Antibiotic-resistant pathogens constitute an important and growing threat to the public health. To understand how important they are, one must recognize that infectious diseases are in aggregate the leading cause of human death worldwide and the third leading cause of human death in the United States. More than 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used to treat these infections. Antibiotic resistance occurs when a microbe acquires a gene, which allows the microbe to inactivate the antibiotic or otherwise nullify its antimicrobial activity. This may occur as a spontaneous, genetic mutation or involve acquisition of a mobile genetic element such as a plasmid, transposon, integron, or gene cassette. It became obvious in the 1940s and 1950s that using an antibiotic to which the microbe was resistant resulted in prolonged suffering and, with serious infections, a higher risk of death than with therapy for infections due to antibiotic-susceptible strains of the same species. In the past decade, there has been an increasing focus on the costs of medical care and it also has become clear that prolonged hospital stay and higher costs result from infections caused by antibiotic-resistant pathogens as compared with infections due to antibiotic-susceptible strains of the same species.

Many different mechanisms of resistance and even...
minor variations on such mechanisms have been described. For example, shortly after penicillin began to be used for clinical therapy, penicillinase was discovered. Since that time, more than 200 different types of penicillinase have been reported. The many different mechanisms of resistance are beyond the scope and focus of this guideline, but it is germane to note that for some microbe–antibiotic pairs, the rate of spontaneous mutation is so frequent that monotherapy with that particular drug will frequently result in the development of antimicrobial resistance and failure of therapy. For example, when isoniazid (INH) is used alone to treat active tuberculosis, more than 70% of patients’ infecting strains develop resistance to INH. Although therapy does not cause the genetic mutation, which occurs spontaneously, it rewards the mutation with a selective advantage to survive. All secondary cases arising from spread from such an index patient exhibit INH resistance. Similarly, significantly higher rates of rifampin resistance are observed after rifampin monotherapy of *Staphylococcus aureus* infection and can be induced in vitro after exposure to rifampin.

Since antibiotic resistance was first documented almost six decades ago, the reasons for its appearance and inexorable increase have been researched and debated. It is clear that antibiotic use has in some way caused this problem. Before penicillin, methicillin, or mupirocin began to be used clinically, resistance to each drug among staphylococci was virtually nonexistent. Likewise, before the use of vancomycin began in the United States, there were no known *Enterococcus faecalis* or *Enterococcus faecium* isolates with vancomycin resistance.

It also is clear that some part of this problem has been due to the spread of resistant strains from patient to patient. The spread of lethal infections from patient to patient via contaminated healthcare workers (HCWs) has been recognized for more than a century and a half since the seminal observations of Holmes and Semmelweis. Darwin’s observations from the same era about natural selection of strains and species best suited to survive within a particular environment help to explain why the problem of antibiotic resistance has been continually amplified most greatly in the healthcare setting, where the prevalence of antibiotic therapy has been highest. The high rate of antibiotic therapy in the healthcare setting means that a strain with a resistance factor enjoys a selective advantage to survive, proliferate, and spread.

The optimal means of control of antibiotic-resistant pathogens has been debated for decades. This guideline focuses on the importance of the spread of antibiotic-resistant pathogens from patient to patient in the healthcare setting and the evidence supporting prevention strategies. Moreover, because most of the available data regarding the transmission of antibiotic-resistant pathogens have focused on methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) during the past two decades, identifying an optimal means for preventing their spread is the primary goal of this guideline. This seems appropriate because healthcare-associated MRSA and VRE infections have increased rapidly during the past decade, these infections are more costly and more lethal than those due to antibiotic-susceptible strains of the same species, and failure to control MRSA and VRE will likely make control of vancomycin-resistant *S. aureus* (VRSA) impossible.

Medline searches of English-language publications from 1966 to 2002 were used on the major topic headings antibiotic resistance, beta-lactam resistance, methicillin resistance, vancomycin resistance, infection control, and control to identify relevant articles. The authors’ personal reference manager files were also used for this purpose. The results of relevant abstract presentations from national meetings regarding infectious diseases or infection control were included when sufficient data were available for interpretation. Most of the available data came from observational studies rather than randomized, controlled trials. Nevertheless, two recent meta-analyses reported that randomized trials, cohort studies, and case–control studies of the same question have usually provided similar results.

**PROPORTION OF MRSA AND VRE INFECTIONS ATTRIBUTABLE TO SPREAD MRSA**

Recent scientific advances regarding the genetic origins of methicillin resistance in *S. aureus* have led to a greater understanding of the epidemiology of MRSA. De novo development of MRSA results when a strain of methicillin-susceptible *S. aureus* (MSSA) acquires a large genetic element, known as staphylococcal cassette chromosome mec (SCCmec). Detailed genetic analysis of MRSA strains from diverse parts of the world has revealed that transfer of SCCmec from a MRSA strain to a MSSA strain has occurred only a few times, and therefore the worldwide emergence of MRSA has resulted from dissemination of only a few clonal types rather than frequent de novo introduction of new MRSA clones. These findings suggest that virtually all patients with MRSA infection or colonization have acquired their MRSA strain from an external source, and therefore control efforts must, in large part, focus on preventing transmission in addition to control of antimicrobial use.

Transmission of MRSA within and between healthcare facilities has been well documented using molecular typing techniques, such as pulsed-field gel electrophoresis (PFGE). Outbreaks involving clonal spread within single facilities have been frequently reported. A large molecular epidemiologic study of MRSA bloodstream isolates collected from five continents demonstrated numerous clusters of clonal dissemination within individual medical centers. Furthermore, geographic clustering of closely related genotypes within cities or geographic regions has been described in several reports, suggesting that spread beyond the boundaries of a hospital is frequent.
The observation that MRSA has been successfully controlled with rigorous infection control practice supports the premise that transmission is the major factor contributing to the increasing prevalence of MRSA. A recent cohort study found that the proportion of patients colonized with MRSA was the most important predictor that new patients would acquire MRSA in an intensive care unit (ICU). Control of clonal MRSA transmission with active surveillance cultures and contact precautions in one neonatal intensive care unit (NICU) outbreak was followed by a 10-year period and approximately 100,000 patient-days in that unit without a single neonate colonized or infected by MRSA.

Success in controlling MRSA has been greatest in countries that adhere to rigorous transmission-based control policies that include active surveillance cultures to identify colonized patients and strict application of barrier precautions for patients colonized or infected with MRSA. In several northern European countries, the prevalence of MRSA is low despite repeated introductions. In Denmark, the prevalence of methicillin resistance among S. aureus blood isolates reached a peak of 33% in the 1960s, but declined steadily after introduction of a policy to control transmission, and has been maintained at less than 1% for 25 years. In Finland and the Netherlands, the prevalence of MRSA has been maintained at lower than 0.5%.

These countries advocate a rigorous national approach to hospital infection control practice that includes surveillance cultures for patients and personnel to identify unrecognized colonization, stringent barrier precautions, cohort nursing, and isolation of patients transferred from outside of the country until they are confirmed to be free of MRSA colonization. It may be argued that the successful control of MRSA in these countries is better explained by their low rate of antibiotic use than by their efforts to prevent transmission. The experience with methicillin resistance in S. epidermidis in the Netherlands suggests that stringent infection control practices, not antibiotic control, have been the most important factor in limiting the emergence of MRSA; approximately 50% to 65% of all S. epidermidis isolates in the Netherlands are methicillin resistant, levels of resistance similar to those seen in countries where MRSA is prevalent. This is notable because surveillance cultures and isolation have not been used for methicillin-resistant S. epidermidis. If antibiotic use in the Netherlands was the major factor in preventing the emergence of MRSA, then similar success at preventing the emergence of methicillin-resistant S. epidermidis would have been expected. On the contrary, in the absence of any infection control practices that target this organism, methicillin-resistant S. epidermidis has been uncontrolled in the Netherlands despite successful control of antibiotic use. Antibiotic consumption in other European countries does not consistently correlate with the prevalence of MRSA. For example, Finland, the United Kingdom, and Italy have similar outpatient antibiotic consumption (19, 18, and 24 defined daily doses per 1,000 inhabitants per day, respectively), but have had marked differences in MRSA prevalence (0.3%, 27.5%, and 50.5% of S. aureus isolates are methicillin resistant, respectively). In one recent report from the Netherlands, there was a 38-fold higher frequency of transmission from patients not suspected of carrying MRSA and thus not in contact precautions than from patients in contact precautions who had surveillance cultures positive for MRSA. This shows a strong, independent effect of preventing transmission in a country considered to have good antibiotic control.

There are few published reports of successful MRSA control solely through changes in antimicrobial use. In one of these hospitals, after initial improvement during the first year of an antibiotic management program, MRSA then increased during the next 5 years despite continuation of that program. The decline in the use of semisynthetic penicillins (eg, methicillin and nafcillin) and the tremendous increase in the use of vancomycin in U.S. hospitals during the past 20 years have not been associated with a reduction in the prevalence of MRSA in the healthcare setting. Instead, MRSA increased significantly during that period in National Nosocomial Infections Surveillance (NNIS) System hospitals. There have been no published reports of MRSA being eradicated through antibiotic control programs alone. On the other hand, interventions leading to eradication of MRSA from individual nursing units or entire hospitals have been based primarily on preventing person-to-person spread with less emphasis on antibiotic control. In summary, the selective advantage enjoyed by MRSA in the presence of antibiotic exposure seems to facilitate patient-to-patient transmission. Nevertheless, the available evidence suggests that antibiotic control alone is unlikely to prevent the emergence and persistence of MRSA in healthcare facilities. Successful interventions will thus most likely require rigorous efforts specifically designed to prevent transmission, similar to those used by multiple countries in Northern Europe that have controlled MRSA.

Historically, MRSA has been isolated almost exclusively in healthcare facilities, suggesting that transmission has occurred primarily in this setting. Evidence of MRSA transmission outside of the healthcare system had been sparse until recent years, when there began to be increasing reports of MRSA infection occurring in patients with little or no direct contact with healthcare facilities. If MRSA becomes widespread in the community, rigorous control of MRSA transmission in healthcare settings would be more difficult to justify. Interpretation of the current literature is complicated by the lack of consistent definitions of “community-acquired” MRSA infection or colonization. Some investigators have classified as community acquired any MRSA infection that does not have its onset during hospitalization, and this includes those with recent or frequent healthcare contact such as dialysis patients or patients who may have recently been discharged from a hospital.
or nursing home.\textsuperscript{60,70} It is probable that a substantial proportion of these patients do not have true community-acquired infections, but rather community-onset infections caused by MRSA that was acquired during prior healthcare contact.\textsuperscript{59,71} Nevertheless, community acquisition has clearly occurred in some areas.\textsuperscript{85,72} In these studies, clonal transmission has accounted for most of the community acquisition. The prevalence of community-acquired MRSA has remained low in countries in Northern Europe, such as Finland, where healthcare-associated MRSA transmission has been controlled even though the relative absence of healthcare-associated isolates should make community-acquired isolates more noticeable.\textsuperscript{31,72,73} The prevalence of MRSA in the community has varied widely by whether subjects have recently been in healthcare facilities, whether they have received antibiotics, and whether the population being accessed is patients in an outpatient clinic or merely citizens of the community. This also has been true in Finland.\textsuperscript{31,73}

Two recent, large prevalence studies focusing on children, because of frequent reports of community-acquired MRSA in children, both found a prevalence of 0.2%.\textsuperscript{74,77} Higher prevalence rates have been noted among patients being admitted to a hospital, usually because of traditional healthcare risk factors.\textsuperscript{71,76} In one of these studies, 415 patients admitted from home known to be previously colonized with MRSA had MRSA surveillance cultures done less than 72 hours from the time of admission; 9 (2.2%) were found to be positive for MRSA. Seven with MRSA (78%) had been admitted to the same hospital within the past year (six in the past 4 months). The other two both had had outpatient clinic visits. On average, each patient had 5.1 chronic illnesses.\textsuperscript{76} In the other study, nursing home residence and home healthcare visits were both significant independent risk factors for MRSA colonization in addition to prior hospital stay and antibiotic use.\textsuperscript{71} Another recent study showed that after patients with healthcare-associated MRSA were discharged from the hospital, 15% of their household contacts were found to carry the same strain of MRSA according to the results of antibiotic susceptibility testing and PFGE.\textsuperscript{77} Although such carriage among household contacts may often be transient, one study found a median duration of carriage among patients colonized with MRSA to be 40 months.\textsuperscript{78} Further study is needed to define the prevalence of community MRSA transmission; currently, the available evidence suggests that most patients with MRSA infection or colonization are likely to have acquired the organism through contact with healthcare, and therefore prevention of transmission in health care should be the focus of MRSA control programs.

**VRE**

The increase in vancomycin resistance among clinically important species of enterococci (\textit{Enterococcus faecalis} and \textit{Enterococcus faecium}) has been caused primarily by the acquisition of clusters of genes (\textit{vanA} and \textit{vanB}) encoding an alternate biosynthetic pathway for the production of peptidoglycan cell wall precursors.\textsuperscript{29} Although the exact origin of vancomycin-resistance genes is unknown, the \textit{vanA} and \textit{vanB} gene clusters are likely the products of a complex evolutionary sequence of genetic transfers.\textsuperscript{80,81} Spontaneous vancomycin-resistance mutations have not been observed, and therefore the de novo appearance of \textit{vanA} or \textit{vanB} glycopeptide resistance through spontaneous genetic mutation in patients exposed to vancomycin is unlikely or impossible.\textsuperscript{82,83} These findings are supported by the results of epidemiologic studies.\textsuperscript{83,84} VRE infection or colonization, therefore, virtually always results from transmission of VRE or from transfer of the vancomycin-resistance gene cluster.\textsuperscript{81,82}

In the United States, VRE is found almost exclusively in patients exposed to healthcare settings. Culture surveys performed in the United States have not yielded \textit{vanA} or \textit{vanB} VRE isolates from healthy individuals, farm animals, or food products.\textsuperscript{81,85,86} These findings suggest that VRE transmission in the United States occurs primarily within healthcare institutions.\textsuperscript{82,87} The situation is different in Europe, where the glycopeptide avoparcin was used for years as a growth promoter in the animal industry and VRE has been identified in the gastrointestinal tract of healthy individuals and farm animals and on processed meat products in grocery stores.\textsuperscript{88-91} In Europe, therefore, it is likely that a substantial proportion of VRE colonization has been acquired through contaminated food products rather than contact with health care.\textsuperscript{82} Avoparcin as a growth promoter was banned for use in the European Union in 1997; several years after the ban, the prevalence of VRE had decreased on some farms but was still detectable at high rates on others.\textsuperscript{92} Recent studies have demonstrated that an \textit{esp} virulence gene is present among clinically significant VRE isolates causing hospital outbreaks in the United States and in Europe, but not in isolates from livestock and healthy people in Europe.\textsuperscript{93,94}

Transmission of VRE within and between U.S. healthcare facilities has been well documented using molecular epidemiologic techniques.\textsuperscript{87,95-100} When VRE outbreaks are detected soon after the organism has been introduced into a facility, molecular typing of the isolates by PFGE usually indicates transmission of a clonal strain.\textsuperscript{87,95-100,102} By contrast, molecular strain typing performed on VRE isolates after the organism has been present in a facility for longer periods of time has generally revealed the presence of multiple clones.\textsuperscript{86,87,97,101-103} Some have interpreted the presence of multiple PFGE types among a sample of VRE isolates from a single institution to indicate the absence of transmission within that facility, arguing that polyclonality is the result of repeated introduction of new VRE strains from outside sources.\textsuperscript{86} However, one molecular epidemiologic study in a hospital with a high VRE prevalence and a polyclonal pattern found that this had developed by the spread of a few strains initially followed by the spread of other strains as they were introduced.\textsuperscript{80} Yet another explanation for polyclonality is horizontal transmission of vancomycin-resistance genes from VRE to different strains of vancomycin-
sensitive enterococci. The vanA gene cluster is carried on a transposon that often is located on conjugative plasmids that can readily transfer between enterococcal strains. The finding of multiple strains of VRE within a healthcare facility, therefore, does not necessarily indicate the introduction of new strains from an outside source, as the horizontal transfer of mobile genetic elements may result in polyclonality even in the absence of new strain introductions.

Epidemiologic studies have consistently identified antimicrobial exposure as a risk factor for VRE culture positivity, and it appears likely that antibiotic exposure facilitates VRE transmission by at least two mechanisms: (1) increasing susceptibility to VRE acquisition by suppressing normal competing flora and providing selective advantage for survival to VRE acquired through cross-transmission; and (2) increasing the likelihood of transmission from colonized patients by increasing the concentration of VRE in the stool, and thereby increasing the probability of environmental or HCW contamination. However, a detailed study of VRE transmission in one medical ICU suggested that infection control practices also exerted a significant influence on VRE transmission rates. The study evaluated the effect of colonization pressure (average daily point prevalence of VRE within the study unit) on VRE acquisition. In a multivariate analysis controlling for colonization pressure, antibiotic pressure, and other factors, colonization pressure was the strongest predictor of VRE acquisition. The model suggested that antibiotic pressure exerted a modest effect on VRE acquisition when colonization pressure was low and less of an effect on acquisition when colonization pressure was high.

The Role of Contamination of HCWs’ Hands

Epidemiologic data have suggested for more than a century and a half that HCWs spread microbes from patient to patient via contaminated hands. In 1847, Semmelweis implemented an antiseptic hand wash that was associated with a significant reduction in maternal mortality due to puerperal fever. A controlled trial showed that refraining from hand hygiene was associated with significantly greater spread of S. aureus than was hand washing with hexachlorophene. In multiple studies, multidrug-resistant organisms, such as MRSA or VRE, have been isolated from the hands, gloves, or both of HCWs involved in the care of infected or colonized patients.

In one study, proximity to patients with VRE (often in other rooms) was the most important risk factor for previously uncolonized patients acquiring the same strain of VRE transmission via the contaminated hands of HCWs was assumed to be an important mechanism. In another study, having the same caregivers as patients with VRE was a significant risk factor, resulting in the same inference. One study found MRSA on hospital computer keyboards used only by clinicians, implying that the clinicians carried these microbes from room to room in the hospital on their hands. Other studies have documented the presence of MRSA or VRE on a variety of other environmental surfaces and equipment, implying that hand contamination may derive in part from touching contaminated surfaces or equipment, implying that hand contamination may derive in part from touching contaminated surfaces or equipment, implying that hand contamination may derive in part from touching contaminated surfaces or equipment.
first of these was Oliver Wendell Holmes, who reviewed data suggesting this possibility for puerperal fever in 1843.3 Zachary et al. found 37% of HCWs' gowns to be contaminated with VRE after care of a patient with VRE122 and Boyce et al. reported that 65% of HCWs' gowns or uniforms were contaminated with MRSA after performing routine “morning care” for patients with MRSA in a wound or urine.132 Similarly, another study showed that 40% of HCWs' gowns were contaminated after care of patients colonized with MRSA or VRE, and that gowns reliably prevented contamination of the clothing beneath them.134 The same investigators also found that when white coats were worn instead of gowns when caring for such patients, they became contaminated 69% of the time with VRE or MRSA after examining a patient and the contaminating organisms were transferred to the hands of the HCWs 27% of the time after touching the white coats.134 In another study, control of a VRE outbreak was attempted using only gloves followed by hand washing for patients with VRE. The investigators found that the outbreak continued unabated and was controlled only when gowns were added to the barriers.36

To date, four of five studies reporting epidemiologic data have shown significantly lower rates of patients becoming VRE culture positive when HCWs used gowns and gloves as compared with gowns alone96,105,115,135,136; one of the four reporting lower rates had simultaneously implemented dramatic reductions in cephalosporin and clindamycin use, making the relative contributions of the different interventions difficult to judge.115 Another of the four reporting lower rates demonstrated that gowns and gloves decreased clonal transmission.136 Many studies have shown convincing control of VRE using contact precautions (ie, wearing a gown and gloves) for colonized patients.95,96,99,102,106,116,137-149 By contrast, there are almost no studies showing effective control of VRE in the absence of contact precautions. One study suggested that universal gloving was as effective as universal use of gloves and gowns.105 Almost half of all patients in both groups became colonized with VRE, however, making it difficult to conclude that VRE was convincingly controlled in either group. Violations of isolation precautions were observed in both groups (21% of the time in the gown and glove group and 38% of the time in the glove group), providing opportunities for transmission in the ICU. Much of the VRE transmission may have occurred elsewhere in the hospital, where such precautions were not being used, before transfer to the ICU; patients who had not received antibiotics before transfer may have been colonized but culture negative on admission. Taken together, the above data suggest that contamination of HCWs' clothing may contribute to the spread from patient to patient.

The Role of Contamination of Equipment

The contaminated faucet handle is a well-known fomite in the healthcare setting, but multiple studies have demonstrated that portable equipment carried by HCWs, such as stethoscopes, tourniquets, sphygmomanometer cuffs, otoscopes, and pagers, also becomes contaminated, like hands, and may serve as a potential vector for antibiotic-resistant pathogens to patients, either via direct contact or by contamination of HCWs' hands.150-156 Such transmission has been documented via portable equipment in one study by Livornese et al.99 They described a VRE outbreak at their facility in which the organism repeatedly was isolated from the rectal probe handles of three electronic thermometers used exclusively on non-isolated patients in the ICU. Restriction endonuclease analysis of plasmid DNA showed that all clinical and environmental isolates were identical. Infection control measures, including removal of the implicated thermometers, active surveillance cultures to detect colonized patients, and contact isolation of patients infected or colonized with VRE, resulted in termination of the outbreak.99 Another study reported a reduction in VRE associated with stopping the use of rectal thermometers.157

The Role of Contamination of the Environment

Hospitalized patients often are confined to hospital beds and surrounded by multiple devices, equipment, and environmental surfaces that can harbor microorganisms. Thus, there is concern that the environment may play a role in the transmission of antimicrobial-resistant pathogens between patients.51,158

Antimicrobial-resistant pathogens have been isolated from a variety of fomites, devices, and environmental surfaces in patients' rooms.86,95,96,112,132,133,159-164 VRE has been isolated from bed rails, wheelchairs, electronic rectal and ear probe thermometers, pulse oximeters, doorknobs, tables over beds, linen, patient gowns, and therapeutic beds.86,95,96,112,132,133,159,160 Environmental contamination has been documented in both outpatient and inpatient settings. In a study by Smith et al.,161 two (28%) of seven previously culture-negative treatment rooms in an outpatient clinic were found to be positive for VRE after a colonized patient was seen for evaluation. Tables next to chairs and treatment chairs were positive for VRE in each room in which contamination was found.161

S. aureus also has been isolated from a wide variety of patient-care items and environmental surfaces: stethoscopes, tables over beds, blood pressure cuffs, floors, charts, furniture, dry mops, and hydrotherapy tanks.132,162-167 Boyce et al. found that 73% of the hospital rooms containing patients infected with MRSA and 69% of the rooms containing patients colonized with MRSA had some environmental contamination; 96 (27%) of 350 surfaces in the rooms of 38 patients colonized or infected with MRSA were positive for MRSA.132 When nurses touched the surfaces in these rooms but not the patients, their gloves became contaminated with MRSA 42% of the time. The percentage of environmental surfaces contaminated has varied in different types of units in different studies (as high as 64% in burn units and as low as 5% in low-risk areas).132,165,166

Both the frequency and the duration of environmental contamination are of concern because laboratory studies have shown that VRE, similar to other enterococ-
ci, can persist on dry environmental surfaces for days to months (range, 7 days to 4 months). VRE has been more difficult to remove from fabric than from vinyl surfaces. Dietz et al. found that MRSA also could survive on the external surface of sterile goods packages for more than 38 weeks. There have been some outbreaks in which persisting VRE contamination of the environment or a particular fomite was implicated as a persistent reservoir and vehicle for transmission.

Few outbreak investigations have implicated the environment in transmission of S. aureus, but most investigations have not focused on this. Nevertheless, in some specialized populations, such as burn patients, exposure to contaminated surfaces or therapy tanks has been identified as a risk factor for transmission. In a recently published investigation, a hand-held shower and a stretcher for showering in the hydrotherapy room in a burn unit were culture positive for the MRSA strain implicated in the outbreak. Improved infection control precautions, including replacement of stretcher showering with bedside sterile burn wound compresses, terminated the outbreak. In another MRSA outbreak, an epidemiologic investigation suggested that hospital-wide dissemination occurred because of patient contacts in the physiotherapy department.

PREVENTING THE SPREAD OF ANTIBIOTIC-RESISTANT PATHOGENS

Use of Active Surveillance Cultures to Identify the Reservoir for Spread and Contact Precautions to Prevent Spread

Multiple studies, involving both endemic and epidemic settings, have shown that implementation of surveillance cultures to identify colonized patients and use of contact precautions for care of colonized patients to prevent contamination of HCWs’ hands, apparel, and equipment have been followed by a significant reduction in the rates of both colonization and infection of the patients with MRSA and VRE. A few studies that did not demonstrate a significant reduction were in countries where all facilities were using active surveillance cultures and contact precautions and described low rates of MRSA and VRE. The probability that so many positive results could have occurred independently merely by chance alone is extremely low. Finding control in so many studies with this approach also shows “consistency of evidence,” suggesting a causal association between programs incorporating active surveillance cultures and contact precautions and control of these pathogens. There also are examples of sustained, long-term control with this approach. This contrasts sharply with the sustained long-term increases in the prevalence of MRSA and VRE infections in U.S. hospitals that have not been using this approach.

Multiple studies have provided additional verification of the efficacy of this approach (ie, beyond the level of evidence demonstrated by a significantly declining incidence following implementation of control measures). The first of these compared the rate of transmission from patients colonized with MRSA who had already been identified by use of active surveillance cultures and placed into contact or droplet precautions (ie, using gown, gloves, and mask) with that from patients colonized with MRSA but not yet identified and thus using only universal or standard precautions, which require barriers to touch any moist body substance or secretion and hand hygiene after patient contacts. The rate of transmission was 15.6-fold higher for patients not yet recognized to be colonized and for whom standard precautions were being used (95% confidence interval, 5.3 to 45.6; P < .0001). This shows high strength of association, another feature important for inferring causality from epidemiologic data. A second comparison showed a 38-fold higher frequency of transmission of MRSA from unidentified, unisolated patients as compared with identified, isolated patients in a Dutch ICU (again using gown, gloves, and mask). A third independent comparison was provided by the results of a conditional logistic regression analysis of risk factors for becoming culture positive for VRE during a hospital outbreak. The most important risk factor for acquiring VRE during this clonal outbreak was proximity to unisolated patients who became culture positive during the preceding 7 days. By contrast, proximity to VRE culture-positive patients being cared for using contact precautions during the preceding 7 days was not a significant risk factor. A dose gradient has also been demonstrated with significantly better control of VRE having been associated with increasing compliance with performance of active surveillance cultures. A dose gradient was also found in a 7-year study of this approach throughout a Canadian province, which demonstrated better control of both MRSA and VRE throughout the province as compliance with surveillance cultures and isolation increased. One study also demonstrated reversibility several times with the VRE infection rate being higher when active surveillance cultures and contact precautions were not used and then declining significantly each time these measures were implemented. Of note, these same control measures shown to work so well for MRSA and VRE have also been used to control multidrug-resistant, gram-negative bacillary infections such as Acinetobacter baumannii and Enterobacter aerogenes. Four more studies have demonstrated that active surveillance cultures and cohort isolation of all colonized patients on an isolation ward successfully controlled healthcare-associated MRSA transmission. None of these four studies clearly stated exactly what measures were used for caring for patients on the isolation ward, but one stated that they were cared for using “strict barrier nursing.” Nevertheless, they show that early identification of the reservoir can prevent spread. One more study used active surveillance cultures, and isolation in negative pressure ventilation rooms with staff wearing masks, gowns, and gloves in addition to a policy for ward closure whenever secondary cases were detected by surveillance cultures suggesting nosocomial spread. This approach was associated with control of MRSA to a low level as evidenced by the occurrence of only 5 MRSA bacteremias in a 1,000-bed, tertiary-care
hospital during a 6-year period. After the relative frequencies of screening, isolation and ward closure were reduced in 1995; however, 18 MRSA bacteremias occurred in 1996 and 74 in 1997.

Because antibiotic therapy has been a critically important risk factor for both colonization and infection with antibiotic-resistant organisms, it also should be recognized that the studies listed above regarding MRSA and most of those involving VRE did not use control of antibiotics other than vancomycin. The latter agent was restricted as part of most VRE control efforts, but efforts to control the use of vancomycin alone without effective measures to prevent transmission have not resulted in the control of VRE.186,198 This does not mean that antibiotics were not important contributing factors. However, it implies that spread was responsible for most of the colonization and infection with such pathogens in these studies and that prevention of spread was thus an important means of control. Stopping all use of antibiotics likely would ultimately result in the disappearance of antibiotic-resistant pathogens. Control of antibiotic use has been recommended for decades194 and most hospitals are reportedly attempting to control excessive and inappropriate use.184 However, the problem of antibiotic resistance keeps growing, which makes preventing spread seem essential.

During the third year of a hospital outbreak of MRSA, 40% of all hospital-acquired S. aureus bloodstream infections and 49% of all S. aureus surgical-site infections were caused by one strain of MRSA.43 During those first 3 years of the outbreak, patients found to have MRSA from routine clinical cultures submitted to the clinical microbiology laboratory had been placed in isolation precautions; but no active surveillance cultures had been implemented; the prevalence of colonization and the incidence of infection kept growing. However, after active surveillance cultures were implemented to detect and isolate the previously unrecognized patients colonized by the outbreak strain, the rate of infection and colonization began to decline for the first time and after a year there was significant reduction in the rate of MRSA infection. This was accomplished without an antibiotic control program.43 This suggests that patients with cultures positive from routinely submitted clinical specimens represent only a small fraction of the reservoir for spread of antibiotic-resistant pathogens. Most of the reservoir for spread was asymptomatic, colonized patients who went unrecognized and unisolated in the absence of active surveillance cultures.43 Several recent studies have confirmed this.177,179 The proportion of VRE-colonized patients who go unrecognized in the hospital in the absence of active surveillance cultures has been large in five studies.105,125,149,166,196

Two recent mathematical models based on epidemiologic data provide additional evidence to support the role of identifying colonized patients. The first suggested that extremely high compliance with hand hygiene (ie, after 80% of patient contacts) could reduce VRE culture positivity in a medical ICU by only approximately one-quarter because of the relatively high rate of transmission when HCWs’ hands were not being cleaned following the remaining 20% of contacts.197 This suggests that relying on hand hygiene alone (ie, without identifying colonized patients for use of contact precautions) is unlikely to control transmission. The mathematical model suggested that surveillance cultures and cohort isolation would result in better control. Another model found that increasing hand hygiene compliance from 0% to 90% in the absence of a program to identify and isolate colonized patients resulted in a reduction in the prevalence of MRSA colonization among patients by approximately one-third.198 The authors of the model concluded that strict isolation measures and surveillance cultures for identifying colonized patients should be considered by those trying to control these pathogens.

One study deserves special mention. This public health initiative used active surveillance cultures in all 32 healthcare facilities in a health district and showed that VRE could be controlled in all facilities in a region.113 This 3-year study is remarkable because rates of VRE infection continued to increase during those 3 years at most other healthcare facilities in the United States. A press release from the Centers for Disease Control and Prevention (CDC) described this effort as a “role model for all other health regions.” Similar efforts on such a large scale have not yet been tried in the United States, but data are available from several countries in Northern Europe that have routinely used active surveillance cultures to identify MRSA-colonized patients and prevent spread as discussed above.31,37,44,48,73 Active surveillance cultures and isolation have also been used successfully to control MRSA and VRE throughout the province of Ontario, Canada, as mentioned above.180 Interventions in a single ward or on a limited number of wards usually can have significant impact;30,46,57,120,138,139,141,142,144,146,148,174 but when transmission is occurring on multiple other hospital wards and between all of the involved wards, control has not been as thorough on the intervention wards as if all spread throughout the facility were being targeted.43,45,49,51,86,102,105,106,137,143,145,147,149,199 Likewise, intervention throughout a single facility can have an important impact, but if all other surrounding facilities also are spreading MRSA, VRE, or both and if patients are shared among the various facilities, then the impact has been less than if all surrounding facilities were employing the same measures.31,37,44,47,48,73,119,137

Most healthcare facilities in the United States have adopted CDC guidelines in effect since 1983, which recommend contact precautions for patients colonized with epidemiologically important antibiotic-resistant pathogens. However, few have used a program of active surveillance cultures to detect patients colonized with such pathogens to prevent transmission using contact precautions.184 If contact precautions are important to prevent spread from colonized patients, then active surveillance cultures are necessary to identify colonized patients because most such patients are never recognized using clinical microbiology cultures. Likewise, identifying colonized patients and placing an isolation sign on the door...
will not control transmission unless hospital policies for contact precautions are enforced for colonized patients.

Control of VRE using active surveillance cultures and contact precautions in Europe will be complicated by the high prevalence of VRE strains that lack virulence factors and have been unassociated with clinical infections. Dutch investigators with extensive experience using this approach in the control of MRSA have recently controlled outbreaks of clinically significant VRE and proposed that molecular typing may be needed to guide preventive efforts in that environment. Some of the same authors recently demonstrated that automated ribotyping could readily and rapidly distinguish clinically relevant strains carrying the esp gene and suggested that this approach could be important for characterizing VRE strains in European hospitals.

Although virtually all of the studies demonstrating success controlling MRSA and VRE have used cultures to detect the organism in samples obtained for active surveillance, recent studies have suggested the possibility that other faster microbial tests such as polymerase chain reaction may soon be useful for such detection.

The Role of Hand Hygiene

Hand hygiene often is said to be the single most important measure for controlling transmission of multidrug-resistant organisms. The CDC has recommended hand washing following patient contacts as a special emphasis of universal precautions since 1987 and has recommended hand washing after all patient contacts as part of standard precautions since 1996. Despite the fact that these recommendations have been enforced as regulations in the United States as part of the blood-borne pathogens standard, most studies assessing the hand hygiene compliance of HCWs before and after the implementation of these requirements have shown low compliance rates, averaging approximately 40% and ranging as low as 10%. Compliance rates often have remained relatively low despite considerable efforts to improve them. For instance, one hospital increased its overall compliance rate from 48% to 66% following the implementation of a multi-year hand hygiene campaign involving “talking walls” designed by psychologists, artists, and infection control specialists to motivate increased compliance. This improvement in compliance differed significantly among HCW groups, with compliance remaining low among physicians and with activities associated with the highest risk of cross-transmission.

Reasons for poor compliance with hand hygiene are complex and complicate efforts to reduce the transmission of antibiotic-resistant pathogens in this manner. Many risk factors for poor compliance with hand hygiene have been identified, including being a physician or a nursing assistant, working in an ICU, working during weekdays, performing activities with a high risk for transmission, and having many opportunities for hand hygiene per hour of patient care. Understaffing and overcrowding also contribute to poor compliance with hand hygiene.

An insufficient number of sinks has been reported as a risk factor, but one recent study reported a decrease in compliance after construction of a new hospital with more sinks that were easier to access and another found that sink availability did not predict compliance. Reasons for not washing hands have included HCWs’ perception that they are at low risk for acquiring infection from patients, an assumption that glove use precludes the need for hand hygiene, and being unaware of guidelines. Skin irritation caused by frequent exposure to soap and water also is an important obstacle to compliance. Given the almost universally low compliance with hand washing between patient contacts, it is clear that greater emphasis should be given to improving hand hygiene practices among HCWs.

The fact that compliance with hand hygiene has been so poor has suggested that any improvement should be associated with lower multidrug-resistant organism infection rates. A recent study coupled mathematical modeling with the results of a cohort study of risk factors for transmission of MRSA in an ICU to predict the potential effectiveness of compliance with hand hygiene and use of cohorting. In this ICU, all patient care required “gloves, disposable aprons, and strict hand hygiene.” In a multivariate analysis, understaffing was the only factor significantly associated with clustered cases (ie, implying transmission). Mathematical modeling suggested that a 12% increase in cohorting of staff with colonized patients or a 12% increase in compliance with hand hygiene during periods of overcrowding and high workload could compensate for staff shortage and prevent transmission. The authors thought that such an increase in hand hygiene under such conditions would be rather unlikely, but with monitoring, feedback, motivational efforts, and a more user-friendly alcohol-based product, such an increase could be possible.

Pittet et al. published the results of a study showing that the overall rate of healthcare-associated infections and the rate of MRSA transmission decreased from 16.9% to 9.9% and from 2.16 to 0.93 episodes per 10,000 patient-days, respectively, while the rate of compliance with hand hygiene improved from 48% to 66%. The consumption of alcohol-based hand rub increased from 3.5 to 15.4 L per 1,000 patient-days during the same period. However, the compliance rates of other infection control measures, which also could have had an impact on MRSA infection and transmission rates, were not presented in the article. For example, active surveillance cultures were implemented to identify and isolate colonized patients. In the first year, 1,863 cultures were processed, but the number of cultures increased progressively during the next 4 years to 10,566 (the same years as the hand hygiene campaign). Because the two interventions were conducted simultaneously and the number of MRSA-colonized patients detected and placed in contact precautions increased more than did compliance with hand hygiene, the relative contribution of the increase in compliance with hand hygiene to the improvement in the MRSA rate is uncertain.
Another study involving two small hospitals reported a large relative reduction in VRE but no significant change in MRSA infection following implementation of a program to increase hand hygiene.220 Two other studies reported a temporal association between control of MRSA NICU outbreaks and switching from chlorhexidine hand wash to triclosan hand wash.221,222 However, both explicitly stated that this was done while continuing all other infection control measures, which included at least weekly active surveillance cultures to identify colonized patients in one221 and active surveillance cultures, gloves, gowns, cohorting, and triclosan bathing of all neonates in the other.222

Thus, although there are abundant data to suggest that transient contamination of HCWs’ hands is often responsible for transmission and that hand hygiene can help, it seems unlikely that hand hygiene, by itself, will result in control of antibiotic-resistant pathogens such as MRSA, VRE, and VRSA. Factors supporting this view include the following: (1) poor compliance with hand hygiene after patient contacts by HCWs is a long-standing problem that will likely take years to correct; (2) there were dramatic increases in MRSA and VRE infections nationwide during the past decade despite the regulatory requirement for universal or standard precautions in all U.S. healthcare facilities throughout that time; (3) studies show significantly lower transmission of MRSA or VRE when colonized patients are identified and cared for using contact precautions; (4) contamination of clothing and equipment occurs frequently when patients are not identified and cared for using contact precautions and appears to contribute to transmission; and (5) there is frequent environmental contamination that may lead to direct transmission to roommates and indirect transmission to other patients via HCWs’ becoming contaminated in a room not known to contain a colonized patient. Therefore, programs to improve hand hygiene practices among HCWs need to be incorporated into comprehensive multidrug-resistant organism control programs that include active surveillance cultures, use of contact precautions, and antibiotic control.

The Role of Gloves

Several investigators have shown that gloves can dramatically reduce hand contamination, transmission of healthcare-associated pathogens, or both.212,223-229 Olsen et al. tested the effectiveness of gloves as a barrier to hand contamination and concluded that gloves prevented hand contamination 77% of the time and decreased bacterial counts 2 to 4 logs when compared with counts taken from the external glove surface.227 Doebbeling et al. reported similar findings in a controlled experimental trial.212 Both studies concluded that gloves greatly reduce the risk of hand contamination, but do not obviate the need for hand washing after their removal. Additionally, VRE has been recovered on 63% of gloves sampled after routine examination of a VRE-colonized patient.122 There are also extensive data documenting environmental contamination with antibiotic-resistant pathogens,86,96,112,132,159,168,169 and one study demonstrated that 42% of HCWs’ gloves became contaminated with MRSA after having contact with only environmental surfaces in the hospital rooms of MRSA patients (ie, without direct contact with the patients).122

During a 2-month period, universal gloving was studied in a few high-risk wards in an institution already performing hospital-wide routine weekly active surveillance cultures for high-risk patients for VRE.230 Universal gloving was employed for all patients not known to be colonized or infected with VRE in addition to full contact precautions for patients known to be infected or colonized by VRE. This intervention was associated with a 5-fold reduction in the incidence density of new acquisition of VRE during the intervention period (relative risk, 0.21; 95% confidence interval, 0.024 to 0.867; P = .025). This implies that universal gloving was an effective measure (ie, as compared with standard precautions) for at least a couple of months on these high-risk wards. How well this would work during a longer period of time has not been demonstrated.

Another study suggested that universal gloving was as effective as universal gowns and gloves for preventing spread of VRE in a medical ICU, but, as discussed above, noncompliance rates of 21% to 38% and the lack of similar precautions throughout 98% of the hospital make evaluation of the time and place of transmission difficult.105 The studies mentioned above suggest that gloves can be an important measure for preventing hand contamination, transmission of epidemiologically important pathogens from colonized or infected patients, or both.

The Role of Gowns

Gowns have been used as part of contact precautions for preventing transmission of VRE and MRSA because of their success in doing so in many studies9,29,30,43,45,47,49,57,96,99,102,106,119,138-147,149,171-173 and because HCWs’ apparel has become colonized when gowns are not worn.122,132,134 One study documented that at least one brand of disposable isolation gown reliably prevented contamination of the HCWs’ clothes beneath the gown.134 Four of five studies with epidemiologic data reported significantly lower rates of patients’ becoming VRE culture positive while HCWs used gowns in addition to gloves as compared with gloves alone.96,105,115,135,136 suggesting that contamination of HCWs’ clothes sometimes leads to transmission and that prevention of this contamination helps prevent transmission.

The Role of Masks for the Isolation of MRSA, Vancomycin-Intermediate S. aureus (VISA), or VRSA

A mask was used as part of contact precautions for MRSA until 1996 when the CDC redefined contact precautions, omitting the use of a mask. The study cited above showing a 15.6-fold higher rate of spread using standard precautions involved use of a mask as part of contact precautions because it preceded 1996.30 It showed
the effect of employing all of the measures being used, however, without showing whether the mask per se was important. This issue has not been studied adequately, but there are several pieces of evidence suggesting that a mask may offer some benefit during isolation of patients colonized or infected with MRSA. First, none of 144 employees were found to be carrying MRSA in the nose despite caring for patients with MRSA during the first 8 months of the NICU outbreak mentioned above for which masks were used. In the same hospital where active surveillance cultures are frequently used and masks were still being used for MRSA isolation, none of 80 internal medicine resident physicians were found to be carrying MRSA despite frequent contact with patients colonized or infected with MRSA who were in isolation. These results resemble those of multiple culture surveys performed in the 1970s and 1980s as part of hospital MRSA outbreak investigations, which found infrequent MRSA carriage by HCWs. By contrast, a more recent, one-time survey of nurses in a hospital that did not report using active surveillance cultures to identify colonized patients found that 37% of nurses were carrying MRSA. House staff in that same hospital underwent culture before and after a particular rotation; 9% were colonized before and 19% after the rotation. In another study, 12 of 26 nurses wearing gowns and gloves but no masks while working on a ward filled with patients colonized or infected with MRSA were found to carry in their noses one or more strains of MRSA from the colonized patients 36 times during a 7-week period. The carriage was usually transient but suggests a higher frequency of transmission to HCWs than previously recognized. Sherertz et al. showed that wearing a simple, surgical mask decreased shedding of MRSA by approximately 75% from a nasally colonized individual who had coryza from experimentally induced rhinovirus infection. Finally, a recent study compared the rate of HCW carriage of MRSA when HCWs wore gowns and gloves to care for MRSA patients as compared with gowns, gloves, and a Technol respirator (Kimberly-Clark, Roswell, GA). A significantly lower rate of colonization was found during the period using the respirator.

Although S. aureus transmission has been assumed to occur primarily via direct or indirect contact with noses becoming colonized because of being touched, some studies published decades ago suggested a role for airborne transmission of S. aureus and several recent studies also support this possibility.

Taken together, the above data suggest that a mask may be of some use in preventing nasal acquisition of MRSA by HCWs, which may in turn help prevent transmission to patients. The CDC has recommended the use of a mask when caring for patients with VISA or VRSA. There are no reasons to suspect that the epidemiology of MRSA and VRSA should differ.

The Role of Antibiotic Control

At least one-third of all hospitalized patients receive a course of antimicrobial therapy during their hospital stay and studies have suggested that a large portion of this use is unnecessary or inappropriate. This pattern of use increases the cost of health care and contributes to the emergence and spread of resistant microorganisms within the healthcare environment. Antibiotic therapy causes an increase in antibiotic resistance in several ways. For microbes with a gene encoding inducible resistance, the presence of certain antibiotics will induce synthesis of enzymes that inactivate that drug, other antibiotics, or both. For most mechanisms of antimicrobial resistance, however, antibiotics result in a higher prevalence of antibiotic resistance in another way. The high prevalence of antibiotic therapy today in health care and especially of broad-spectrum antibiotic therapy ensures that any microbe with almost any mechanism of resistance will enjoy a selective advantage to survive, proliferate, and spread. Recommendations against inappropriate use, excessive use, or both of antibiotics have been made for decades.

When a culture is performed, it often shows colonizing flora, which should not usually be treated. Exceptions to this rule are covered in the next section regarding suppression, eradication, or both of colonization for infection control purposes. Antibiotic therapy should be given at the correct dose for an appropriate duration. An inadequate dose, duration, or both may make evolution of resistance in an infecting organism more likely. An excessive duration may make development of resistance among colonizing flora in the gastrointestinal tract more likely.

The risk of MRSA colonization has been shown to relate to the frequency and duration of prior antimicrobial therapy, and several studies have recently documented a higher risk following therapy with fluoroquinolones in particular. These data have led to suggestions that antibiotics in general and fluoroquinolones in particular must be used prudently in institutions where MRSA is endemic. Three studies have reported a decline in MRSA following reductions in the use of certain antibiotics, but in two of these studies new infection control measures were also simultaneously implemented. One involved switching from a third-generation to a first-generation cephalosporin for perioperative prophylaxis, another involved major reductions in the use of third-generation cephalosporins and clindamycin, and the third involved restriction of the use of both ceftazidime and ciprofloxacin as well as rotating use of other beta-lactams. The risk of VRE colonization has been associated with the use of multiple antimicrobial classes, including glycopeptides, third-generation cephalosporins, and antibiotics with potent anaerobic activity. Two studies reported that greatly reducing or stopping the use of ceftazidime and switching to piperacillin/tazobactam was associated with a two-thirds relative reduction in the prevalence of VRE. Although this is encouraging, one of the two studies made multiple changes at once, including some new measures for preventing spread,
making it difficult to see the effect of each individual measure.\textsuperscript{115} Another recent study reported that VRE continued to increase despite an 85% relative reduction in the use of third-generation cephalosporins.\textsuperscript{116} One study suggested that restriction of vancomycin using unit-specific practices was associated with a modest reduction of VRE prevalence in ICUs (ie, a 7.5% reduction as compared with ICUs that did not implement unit-specific practices in which VRE prevalence increased by 5.7% during the 1.25-year follow-up period).\textsuperscript{269} By contrast, Donskey et al. found that the use of ticarcillin-clavulanate and ceftriaxone resulted in the development of high-level VRE colonization in the mouse model, whereas the use of piperacillin/tazobactam did not.\textsuperscript{270} All three antibiotics are secreted in significant concentration into the bile, but piperacillin/tazobactam has significantly greater activity against many enterococcal strains. The effect of piperacillin/tazobactam on VRE colonization may represent a balance between inhibition due to antienterococcal activity and promotion due to antianaerobic activity. The mouse model findings are consistent with findings from clinical studies.\textsuperscript{115,119,266} Additionally, the use of antianaerobic antimicrobials in mice and humans already known to be colonized with VRE has been shown to promote persistent, high-level VRE colonization.\textsuperscript{113,270}

It now appears that the specific antibiotic selected should depend on the VRE colonization status of the patient. Once a previously uncolonized individual is exposed, VRE establishment is likely related to the effect of the antibiotic on the intestinal flora. The intrinsic activity of the antibiotic against the colonizing strain, the amount of biliary excretion, and the amount of active antibiotic in the intestinal tract are important factors in determining the effect of the antibiotic on the gut flora.\textsuperscript{267} Therefore, to prevent the establishment of VRE intestinal colonization, the use of agents with little or no activity against enterococci, such as third-generation and fourth-generation cephalosporins, should be kept to the minimum necessary in patients not known to be VRE colonized. To prevent persistent high-density VRE colonization, antianaerobic agents should be kept to the minimum necessary in patients known to have intestinal VRE colonization.

The Role of Suppression of Colonization, Eradication of Colonization, or Both

Suppression of carriage, eradication of carriage, or both have been used adjunctively at times to help control the spread of MRSA.\textsuperscript{30,44,57,176,190,191,271-274} Because HCWs can become colonized and spread MRSA to patients, control has sometimes necessarily involved eradication of MRSA colonization in HCWs.\textsuperscript{30,44,272} Treating colonized or infected HCWs who were epidemiologically implicated in outbreaks has helped control outbreaks.\textsuperscript{275-277} For healthy HCWs, topical treatment with intranasal mupirocin ointment twice daily for 5 days was associated with a 91% reduction in the prevalence of \textit{S. aureus} carriage, but recolonization was noted in 26% of decolonized HCWs within 4 weeks.\textsuperscript{278} One of these studies with longer follow-up showed that 48% of those undergoing treatment were culture positive after 6 months.\textsuperscript{279} Another study showed that eradication of nasal colonization in HCWs resulted in a significant decrease in hand contamination by the same strain.\textsuperscript{280} This strategy also has been used perioperatively to prevent surgical-site infection and periodically to prevent bacteremia in colonized patients receiving dialysis.\textsuperscript{281,282}

Use of mupirocin to eradicate MRSA colonization was studied in a randomized, controlled trial of colonized hospital patients. Eradication was reported in 25% of those receiving intranasal mupirocin twice daily for 5 days and a daily bath with chlorhexidine for 7 days as compared with 18% of those receiving placebo nasal ointment and the week of daily baths with chlorhexidine.\textsuperscript{283} Persistent carriage was linked to carriage at sites other than the nose.\textsuperscript{284} A much higher success rate was reported for eradicating MRSA from hospitalized patients using a protocol that included mupirocin intranasal ointment three times daily, daily chlorhexidine baths, systemic therapy with a regimen containing rifampin and at least one other systemic drug to which MRSA was susceptible (usually minocycline or trimethoprim-sulfamethoxazole), removal and replacement of foreign bodies (eg, endotracheal tubes, percutaneous endoscopic gastrostomy tubes, or catheters) halfway through the treatment course, and brief disinfection of the hospital room daily during the treatment course, which usually lasted for 2 weeks.\textsuperscript{272}

Any program attempting eradication of carriage should incorporate plans for routine susceptibility testing because eradication is less likely when the drugs selected are inactive against the colonizing strain and widespread mupirocin resistance has developed due to spread in facilities using mupirocin extensively.\textsuperscript{285,286}

The Role of Environmental Disinfection

Facilities should develop cleaning and disinfection policies to control environmental contamination with antimicrobial-resistant pathogens such as VRE, MRSA, and VISA or VRSA.\textsuperscript{158,287} In addressing the cleaning and disinfection of environmental surfaces, the Spaulding classification, which divides instruments into critical, semicritical, and noncritical categories requiring different levels of disinfection and sterilization, and the recommendations of manufacturers have been important.\textsuperscript{287,290} These policies should consider the use of the surface or object, the amount of contact with the patient, and the materials or special qualities of the surface or object. In addition, environmental surfaces may be more (bed rails or doorknobs) or less (walls or ceilings) frequently involved in hand contact. For those areas that have substantial hand contact, cleaning may need to be more frequent and more stringent.\textsuperscript{158}

It has been suggested that general routine cleaning and disinfection of housekeeping surfaces and patient-care surfaces should be adequate for inactivation of these organisms.\textsuperscript{291,292} MRSA and VRE are susceptible to many
low-level and intermediate-level disinfectants, quaternary ammonium compounds, phenolics, and iodophors (with proper dilutions). 158,291-295 Studies have shown that an array of dilutions of quaternary ammonium, phenolic, and iodophor germicidal are equally effective in vitro for VRE and vancomycin-susceptible Enterococcus (VSE) and for MRSA and MSSA. 296,298 Rutala et al. evaluated multiply resistant bacteria, including MRSA and VRE (as well as several other gram-negative and gram-positive bacteria), and found that antibiotic-resistant strains did not exhibit increased resistance to the disinfectants studied, including phenolics and quaternary ammonium. 292

Although routinely used disinfectants are as active against MRSA and VRE as they are against MSSA and VSE, 292,293 more thorough application of the disinfectant by “drenching the surface” or “active damp scrubbing” has been found to more reliably remove VRE from environmental surfaces in the healthcare setting than does quick wiping with a cloth lightly sprayed with the same disinfectant. 161,169,294 Falk et al. reported control of a VRE outbreak in a burn unit only after an increase in the intensity of environmental disinfection (associated with a decrease in the proportion of environmental cultures positive, from 29% to 1%). 169 The cleaning intensification included an in-service for housekeeping personnel, an assigned daily cleaning time, additional cleaning during later shifts in the day, and a checklist system to track cleaning in the units involved in the outbreak. Byers et al. found that 16% of hospital room surfaces remained contaminated by VRE after routine terminal disinfection, which involved spraying a cleaning rag with a quaternary ammonium disinfectant and quickly wiping surfaces. In contrast, the authors found that enhanced disinfection with a new “bucket method” (cleaning rag dipped in bucket with the same disinfectant, drenching all surfaces, leaving surfaces wet for 10 minutes, and then wiping dry with clean towels, as well as antimicrobial treatment of carpet) resulted in uniformly negative cultures. Byers et al. found that conventional cleaning took an average of 2.8 disinfections to eradicate VRE from a hospital room, whereas only one cleaning was required with the bucket method. Smith et al. reported that traditional disinfection with a phenolic disinfectant, which involved spraying the surface and then immediately wiping it dry with a paper towel, did not reliably remove VRE from the surfaces. By contrast, “active damp scrubbing” with the same phenolic disinfectant was associated with uniformly negative cultures. Another recent investigation concluded that rigorous cleansing of the environment helped to control a MRSA outbreak when added to other control measures (surveillance cultures, isolation of colonized patients, eradication of colonization, ward closure for multiple cases, and an educational program regarding infection control measures including hand washing and use of an alcohol hand gel). 295 Thus, facilities should review their cleaning methods and intensity and consider adopting such enhancements if needed. Antibiotic-resistant pathogens are sensitive to routinely used hospital disinfectants, but it is essential that correct and meticulous cleaning and use of disinfectants be performed. Care must be taken to see that the proper amount, dilutions, and contact time of germicidal agents are used consistently. Although routine environmental cultures are not recommended, 158,298 in the setting of ongoing transmission of VRE, cultures of the environment can assist in validating the effectiveness of cleaning and disinfection procedures. Directed cultures should be done with the assistance of microbiology and infection control personnel. 158

The Role of Equipment Disinfection

As mentioned above, multiple studies have demonstrated that portable healthcare equipment, such as stethoscopes, tourniquets, sphygmomanometer cuffs, electronic thermometer handles, otoscopes, and pagers, also becomes contaminated, like hands, and can serve as a potential vector for antibiotic-resistant pathogens to patients, either via direct contact or by contamination of clinicians’ hands. 150-156,296 Disinfection of such equipment with 70% isopropyl alcohol has been shown to decrease bacterial counts significantly. 122,151,155 Therefore, routine disinfection of equipment between patient contacts could help prevent transmission of such pathogens.

The Role of Information Management

A hospital computer system can be used to store information regarding long-term isolation indicators for patients known to be colonized with antibiotic-resistant pathogens such as MRSA or VRE. With optimal programming, this can come up automatically whenever the patient enters the healthcare system, whether in the hospital, emergency department, outpatient clinic, or a diagnostic or procedure area, providing an alert to HCWs who may be interacting with the patient for the first time and are unaware of the requirement for isolation. This was done at the University of Geneva Hospitals and resulted in a significant improvement in isolation of such patients on readmission. 297

Cost-effectiveness

A variety of studies have been conducted of the impact of S. aureus infections. Wakefield et al. assessed the extra costs due to serious S. aureus nosocomial infections and found that 77% of the costs of these infections were related to per diem costs for the extra days spent in the hospital, 21% were due to antimicrobials for treating the infections, and 2% were due to laboratory costs incurred for diagnosing and treating the infections. 298 In another study, the same authors estimated the incremental costs associated with S. aureus healthcare-associated infections and found that they prolonged the mean hospital stay by 20 days. 299 Arnow et al. assessed the consequences of catheter-related infection and concluded that S. aureus was responsible for higher mean costs than were other pathogens. 300 They found that S. aureus catheter-related bloodstream infections resulted in excess costs that were 1.64-fold higher than those for all episodes of catheter-related bloodstream
infection (ie, including those due to *S. aureus*). This implies that *S. aureus* actually caused a greater increase in cost than 1.64-fold as compared with all other pathogens. Another study reported that *S. aureus* infection was associated with “approximately twice the length of stay, deaths and medical costs of typical hospitalizations.”301 These results are of interest because the excess costs of MRSA infections are often compared with those of MSSA infections rather than with those of all nosocomial infections.

Abramson et al. calculated an excess attributable cost of $27,083 for MRSA bloodstream infection versus $9,661 for MSSA bloodstream infection.302 Similarly, Carmeli et al. compared patients with MRSA bloodstream infection with those with MSSA bloodstream infection in multivariate analyses; those with MRSA bloodstream infection had increased lengths of hospital stay and hospital charges.16 They concluded that MRSA bloodstream infections resulted in an estimated increase in costs to their hospital of $235,000 per year. The same authors conducted a meta-analysis of 31 cohort studies and concluded that MRSA bloodstream infection was significantly more lethal, resulting in almost a doubling of the case fatality rate after adjustment for other predictors such as underlying severity of illness.15 Cheng et al. found that when compared with patients with MSSA bloodstream infections, patients with MRSA bloodstream infections had prolonged hospitalization, higher antimicrobial costs, and higher mortality.303 Recently, Stone et al. performed a meta-analysis of the attributable costs of a variety of healthcare-associated infections.304 They found that MRSA infections were associated with a mean attributable cost of $35,367. In a cohort study of surgical patients from January 1994 through November 2000, Engemann et al. found that when compared with MSSA, patients with MRSA surgical-site infections had prolonged hospital admissions (median, 15 vs 10; *P* < .001), increased hospital charges (median, $92,363 vs $52,791; *P* < .001), and higher mortality (20.7% vs 6.7%; *P* < .001).17 The two latter associations remained significant in a multivariate analysis after adjusting for multiple covariates including American Society of Anesthesiologists (ASA) score. Kaye et al. compared patients with MRSA infections with two types of control groups: uninfected patients and patients infected with MSSA. In both sets of analyses, MRSA was associated with significantly higher mortality, hospital stay, and hospital charges.305

Significant but with wide confidence intervals, and four that tended to have greater statistical power reported significant increases in mortality with odds ratios of 2 to 3.18 Stosor et al. found that VRE bloodstream infection was associated with increased length of stay and hospital costs ($27,000 per episode) as compared with VSE bloodstream infection among patients with similar underlying severity of illness.300 Song et al. found that VRE bloodstream infection was associated with a 19-day increase in hospital stay and increased hospital charges when compared with uninfected patients with similar baseline severity of illness ($79,589 per episode).14 A more recent study by Kaye et al. concluded that VRE infection was associated with significantly higher mortality and hospital charges as compared with either uninfected control patients or patients with VSE infections after adjustment for other predictors.305

The significantly higher costs of MRSA and VRE infections (than of those due to MSSA and VSE, respectively) suggest that effective control of these antibiotic-resistant pathogens would result in cost savings. A low rate of bloodstream infections due to these two antibiotic-resistant pathogens at a hospital using a program of active surveillance cultures for identifying the reservoir for spread to prevent transmission resulted in annual cost savings ranging from $884,586 to $2,933,312 when compared with hospitals of comparable size and complexity that were not employing such control measures.317 At Westchester County Medical Center, Montecalvo et al. found that the implementation of an active surveillance and isolation program for VRE terminated an outbreak, reduced the prevalence of VRE colonization, and was cost-effective, with reported annual cost savings of $189,318.320 At a hospital that had controlled a large outbreak and then kept the prevalence of VRE low during the next 2 years, Muto et al. compared the costs of active surveillance cultures and contact isolation with the attributable costs of VRE bloodstream infections that occurred at a much higher rate at a hospital of similar size and complexity not using this approach to prevent spread. The excess costs of VRE bloodstream infections were estimated to cost the comparison hospital 3-fold more than the costs of active surveillance cultures and contact isolation at the hospital using these measures to prevent spread (ie, $761,320 in attributable costs for 28 extra VRE bloodstream infections during a 2-year period at the comparison hospital vs $253,099 for surveillance cultures and isolation at the hospital proactively preventing spread). It was noted that adding the excess costs of infections at body sites other than the bloodstream would have resulted in an even larger difference.314

For MRSA, six cost-benefit analyses have been performed. Jernigan et al. assessed the cost and benefit at a university hospital where active surveillance cultures were performed for high-risk patients.45 They estimated that an active surveillance culture program would save between $20,062 and $462,067 annually while preventing 8 to 41 MRSA infections. Chaix et al. performed a cost-benefit analysis of control of endemic MRSA in an ICU.46 The mean total costs of treating MRSA patients exceeded those of their matched controls by $9,275; the excess
medical and total costs incurred by MRSA-infected patients who survived were $4,380 and $10,560, respectively. The total extra cost of contact isolation, including supplies and screening for MRSA, was $655 to $705 per patient. The total cost of the control program ranged from $340 to $1,480 per patient. Chaix et al. concluded that a reduction of the MRSA infection rate by just 14% would make such a containment program cost-beneficial. The authors concluded that “a strategy of targeted screening and isolation dominates other strategies over a range of MRSA carriage rates on admission, efficacy of the control program and infection rates following transmission.”

A third cost-benefit analysis of controlling MRSA infections in this manner compared the costs of controlling spread of MRSA using this proactive approach in the NICU of one hospital with the costs of not taking this approach in another NICU in another hospital where a MRSA outbreak continued uncontrolled for 51 months during which time there were 75 MRSA bloodstream infections with 14 resulting in death. The estimated attributable excess cost of the 75 MRSA bloodstream infections in the comparison NICU was $1,306,600, which exceeded the cost estimates for surveillance cultures and contact precautions in the other NICU by 19- to 27-fold. This would have been the savings if the two units had had equal rates of Staphylococcus aureus bloodstream infection because of the significantly higher cost of MRSA as compared with MSSA bloodstream infection. A fourth cost-effectiveness analysis concluded that a 1-year screening program was cost-effective because of reduced transmission and resulting lower costs of isolation. A fifth study found that the cost of gowns used for contact precautions decreased significantly after implementation of a program of active surveillance cultures and immediate presumptive contact precautions for all new admissions to an ICU until the results of surveillance cultures were confirmed to be negative. In the first 3 months of using this approach, the incidence rate of MRSA decreased from 5.4 per 1,000 patient-days to 1.6 per 1,000 patient-days and overall gown use decreased by 40% (P < .001). A sixth study concluded that it would be cost-beneficial to use screening cultures and contact precautions to control MRSA infections in ICUs and that it would be more cost-beneficial to place all ICU admissions in contact precautions and perform screening cultures than it would be to do the same for different subsets. The cost-benefit studies mentioned above have all focused on implementing control measures in a single ward or a single hospital. Simultaneous implementation throughout all healthcare facilities would probably make implementation in any single facility more effective. Likewise, the cost of gaining and maintaining control will probably be reduced in that facility because of similar measures being implemented in all other facilities.

Some have recommended the use of universal barrier precautions to prevent the spread of antibiotic-resistant pathogens such as MRSA and VRE. Universal gloving has been studied and has been shown to work better for preventing the spread of VRE than standard precautions in four high-risk wards during a 2-month period. However, this was in addition to contact precautions for known patients known to be colonized or infected with VRE. Four of five other studies with epidemiologic data suggested that contact precautions with gowns and gloves worked better than gloves alone for preventing the spread of VRE. Additionally, a high rate of clothing contamination has been found that was prevented when gowns were worn. Of the various universal barrier options, universal gloving would cost the least but would be associated with a higher transmission rate than other options. The highest cost of any universal barrier option would come from universal gown and glove isolation. Surveillance cultures and contact precautions would have an intermediate cost that would depend primarily on the prevalence of patients requiring isolation. Implementing contact precautions for patients with an expected prevalence exceeding 5% to 10% pending the results of surveillance cultures and discontinuing isolation for those with negative cultures would combine elements of both approaches and result in optimal control at a lower price than using universal gown and glove precautions for all patients for the entire hospital stay.

The above cost-benefit analyses were usually conservative and did not attempt to include all cost savings that might accrue from preventing MRSA and VRE infections. Nevertheless, they show that MRSA and VRE infections are responsible for increased duration of hospitalization, increased costs, and higher mortality. Furthermore, they demonstrate that an infection control program that emphasizes early identification of these patients through active surveillance cultures and contact isolation for preventing transmission reduces the prevalence and incidence of both colonization and infection, improves patient outcomes, and reduces healthcare costs. The recent emergence of VRSA, which has not yet been submitted to cost-effectiveness studies, will likely lead to even greater cost-effectiveness of controlling MRSA and VRE. This is because of the twin prospects that (1) VRSA will emerge in places where MRSA and VRE are allowed to spread out of control and (2) there will likely be greater costs for VRSA infections than for MRSA infections (because VRSA is resistant to more antibiotics and, on average, VRSA infections therefore will probably persist longer). A VRSA infection may require therapy with newer agents such as synergicid and linezolid; the acquisition costs for these agents in one hospital pharmacy were recently reported to be 5- to 17-fold higher than the cost for vancomycin. In a recent study, patients with infections due to MRSA strains with reduced susceptibility to vancomycin exhibited higher hospital mortality than did matched patients with infections due to MRSA strains fully susceptible to vancomycin despite adjustment for other predictors of hospital mortality.

RECOMMENDATIONS

I. Active Surveillance Cultures to Identify the Reservoir for Spread

1. Implement a program of active surveillance cultures and contact precautions to control the spread of epidemiolog-
ically significant antibiotic-resistant pathogens known to be spreading in the healthcare system via direct and indirect contact. (IA)29,30,43,45-47,49,57,96,99,102,106,119,138-147,149,171-173,176

2. Surveillance cultures are indicated at the time of hospital admission for patients at high risk for carriage of MRSA, VRE, or both. (IB)71,76,177,320,321

3. Periodic (eg, weekly) surveillance cultures are indicated for patients remaining in the hospital at high risk for carriage of MRSA, VRE, or both because of ward location, antibiotic therapy, underlying disease, duration of stay, or all four. (IA)30,57,102,137,141,147-149,174,181

4. In facilities found to have a high prevalence on initial sampling, a facility-wide culture survey is indicated to identify all colonized patients and allow implementation of contact precautions. (IB)102,145,322

5. Because transmission occurs throughout the healthcare system, these measures should be implemented in all types of healthcare facilities throughout the system. (IB)119,161,176,182,323

6. The frequency of active surveillance cultures should be based on the prevalence of the pathogen and risk factors for colonization. For example, more frequent cultures are needed in a facility where 50% of all S. aureus isolates are MRSA than in one where less than 1% of all S. aureus isolates are MRSA. (IB)30,43,45-47,49,57,96,99,102,106,119,138,147,149,171-173,176

7. The goal of this program should be to identify every colonized patient, so that all colonized patients are cared for in contact (or cohort) isolation to minimize spread to other patients. (IB)30,43,45-47,49,57,96,99,102,106,119,138,147,149,171-173,176

8. Surveillance cultures for VRE should use stool samples or swab samples from the rectum or perirectal area. Polymerase chain reaction, culture with broth enhancement, and quantitative stool culture have each been more sensitive than directly plated rectal or perirectal swab cultures, but the latter have been associated with control of infections and can be recommended as effective and cost-effective until less costly methods of using the other procedures become available. (IB)99,102,106,119,138,147

9. VRE patients can be routinely cohorted with other VRE patients. (II)102,106,145

10. Surveillance cultures for MRSA should always include samples from the anterior vestibule of the nose. (IB)78,315,324

11. If present, areas of skin breakdown should also be sampled for MRSA. (IB)315,324

12. Throat cultures have been shown to detect S. aureus and MRSA with sensitivity equal to or greater than that of nasal cultures in multiple patient populations. If used, the throat swab can be plated onto the same agar as the nasal swab. This would enhance sensitivity without adding the cost of an extra culture. (IB)67,74

13. Perirectal–perineal cultures have been shown to detect MRSA with high sensitivity in certain patient populations, but the perirectal–perineal area should not be selected as the only site for culture. (IB)315,324,325

14. Patients colonized or infected with MRSA isolates can be cohorted with other MRSA patients. (II)30,43,45

15. Patients with MRSA isolates that are eradicable because of known susceptibility to multiple drugs useful for eradication (eg, mupirocin, rifampin, minocycline, trimethoprim-sulfamethoxazole, or all four) should not be cohorted with those with isolates resistant to these drugs, if eradication will be used as an adjunctive measure. (II)272

16. In certain settings, such as nursing homes and psychiatric wards, identification of colonized patients is important, but contact precautions may require modification allowing for social contact while limiting physical contact. (II)119,182,323

II. Hand Hygiene

1. HCWs should be encouraged to decontaminate (clean) their hands with an antiseptic-containing preparation before and after all patient contacts. (IA)121,326-330

2. Soap and water hand washing is required when hands are visibly dirty or visibly contaminated with blood, body fluids, or body substances. (IA)331

3. When hands are not visibly contaminated with blood, body fluids, or body substances, use of an alcohol hand rub containing an emollient should be encouraged. (IB)315,332,334

4. Lotion compatible with (ie, that does not inacti-
vate) the antiseptic being used should be provided for use by HCWs. (II)219,234
5. Monitoring of hand hygiene compliance and feedback to HCWs should be done to motivate greater compliance. (IB)215,234

III. Barrier Precautions for Patients Known or Suspected to Be Colonized or Infected With Epidemiologically Important Antibiotic-Resistant Pathogens Such as MRSA or VRE
1. Gloves should always be worn to enter the room of a patient on contact precautions for colonization or infection with antibiotic-resistant pathogens such as MRSA, VRE, VISA, or VRSA. (IA)122,132,212,225-230
2. Gowns should always be worn as part of contact precautions for all patient and environmental contact with patients known to be colonized by antibiotic-resistant pathogens such as MRSA, VRE, VISA, or VRSA, except when there is no direct contact with patient or environmental surfaces. (IA)29,30,43,45-47,49,57,59,96,99,102,106,119,122,135,136,138,147,148,171-173,176,345
3. Universal gown and glove use or universal gloving alone also can be considered for adjunctive control on high-risk wards among patients with surveillance cultures pending. (IB)37,44,105,216,318,346
4. Masks should be worn as part of isolation precautions when entering the room of a patient colonized or infected with MRSA, VRE, VISA, or VRSA to decrease nasal acquisition by HCWs. (II)30,123,124,129,231,232
5. To prevent persistent high-density VRE colonization, decrease the use of antianaerobic agents in patients with known VRE intestinal colonization (if possible and appropriate for care of the individual patient being treated). (II)115,269
6. To help prevent persistent carriage of MRSA, reduce the use of antibiotics and particularly fluoroquinolones to the minimum necessary in institutions where MRSA is endemic. (IB)225,238
7. Avoid therapy for colonization except when suppression or eradication of colonization is being attempted using an evidence-based approach for infection prevention, for psychological benefit of the patient, or for cost benefit (ie, by reducing the need for long-term isolation). (IB)272,285,286

V. Decolonization or Suppression of Colonized Patients
1. Consider MRSA decolonization therapy for both patients and HCWs as an adjunctive measure for controlling spread of MRSA in selected populations when appropriate. (IB)30,116,271,272,275-277
2. Any program of decolonization therapy should incorporate routine susceptibility testing, as selection of inactive agents is less likely to achieve eradication. (II)272,285,293
3. Widespread use, prolonged use, or both of decolonization therapy should be avoided, because this has been associated with the evolution and spread of antibiotic-resistant strains, undermining the effectiveness of the control effort. (IB)285,286

VI. Other
1. Educational programs should be conducted to ensure that HCWs understand why antibiotic-resistant pathogens are epidemiologically important, why prevention of spread is critically necessary for control, and which measures for preventing spread have proven effective. (IB)215,220
2. Ensure that the hospital method of disinfecting hospital surfaces for antibiotic-resistant organisms (especially VRE) has been shown to be adequate based on the results of studies of such methods in the healthcare setting or perform cultures in the room of discharged patients to confirm the adequacy of terminal cleaning. This requires review of the disinfectant agent, method and meticulousness of cleaning, dilutions, and contact time. (IB)192,161,169,284
3. Use the hospital computer system to record long-term isolation indicators for patients colonized with MRSA, VRE, VISA, or VRSA so that on return the computer will provide an alert regarding the need for isolation. (IB)297
4. Dedicate the use of noncritical patient-care equipment to a single patient (or cohort of patients infected or colonized with the pathogen requiring precautions) to avoid sharing between patients. If use of common equipment or items is unavoidable, then adequately clean and disinfect them before use for another patient. (IB)299,150,155,296

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