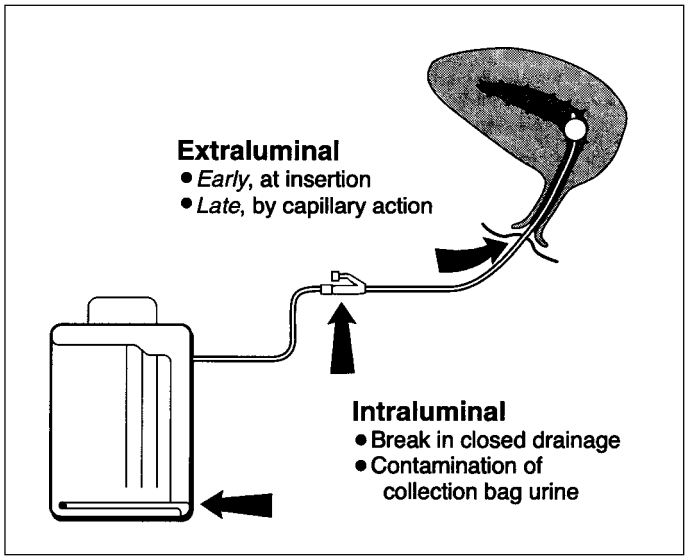

Figure 1. Routes of entry of uropathogens to catheterized urinary tract.

Recent studies suggest that CAUTIs most frequently stem from microorganisms gaining access to the bladder extraluminally, but both routes are important (Table 2) (16). Some studies suggest that the extraluminal route may be of greater relative importance in women because of the short urethra and its close proximity to the anus (17). Investigators have found that antecedent heavy periurethral cutaneous colonization is an important risk factor for CAUTI in both men and women (17,18).

Table 2. Mechanisms of catheter-associated urinary tract infection, based on a prospective study of 1,497 newly catheterized patients who had 235 new-onset infections (16)

	Organisms causing CAUTI[a]			
Mechanism of CAUTI	Gram-positive cocci (n=44)	Yeasts (n=34)	Gram-negative bacilli (n=37)	Overall (n=115)
Extraluminal	79%	69%	54%	66%
Intraluminal	21%	31%	46%	34%

[a]Percentages refer to organisms in which the mechanism of infection could be determined. For comparison of gram-positive cocci and yeasts vs. gram-negative bacilli, p = 0.007.
CAUTI = catheter-associated urinary tract infection.

Most infected urinary catheters are covered by a thick biofilm containing the infecting microorganisms embedded in a matrix of host proteins and microbial exoglycocalyx (Figure 2). A biofilm forms intraluminally, extraluminally, or both ways, usually advancing in a retrograde fashion (19). The role of the biofilm in the pathogenesis of CAUTI has not been established. However, antiinfective-impregnated and silver-hydrogel catheters (20-26), which inhibit adherence of microorganisms to the catheter surface, significantly reduce the risk of CAUTI, particularly infections caused by gram-positive organisms or yeasts, which are most likely to be acquired extraluminally from the periurethral flora (16). These data suggest that microbial adherence to the catheter surface is important in the pathogenesis of many, but not all, CAUTIs. Infections in which the biofilm does not play a pathogenetic role are probably caused by mass transport of intraluminal contaminants into the bladder by retrograde reflux of microbe-laden urine when a catheter or collection system is moved or manipulated (Figure 1, Table 2).

A prospective study in which catheterized patients were cultured daily by a technique capable of detecting very low-level bacteriuria, as low as 1 CFU/mL (7), showed that isolation of any microorganisms from an intraluminal specimen, even 3-4 CFU/mL, is highly predictive of CAUTI. If intercurrent antimicrobial therapy is not given, the level of bacteriuria or candiduria almost uniformly increases to $>10^5$ within 24-48 hours (Figure 3), demonstrating the vulnerability of the catheterized urinary tract to infection once any

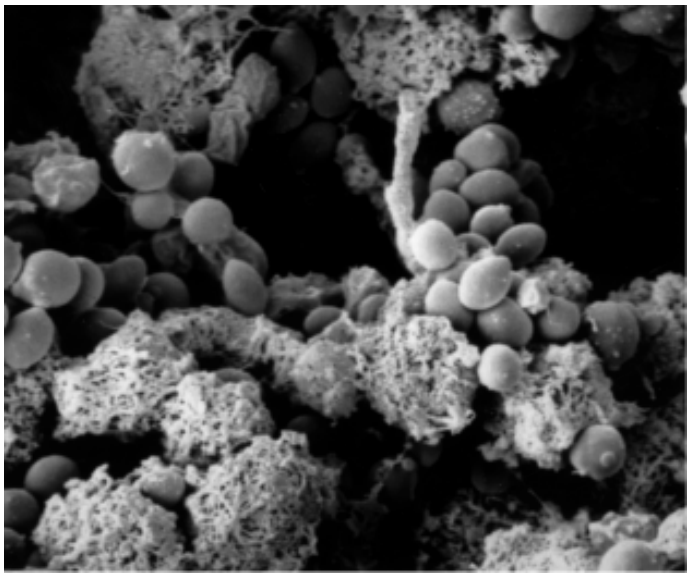

Figure 2. Scanning electron micrograph of an infected catheter showing dense and complex biofilm on the extraluminal surface. Urine culture at catheter removal yielded *Candida albicans* 10^4 CFU/mL and *C. glabrata* 10^4 CFU/mL (X 5000).

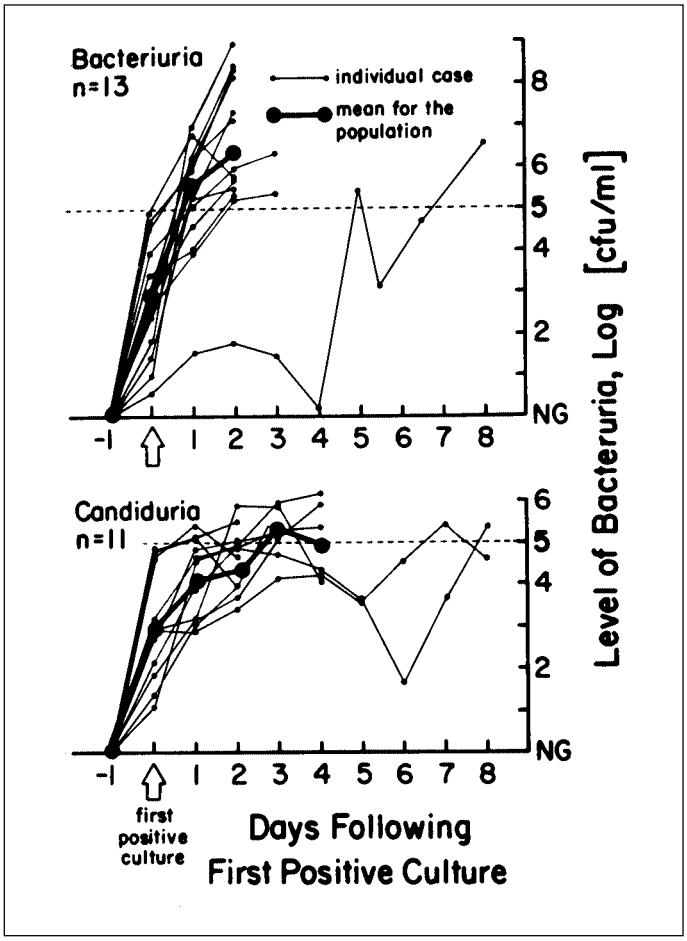

Figure 3. Rate of progression of bacteriuria and candiduria in 25 catheterized patients once any microorganisms were detectable in urine culture. Once organisms appeared in urine, low-level bacteriuria progressed very rapidly to levels $>10^5$ organisms per milliliter in 12 of the 14 cases within 2 days. Candiduria progressed less rapidly: in 9 of 11 cases, a concentration of $>10^5$ organisms per milliliter was reached within 3 days (7).

microorganisms gain access to the lumen of the catheter and the bladder. The very heavy use of systemic antimicrobial drugs in catheterized patients, which has been found in most studies (5-13), probably keeps the rate of CAUTI considerably lower than it would be otherwise, but unfortunately selects for the resistant organisms that produce most nosocomial CAUTIs (Table 1).

Definition of CAUTI

Most clinicians use a clean-voided specimen showing $>10^5$ CFU/mL as the criterion for "significant" bacteriuria (i.e., true infection) for noncatheterized patients (4). However, once any microorganisms are identified in urine from a patient's indwelling catheter, unless suppressive antimicrobial-drug therapy is being given or started, progression to concentrations $>10^5$ CFU/mL occurs predictably and rapidly, usually within 72 hours (Figure 3) (7). Thus, most authorities consider concentrations $>10^2$ or 10^3 CFU/mL, in urine collected with a needle from the sampling port of the catheter, to be indicative of true CAUTI. This concentration can be reproducibly detected in the laboratory, and this definition is useful for therapeutic decisions and epidemiologic research (1-7).

Risk Factors for CAUTI

Large, prospective studies in which catheterized patients were cultured daily and which used multivariable techniques of statistical analysis identified risk factors independently predictive of increased risk for CAUTI (27-30; Table 3). Females have a substantially higher risk than males (relative risk [RR] 2.5-3.7), and patients with other active sites of infection (RR 2.3-2.4) or a major preexisting chronic condition (such as diabetes [RR 2.2-2.3], malnutrition [RR 2.4], or renal insufficiency [RR 2.1-2.6]) also are at higher risk. Inserting the catheter outside the operating room (RR 2.0-5.3) or late in hospitalization (RR 2.6-8.6), presence of a ureteral stent (RR 2.5), or using the catheter to measure urine output (RR 2.0) further increase the risk.

The most important, potentially modifiable risk factor, identified in every study, is prolonged catheterization, beyond 6 days (RR 5.1-6.8); by the 30th day of catheterization, infection is near-universal. A large, prospective study monitored compliance on a daily basis with seven recommended precepts for catheter care, including closed drainage, dependent drainage including proper position of the drainage tubing and collection bag, and protection of the drainage port; the only violation predictive of an increased risk of CAUTI was improper position of the drainage tube, above the level of the bladder or sagging below the level of the collection bag (RR 1.9) (27).

Antimicrobial-drug therapy has been shown to be protective against CAUTI for short-term catheterizations (RR 0.001-0.4) but clearly selects for infection caused by multidrug-resistant microorganisms, such as *P. aeruginosa*, and other resistant gram-negative bacilli, enterococci, and yeasts (Table 1) (1-10,15).

Table 3. Risk factors for catheter-associated urinary tract infection, based on prospective studies and use of multivariable statistical modeling (27-30)

Factor	Relative risk
Prolonged catheterization >6 days	5.1-6.8
Female gender	2.5-3.7
Catheter insertion outside operating room	2.0-5.3
Urology service	2.0-4.0
Other active sites of infection	2.3-2.4
Diabetes	2.2-2.3
Malnutrition	2.4
Azotemia (creatinine >2.0 mg/dL	2.1-2.6
Ureteral stent	2.5
Monitoring of urine output	2.0
Drainage tube below level of bladder and above collection bag	1.9
Antimicrobial-drug therapy	0.1-0.4

Guidelines for Preventing CAUTI

Several catheter-care practices are universally recommended to prevent or at least delay the onset of CAUTI: avoid unnecessary catheterizations; consider a condom or suprapubic catheter; have a trained professional insert the catheter aseptically; remove the catheter as soon as no longer needed; maintain uncompromising closed drainage; ensure dependent drainage; minimize manipulations of the system; and separate catherized patients (1-4). However, few of these practices have been proven to be effective by randomized controlled trials.

Avoid Unnecessary Catheterizations

Use of indwelling urethral catheters should be limited to patients requiring relief of anatomic or physiologic outlet obstruction; patients undergoing surgical repair of the genitourinary tract (to facilitate healing); critically ill or postoperative patients who need their urinary output accurately measured; and debilitated, paralyzed, or comatose patients (to prevent skin breakdown and infected pressure ulcers). When no longer needed, the catheter should be promptly removed (31).

Consider Alternatives to Urethral Catheterization

Suprapubic catheterization is more comfortable and acceptable to the patient and may be associated with a lower incidence of CAUTI (32). For incontinent males who do not have bladder outlet obstruction, condom drainage, while not free from nosocomial urinary tract infections, appears to be associated with a lower risk than indwelling urethral catheters (33).

Insertion Using Aseptic Technique

Catheters should be inserted by trained health-care professionals using aseptic technique, including sterile gloves, a fenestrated sterile drape, and an effective cutaneous antiseptic, such as 10% povidone-iodine or 1% to 2% aqueous chlorhexidine.

Closed Drainage

After a catheter is inserted, uncompromising maintenance of closed drainage is of the highest priority and can keep the overall risk of CAUTI <25% for up to 2 weeks of catheterization (5,6).

Ensure Dependent Drainage

The collection tubing and bag should always remain below the level of the patient's bladder, but the drainage tubing should always be above the level of the collection bag.

In one large prospective study, this was the only catheter-care violation associated with a significantly increased risk of CAUTI (RR 1.9) (27).

Urine Collection

The catheter and the drainage system should be manipulated as little as possible, and urine output should be monitored hourly only when clearly indicated by the patient's condition.

Other Practices

If feasible, separating catheterized patients geographically on a patient-care unit may reduce the risk of cross-infection with multidrug-resistant nosocomial organisms such as *Serratia, Klebsiella, Pseudomonas,* and *Enterobacter* (34).

Systemic antimicrobial prophylaxis with trimethoprim-sulfamethoxazole, methenamine mandelate or, especially, a fluoroquinolone, can reduce the risk of CAUTI for short-term catheterizations (35). Although use of antimicrobials in this way may reduce the rate of CAUTI, infections that do occur are far more likely to be caused by antibiotic-resistant bacteria and yeasts (1-10). Since most CAUTIs are asymptomatic and do not result in urosepsis (13), it is difficult to justify antimicrobial therapy of asymptomatic bacteriuria other than for granulocytopenic or other severely immunocompromised patients, patients scheduled for urologic surgery, pregnant women, patients with *Serratia* CAUTI, or patients about to have their catheter removed. The societal benefits of antibiotic prophylaxis in immunocompetent catheterized patients to prevent largely asymptomatic CAUTIs are dubious.

Novel Technology

Technologic innovations to prevent nosocomial infection are most likely to be most effective if they are based on a clear understanding of the pathogenesis and epidemiology of the infection (36). Novel technologies must be designed to block CAUTI by either the extraluminal or intraluminal routes or both (Figure 1). Technologic innovations have been proposed and evaluated during the past 25 years but have not proven conclusively beneficial (1-5). Among these innovations are using antiinfective lubricants when inserting the catheter; soaking the catheter in an antiinfective antimicrobial-drug solution before insertion; regular metal cleansing or periodically applying antiinfective creams or ointments to metals; continuously irrigating the catheterized bladder with an antiinfective solution through a triple-lumen catheter; or periodically instilling an antiinfective solution into the collection bag (Table 4). Bladder irrigation with antimicrobial-drug solutions has not only shown no benefit for prevention but has been associated with a strikingly increased proportion of CAUTIs caused by microorganisms resistant to the drugs in the irrigating solution (37).

Given the widely accepted importance of closed catheter drainage, efforts have been made to seal the connection between the catheter and collection tubing. An initial trial with a novel catheter showed a modest benefit and suggested a reduction in hospital deaths (38); however, follow-up studies have not demonstrated a reduction in CAUTI with a sealed catheter-collecting tube junction (39,40).

Medicated catheters, which reduce adherence of microorganisms to the catheter surface, may confer the greatest benefit for preventing CAUTI. Two catheters impregnated with antiinfective solutions have been studied in randomized trials, one impregnated with the urinary antiseptic nitrofurazone (20) and the other with a new broad-spectrum antimicrobial-drug combination, minocycline and rifampin (21). Both catheters showed a significant reduction in bacterial CAUTIs; however, the studies were small, and selection of antimicrobial-drug resistant uropathogens was not satisfactorily resolved.

Table 4. Studies of novel technologies for preventing catheter-associated urinary tract infection

Technologic innovation (ref)	Risk reduction in randomized trials
Antiinfective lubricant (2)	Unproven
Sealed catheter-collection tubing junctions (38-40)	Unproven
Antireflux valves (2)	Unproven
Continuous irrigation of bladder with antiinfective solution (2,37)	Unproven
Instillation of antiinfective into collection bag (2)	Unproven
Antiinfective catheter material	
Antimicrobial drug-impregnated	
Nitrofurazone (20)	0.7 (0.3[a])
Minocycline-rifampin (21)	0.4
Silver oxide (29,30,42)	Unproven
Silver-hydrogel (22-25,26,42)	0.2-0.7

CAUTI = catheter-associated urinary tract infection.
[a]For bacterial CAUTI.

The universal presence of a biofilm on the surface of an infected catheter (19) (Figure 2) has prompted hope that coating the catheter surface with an antiseptic, such as a silver compound, might reduce the risk for CAUTI. However, silver oxide-coated catheters, which had been initially reported to show promise, did not show efficacy when studied in large, well-controlled trials (29,30). In one of the trials, male patients with the coated catheter who did not receive systemic antibiotics had a paradoxical and inexplicably increased risk for CAUTI (30).

A silver-hydrogel catheter has been developed that inhibits adherence of microorganisms to the catheter surface in vitro; tested microorganisms include resistant enterococci, staphylococci, Enterobacteriaceae, *P. aeruginosa*, and yeasts (41). Small comparative but nonblinded trials have shown this product prevents CAUTI (22-25,42) (Figure 4). In a recent, large, double-blinded trial in 850 patients (26), the silver-hydrogel catheter reduced the incidence of CAUTI 26% (25.7 vs. 15.4 per 100 catheters, RR 0.74, p =0.04) (27). The greatest benefit was preventing infections caused by gram-positive organisms, enterococci and staphylococci (RR 0.45, p <0.001), and *Candida* (RR 0.80), microorganisms that usually gain access to the bladder extraluminally (16). The catheter conferred no protection against CAUTIs with gram-negative bacilli, which most often gain access intraluminally (16). Use of the silver-hydrogel catheter was not associated with an increased incidence of infections caused by antibiotic-resistant bacteria or *Candida*, and in vitro susceptibility testing of isolates from both treatment groups showed no infections caused by silver-resistant microorganisms. Cost-utility analysis indicates that use of this catheter could bring substantial cost savings to health-care institutions (Table 5).

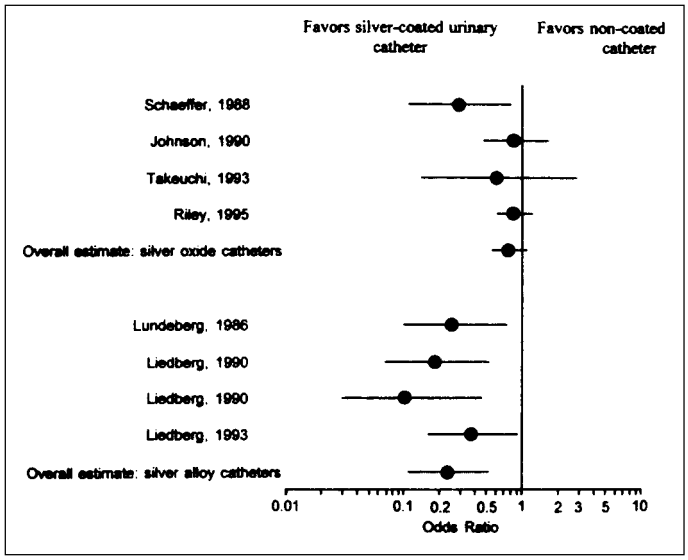

Figure 4. Meta-analysis of published prospective randomized trials of silver oxide and silver alloy-hydrogel catheters. Data suggest that silver-hydrogel catheters can substantially reduce the risk for CAUTI (42).

Table 5. Cost-benefit evaluation (restricted to direct hospital costs) of the silver-hydrogel catheter

Assumptions of analysis	
Proportion of CAUTIs diagnosed clinically	65%
Cost of each diagnosed CAUTI	~$1000[a]
Added acquisition cost of a silver-hydrogel catheter	~$5
Incremental hospital costs, per 100 catheters:	
Using standard urinary catheters (26 CAUTIs, 17 diagnosed)	$17,000
Using silver-hydrogel catheters (15 CAUTIs, 10 diagnosed)	$10,000
Added cost of catheters	$500[b]
Total costs	$10,500
Potential savings per 100 catheters	$6,500

[a]Based on studies showing that a diagnosed nosocomial CAUTI adds approximately $1,000 to direct costs of hospitalization (14); CAUTI = catheter-associated urinary tract infection.
[b]Cost of preventing a CAUTI: approximately $71.

The Future

The first major advance for preventing CAUTI since the wide-scale adoption of closed drainage 35 years ago is the development of catheters with antiinfective surfaces. These advances should not be considered the final answer, however. Other technologies that should be pursued include new, more potent antiinfective materials; microbe-impervious antireflux valves; urethral stents; conformable (collapsible) urethral catheters; and vaccines for enteric gram-negative bacilli and staphylococci. Antiseptics are far more likely than antibacterials to confer greater resistance to surface colonization and not to select for infection with antimicrobial-drug resistant bacteria or yeasts (43). New surface technologies that release far greater quantities of ionic silver or other antiinfective agents into the aqueous environment contiguous to the catheter surface might even prevent CAUTIs caused by intraluminal contaminants.

In uncontrolled trials, urethral stents have provided a less-invasive alternative to catheter drainage for men with outlet obstruction caused by prostatic hypertrophy or cancer (44). A conformable catheter, with a collapsible intraurethral segment that may cause less trauma to the urethra, has been developed but has not been tested clinically and is not commercially available. These and other alternatives to the rigid urethral catheter, such as a condom catheter for female patients (45), need to be evaluated in controlled, randomized trials.

The greatest hope for a major reduction in CAUTI and indeed all nosocomial infections is likely to be vaccines against important nosocomial multidrug-resistant pathogens, such as the enteric gram-negative bacilli and staphylococci.

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New Disinfection and Sterilization Methods

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New disinfection methods include a persistent antimicrobial coating that can be applied to inanimate and animate objects (Surfacine), a high-level disinfectant with reduced exposure time (ortho-phthalaldehyde), and an antimicrobial agent that can be applied to animate and inanimate objects (superoxidized water). New sterilization methods include a chemical sterilization process for endoscopes that integrates cleaning (Endoclens), a rapid (4-hour) readout biological indicator for ethylene oxide sterilization (Attest), and a hydrogen peroxide plasma sterilizer that has a shorter cycle time and improved efficacy (Sterrad 50).

The need for appropriate disinfection procedures is highlighted by the multitude of outbreaks resulting from improperly decontaminated patient-care items. Because sterilizing all such items is unnecessary, hospital policies need to identify whether cleaning, disinfection, or sterilization is indicated based primarily on an item's intended use but considering other factors including cost. We review new methods of disinfection and sterilization. Criteria for inclusion were technologies cleared in 1999 or 2000 by the Food and Drug Administration (FDA) or submitted to the FDA or Environmental Protection Agency (EPA) but not yet cleared (Table 1). These technologies have the potential to improve patient care, but in general their antimicrobial activity has not been independently validated.

Table 1. New methods in disinfection and sterilization

Process	Agent	Regulatory agency action
Disinfection	Ortho-phthalaldehyde (Cidex OPA)	FDA cleared, October 1999
	Antimicrobial coating (Surfacine)	Not FDA/EPA cleared
	Superoxidized water (Sterilox)	Not FDA/EPA cleared
Sterilization	Liquid sterilization process (Endoclens)	Not FDA cleared
	Rapid readout ethylene oxide biological indicator (Attest)	Not FDA cleared
	New plasma sterilizer (Sterrad 50)	FDA cleared, Jan 1999

Rational Approach to Disinfection and Sterilization

More than 25 years ago, Spaulding devised an approach to disinfection and sterilization of patient-care items or equipment that has proved to be so clear and logical that it has been retained, refined, and successfully used by infection control professionals (1). Spaulding believed that how an object should be disinfected depended on its intended use. The three categories he described were critical, semicritical, and noncritical. Critical objects (those that enter sterile tissues or the vascular system or through which blood flows, such as implanted medical devices) should be sterile when used. Semicritical items (that touch mucous membranes or nonintact skin, e.g., endoscopes, respiratory therapy equipment, and diaphragms) require high-level disinfection (i.e., elimination of all microorganisms except high numbers of bacterial spores). Noncritical items (bedpans, blood pressure cuffs, and bedside tables) require only low-level disinfection.

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Ortho-phthalaldehyde: A New Chemical Sterilant

Ortho-phthalaldehyde (OPA) received clearance by FDA in October 1999. OPA solution is a clear, pale-blue liquid (pH 7.5), which typically contains 0.55% OPA. OPA has demonstrated excellent microbiocidal activity in in vitro studies (2,3). For example, it has shown superior mycobactericidal activity (5-log$_{10}$ reduction in 5 minutes) compared with glutaraldehyde. The mean time required to effect a 6-log$_{10}$ reduction for *M. bovis* using 0.21% OPA was 6 minutes, compared with 32 minutes using 1.5% glutaraldehyde (Table 2) (4). When tested against a wide range of microorganisms, including glutaraldehyde-resistant mycobacteria and *Bacillus subtilis* spores (5), OPA showed good activity against the mycobacteria tested, including the glutaraldehyde-resistant strains, but 0.5% OPA was not sporicidal within 270 minutes of exposure. Increasing the pH from its unadjusted level (about 6.5) to pH 8 improved sporicidal activity.

OPA has several potential advantages compared with glutaraldehyde. It requires no activation, is not a known irritant to the eyes and nasal passages, has excellent stability over a wide range of pH (pH 3-9), does not require exposure monitoring, and has a barely perceptible odor. Like

Table 2. Activity of glutaraldehyde and ortho-phthalaldehyde against *Mycobacterium bovis*

Disinfectant	Time for 6-log$_{10}$ reduction[a]
1.5% glutaraldehyde	28-36 minutes
2.5% glutaraldehyde	14-18 minutes
0.21% ortho-phthalaldehyde	4.8-6.3 minutes

[a]Range of values from two different laboratories (4).

glutaraldehyde, OPA has excellent material compatibility. A potential disadvantage is that OPA stains proteins gray (including unprotected skin) and thus must be handled with caution (i.e., use of gloves, eye protection, fluid-resistant gowns when handling contaminated instruments, contaminated equipment, and chemicals) (2,3). Limited clinical studies of OPA are available. In one clinical-use study of 100 endoscopes exposed for 5 minutes to OPA, a $\geq$ 5-$\log_{10}$ reduction in bacterial load occurred, and OPA was effective over a 14-day usage cycle (6). Manufacturer's data show that OPA will last longer before reaching its minimum effective concentration limit (about 82 cycles) compared with glutaraldehyde (after 40 cycles) in an automatic endoscope reprocessor (7). Disposal must be in accordance with local and state regulations. If OPA disposal in the sanitary sewer is restricted, glycine (25 g/gallon) can be used to neutralize the OPA and make it safe for disposal.

The high-level disinfectant label claims for OPA solution at 20°C vary: 5 minutes in Europe, Asia, and Latin America; 10 minutes in Canada; and 12 minutes in the United States. FDA clearance was based on a "simulated-use" test requirement for a 6-$\log_{10}$ reduction of resistant bacteria suspended in organic matter and dried onto an endoscope. Since this test does not include cleaning, an essential component of disinfection of reusable devices (e.g., endoscopes), it is likely that the time required for high-level disinfection of a medical device by OPA would be less than 12 minutes. Efficacy test results using mycobacteria support a 5-minute exposure time at room temperature for OPA with a greater than 5-$\log_{10}$ reduction. Canadian regulatory authorities require a 6-$\log_{10}$ reduction in mycobacteria (this requires approximately 6 min) and allow only 5-minute exposure time intervals; thus, the exposure time for Canadians was set at 10 minutes (CG Roberts, pers. commun., Feb 2000).

Surfacine: A New Antimicrobial Agent

Contaminated environmental surfaces have been associated with transmission of certain nosocomial pathogens, principally vancomycin-resistant *Enterococcus* spp. (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile*. The incidence of nosocomial infections caused by VRE in particular has dramatically increased in the past decade. Cross-transmission is thought to result from transient hand carriage by hospital personnel, who may potentially be colonized directly from contact with colonized or infected patients or indirectly by contact with a contaminated environmental surface. Cultures of surfaces in rooms of patients colonized or infected with VRE have yielded positive cultures in 7% to 37% of samples. Molecular analysis of VRE strains involved in outbreaks has in some cases demonstrated that isolates obtained from the environment were identical to the outbreak strain (8).

Antibiotic-resistant pathogens such as VRE and MRSA possess similar susceptibility to disinfectants as antibiotic-susceptible strains (9,10). However, commonly used surface disinfectants such as phenols and quaternary ammonium compounds, while effective in eliminating these pathogens, do not have residual activity. Hence, after disinfection, surfaces may rapidly be recontaminated.

Surfacine is a new, persistent antimicrobial agent that may be used on animate or inanimate surfaces. It incorporates a water-insoluble antimicrobial compound (silver iodide) in a surface-immobilized coating (a modified polyhexamethylenebiguanide) that is capable of chemical recognition and interaction with the lipid bilayer of the bacterial outer cell membrane by electrostatic attraction. The intimate microbial contact with the surface results in transfer of the antimicrobial component (silver) directly from the coating to the organism. Microorganisms contacting the coating accumulate silver until the toxicity threshold is exceeded; dead microorganisms eventually lyse and detach from the surface. The amount of silver present and the number of microorganisms in contact with the treated surface determine how long the coating is effective. Preliminary studies show that treated surfaces result in excellent elimination of antibiotic-resistant bacteria (e.g., VRE) inoculated directly on various surfaces at challenge levels of 100 CFU/sq inch for at least 13 days (Table 3) (11). Antimicrobial activity is retained when the surface is subjected to repeated dry wiping or wiping with a quaternary ammonium compound. Data available from the manufacturer demonstrate inactivation of bacteria, yeast, fungi, and viruses when the product is applied at challenge levels of up to 10^6 CFU/mL. Sustained antimicrobial activity has been shown for the tested microorganisms. Inactivation times for microorganisms vary.

This persistent antimicrobial agent transfers the active biocide (silver) "on demand" directly to the organism without elution of silver ions into solution. The coating, therefore, functions in a chemically intelligent way, i.e., antimicrobial response is triggered only upon microbial contact. The mechanism of silver release differs from that of conventional, topically applied silver compounds (e.g., silver nitrate and silver sulfadiazine), which work by generating a bactericidal level of silver ions. (The ions are released into aqueous solution either by silver oxide or dissolution of the silver salt.)

This new antimicrobial agent can be applied to animate and inanimate surfaces by dipping, brushing, or spraying without prior surface treatment. The coating does not undergo photoreduction, degradation, or color change when exposed to intense UV irradiation (4 mW/cm^2 for 2 hr). This new antimicrobial agent has excellent adhesion to virtually all substrates, is optically clear, and does not delaminate, flake, or crack. Treated surfaces subjected to a wipe test retained their antimicrobial efficacy (Table 3) (11). Permanently treated surfaces remained chemically inert and retained their biocidal activity after exposure to various physical and chemical stresses such as temperature (tested from –20°C to 130°C), solvents (alcohol), solutions with a pH of 4 to 10, solutions of high ionic strength, and sterilization by conventional methods (e.g., steam, ethylene oxide, gamma-irradiation). The coating contains low levels of silver iodide (approx. 10 µg/cm^2 of coated surface), and coated surfaces are resistant to biofilm formation. Surfacine does not cause mammalian cell toxicity and passes the acute systemic toxicity tests recommended by the U.S. Pharmacopeia (SP Sawan and S Subramanyan, pers. commun., 2000).

Table 3. Effect on vancomycin-resistant Enterococcus (VRE) survival of wiping Surfacine on a treated surface over an extended period

Surface	Intervention	Day 1	Day 6	Day 13
Formica	Control	50	95	120
	Treated	0 (100%)[a]	0 (100%)	0 (100%)
	Treated & wiped	0 (100%)	0 (100%)	0 (100%)

[a]Percent reduction of VRE counts per Rodac plate ([treated/control] x 100) (11).

If novel surface treatments such as this product prove to be effective in significantly reducing microbial contamination, are cost-effective, and have long-term residual activity, they may be extremely useful in limiting transmission of nosocomial pathogens. The antimicrobial activity of this coating makes it potentially suitable for a wide range of applications, including disinfection of surfaces, microporous filters, and medical devices and use as a topical ointment or hand antiseptic.

A New Disinfectant: Superoxidized Water

The concept of electrolyzing saline to create a disinfectant is appealing because the basic materials, saline and electricity, are cheap and the end product (water) is not damaging to the environment. A commercial adaptation of this process, Sterilox, is available in the United Kingdom. The mode of action is not clear but probably relates to a mixture of oxidizing species. The main products are hypochlorous acid at a concentration of approximately 144 mg/L and free chlorine radicals. This disinfectant is generated at the point of use by passing a saline solution over titanium-coated electrodes at 9 amps. The product generated has a pH of 5.0-6.5 and an oxidation reduction potential of >950 mV. Equipment to produce the product may be expensive because parameters such as pH, current, and redox potential must be closely monitored. The solution has been shown to be nontoxic to biological tissues. Although the solution is claimed to be noncorrosive and nondamaging to endoscopes, one flexible endoscope manufacturer has voided the warranty on its endoscopes because superoxidized water was used to disinfect them (12).

The antimicrobial activity of this new sterilant has been tested against bacteria, mycobacteria, viruses, fungi, and spores (13-15). Recent data have shown that freshly generated superoxidized water is rapidly effective (<2 minutes) in achieving a 5-$\log_{10}$ reduction of pathogenic microorganisms (*Mycobacterium tuberculosis*, *M. chelonae*, poliovirus, HIV, MRSA, *Escherichia coli*, *Candida albicans*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*) in the absence of organic loading. However, the biocidal activity of this disinfectant was substantially reduced in the presence of organic material (5% horse serum) (14). Additional studies are needed to determine if this solution may be used as an alternative to other disinfectants.

Endoclens: A New Liquid Chemical Sterilization System

A new automated endoscope-reprocessing system has been submitted to FDA for clearance. The system is designed to provide rapid, automated, point-of-use chemical sterilization of flexible endoscopes and consists of a computer-controlled endoscope-reprocessing machine and a new, proprietary liquid sterilant that uses performic acid. The sterilant is produced, as needed by the machine, by automatic mixing of the two component solutions of hydrogen peroxide and formic acid. This sterilant is fast-acting against spore-forming bacteria (Table 4). The system's major features are an automatic cleaning process, capability to process two flexible scopes asynchronously, automated channel blockage and leak detection, filter water rinsing and scope drying after sterilization, hard-copy documentation of key process parameters, user-friendly machine interface, and total cycle time less than 30 minutes. The reprocessor can also be disinfected automatically to prevent infection or pseudoinfection.

Table 4. Activity of performic acid against spore-forming bacteria[a]

	Lot 1	Lot 2
Bacillus subtilis[b]	0/30 growth	0/30 growth
B. subtilis[c]	0/30 growth	0/30 growth
Clostridium sporogenes[b]	0/30 growth	0/30 growth
C. sporogenes[c]	0/30 growth	0/30 growth

[a]Methodology: AOAC Sporicidal Activity Test, 10-min exposure; 1800 ± 500 ppm performic acid; hard water/aged starting solution at 44 ±2°C.
[b]Silk sutures.
[c]Porcelain cylinders.

The reprocessor can independently process two endoscopes at the user's discretion since it has two washing/sterilization bays. The endoscopes are attached to special holders (racks), which slide into the machine bays located in the front of the machine and provide a connection between the reprocessor and the endoscope's inner channels. The endoscope racks are designed to accommodate all types of flexible endoscopes. During washing, enzymatic detergent is automatically dispensed, diluted with warm water (45ºC), and sprayed onto the exterior endoscope surfaces and pumped through the endoscope lumens. The enzymatic detergent is pumped through the lumens with alternating pulses of compressed air to assist in removing any adhering material. Cleaning studies performed by the manufacturer using a synthetic soil show the system can satisfactorily clean and rinse detergents from an endoscope in preparation for point-of-use sterilization.

The concentration and temperature of the mixed chemicals are automatically measured by the machine with refraction and temperature sensors. Once pumped into the washing/sterilization bay, the sterilant is vigorously sprayed over all exterior endoscope surfaces and pumped through all endoscope lumens to sterilize the scope. Simulated-use studies with resistant spores suspended in 5% serum and inoculated on scope surfaces and inside lumens have demonstrated the effectiveness of the sterilant.

All water used for washing/sterilization and rinsing is filtered through a 0.2-µm filter. The scopes are dried when the cycle is completed by using filtered compressed air that is sprayed over the exterior scope surfaces and through the interior lumens through the same connections used for the washing and sterilization steps.

The total cycle time for scope testing, washing, sterilization, and drying is less than 30 minutes. Upon completion of each cycle, the reprocessor prints a hard-copy record as well as retaining a record in memory, accessible through its floppy disk drive. Printer parameters are printed at the completion of each cycle and include scope identification, processing date, key cycle parameters, space for insertion of patient name or identification number, procedure type, and date (16; CG Roberts, pers. commun., 2000).

Attest Ethylene Oxide (EO) Rapid Readout

EO has been widely used as a low-temperature sterilant since the 1950s. It is the most commonly used process for sterilizing temperature- and moisture-sensitive medical devices and supplies in U.S. health-care institutions. Until

December 1995, EO sterilizers were combined with a chlorofluorocarbon stabilizing agent, but these agents were phased out because they were linked to destruction of the earth's ozone layer. Alternative technologies currently available and cleared by FDA include 100% EO and EO with different stabilizing gases, such as carbon dioxide (CO_2) or hydrochlorofluorocarbon (17). A new rapid readout EO biological indicator, designed for rapid and reliable monitoring of EO sterilization processes, is available outside the United States but has not yet been cleared by FDA.

Sterilization (the complete elimination or destruction of all forms of microbial life) is recommended for all "critical" medical items, such as surgical instruments, cardiac and urinary catheters, implantable devices (e.g., heart valves), and needles. Because it is essential to ensure sterilization of critical items, monitoring of the sterilization process is advised. Monitors may be mechanical, chemical, or biological. Biological monitors are recommended because, unlike chemical indicators, they measure the sterilization process directly by using the most resistant microorganism (e.g., *B. subtilis*), not by merely testing the physical and chemical conditions necessary for sterilization (18,19).

The new rapid readout EO biological indicator will indicate an EO sterilization process failure by producing a fluorescent change, which is detected in an auto-reader within 4 hours of incubation at 37ºC, and a visual pH color change of the growth media within 96 hours of continued incubation. The rapid readout EO biological indicator detects the presence of *B. subtilis* by detecting the activity of an enzyme present within the *B. subtilis* organism, beta-glucosidase. The fluorescence indicates the presence of active spore-associated enzyme and a sterilization process failure. The rapid readout EO biological indicator also detects acid metabolites produced during growth of the *B. subtilis* spore. The acid metabolites are the result of a series of enzyme-catalyzed reactions that occur during spore growth. The growth produces a pH change in the medium that causes the medium to change color from green to yellow, indicating an EO sterilization process failure.

For hospital use, a monitor should be easy to use, inexpensive, and not subject to exogenous contamination; provide positive results as soon as possible after the cycle so that corrective action may be taken; and provide positive results only when the sterilization parameters (e.g., EO concentration, humidity, time, temperature) are adequate to kill microbial contaminants. However, the biological indicator should not be so resistant that it causes needless recall and overprocessing (18). The rapid readout EO biological indicator has potential for substantially improving assessment of EO cycles. According to manufacturer's data, the enzyme was always detected whenever viable spores were present. This was expected because the enzyme is relatively EO resistant and is inactivated at a slightly longer exposure time than the spore.

The rapid readout EO biological indicator can be used to monitor 100% EO, EO-chlorofluorocarbons, and EO-hydrochlorofluorocarbon mixture sterilization cycles. It has not been tested in EO-CO_2 mixture sterilization cycles. The self-contained design (i.e., it contains both the spore strip and growth media) of the indicator makes it easy to use in the department where the sterilizer is located. The rapid readout EO biological indicator should be placed in a test pack (e.g., the Association for the Advancement of Medical Instrumentation) and placed in a full sterilizer load in the most challenging area for the sterilizer (for EO placement should be in the center). Data show that the 4-hour fluorescent sensitivity of this indicator is ≥ 97%, on the basis of the number of visual growth-positive indicators after 168 hours (7 days) of incubation at 37ºC. In fact, all the 7-day growth-positive indicators were detected by fluorescence within 4 hours of incubation (Table 5), indicating that if there is no fluorescence at 4 hours, no growth-positive indicators will be detected with continued incubation.

The ability to monitor EO cycles in a surgical suite or central processing and to have results in 4 hours should enable operating room staff to intercept improperly sterilized items either before use or before a surgery ends. If a hospital could quarantine the load for the 4-hour readout, the need for recalls of potentially nonsterile packages and for informing physicians about the use of nonsterile medical devices could be eliminated. New indicator technologies such as the rapid readout EO biological indicators are likely to improve patient safety (20, PM Schneider, pers. commun., 2000).

Table 5. Sensitivity of Attest rapid readout ethylene oxide biological indicator

Sterilization process	Incubation temp. (°C)	No. tested	No. growth positives (168 hr)	False-negatives (4 hr)	Sensitivity (4 hr)
37°C 600 mg EO/L, 60% relative humidity	37	1,100	752	0	100%
54°C 600 mg EO/L, 60% relative humidity	37	1,300	842	0	100%

A New Low-Temperature Sterilization Technology: Hydrogen Peroxide Plasma

Alternative technologies to sterilize temperature-sensitive equipment are being developed. A new hydrogen peroxide plasma sterilizer, the Sterrad 50, was recently cleared by FDA. It is a smaller version (44-L sterilization chamber) of the Sterrad 100 (73-L sterilization chamber), cleared in 1991. The Sterrad 50 contains a single shelf for placement of instruments to be sterilized within a rectangular chamber, whereas the Sterrad 100 has two shelves and a cylindrical chamber. The operational design of the two sterilizers is similar except that the Sterrad 50 consists of two hydrogen peroxide vapor-diffusion stage-plasma cycles. The sterilization cycles of the Sterrad 50 and Sterrad 100 are 45 minutes and 72 minutes, respectively.

The Sterrad 50 was equally as effective as EO in killing approximately 10^6 *B. stearothermophilus* spores present in the center of narrow-lumen stainless steel tubes (Table 6).

Table 6. Comparative evaluation of sporicidal activity of new low-temperature sterilization technologies (21,22)

Sterilization method	Units positive/units tested			
	LTU,[a] 3 mm	LTU 2 mm	LTU 1 mm	SL,[b] 3 mm
EO-HCFC	0/50	0/40	0/40	0/50
Sterrad 100S	0/50	0/40	0/40	0/40
Sterrad 50	0/30	0/30	0/30	0/30
Sterrad 100	2/40	3/40	37/50	0/40

[a]LTU = lumen test unit.
[B]SL = straight lumen.

The Sterrad 50 and EO sterilized the carriers in even the smallest-lumened device, which was 1 mm in diameter (21).

Conclusions

New sterilization and disinfection technologies may provide significant advantages over existing technologies (Table 7). However, data currently available have primarily been generated by the manufacturers and need to be independently validated. If these new technologies are demonstrated to be effective, their cost-effectiveness compared with standard technologies should be assessed. These new technologies hold the promise of improved patient care.

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Table 7. Comparison of new and standard disinfection and sterilization technologies

Technology		Comparison of new with standard technology		
New	Standard	Advantages	Disadvantages	Future needs
OPA	Glutaraldehyde	-Shorter process time (12 vs. 45 min) -No activation -Not a known irritant to eyes and nasal passages -No vapor ceiling limit -Weak odor	-Stains protein gray -Higher cost	-Additional studies of antimicrobial efficacy -Cost-effectiveness study -Study of effectiveness in actual clinical use -Verification of more cycles per solution than glutaraldehyde
Surfacine	Disinfectants (phenolics quaternary ammonium); Antiseptics (alcohol, iodophor, chlorhexidine gluconate)	-Antimicrobial persistence (>13 days) -May be used on animate and inanimate surfaces -Broad antimicrobial spectrum -Transfers active agent (silver) to microbes on demand without elution -Resistant to forming biofilm -No toxicity to mammalian cells	-Cost?	-Assess microbicidal activity against broad spectrum of pathogens -Demonstration of efficacy to reduce nosocomial infections -Human safety and toxicity data for use as an antiseptic -Demonstrate antimicrobial activity in presence of organic matter
Super-oxidized water	High- or low-level disinfectants; antiseptics	-Basic materials (saline and electricity) inexpensive -End product not damaging to environment -Nontoxic to biological tissues	-Production equipment expensive due to monitoring -Endoscope compatibility unknown -Decreased efficacy in presence of organic matter -Limited-use life (must be freshly generated)	-Evaluation of endoscope compatibility -Cost-effectiveness study
Endoclens	None	-Device automatically cleans and sterilizes -Rapid cycle time (<30 min) -Tests endoscope for channel blockage and leaks -Advantages of automated process (e.g., consistent exposure to sterilant, filtered water rinse, operator convenience)	-Cost? -Used for immersible instruments only -Point-of-use system, no long-term storage	-Cost-effectiveness study -Study of effectiveness in actual clinical use -Assessment of microbicidal activity
EO rapid readout	48-hr spore readout biological indicator	-Rapid (4-hr), reliable assessment of sterilization efficacy -Prevents recall of released sterilization loads	-Cost? -Not tested with EO and CO_2 mixtures	-Cost-effectiveness study -Validation of claimed 100% sensitivity
Plasma sterilizer	Hydrogen peroxide gas plasma sterilizer	-Use of two hydrogen peroxide diffusion-plasma stage cycles is a more effective sterilization process -Reduced cycle time (45 min) -Various sized units available -Leaves no toxic residues	-Cost? -Endoscopes with lengths >40 cm or a diameter of <3 mm cannot be processed	-Cost-effectiveness study -Study of effectiveness in actual clinical use

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Engineering Infection Control through Facility Design

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Many medical centers have modified their facility design to provide a safer environment for patients. From an infection control perspective, the primary objective of hospital design is to place the patient at no risk for infection while hospitalized. We describe historical landmarks about hospital design, modern facility design, and specific designs to prevent acquisition and spread of infections such as tuberculosis and aspergillosis.

While most hospitals are designed to control the spread of infection, this was not always the case. During the evolution of health care, most patients were cared for outside the hospital, and only the poor and disadvantaged received inpatient treatment. For most hospitals, care of the sick became difficult or unwanted. For example, when the statutes of the hospital of St. John, Bridgewater, were developed in 1219, Bishop Joscelin of Bath and Wells commented that "No lepers, lunatics, or persons having the falling sickness or other contagious disease, and no pregnant women or sucking infants, and no intolerable persons, even though they be poor and infirm, are to be admitted in the house; and if any such be admitted by mistake, they are to be expelled as soon as possible" (1). There are many similar cases of medieval English hospitals where admittance of sick persons was discouraged (2).

Puerperal Fever

The delivery of babies in hospital is a relatively recent phenomenon: it evolved during the last half of the 20th century. Before then, maternity hospitals were not considered safe because of relatively high rates of death. It was not until the observations of Oliver Wendell Holmes and Ignaz Semmelweis that puerperal fever was thought to be a communicable disease transmitted from health-care workers to patients.

Semmelweis hypothesized that puerperal fever was spread by the hands of physicians and midwives. He noted that at the Vienna Lying-In Hospital the death rate was almost 10% for women who delivered in Division I, compared with 3% for women in Division II (3). Semmelweis' investigation determined that food, water, ventilation, or socioeconomic class did not account for these discrepancies. However, he observed that patients with prolonged labor were at increased risk and children born to infected mothers were also more likely to become ill. Conversely, women whose babies were born outside the hospital were less likely to develop fever. Semmelweis also noted that infection in Division I occurred sporadically and in clusters, whereas in Division II, no clustering occurred.

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His analysis revealed that medical students, who were responsible for deliveries in Division I, often performed autopsies before assisting in deliveries, while midwives, who worked in Division II, did not. He theorized that disinfecting hands could prevent transmission of infection from a diseased cadaver to a pregnant patient (3). Therefore, on May 15, 1847, he required all medical students to wash their hands with chlorinated lime before assisting in deliveries, which resulted in a dramatic outcome (Figure).

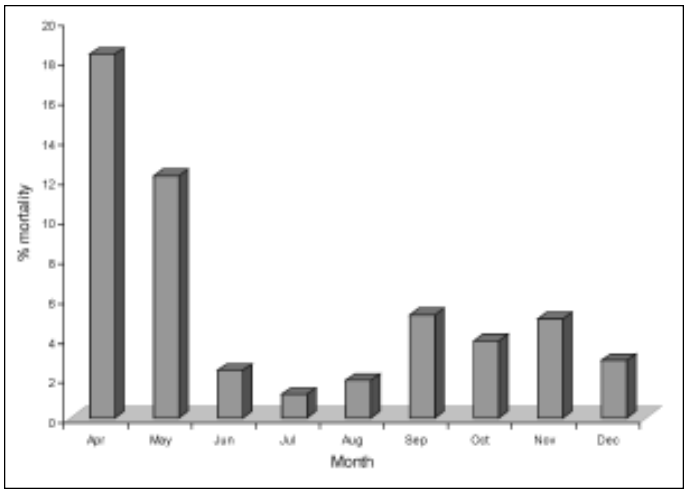

Figure. Division I rates of death, April-December 1847.

Florence Nightingale

Florence Nightingale made many observations about hospital design based on her experiences during the Crimean War. Her ideas regarding a sanitary environment meant rejecting the 18th-century concept of long hospital corridors. She commented that double wards were objectionable on every account primarily because they prevented nurses from being able to assess all their patients at the same time (4). She also observed that open windows interfered with the ventilation of hospital wards and allowed air from the wards to pass into the corridors. Nightingale believed that respiratory secretions were potentially dangerous, especially

among the sick. Therefore, she said that depriving patients of appropriate ventilation "is nothing but manslaughter under the garb of benevolence" (5). Finally, she believed the sick should be isolated and that hospitals should be no more than two stories high. It was her contention that taller buildings interfered with sunlight and ventilation.

Johns Hopkins Hospital

In 1875, after a large donation from Johns Hopkins, plans were developed to build a hospital in Baltimore, Maryland. Of five construction plans, two were substantially influenced by infection control. Norton Folsom, superintendent of Massachusetts General Hospital, believed that the hospital should be well ventilated and provide an isolation ward "for the occasional case so contagious or unpleasantly smelly that it cannot remain under the same roof with others" (6). A New York physician, Stephen Smith, believed that contagious patients should be separated from each other. In his plan, Smith classified patients into one of four categories: acutely contagious cases; uncomplicated infections and fever cases; acute medical and surgical cases; and completely noninfectious chronic disease cases. Further, he suggested that properly separating patients, with appropriate ventilation, was the most important facet of hospital planning.

Private Rooms

In 1920, Asa Bacon of Chicago's Presbyterian Hospital noted that hospitals are hotels for sick people. One disgruntled patient commented to him following his discharge, "When I return, put me in a closet rather than in the ward!" (7). Bacon concluded that the most efficient hospital would contain all private rooms. His vision included a private toilet and lavatory in each room; a central kitchen and serving station; central linen supply instead of linen rooms on each floor; elimination of long corridors; dumbwaiters direct from central supply rooms; and pneumatic tubes to carry written requisitions. Bacon proposed these innovations 80 years ago, and today we take them for granted as integral to the modern medical center.

Aberdeen Royal Infirmary

The Royal Infirmary in Aberdeen, Scotland, was specifically designed to prevent hospital-acquired infections in the surgical unit (8). Based on the recommendations of the Infirmary's Department of Bacteriology, no room had more than four beds, and 41% of the rooms were private or had only one bed. In addition, 10 private rooms surrounding central nurses' station were designed for "intensive nursing care." All rooms were mechanically ventilated, and 75% of the air was cleaned and then recirculated. The design also included an ISPIN (isolation, pre- and postoperative care including intensive nursing) unit with all private rooms placed between the operating room and the wards. This allowed "clean" surgeries to be separated from those with the potential of infection.

Modern Design

To minimize the risk for infection in hospitalized patients, infection control professionals should participate in facility design from a building's inception (9). This allows for identifying potential infection control issues early and provides an opportunity to design solutions prospectively. Infection control professionals also play an important role in educating architects, engineers, and construction workers about potential infection control risks and appropriate methods for reducing them. Because infection control professionals are often the only personnel with a clinical background working on the construction project, they need to visit the construction site frequently and completely understand the extent of the project. Because of the profound implications of inadequate oversight by infection control professionals, these expectations should be included in the hospital building contract (10). In addition, if the policies and procedures set forth by the infection control team are consistently ignored, the institution should fine the contractors.

As part of the planning process for constructing a new facility, an infection control risk assessment should be conducted to determine the potential risk for transmission of microorganisms within the hospital. In general, the risks can be classified as infections transmitted by air, water, or environment. The association between construction and the development of aspergillosis in immunocompromised patients has been known for decades (11), as has the association of hospital-acquired legionellosis and potable water (12). More recently, contamination of the hospital environment has been associated with transmission of *Clostridium difficile* (13), methicillin-resistant *Staphylococcus aureus* (MRSA) (14), and vancomycin-resistant enterococci (VRE) (15).

Preventing Aspergillosis

Aspergillus spp. are ubiquitous fungi, typically found in soil, decaying vegetation, and dust. *Aspergillus* spores are easily suspended in the air and survive for prolonged periods. Because of their size, they are easily inhaled, which can lead to invasive infection of both the upper and lower respiratory tracts in a susceptible host.

Epidemiologic evidence clearly correlates hospital acquisition of aspergillosis with *Aspergillus* spore counts (16). Therefore, installation of HEPA filters is essential in locations housing patients at high risk. While achieving a spore-free environment is an admirable goal, minimal concentrations of fungal spores in the environment are considered safe. In our new hospital, Northwestern Memorial, in Chicago, Illinois, the entire building is HEPA filtered because of the increasing number of immunosuppressed patients. Before opening the hospital, we performed air sampling to ensure the efficacy of the HEPA filter system and found that the composite fungal concentration and the *Aspergillus* spp. spore count were consistent with a highly filtered environment (Table).

Table. Indoor air quality at Northwestern Memorial Hospital

Location[a]	Composite fungal concentration (CFU/m^3)	*Aspergillus* spp. (CFU/m^3)
16W	5.7	0.7
15E[b], 15W	0.04	0.0
11E[c]	0.0	0.0
MICU	0.7	0.0
SICU	1.4	0.0
Operating rooms	0.6	0.0
Lobby	1.0	0.3

[a]MICU = medical ICU; SICU = surgical ICU.
[b]Bone marrow transplant unit.
[c]Solid organ transplant unit.

Prevention of aspergillosis is particularly important for patients undergoing solid organ and bone marrow transplantation. In bone marrow transplant units, the air should be HEPA filtered with the air pressure in the room positive in relation to the corridor. In addition, rooms should be tightly sealed, especially around windows, and the air exchange rate should be high (≥15 per hour) (17).

Preventing Tuberculosis (TB)

Proper health-care facility design can prevent hospital transmission of TB to patients and health-care workers. Ultimately, the interventions necessary to prevent hospital transmission of TB depend on the incidence of this disease in the community and have been published in detail (18). The Centers for Disease Control and Prevention recommends that patients requiring isolation for TB be placed in a room with negative airflow. These rooms should have frequent air exchanges (≥12 per hour), and the air should be exhausted to the outside without recirculation. Doors to the rooms should be self-closing, and the walls, windows, ceiling, floor, and penetrations well sealed. These rooms should be monitored to ensure that they remain under negative pressure when occupied by a TB patient.

Infection control professionals play a substantial role in determining the appropriate location of negative-airflow rooms when a hospital is being designed. Ideally, they should be located in areas where patients at high risk will be cared for (e.g., emergency department, recovery room, bronchoscopy suite, ambulatory clinic, medical units).

Preventing Legionellosis

Legionella is an important cause of community- and hospital-acquired lower respiratory tract infections. Person-to-person transmission of this organism has not been documented. Rather, infection is exclusively acquired from the environment, and hospital acquisition is well recognized (12,19,20). The most consistent observation about health-care acquired legionellosis is its association with potable water. The highest concentrations of the organism are found in hot-water storage tanks, cooling towers, and condensers.

Effective methods for disinfecting the hospital water supply include chlorination, thermal eradication, UV light, and metal ionization (16). At our new medical center, we elected to install a copper-silver ionization system. Despite the potential presence of *Legionella* in the water supply, routine culturing of water in the absence of proven or suspected hospital transmission is not recommended (21).

Hospital Environment as a Risk for Infection

Hospital design should ensure that patients, especially immunocompromised patients, are at no greater risk for infection within the hospital than outside. Because the microbial flora of a health-care facility can be influenced by its design, infection control professionals play a major role in this aspect.

Bacteria on hospital floors predominantly consist of skin organisms, e.g., coagulase-negative staphylococci, *Bacillus* spp., and diphtheroids (22); *S. aureus* and *Clostridium* spp. can also be cultured. However, infection risk from contaminated floors is small. Gram-negative bacteria are rarely found on dry floors, but may be present after cleaning or a spill. Nevertheless, these organisms tend to disappear as the surface dries (23).

The survival of microbes on carpeting, however, is different: they are present in larger numbers on this surface and they pose a greater risk for infection. Therefore, carpets should be vacuumed daily and periodically steam cleaned. Carpeting should be avoided in high-risk areas because the cleaning process may aerosolize fungal spores. Regardless of the flooring chosen, it should be easily cleanable and water resistant (9).

In general, pathogenic microorganisms do not readily adhere to walls or ceilings unless the surface becomes moist, sticky, or damaged (23). Little evidence exists that walls and ceilings are a major source for hospital infection. Wall coverings should be fluid resistant and easily cleaned, especially in areas where contact with blood or body fluids may occur (e.g., laboratories, operating rooms). Finishings around plumbing fixtures should be smooth and water resistant (9). In addition, pipe penetrations and joints should be tightly sealed. Acoustical tiles should be avoided in high-risk areas because they may support microbial growth when wet. False ceilings may harbor dust and pests that may contaminate the environment if disturbed, so should be avoided in high-risk areas unless adequately sealed. Ideally, walls and ceilings should have a smooth, impervious surface that is easy to clean with minimal likelihood of dust accumulation.

Infection control professionals are often consulted to recommend appropriate finishes and fixtures. The best finishes are durable and easy to clean. Surfaces that are porous or textured may be difficult to clean and might therefore harbor potentially pathogenic microbes (10). Furniture is thought to be a minor infection risk, but prolonged survival of VRE on chairs (24) and other environmental surfaces has been documented (25). MRSA and VRE have also been recovered from privacy curtains, scrub suits, and plastic aprons (26); whether contamination of these surfaces poses a risk to patients is unknown. However, survival of these pathogens for even a short time increases the possibility of their being acquired by patients or health-care workers and spread from one person to the next.

Handwashing is the single most important method to prevent hospital infections. Each patient room, examination room, and procedure room needs at least one sink (9). Optimally, it should be as close to the entrance of the room as possible and be large enough to prevent splashing. Too shallow a sink may cause contamination of hands by bacteria residing in the drain; this was linked to a hospital outbreak of multidrug-resistant gram-negative bacilli (27). Each sink should be equipped with a hands-free control, soap dispenser, and paper towel holder. Access to examination gloves and a trash receptacle should be readily available. We installed a dedicated sink at the entrance to every patient room to facilitate handwashing by health-care workers.

Summary

The design of health-care facilities has undergone substantial changes in large part because patients with impaired host defenses now represent an increasing proportion of hospitalizations. As a result, both design and renovation of these facilities present unique challenges and opportunities for infection control professionals, who are often the only clinical staff associated with construction projects. Early involvement in the process can make appropriate communication easier and protect patient safety.

Ultimately, while time-consuming, participation in hospital design, construction, and renovation can serve as another marker of how infection control professionals improve the quality of patient care.

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Can Managed Health Care Help Manage Health Care-Associated Infections?

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Managed-care organizations have a unique opportunity, still largely unrealized, to collaborate with health-care providers and epidemiologists to prevent health care-associated infections. Several attributes make these organizations logical collaborators for infection control programs: they have responsibility for defined populations of enrollees and for their overall health, including preventive care; they possess unique data resources about their members and their care; and they are able to make systemwide changes in care. Health care-associated infections merit the attention and effort of managed-care organizations because these infections are common, incur substantial illness and costs, and can be effectively prevented by using methods that are unevenly applied in different health-care settings. Both national and local discussions will be required to enable the most effective and efficient collaborations between managed care organizations and health-care epidemiologists. It will be important to articulate clear goals and standards that can be readily understood and widely adopted.

The term managed care connotes a commitment to improving the delivery of health care. Most of the U.S. population receives its health care through some form of managed care (1). Thus, managed-care organizations have an enormous potential to affect the incidence and management of infectious diseases in their patients. Health care-associated infections, which are common, serious, and costly adverse outcomes of medical care, have been identified by a recent Institute of Medicine Report as among the most pressing problems of medical care (2).

The potential for managed-care organizations to improve prevention and management of infections derives from four of their defining characteristics. Such organizations are responsible for defined populations in all health-care settings and for the overall health (including health promotion and disease prevention) of their members; they create and use detailed information about their members, their health status, and the medical care they received (although this information is usually not complete, it is typically more comprehensive than that available from other sources); and they are able to make systemwide changes in care, including disseminating guidelines, supporting interventions to improve outcomes, feeding back actual performance data to providers, and setting standards. In each of these respects, managed-care organizations resemble traditional public health agencies, which have played an important role in reducing health-care associated infections.

Managed care's population base and health system strengths, combined with its involvement in the delivery of care to specific persons, create the opportunity to use new capabilities and resources to address healthcare-associated infections. Since this opportunity is still largely unrealized, there are relatively few directly relevant examples. The following three, dealing with prevention of neonatal group B streptococcal infection, surveillance for tuberculosis (TB), and surveillance for postoperative infection, illustrate ways in which managed care can contribute to the prevention or control of serious infections. Although the first two examples are not health care-associated per se, health-care epidemiologists are often involved in hospitals' programs to prevent, identify, manage, and report them.

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Examples of Managed-Care Organizations' Contributions to Prevention and Control of Infectious Diseases

Neonatal Group B Streptococcal Infection

Adoption of guidelines developed by the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, and the American College of Obstetrics and Gynecology has led to a profound reduction in the occurrence of early onset neonatal Group B streptococcal infection (3). These guidelines changed the recommended date for screening pregnant women for vaginal or rectal carriage of group B streptococcus to weeks 35 to 37 of pregnancy, instead of the second trimester. The guidelines also recommend initiating prophylaxis at least 4 hours before delivery. Although the impact of these and other aspects of the guidelines is evident (3), their implementation poses new challenges to the health-care system. For example, ensuring effective communication between the physician's office, the microbiology laboratory, and hospital is essential, since the 35-to 37-week screening cultures are usually performed in obstetricians' offices, while the culture results are needed promptly in the hospital to guide management before delivery. This and other challenges have meant that the guidelines are imperfectly implemented in some settings and

that developing systems that monitor adherence to guidelines is difficult.

Group Health Cooperative of Puget Sound, working in collaboration with CDC, demonstrated the potential for rapid implementation of these guidelines (4). The managed-care organization's obstetricians and administrative staff created systems that facilitated a shift from their prior practice of performing screening cultures at the end of the second trimester of pregnancy to weeks 35 to 37 (Figure 1). Working in conjunction with hospital personnel, they created systems to speed communication of these culture results to the obstetrical services and made other changes in hospital procedures that led to a sharp increase in the proportion of culture-positive women who received antibiotics at least 4 hours before delivery, with no commensurate increase in antimicrobial-drug administration to women who were not colonized with group B streptococcus (Figure 2). This example shows the ability of a managed-care organization to enhance the dissemination of guidelines, improve coordination of care, and monitor adherence to guidelines. This form of coordination is most straightforward in staff model managed-care organizations, such as Group Health Cooperative, but other types of managed-care organizations can use some elements of this approach.

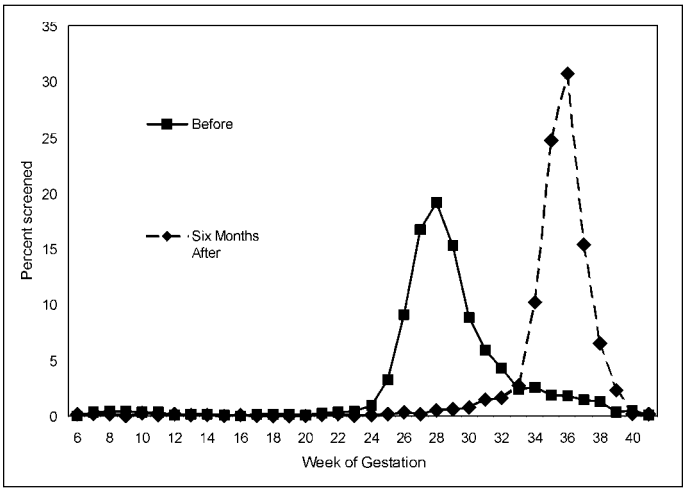

Figure 1. Stage of pregnancy at which group B streptococcal screening specimen was obtained. A prompt shift from second trimester (squares) to weeks 35 to 37 (diamonds) of pregnancy occurred after new guidelines were introduced at Group Health Cooperative of Puget Sound (4).

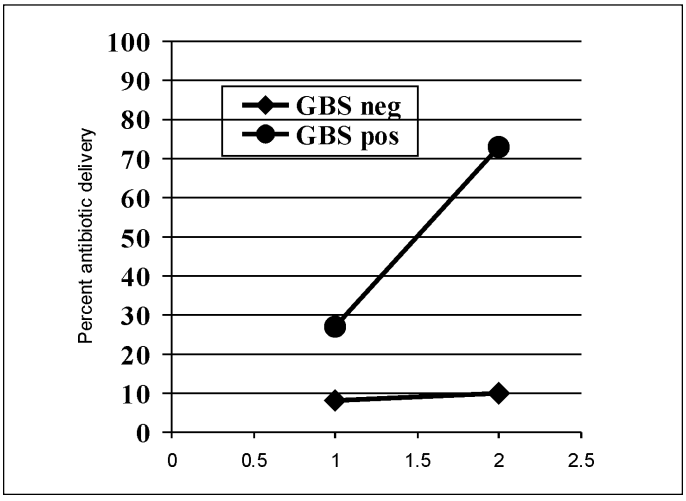

Figure 2. The proportion of women positive for group B streptococcus who started intrapartum chemoprophylaxis at least 4 hours before delivery (squares). For comparison, women without group B streptococcus (diamonds) are also shown (4).

TB Surveillance and Management

A second example illustrates collaboration between managed-care organizations, clinicians, and public health agencies. Both providers and microbiology laboratories are required to report TB to departments of health. However, there is no effective mechanism to assess the completeness of clinicians' reporting of cases when no positive laboratory culture exists. In Massachusetts, a large managed-care organization examined its electronic diagnosis and treatment data, in conjunction with review of the medical records of patients with diagnoses or treatments consistent with TB. When data from the managed-care organization were compared with public health department records (5), 78% of cases were found by both, but the managed-care data revealed an additional 18% of reportable cases previously unknown to the public health department. Most of these cases had no positive culture, and therefore no laboratory-based reports had been generated.

Two additional notable findings emerged from this study. Although the managed-care organization had a rich array of data types available, pharmacy dispensing data alone proved to be the most useful information for identifying patients with active TB, almost all of whom were identifiable because they received at least two anti-TB drugs. Because these drugs are not often used for other purposes, it proved unnecessary to impose further conditions, such as requiring the drugs to be dispensed repeatedly or to be dispensed at the same time. In practice, the drugs were usually dispensed repeatedly and at the same time.

In addition, assessing the frequency and amount of dispensed drugs identified several persons who were poorly compliant with their treatment regimen, but who had not been recognized as such by their clinicians (6). If this result is confirmed in other settings, monitoring the dispensing of drugs for anti-TB therapy may become an important adjunct to TB surveillance and control programs. This investigation could only have been performed effectively in a managed-care setting, where access to diagnosis and treatment data and medical records existed. However, it produced a result that is applicable to other health-care settings in which there is only automated pharmacy data. In principle, this type of reporting could be performed by individual pharmacies or national pharmacy benefit management companies.

Surveillance for Surgical Site Infection

Collaboration between managed-care organizations and hospitals has provided convincing evidence that most surgical site infections are diagnosed after patients are discharged from the hospital, and many patients never return for care of the infection to the facility in which surgery was performed (Figure 3) (7). Further, this trend is increasing as patients are discharged on, or shortly after, the day of surgery. Because

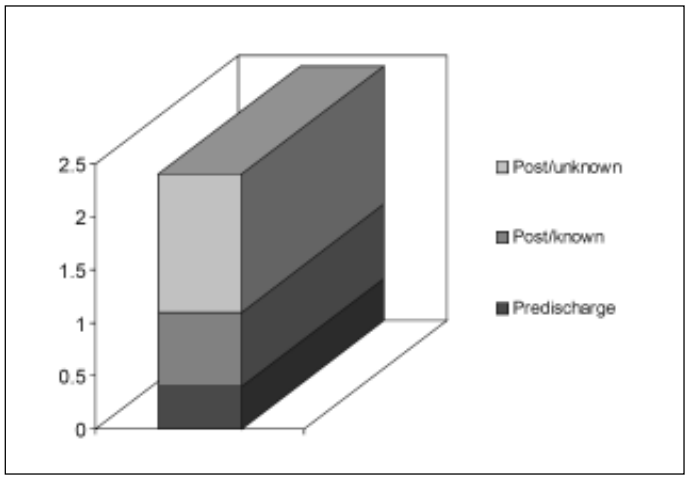

Figure 3. The proportion of postoperative surgical site infections first identified before and after discharge from hospital in which surgery was performed. Light gray bar (Post/unknown) shows infected patients who did not return to the hospital at which surgery was performed. The units on the ordinate are percentages of all procedures (7).

managed-care organizations have information on postoperative care delivered at all sites, including ambulatory settings and other hospitals, they can collaborate with hospitals that perform surgery on their members in conducting postdischarge surveillance that is otherwise difficult if not impossible to perform. Current work supported by CDC's Prevention Epicenters program is focused on developing methods to allow efficient use of computerized data to conduct ongoing surveillance, in conjunction with the hospitals in which surgery is performed (8). In a study of coronary artery bypass surgery performed at five hospitals, data from a managed-care organization identified twice as many surgical site infections as were identified by hospital-based surveillance (9). If this work is successfully extended, it should be possible to use existing automated data to enhance current surveillance capabilities, allowing uniform, objective surveillance for essentially all surgical procedures. This computer-based surveillance could supplement or in some cases replace existing hospital-based efforts that absorb considerable time and effort of skilled infection control professionals, resulting in a more complete and accurate monitoring system.

Developing Collaborations Between Managed Care and Delivery Systems

Successful collaborations require the identification of topics that both sides (the hospital-based health-care epidemiology community and managed-care organizations) agree are important. Therefore, the first step is to assign appropriate priority to health care-associated infections so that both parties can make informed decisions about the value of collaboration.

Setting Priorities

Managed-care organizations are accountable to the purchasers of their care. Usually these are employers, who fund services on behalf of their employees, or government agencies, who contract for services on behalf of Medicaid recipients, Medicare beneficiaries, or government employees. Managed-care organizations are also accountable to their members, and in some cases to accrediting agencies, such as the National Committee for Quality Assurance. Thus, managed-care organizations typically assign priorities on the basis of several considerations, including impact on members' health, members' preferences, cost and cost-effectiveness, society's preferences, and quality of care.

In assessing the impact of programs that address specific health problems, managed-care organizations consider a problem's burden of illness to their members, focusing on common, serious problems like asthma or osteoporosis. They also consider the strength of evidence that interventions can improve health outcome. An example is a standard, adopted by many managed-care organizations, for using beta-adrenergic blockers in survivors of myocardial infarction. This standard was adopted after it was appreciated that use of this relatively safe and simple treatment was not nearly as common as was appropriate, despite substantial clinical evidence of benefit.

Managed-care organizations also give priority to their members' preferences, even when they have no direct bearing on health outcomes or when clinical evidence is lacking. These organizations commit considerable resources to understanding issues that are important to their members and tracking their members' satisfaction. In addition to attending to members' perception of the quality of care they receive, managed-care organizations give priority to minimizing waiting time for appointments, the appearance of offices and inpatient facilities, and many other issues not directly related to health status.

Cost and cost-effectiveness are often important drivers of such organizations' decisions. These decisions are sometimes made from the purchaser's perspective, as in provision of pneumococcal immunizations for the elderly. At other times, decisions about cost-effectiveness are made from a societal perspective. Examples include smoking cessation or mammography screening programs, which typically yield their cost savings far enough in the future that the persons who avoid the adverse health outcomes are unlikely to still be members of the managed-care organization that paid for the care. In making these choices, managed-care organizations typically focus on the 25 conditions that account for nearly 80% of health-care costs (10).

Several dozen quality-of-care benchmarks are represented in managed-care organizations' accreditation standards (11). Examples include mandated performance with regard to childhood and adult immunization programs, cancer screening, diabetes care, substance abuse and mental health, and prenatal care.

Data Issues

Collaborations between managed-care organizations and the health-care epidemiology community are most likely to be successful when the managed-care organizations take advantage of their enrollment and demographic information, pharmacy dispensing data, and claims files. Such information is usually available in electronic databases and is used most often. Work with these data typically involves relatively small marginal costs, once the programs to create them are developed. In contrast, it is typically quite difficult for managed-care organizations to provide information from noncomputerized records, such as office records. Similarly, information on care that is delivered in hospitals or other

organizations with which they contract for services may not be easily available unless these services generate an itemized bill for payment. For example, a managed-care organization would have information on intravenous antimicrobial-drug therapy delivered by a home-care company if the managed-care organization were charged for individual medications, but not for the same treatment if the charge for drugs were bundled into an overall medication administration fee.

Rationale for Collaborations

Benefit to Managed-Care Organizations

Health care-associated infections merit the attention and effort of managed-care organizations according to the criteria noted above because these infections are common, they incur substantial illness and costs, and effective prevention methods exist but are currently unevenly applied in different health-care settings.

The Institute of Medicine Report highlighted postoperative infection as one of the most important categories of adverse events associated with medical care (2). One reason the burden of these infections is difficult to appreciate is that the impact of the adverse event is often "lost" in the overall outcome of the condition being treated. Thus, the fact that almost 20% of patients require ≥9 days of antibiotic therapy because of confirmed or suspected infection after coronary artery surgery is not ordinarily a separately identified outcome of this procedure. However, the total cost of these infections in inpatients alone is estimated to be several billion dollars per year. Additionally, costs of infections that occur outside the hospital have not been adequately measured. Reductions in the occurrence of these infections could contribute to decreasing both illness and costs of care.

Evidence suggests that carefully implemented programs to prevent these infections are effective. Examples include reductions in bloodstream infections in intensive care units, postoperative surgical site infections, ventilator-associated pneumonias, and urinary tract infections. An additional reason that infection control programs merit the attention of managed-care organizations is that they are often the best organized and most effective quality improvement and error reduction programs in many hospitals. The National Nosocomial Infections Surveillance study has demonstrated how coordinated but decentralized systems can collect essential data about quality of care and make meaningful improvements in outcomes (12). Support of infection control programs in hospitals, nursing homes, and other facilities would create opportunities for managed-care organizations to engage more directly in the care provided by these facilities.

Benefit to Infection Control Programs

Managed care can contribute to infection control programs in several ways. It can help make infection control a priority for the entire health-care industry by jointly developing quality benchmarks with hospitals, nursing homes, and other components of the delivery system. The current interest in reducing medical errors can be an important foundation for such work. Managed care can use both its data and its ability to coordinate systemwide interventions to collaborate in research. Examples include better assessment of the epidemiology, risk factors, and consequences of health care-associated infections, as well as assessment of surveillance and prevention methods. Managed care can also have an impact through its considerable ability to bring about change in systems of care. The remarkable shift in the timing of group B streptococcus screening to a different stage of pregnancy in a single staff model managed-care organization demonstrates this potential. Managed care can play an important role in improving surveillance for these infections by contributing data about care delivered outside hospitals and integrating data across hospitals and other delivery sites. It can also assist in the implementation of infection control programs, especially in delivery sites such as physicians' offices, which currently have little organizational framework in which to develop or monitor such systems.

The Path to a More Robust Managed Care: Infection Control Collaboration

To take advantage of the potential benefits to patients, health-care epidemiologists need to strengthen the rationale for managed-care organizations to recognize the importance of health care-associated infections and the potential benefits of improved infection control programs. Most managed-care organizations, like other parts of the delivery system, are fully extended, so the addition of infection control priorities will require them either to displace an existing quality benchmark activity or to expand their roles, which will necessitate passing on new costs to their purchasers.

Both national and local discussions will be required to make the case for infection control collaborations. Nationally, the infection control parties best positioned to articulate overall themes and identify specific areas for collaboration are CDC, the Society of Healthcare Epidemiologists of America, and the Association for Professionals in Infection Control and Epidemiology (APIC). In the managed-care arena, the American Association of Health Plans, the Health Insurance Association of America, the Blue Cross Blue Shield Association, and the managed-care organizations with nationwide memberships are logical participants in these discussions. Other participants in discussions should include accrediting agencies, such as the National Committee on Quality Assurance and the Joint Commission on Accreditation of Healthcare Organiations, and purchasers, such as the Washington Business Group on Health, the National Business Coalition on Health, and the Health Care Financing Administration. Local discussions between individual health-care facilities and the managed-care organizations with which they work will proceed more quickly within the context of a framework that emerges from national discussions.

Developing explicit technical standards for collecting and reporting infection surveillance data will also be important. This is necessary both to ensure that meaningful and interpretable information is collected and to allow the efficient development and dissemination of programs to perform the required work. This strategy has proved useful for other managed-care benchmarking activities, and it should be extended to the managed-care infection control arena. The actual work of creating technical standards is likely to require working groups with broad representation and deep technical expertise. Issues that need to be addressed include relatively straightforward ones of data availability, definitions, and reporting standards, plus some that will address new issues, such as the value of aggregating data across managed-care organizations and development of performance benchmarks.

Finally, it will be important to recognize that both parties to this discussion are evolving rapidly, as is health care itself. This means there will be a need for sustained engagement between managed care and health-care epidemiologists.

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Health-Care Quality Promotion through Infection Prevention: Beyond 2000

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Health-care value purchasing, complex health-care systems, and information technology are the three most important change drivers influencing the interrelated themes of the 4th decennial conference: accountability, quality promotion through infection prevention across the health-care delivery system, and medical informatics. Among the change drivers influencing themes of future conferences may be a societal mandate for health promotion and health-care access for all.

Tempora mutantur, nos et mutamur in illis.
Times change, and we change with them.
Owen's Epigrammata, 1615

Globalization, population demographics, and biotechnology are examples of change drivers that influence our social lives, businesses, and government. These forces create a changing environment to which organizations must adapt. Change drivers also affect our health-care system and were reflected in the themes of this decennial conference.

In 1970, the rising cost of medical care in the fee-for-service environment was a major change driver. Risk management also became an important force, in response to the increase in medical malpractice claims and awareness that health care-associated infections could lead to litigation. In 1970, reducing the frequency of both endemic and epidemic hospital infections was emphasized, as well as emerging pathogens and antimicrobial-drug resistance (1).

Ten years later, health-care economics was still an important force, this time manifest by the onset of prospective reimbursement and diagnosis-related groups as the basis for payment. In addition, standards for hospital accreditation relevant to infection control had a major impact on the profession. The 1980 themes included the critical role of surveillance and infection control personnel in preventing infection and the importance of risk stratification in interpreting infection rates (2).

By 1990, the broadening market penetration of managed care and the reduced emphasis on hospital in-patient care were key change drivers. The effects of the "quality assurance movement" were also evident, along with the enormous impact of the HIV epidemic. A major theme in 1990 was increasing severity of illness and hence, increasing infection risk among hospital patients (3). For the first time, infections in nonhealth-care settings received attention, as well as occupational infections, including HIV and other bloodborne pathogens.

Among many factors influencing the profession of health-care epidemiology and infection control in the 1990s, three were deemed to have the most potent impact: health-care value purchasing, the increasing complexity of health-care systems and health care, and advances in medical information technology. Hence, three major themes emerged: accountability, or demonstrating the attributable impact of infections and the cost-effectiveness of prevention interventions; extension of health-care quality promotion and infection prevention programs to include the entire health-care delivery system; and innovative uses of medical informatics to enhance the overall impact of our profession.

Health-Care Value Purchasing

Health-care expenditures are once again increasing at an alarming rate, despite extensive efforts to control costs through managed care and other strategies. Consumers, third-party payers, and politicians are demanding that the delivery system be accountable for the value of these expensive purchases. Health-care value in simple terms is directly proportional to quality and inversely proportional to cost. Ideally, the goal is to obtain the highest quality health care at an affordable price. From the business perspective, as the cost of health care per covered employee life increases, corporate profit margins shrink. Investments in high-quality prevention and care services that reduce the need for more expensive care in the future make good business sense for employers. Hence, many corporations have a strong incentive to maximize both short- and long-term value of the health-care benefits they purchase for employees. As a result, large purchasing coalitions have emerged and now exert considerable influence on the prevention and treatment services provided by the health plans they support.

Accountability in Health-Care Quality Promotion

Value purchasing is driving major changes in the delivery system and new standards for the entire health-care industry. To survive in this environment, we must first provide the evidence that quality promotion and infection prevention programs contribute to health-care value and then help shape new standards for quality and safety. The first major conference theme, accountability, is a direct response to the powerful influence of value purchasing on our profession. Accountability requires documenting the attributable impact of health care-associated infections on health-care outcomes and cost. We must measure the impact of infections on patient outcomes, satisfaction, and cost of care through credible

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research and use this information to justify goals for prevention interventions and the need for resources.

Evidence alone is not sufficient to convince decision-makers that infection prevention is a critical component of quality promotion and adds value to the delivery system. We must effectively communicate this information, not only to our traditional constituents, but also to health-care administrators, organizations, accreditors, regulators, and perhaps most importantly, purchasers and consumers. Effective communication will require some revision in our vocabulary and a "multilingual" approach that includes concepts traditionally embraced by other disciplines.

Health-care epidemiologists and infection control professionals are in the business of infection prevention. Quality managers and accreditors are in the business of continuous quality improvement. Health-care purchasers and consumers are in the business of promoting patient safety and health-care value. Each of these three groups has its language (Table), but essentially all are talking about the same things.

"Nosocomial" is a word with a precise meaning that remains obscure to many within the health-care system and to most outside of it. "Surveillance" is another term that effectively communicates an important concept within our profession but has completely different meanings outside the epidemiology and public health community. We accept the concept that some health care-associated infections are preventable. However, when this same concept is presented as "some health care-associated infections are due to medical errors," many are not so accepting. Until we achieve a "no name, no blame, no shame" atmosphere, "medical error prevention" perhaps should be framed as "patient safety promotion." Words that obscure the problem, miscommunicate our purpose, or alarm constituents must be avoided if we are to convince decision-makers to invest in our prevention programs.

Accountability also requires that the success (or failure) of quality promotion efforts, including infection prevention programs, be measured. Proposed measurements of quality generally encompass three main areas: health-care outcomes and cost, processes of care that serve as indicators or surrogates of outcomes, and patient or consumer satisfaction.

Traditional health-care epidemiology has not emphasized measurement of outcomes or patient satisfaction. We do have enormous expertise in measuring processes of care (e.g., infection rates, invasive device utilization, antimicrobial-drug use). In addition, we have considerable experience in creating scientifically valid performance measures and benchmarks for intramural or external comparisons. The National Nosocomial Infections Surveillance (NNIS) system is perhaps the largest and certainly the longest ongoing system for monitoring adverse events in hospitals. In the 1990s, rates of infections monitored in NNIS hospitals declined by >30%, suggesting that NNIS benchmarking is an effective quality promotion program in facilities that have invested in the infection control staff necessary for participation (4). Preliminary data also suggest that performance measurement, benchmarking, and feedback systems can improve antimicrobial-drug use and reduce antimicrobial-drug resistant infections among intensive care patients. This approach is likely to have broad utility in preventing adverse events and promoting patient safety in other domains and venues.

Table. Perspectives on health-care quality

Perspective	Infection control	Continuous quality improvement	Patient safety
Focus	Adverse health events	Indicators	Errors, near misses
Determinants	Risk factors	Patient mix	Root cause, human factors
Monitoring	Surveillance, response	Performance measurement, improvement	Reporting, learning
Goal	Prevention	Performance improvement	System improvement
Key professionals	Health-care epidemiologists, infection control professionals	Quality managers, accreditation officials	Systems engineers health-care purchasers, consumers

Measuring adverse event rates is most appropriate when the numerator is not expected, at least in the short run, to be zero (i.e., when there is a reasonable expectation that an event occurs often enough to merit attention and is not entirely preventable). Health care-associated infections certainly fall into this category, as do many other complications of health care. From the perspective of those responsible for ensuring quality care to a population of patients, monitoring and comparing rates can be extremely helpful in diagnosing the need for prevention programs at the local level. Likewise, facilities with rates well below those observed in comparable facilities serving comparable patients can be confident that their care is not deficient in that dimension.

However, we must also consider the perspective of the individual patient, who is much more concerned about the cause and consequences of his or her infection than with the facility's infection rate. Even in facilities with low infection rates, some individual infections are likely to be preventable. Overreliance on rates can create complacency and lost opportunities to learn from these events and prevent them in the future. The Institute of Medicine report "To Err is Human–Building a Safer Health System" drew national attention to the relevance of this perspective and has legitimized the value of assessing the causes of individual adverse events, errors, and near-misses (5). Likewise, the Joint Commission on Accreditation of Health-Care Organizations requires facilities to investigate sentinel events, identify their root causes, and take action to prevent them in the future (see URL: www.jcaho.org/sentinel/sentevnt_frm.html.)

Complexity of the Health-Care Delivery System

An elderly patient admitted to a hospital with severe community-onset pneumonia may be evaluated in the emergency department, visit the radiology department for a state-of-the-art imaging procedure, and then be admitted to the intensive care unit for mechanical ventilation. Once stable, the patient could have a brief stay in a step-down unit before being transferred to a medical ward. Movement from one room to another or from one ward to another is likely because bed or room changes often are needed to accommodate staffing shortages or isolation room requirements. As soon as possible, the patient will be transferred to a skilled nursing facility and then finally, if all goes well, to home care or home with ambulatory care follow-up. Along the

way, the patient will have contact with many health-care personnel, including nurses, respiratory therapists, technicians, phlebotomists, dieticians, housekeepers, physicians, consultants, fellows, house staff, and students. In addition, the patient will encounter an amazing array of medical devices and monitors, undergo dozens of laboratory tests, and receive numerous oral and intravenous medications.

The systems of health-care delivery, for even a fairly simple problem, are both dynamic and incredibly complex. Patient transfers and complicated interactions between patients, personnel, and the processes of care (each allowing opportunities for adverse events or errors) present formidable challenges to quality health care and effective intervention programs. Clearly, the increasing complexity of health care is a major change driver affecting virtually every domain of our profession.

Quality Promotion through Infection Prevention across the Spectrum of Health-Care Delivery

The urgent need for enhanced infection prevention programs in nonhospital settings has been acknowledged for more than a decade. However, programs to effectively address this need have been slow to evolve because of lack of information about the incidence and impact of infections; lack of validated methods to monitor infections, antimicrobial-drug use, and resistance; and lack of evidence to document the cost-effectiveness of prevention programs outside hospitals. These deficits can be overcome with research, demonstration programs, and other creative enterprises. However, some contributing factors present more difficult challenges: scant resources for hiring and developing the needed staff; lack of regulatory and accreditation standards to ensure that truly effective program components are in place; and perhaps most importantly, lack of focused leadership and commitment from professional and governmental organizations.

The complexity of the delivery system demands new strategies to achieve meaningful improvements in quality and patient safety. The movement of patients through various health-care settings provides strong support for integrating prevention programs to encompass the entire system of care. Until the patient or patient population, rather than the venue of care, is seen as the organizing principle for these activities, effectiveness will be compromised and new prevention opportunities will be missed. For example, monitoring programs may need to measure not only the use of antimicrobial drugs in the intensive care unit, but also their use in patients with diabetes or in geriatric patients as they move in and out of various venues of care. If trends toward increased integration of care continue, then integrating infection prevention and quality promotion efforts will be essential.

Information Technology

The computer age slowly emerged during the last three decades. The 1970 proceedings include a paper describing the use of computer-compatible formats for infection surveillance (6). By 1980, many hospitals had computerized laboratory information systems sufficient to conduct some laboratory-based surveillance and monitor antimicrobial-drug susceptibility. By 1990, systems had evolved to include consideration of the electronic medical record as a key component of surveillance and intervention programs. However, the computer age has clearly given way to the explosive onset of the information age. In 2000, we have access to more information than we dreamed possible even 5 years ago, we can instantaneously exchange that information with anyone, and we can disseminate useful prevention tools anywhere in the world. We are enjoying the benefits of a technologic capacity that far exceeds our own capacity to make effective use of it, a capacity that will revolutionize our profession.

Quality Promotion through Informatics

Medical informatics is the scientific field that uses computer technology and communication systems to retrieve, exchange, and optimize use of biomedical information and data for making health-care decisions and solving problems. Computer order entry, on-line decision support, and immediate feedback about treatment decisions are now recognized as key opportunities for improving medical care. With the advent of integrated systems, data repositories, and robust analytic tools, electronic surveillance for infections, antimicrobial-drug resistance, and related adverse health events is a realistic goal.

The technology to create local, regional, national, and international networks for communicating health information and providing decision support already exists. E-mail, list-serves, and other informal networking strategies are in wide use. Plans are already under way for integrated state-based electronic notifiable disease reporting, which includes electronic laboratory data reporting protocols (See URL: http://www.cdc.gov/nchs/otheract/phdsc/presenters/nedss.pdf). Programs to link local users in health-care facilities with local and state health departments and CDC have received increasing priority and funding as a component of bioterrorism preparedness and response activities (See URL: http://www.phppo.cdc.gov/han/). Creating effective internet-based bidirectional communication channels between the health-care delivery system and the public health system is likely to optimize detection, prevention and control of many emerging health problems.

A complex system such as health-care delivery involves factors that interact in a very complicated manner. Reducing a complex system to its simplest terms (e.g., disease or no disease, risk factor or no risk factor) is one of the strengths of epidemiology. However, this approach is not sufficient for understanding health-care systems and the factors affecting outcomes. Fortunately, advances in systems engineering, computer science, and complexity research have produced new tools for understanding complex systems with important applications in patient safety and health-care quality promotion. It is now possible to mine the large data repositories that contain data from patients, providers, facilities, and plans to identify important trends, evaluate outcomes and costs, and detect associations that may lead to quality promotion interventions. New tools for data mining, which are adept at handling large and robust data sets and tolerate missing or sometimes inaccurate data elements, enhance the feasibility of this process and are already in use for evaluating emerging infections (7). Use of neural network analytic software is in its infancy, but several creative applications have demonstrated its utility, including clinical prediction rules to aid diagnosis (8,9). These and similar tools help generate new hypotheses that aid understanding of the system or lead to evaluation of new intervention targets.

Beyond 2000

Times change, and CDC must change along with them. The Hospital Infections Program has redefined its mission–to protect patients, protect health-care personnel, and promote health-care quality–and initiated a reorganization to more effectively accomplish its priority program objectives. This process is reflected in the new name, Division of Healthcare Quality Promotion, which became effective January 1, 2001. The name change does not signal an end to more than four decades of successful infection prevention and control activities or a new move into "quality." Rather, it reflects what always has been true: infection prevention is a critically important component of quality promotion. To paraphrase Dr. Richard Wenzel's statement in 1990, infection control is the premier program for quality promotion in U.S. hospitals. It makes no sense to ask whether infection control should expand to include quality promotion; infection control has, from its inception, been quality promotion (10).

The core activities in health-care epidemiology and infection control—cluster and outbreak investigations, case-control studies to identify risk factors, surveillance and response, laboratory investigation, intervention efficacy and effectiveness studies–are tools with broad applicability to many domains of health-care quality. We can lend these tools to our colleagues in other disciplines and, in turn, benefit from their tools–root cause analysis, human factors research, hazards analysis, economic assessment—as we pursue common goals. We have a unique opportunity to experience, and, more importantly, to lead the development of consilience, the linkage of facts and fact-based theory across disciplines to create a common basis for new explanation or action, in health-care quality promotion (11).

First, the experience gained from preventing health care-associated infections must be generalized to encompass a broader set of adverse events. The progression is logical: from catheter-associated infections to device-associated infections to device-associated complications; likewise, from surgical site infections to procedure-associated infections to procedure-associated complications; from antimicrobial-drug resistance to medication complications. Together these three generic categories–device, procedure, and medication complications-account for most adverse events and medical errors that affect patient and provider safety, and hence are priority targets for quality promotion efforts. Building on the lessons learned from hospital infection control is one way to achieve rapid success in preventing these related complications. Second, multidisciplinary collaborations are essential to instigate innovative prevention research, identify new applications for old prevention strategies, maximize synergy among the broad array of professionals engaged in quality promotion efforts, minimize overlap, and conserve scarce resources.

In summary, health-care value purchasing, increasingly complex health-care systems, and information technology are the three most important change drivers that influenced the inter-related themes of the 4th Decennial Conference: accountability, quality promotion through infection prevention across the health-care delivery system, and medical informatics. Among the change drivers influencing the themes of the 5th International Conference may be a societal mandate for health promotion and health-care access for all. We can hope that market forces demand that "caring"–for patients and their providers–assumes the highest value in health-care purchasing decisions. Until we put the caring back into the health-care delivery system, we cannot hope to be successful with any quality promotion effort.

Successful consilience among professionals with complementary skills and capacities working in concert to solve quality of care problems would be an exciting future theme. Prevention "success stories" would be another, perhaps including such topics as elimination of occupational needle injuries, complete adherence to immunization guidelines among patients and providers, and substantial reductions in the incidence of antimicrobial drug-resistant infections. Likewise, dramatic reductions in benchmark rates of infections, other adverse events, and medical errors in all health-care venues, a sign that successful measurement and prevention programs have been implemented across the entire system, would be a wonderful theme for the future. Finally, we may fervently hope that the 5th Decennial Conference will celebrate success in accomplishing the single most important factor necessary to promote health-care quality—a system that fosters joy and balance in the lives of health-care providers and the time for them to express their caring and concern for patients.

Dr. Gerberding is director of the Division of Healthcare Quality Promotion (formerly the Hospital Infections Program) at CDC and associate professor of medicine (infectious diseases) and epidemiology at the University of California, San Francisco. She has conducted many research investigations on infection prevention among patients and their care providers and contributed to the development of prevention guidelines and policies at the local, state, national, and international levels.

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Upcoming Events

Fourth Annual Conference on Vaccine Research
Arlington, Virginia
April 23-25, 2001

The conference is sponsored by the National Foundation for Infectious Diseases, in collaboration with the Centers for Disease Control and Prevention; the National Institute of Allergy and Infectious Diseases, National Institutes of Health; the International Society for Vaccines; the Agricultural Research Service, U.S. Department of Agriculture; the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration; the Albert B. Sabin Vaccine Institute; and the World Health Organization.

The meeting will focus on research and development of vaccines and associated technologies for the control of human and veterinary diseases through immunization. Program announcements and forms for registration and hotel reservations are available from www.nfid.org/conferences/vaccine01/ and by request to the National Foundation for Infectious Diseases, Suite 750, 4733 Bethesda Avenue, Bethesda, MD 20814-5228; telephone: 301-656-0003, ext. 19; fax: 301-907-0878; e-mail: info@nfid.org

Seventh International Course on Dengue: A Challenge for the Third Millennium
Pedro Kourí Tropical Medicine Institute, Havana, Cuba
August 13–24, 2001

The course is sponsored by the World Health Organization (WHO) Collaborating Centers for Viral Diseases and for Training and Research on Medical Malacology and Biological Control of Vectors and Intermediate Hosts of the Pedro Kourí Tropical Medicine Institute, and the Pan-American Health Organization and the Special Program of Research and Training for Tropical Diseases, WHO.

The course is intended for physicians, microbiologists, infectious disease specialists, biochemists, epidemiologists, entomologists, and technologists involved in the prevention and control of dengue. Presentations (in Spanish) will cover the following general areas: laboratory diagnosis; entomology, vector control, and community participation; and clinical and pathologic aspects of dengue and dengue hemorrhagic fever.

Applications should be sent by fax or e-mail before July 1, 2001; include name and postal address, telephone, telex, fax, e-mail address, a short curriculum vitae, and the practical session of interest; and be sent to Prof. María G. Guzmán, Instituto "Pedro Kourí," Autopista Novia del Mediodía, Km 6, P.O. Box 601, Mnao. 13, Ciudad Havana, Cuba; telephone: 53-7-220450, 53-7-220633; fax: 53-7-246051; e-mail: lupe@ipk.sld.cu. Additional information is available at http://www.sld.cu/instituciones/ipk/eventoipk/cdengue.htm

Intensive Review Course in Clinical Tropical Medicine and Travelers' Health
San Francisco, California
October 23-24, 2001

This two-day course is sponsored by the American Society of Tropical Medicine and Hygiene (ASTMH) in cooperation with the American Committee on Clinical Tropical Medicine and Travelers' Health. The course will provide a broad overview of core topics (e.g., tropical illness caused by viral, bacterial, mycobacterial, protozoal, helminthic and ectoparasitic agents; pre- and post-travel consultations; immunizations and evaluations; and the proper care of moderate- to high-risk travelers). It is designed for all health-care providers in this specialty and for physicians planning to take the ASTMH-sponsored certification examination in clinical tropical medicine and travelers' health, to be administered on November 10, 2001, in Atlanta, Georgia, before the ASTMH 50th Annual Meeting.

For additional information, please contact ASTMH (telephone: 847-480-9592; e-mail: astmh@astmh.org) or visit the ASTMH web site at http://www.astmh.org.

Updates in Special Bacterial Pathogens
Hilton Atlanta Hotel and Towers
Atlanta, Georgia
November 10-11, 2001

This 1 1/2-day course, sponsored by the American Society of Tropical Medicine and Hygiene (ASTMH) in cooperation with the American Committee on Clinical Tropical Medicine and Travelers' Health, will focus on new developments in special bacterial pathogens (e.g., those that cause plague, anthrax, botulism, melioidosis, and shigellosis). The course will immediately precede the ASTMH 50th Annual Meeting.

For additional information, please contact ASTMH (telephone: 847-480-9592; e-mail astmh@astmh.org) or visit the ASTMH web site at http://www.astmh.org.

50th Annual Meeting of the American Society of Tropical Medicine and Hygiene
Hilton Atlanta Hotel and Towers
Atlanta, Georgia
November 11-15, 2001

The annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) will include basic research on disease agents and mechanisms of pathogenesis at the molecular level; new diagnostic methods; vaccine and drug design and evaluation; epidemiologic investigations; public health interventions; economic analyses of tropical disease impact; and vector biology and control. Highlights of the 2001 meeting include sessions on DNA vaccines, molecular parasitology, pathogenesis of malaria, cytokines and parasite antigens, epidemiology of tropical diseases, and mucosal immunity. ASTMH has issued a call for papers, with a deadline of June 1, 2001, for online abstract submissions at http://abstract.cornetser.com.

For additional information, please contact ASTMH (telephone: 847-480-9592; e-mail: astmh@astmh.org) or visit the ASTMH web site at http://www.astmh.org.

Ignaz Philipp Semmelweis (1818-65), a Hungarian obstetrician educated at the universities of Pest and Vienna, introduced antiseptic prophylaxis into medicine.

In the 1840s, puerperal or childbirth fever, a bacterial infection of the female genital tract after childbirth, was taking the lives of up to 30% of women who gave birth in hospitals. Women who gave birth at home remained relatively unaffected. As assistant professor on the maternity ward of the Vienna General Hospital, Semmelweis observed that women examined by student doctors who had not washed their hands after leaving the autopsy room had very high death rates. When a colleague who had received a scalpel cut died of infection, Semmelweis concluded that puerperal fever was septic and contagious. He ordered students to wash their hands with chlorinated lime before examining patients; as a result, the maternal death rate was reduced from 12% to 1% in 2 years. Nevertheless, Semmelweis encountered strong opposition from hospital officials and left Vienna in 1850 for the University of Pest.

As a professor of obstetrics at the University of Pest Hospital, he enforced antiseptic practices and reduced the death rate from puerperal fever to 0.85%. However, Semmelweis' findings and publications were resisted by hospital and medical authorities in Hungary and abroad. After a breakdown, he entered a mental hospital in Vienna, where he died of an infection contracted during an operation he had performed.

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Editorial Policy and Call for Articles

Emerging Infectious Diseases is a peer-reviewed journal established expressly to promote the recognition of new and reemerging infectious diseases around the world and improve the understanding of factors involved in disease emergence, prevention, and elimination.

The journal has an international scope and is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health, as well as from specialists in economics, demography, sociology, and other disciplines. Inquiries about the suitability of proposed articles may be directed to the Editor at 404-371-5329 (tel), 404-371-5449 (fax), or eideditor@cdc.gov (e-mail).

Emerging Infectious Diseases is published in English and features the following types of articles: Perspectives, Synopses, Research Studies, Policy Reviews, and Dispatches. The purpose and requirements of each type of article are described in detail below. To expedite publication of information, we post journal articles on the Internet as soon as they are cleared and edited.

Chinese, French, and Spanish translations of some articles can be accessed through the journal's homepage at www.cdc.gov/eid. Articles by authors from non-English-speaking countries can be made simultaneously available in English and in the author's native language (electronic version of the journal only).

Instructions to Authors

Manuscript Preparation

Follow "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (Ann Intern Med 1997:126[1]36-47) (http://www.acponline.org/journals/annals/01jan97/unifreqr.htm).

Begin each of the following sections on a new page and in this order: title page, abstract, text, acknowledgments, references, tables, figure legends, and figures.

Title page. Give complete information about each author (i.e., full name, graduate degree(s), affiliation, and the name of the institution in which the work was done). Also provide address for correspondence (include fax number and e-mail address).

Abstract and key words. Avoid citing references in the abstract. Include up to 10 key words; use terms listed in the Medical Subject Headings from Index Medicus (http://www.nlm.nih.gov/mesh/meshhome.html).

Text. Double-space everything, including the title page, abstract, references, tables, and figure legends. Type only on one side of the paper and number all pages, beginning with the title page. Indent paragraphs 5 spaces; leave no extra space between paragraphs. After a period, leave only one space before beginning the next sentence. Use Courier font size 10 and ragged right margins. Italicize (rather than underline) scientific names when needed.

Electronic formats. For word processing, use WordPerfect or MS Word. Send graphics in native format or convert to .TIF (Tagged Image File), or .EPS (Encapsulated Postscript) formats. The preferred font for graphics files is Helvetica. Convert Macintosh files into one of the suggested formats. Submit slides or photographs in glossy, camera-ready photographic prints.

References. Follow the Uniform Requirements style. Place reference numbers in parentheses, not in superscripts. Number citations in order of appearance (including in text, figures, and tables). Cite personal communications, unpublished data, and manuscripts in preparation or submitted for publication in parentheses in text. Consult List of Journals Indexed in Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title in full. List the first six authors followed by "et al."

Tables and figures. Create tables within the word processing program's table feature (not columns and tabs within the word processing program). For figures, use color as needed; send files, slides, photographs, or prints. Figures, symbols, lettering, and numbering should be clear and large enough to remain legible when reduced. Place figure keys within the figure.

Manuscript Submission

Include a cover letter verifying that the final manuscript has been seen and approved by all authors.

Submit three copies of the original manuscript with three sets of original figures and an electronic copy (on diskette or by e-mail) to the Editor, Emerging Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., MS D 61, Atlanta, GA 30333, USA; e-mail eideditor@cdc.gov.

Types of Articles

Perspectives, Synopses, Research Studies, and Policy Reviews: Articles should be approximately 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch.

Perspectives: Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases or related issues. Perspectives may also address factors known to influence the emergence of diseases, including microbial adaptation and change; human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Synopses: This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. Use of subheadings in the main body of the text is recommended. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text. Photographs and illustrations are encouraged.

Research Studies: These articles report laboratory and epidemiologic results within a public health perspective. Although these reports may be written in the style of traditional research articles, they should explain the value of the research in public health terms and place the findings in a larger perspective (e.g., "Here is what we found, and here is what the findings mean").

Policy Reviews: Articles in this section report public health policies that are based on research and analysis of emerging disease issues.

Dispatches: These brief articles are updates on infectious disease trends and research. The articles include descriptions of new methods for detecting, characterizing, or subtyping new or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination programs are appropriate. Case reports are also welcome. Dispatches (1,000 to 1,500 words) need not be divided into sections. Provide a short abstract (50 words); references, not to exceed 10; figures or illustrations, not to exceed two; and a brief biographical sketch.

Book Reviews: Short reviews (250 to 500 words) of recently published books on emerging disease issues are welcome.

Letters: This section includes letters that give preliminary data or comment on published articles. Letters (500 to 1,000 words) should not be divided into sections, nor should they contain figures or tables. References (not more than 10) may be included.

News and Notes: We welcome brief announcements (50 to 150 words) of timely events of interest to our readers. (Announcements can be posted on the journal web page only, depending on the event date.) In this section, we also include summaries (500 to 1,500 words) of conferences focusing on emerging infectious diseases. Summaries may provide references to a full report of conference activities and should focus on the meeting's content.