Patients in intensive care units (ICUs) are at greatly increased risk of developing health care-associated infections (HAIs) [1]. More than 70% of the bacteria that cause HAIs are resistant to at least one of the antimicrobials commonly used to treat these infections [2]. Two such pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are responsible for a considerable proportion of ICU infections that are associated with increased morbidity, mortality, and costs [3–5]. In this review, we discuss the epidemiology of colonization and infection by MRSA and VRE and provide an update on practices for prevention of transmission and infection by MRSA and VRE in the ICU.

**EPIDEMIOLOGY AND MECHANISMS OF RESISTANCE**

MRSA is the major cause of HAIs worldwide [6]. Among ICUs in the United States, the proportion of methicillin resistance among *S. aureus* isolates increased from 35.9% in 1992 to 64.4% in 2003 [4]. Approximately 8% of patients are colonized with MRSA upon admission, and an average of 5% will acquire MRSA colonization in the ICU [7,8]. A comparison study of academic tertiary care facilities found medical ICUs had higher MRSA admission prevalence rates than surgical ICUs, whereas surgical ICUs had a higher incidence rate [7]. *Enterococcus* is the third most common pathogen associated with HAIs, with 33% resistant to vancomycin [9]. VRE infection is associated with increased ICU cost and increased length of stay [10]. Incidence of ICU-acquired VRE varies among regions and countries. For example, in the United States, Warren et al [11] reported a VRE incidence of 27 cases per 1000 patient ICU days, whereas Kohlenberg et al [12] reported a mean incidence of 0.29 cases per 1000 patient ICU days in Germany.

Understanding the mechanisms that allow development of resistant strains of *S. aureus* and *Enterococcus* species is important to devise preventive strategies. Methicillin resistance in MRSA is determined by the staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element that carries the mecA gene. The mecA gene codes for an additional penicillin-binding protein (PBP) that has a reduced affinity towards methicillin (PBP2a/PBP2’). This results in a reduced ability to bind to the bacterial cell wall and inhibit synthesis [13,14]. Study of molecular epidemiology has identified MRSA as originating from 8 major variants of the mecA gene [15]. The majority of MRSA infections are caused by strains belonging to a few internationally disseminated clones [14]. The first identified strains were associated with infections in hospitalized patients (hospital-associated MRSA), but community-associated MRSA strains have since emerged and have become established established globally, including in health care institutions [16].

Community-acquired MRSA can cause severe infections in health hosts [17]; possible explanations include...
increased CA-MRSA virulence due to the acquisition of mobile genetic elements, namely those containing Panton-Valentine leukocidin (PVL) [18] or increased expression of core genome-encoded virulence genes, such as phenol-soluble modulin (PSM) cytolsins, α-toxin, and other virulence determinants [19].

Enterococcus is intrinsically resistant to several antimicrobial drugs, with resistance to vancomycin encoded by several clusters of genes known as vancomycin resistance gene clusters (eg, vanA, vanB). The gene clusters generate resistance through multiple pathways which encode enzymes to determine the structure of peptidoglycan precursors [20,21]. Genetically diverse, hospital-associated VRE outbreaks have been associated with single clones, multiple clones, and changing molecular epidemiology over time [21]. While up to 25% of the VRE genome includes acquired elements, the majority of hospital-associated infections are traced to a few clonal complexes, which differ from community-associated VRE strains [22].

The evolution of these efficient mechanisms that promote drug resistance has made it extremely challenging to eradicate organisms such as MRSA and VRE. However, advances in recent years have furthered our understanding of the epidemiology, pathogenesis, and methods of prevention and containment.

**RISK FACTORS FOR COLONIZATION AND INFECTION**

**MRSA**

The risk factors underlying MRSA colonization and infection in the ICU setting can be categorized as either patient/host or environmental factors. A wide range of patient-level factors is associated with MRSA colonization upon admission. General principles regarding the transmission of MRSA in the community include close contact with colonized or infected individuals, breaks in the skin, crowded living conditions and poor hygiene. These factors, alone or in combination, are thought to underlie observed outbreaks among sports teams, military personnel, correction facilities, American Indian communities, and daycare centers [23–34].

Two recently published systematic reviews have summarized important patient-level factors associated with MRSA colonization at the time of hospital admission. Forster et al [35] examined 27 studies and identified previous admission to hospital, transfer from nursing home or long-term care facility, and previous antibiotic use as the top 3 factors associated with MRSA colonization. A similar review conducted by McKinnell and colleagues [36] found that prior hospitalization, nursing home contact, recent antibiotic use, and exposure to health care-associated pathogens (MRSA carriage, VRE carriage, or Clostridium difficile infection) were found to portend the highest risk. Specific comorbid conditions also conveyed an increased risk, including congestive heart failure, chronic wounds/bedsores, diabetes mellitus, pulmonary disease, immunosuppression, urinary catheter, and renal failure/dialysis. It is clear that healthcare contacts, especially recent hospitalization, residence in a long-term care facility, and antibiotic use, are significant risk factors for MRSA colonization [37–39].

In contrast to those already colonized with MRSA, some patients acquire MRSA during hospitalization. In these cases, transmission via hands of healthcare workers is likely the most common mechanism for spread of MRSA [6,40–42]. An understaffed ICU has also been cited as a potential risk factor for ICU MRSA transmission, perhaps due to sacrifices in hand hygiene practices by overextended staff [6]. Additional factors associated with increased risk of nosocomial MRSA acquisition include duration of antibiotic therapy, exposure to quinolone or macrolide antibiotics, length of hospital stay, enteral feeding, post-surgical status, insertion of central line or urinary catheter during admission, ICU admission, and proximity to another patient with MRSA infection or colonization [43–45]. A summary of risk factors for MRSA acquisition is shown in Table 1. Regardless of whether MRSA colonization precedes admission or occurs due to nosocomial spread, it is associated with increased risk of developing a HAI [46–49]. In 2 large prospective observational cohort studies, the hazard ratios of MRSA colonization developing into S. aureus infections during the ICU stay were 3.84 and 4.70, respectively [50,51]. High levels of concordance between MRSA colonization strains and HAI strains have also been reported [52]. Nasal colonization with S. aureus has also been identified as an independent risk factor for developing ventilator-associated pneumonia (VAP) and bacteremia [53,54]. A case series of ICU patients with S. aureus nasal colonization who developed lower respiratory tract infections demonstrated genetically identical nasal and bronchial strains in 15/16 cases [55]. This finding strongly suggests that nasopharyngeal colonization with S. aureus contaminates oral secretions that are aspirated by critically ill patients, resulting in subse-
Reducing MRSA/VRE Transmission

quent pneumonia. In a long-term outcomes study among a matched cohort of veterans, MRSA colonization was associated with an increased risk of infection-related readmission and mortality [56]. These findings reflect the critically important nature of measures designed to curb nosocomial transmission and acquisition of MRSA, especially among the vulnerable ICU population.

VRE

As with MRSA, risk factors associated with VRE colonization include both patient-level and ICU-level (or environmental) factors [57]. Examples of patient-level factors include previous antimicrobial exposure [58–62], underlying medical illnesses such as chronic renal failure requiring hemodialysis [11,63], length of hospital or ICU stay [11,59,64,65], and recent exposure to health care facilities. ICU-level factors of relevance are the prevalence of VRE in the unit, with high levels of endemicity leading to higher risk of colonization and transmission.

Antibiotic use is a major risk factor for VRE acquisition, although the type and class of antibiotic varies considerably across studies; the most frequently identified antibiotics are broad-spectrum cephalosporins, vancomycin, and anti-anaerobic agents [58,62,64]. Patients with chronic liver disease and post-transplantation are at exceedingly high risk for VRE acquisition [59]. In a recent study by Pan [66], for example, the authors found that the incidence of newly acquired VRE was 21.9 per 1000 patient-days in an ICU setting. On multivariate analysis, the authors found that, similar to other reports [11,59,67], length of stay in the ICU was associated with increased risk of VRE acquisition, with each additional day of stay increasing risk of VRE by 1.03 times. Warren et al undertook a prospective cohort study involv-

Table 1. MRSA Risk Factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>McKinnell 2013 [164]</td>
<td>Meta-analysis</td>
<td>Prior hospitalization, nursing home exposure, history of health care-associated pathogens (MRSA carriage, Clostridium difficile infection, VRE carriage), CHF, DM, pulmonary disease, renal failure, immunosuppression</td>
</tr>
<tr>
<td>Forster 2013 [35]</td>
<td>Systematic review</td>
<td>Previous admission to hospital, previous antibiotic use, age, gender, chronic skin lesions, chronic illness, nursing home/long-term care transfer, urinary or intravenous catheter, history of surgery, DM, prior MRSA colonization/infection, hospital-to-hospital transfer, heart disease, enteral nutrition, male-male sex, combined social factors (homelessness, promiscuity, IVDA), spinal cord injury</td>
</tr>
<tr>
<td>Jernigan 2003 [38]</td>
<td>Case-control</td>
<td>Hospital admission in previous year, chronic illness, admission to nursing home, hospitalization of 5 days or longer in preceding year</td>
</tr>
<tr>
<td>Denkinger 2013 [165]</td>
<td>Retrospective cohort</td>
<td>Age &gt; 65 years</td>
</tr>
<tr>
<td>Boisseau 2012 [166]</td>
<td>Cross-sectional</td>
<td>Health care worker</td>
</tr>
<tr>
<td>Fritz 2012 [167]</td>
<td>Cross-sectional</td>
<td>Close household contact with MRSA</td>
</tr>
<tr>
<td>Rafee 2012 [168]</td>
<td>Cross-sectional</td>
<td>Close household contact with MRSA</td>
</tr>
<tr>
<td>Schechter-Perkins 2011 [169]</td>
<td>Prospective cohort</td>
<td>DM, HIV, MRSA history, IVDA, hospital admission in previous year, jail in past year, contact sports, long-term care facility</td>
</tr>
<tr>
<td>Bisaga 2008 [170]</td>
<td>Prospective cohort</td>
<td>Emergency department workers</td>
</tr>
<tr>
<td>Suffoletto 2008 [171]</td>
<td>Prospective cohort</td>
<td>Emergency department workers</td>
</tr>
<tr>
<td>Cantar 2006 [43]</td>
<td>Case-control</td>
<td>Insertion of central line or urinary catheter during admission, surgical site infection</td>
</tr>
<tr>
<td>Furuno 2006 [37]</td>
<td>Prospective cohort</td>
<td>Hospital admission in previous year, antibiotics within previous year</td>
</tr>
<tr>
<td>Young 2004 [172]</td>
<td>Retrospective cohort</td>
<td>Homelessness, IVDA</td>
</tr>
<tr>
<td>Salgado 2003 [173]</td>
<td>Meta-analysis</td>
<td>Close contact with MRSA colonized individual, health-care exposure</td>
</tr>
<tr>
<td>Graffunder 2002 [44]</td>
<td>Case-control</td>
<td>Hospital length of stay, antibiotic exposure (levofloxacin, macrolides), previous hospitalization, enteral feedings, surgery</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; DM = diabetes mellitus; IVDA = intravenous drug abuse.
ing 519 patients admitted to the ICU for more than 48 hours [11]. Seventy-four (21%) of 352 patients were subsequently colonized with VRE. The median time to development of a positive VRE culture after ICU admission was 6 days. Increased mean APACHE II score on ICU admission (P = 0.002), sucralfate use (P = 0.003), vasopressor use (P = 0.01), tracheostomy in the ICU (P = 0.02), and C. difficile diarrhea (P = 0.002) appeared to be associated with VRE acquisition.

It appears that VRE acquisition is often associated with the sick subgroup of patients, and risk factors generally associated with VRE colonization and infection co-relate with disease chronicity and severity of illness. Length of hospitalization, ICU stay, hemodialysis, or transplantation may all be markers of disease severity. A summary of risk factors for VRE acquisition is shown in Table 2.

**REDUCING TRANSMISSION—MRSA AND VRE PREVENTION STRATEGIES**

Evidence-based guidelines developed by the Centers for Disease Control (CDC) Hospital Infection Control Practices Advisory Committee (HICPAC) for prevention of MRSA and VRE are available [68]. Several recently conducted well-designed clinical trials also provide additional insight that may be particularly helpful in the ICU setting [69]. A summary of the MRSA prevention guidelines issued by the CDC and included in its “MRSA toolkit” is provided in Table 3. A similar guideline on prevention of VRE [70], published more than a decade ago, has similar elements. Table 3 shows a side-by-side comparison of these elements. Unfortunately, despite these guidelines and extensive research regarding prevention and control, considerable controversy exists as to the most effective approaches. As such, these recommendations should be tailored to meet the needs of the specific ICU setting.

**Antimicrobial Stewardship**

Antibiotic use is a major driver of antibiotic resistance. A meta-analysis by de Bruin and Riley [71] studied the effect of vancomycin usage on VRE colonization and infection. A total of 12 articles describing 13 studies were included; none were randomized controlled trials.

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**Table 2. VRE Risk Factors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Risk Factors</th>
</tr>
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<tbody>
<tr>
<td>Bonten 1996 [60]</td>
<td>Prospective cohort</td>
<td>Age (55.5 [48–71] vs 40 [30–54] years, P &lt; 0.01). Previous use of a third-generation cephalosporin was more common in the 13 ventilated patients who acquired VRE than in the 25 who did not acquire VRE (11 [85%] vs 10 [40%], P &lt; 0.01). Previous use of parenteral vancomycin was more common in ventilated patients who acquired VRE than in those who did not (7 [54%] vs 6 [24%], P = 0.06).</td>
</tr>
<tr>
<td>Ostrowsky 1999 [59]</td>
<td>Prospective cohort</td>
<td>Length of stay, history of transplantation, use of 2nd- or 3rd-generation cephalosporins</td>
</tr>
<tr>
<td>Carmeli 2002 [58]</td>
<td>Case-control</td>
<td>Comorbid illness, infection or colonization with MRSA/CDAD in the last year, broad-spectrum antibiotics such as cephalosporins and metronidazole</td>
</tr>
<tr>
<td>Padaglione 2003 [62]</td>
<td>Prospective cohort</td>
<td>Admission to the hemodialysis unit, antibiotics such as carbapenems and ticarcillin-clavulanic acid</td>
</tr>
<tr>
<td>Furtado 2005 [64]</td>
<td>Prospective cohort</td>
<td>Length of stay</td>
</tr>
<tr>
<td>Se 2009 [67]</td>
<td>Neurosurgical ICU</td>
<td>Length of stay &gt; 2 weeks, GCS &lt; 8, Foley catheter placed longer than 2 weeks, Presence of nearby VRE-positive patients</td>
</tr>
<tr>
<td>Huang 2011 [65]</td>
<td>Retrospective case-cohort</td>
<td>Length of stay, hemodialysis (OR = 2.60, CI: 1.19, 5.70), low albumin (OR = 2.07, CI: 1.12, 3.83), fluoroquinolones (OR = 1.90, CI: 1.14, 3.17), third-generation cephalosporins (OR = 1.89, CI: 1.15, 3.10)</td>
</tr>
<tr>
<td>Batistao 2012 [63]</td>
<td>Prospective cohort</td>
<td>Hemodialysis, prior antibiotic use, prior carbapenem use</td>
</tr>
<tr>
<td>Pan 2013 [66]</td>
<td>Prospective case control (SICU)</td>
<td>Length of stay</td>
</tr>
</tbody>
</table>

GCS = Glasgow coma score.
All studies were quasi-experimental and lacked control groups. Among all studies, less than half (46%) implemented vancomycin reduction measures as the sole type of intervention [72–76]. The remaining studies implemented other infection control modalities and or restricted the use of other antimicrobials [77–83]. Although all
studies that implemented vancomycin restriction alone as a single strategy showed a decline in vancomycin usage, only 2 of these [74,75] showed a relative risk reduction in VRE acquisition post-intervention. Also, studies that restricted vancomycin alone revealed a trend towards lower efficacy in reducing VRE colonization and infection (33%) when compared with those that used additional measures (71%). While judicious antibiotic use should always be practiced, the evidence for vancomycin restriction as a sole intervention to control VRE is scant. It may be that other antibiotics are as big or bigger drivers of resistance in enterococci than vancomycin. For example, a growing body of literature supports antibiotic restriction, especially fluoroquinolones, for reducing MRSA. In several time-series quasi-experimental studies, restriction of fluoroquinolones was associated with reduced trends in MRSA infections in the acute care setting, and consideration should be given to monitor and optimize fluoroquinolone use in the ICU setting [84,85].

Antimicrobial stewardship programs are fundamental to optimizing antibiotic use in the ICU and the authors strongly recommend that all ICUs should have such a program in place.

Educational Interventions
Infection control and multidrug-resistant organism (MDRO)–specific education programs for health care workers is a core principle of the CDC’s prevention guidelines. The HICPAC VRE guideline also explicitly states “continuing education programs for hospital staff (including attending and consulting physicians, medical residents, and students; pharmacy, nursing, and laboratory personnel; and other direct patient-care providers) should include information concerning the epidemiology of VRE and the potential impact of this pathogen on the cost and outcome of patient care [70].” A systematic review published in 2008 [86] that included 26 studies showed that such interventions to prevent HCAIs are usually successful; in this review, 20 of 26 studies showed a statistically significant decrease in infection rates, with risk ratios ranging from 0 to 1.6. Education was usually part of a broader array of infection control interventions. While clearly essential, education alone is unlikely to have a sustained impact on reducing MRSA and VRE infections.

Infection Control Measures
Major infection control interventions include hand hygiene, the use of personal protective equipment (PPE), and cohorting. These measures can be grouped into “horizontal” (or global) vs. “vertical” (or targeted) strategies. Although not mutually exclusive, horizontal approaches are designed to have an impact on multiple pathogens (pathogen nonspecific), whereas vertical approaches are designed to reduce the impact of specific pathogens (such as VRE). For the purposes of this review, we will discuss both strategies for containment of MRSA and VRE. Horizontal strategies include hand hygiene, universal gloving and/or gowning, environmental cleaning, and daily bathing with chlorhexidine. Vertical strategies include screening for either MRSA or VRE followed by placement in contact precautions and decolonization with mupirocin.

Hand Hygiene
Hand washing is fundamental to reducing transmission of MDROs in health care institutions; however, optimal compliance is hard to achieve and sustain. Barriers to adherence may include unavailability of sinks or hand hygiene materials (eg, alcohol-based gels, gloves) time constraints, forgetfulness, or lack of knowledge [87–95]. Several monitoring strategies have been evaluated to increase compliance with hand hygiene. Most involve direct observation followed by performance assessment and feedback.

Trials examining the impact of improvements in hand hygiene compliance on HAIs in the ICU setting have largely found benefit, although not all studies showed a decline in HAI. In a prospective crossover trial, Rupp et al [96] found dramatic improvements in compliance with hand gel availability, but this did not translate to decreased nosocomial MRSA infections. Venkatesh et al [97] carried out a before-and-after interventional prospective study in a hematology unit in a tertiary level hospital to evaluate the use of an electronic method of surveillance to determine compliance with hand hygiene. The authors also used rates of horizontal transmission of VRE as a secondary end-point. Results of the study showed that hand hygiene compliance improved from 36.3% at baseline to 70.1%. This represented an OR of 4.1 (95% confidence interval, 3.7–4.5), which the authors attributed to the use of automated alerts. VRE transmission rates before and during intervention were not statistically different, but the rates of infection were lower at 1.0 per month in comparison with 4.7 infections per month in the preceding 6 months (P = 0.096).

While improved hand hygiene may result in significant reductions in HAIs [40], research indicates hand hygiene
alone influences about 40% of infections in the ICU setting [98]. As such, hand hygiene should be viewed as a necessary component of a comprehensive infection control program [99]. Despite the success of hand hygiene in reducing HAIs in the ICU, effective strategies to improve compliance remain elusive even under study conditions and further research is needed in this area [100].

**Personal Protective Equipment**

Tenorio et al [101] conducted a study to assess the effectiveness of gloving in the prevention of hand carriage of VRE by health care workers. The study showed that among 50 health care workers who had contact with patients colonized with VRE, 6 carried a similar patient strain even prior to known contact, and 17 of 44 (69%) had a patient-related VRE strain on their gloves after contact. This suggests a relatively high rate of colonization after usual patient-care contact. Factors associated with acquisition of VRE on gloves included duration of contact, contact with a patient’s body fluids, presence of diarrhea in a patient, mean VRE colony counts on a patient’s skin, and number of body sites colonized with VRE. Although gloves reduced the risk of VRE acquisition of VRE by 71% (ie, 12/17 did not have VRE on their hands after de-gloving) the protection afforded by gloves was incomplete. As such, hand hygiene after glove removal is recommended.

Slaughter et al [102] compared the use of personal protective equipment in the acquisition of VRE. During this study, 93 patients in glove-and-gown rooms and 88 patients in glove-only rooms had similar rates of VRE at baseline entry into the ICU and after the intervention. Mean times to colonization among the patients who became colonized were 8.0 days in the glove-and-gown group and 7.1 days in the glove-only group. None of these comparisons were statistically significant and the authors concluded that the universal use of gown and gloves was no better than the use of gloves alone in preventing VRE colonization.

A recent cluster randomized trial compared the effect of universal PPE (ie, gowning and gloving) with usual care for reducing acquisition of MRSA or VRE as a composite outcome [103]. The study did not find that universal gowning and gloving reduced VRE or MRSA acquisition but found a 40% decline in MRSA acquisition in the intervention ICUs compared with baseline rates of MRSA. No major adverse effects of universal gowning and gloving were noted in this study. A thoughtful editorial commenting on this article proposes that several aspects of the study deserve consideration, including the possibility of false-negative screening tests for VRE, which may have partially accounted for the negative primary outcome [69].

Based on these studies, it appears that the use of barrier precautions may be of value more for MRSA than VRE but further studies are needed to examine its impact on other types of pathogens, including new and emerging MDROs. Until further evidence becomes available, routine gowning and gloving may be of value in units with a high prevalence of MRSA.

**Environmental Cleaning**

Accumulating data suggests that the environment may play a major role in transmission of pathogens. MRSA has the ability to survive for days to weeks on inanimate objects [104–107]. Environmental contamination results in contamination of staff clothing and gloves [107,108] and is highly correlated with colonization strains among inpatients [109]. Although some studies of enhanced cleaning techniques and increased environmental services staff time have demonstrated reductions in MRSA outbreaks [110–112], the results are not universally favorable [113,114] and further studies are needed to examine the impact of environmental cleaning on rates of MRSA colonization or infection.

Several studies have implicated contaminated equipment as vectors for transmission of VRE during outbreaks [115–117], but the direction of fomite transfer from patient to environment has been difficult to ascertain. VRE have been found frequently on a variety of inanimate objects and surfaces in different health care environments [118–123], including gloved or ungloved hands of health care workers [101,124,125]. Hayden et al [126] determined the effect of improved environmental cleaning on VRE acquisition rates. This study was a pre-and-post intervention study carried out in a 21-bed medical intensive care unit (MICU) in a tertiary hospital over several phases. The intervention included the creation of a unique and improved cleaning program, as well as in-services to housekeeper services, education of the MICU staff, and a hand hygiene campaign. The results of the study showed decreased acquisition of VRE from 33.47 cases per 1000 patient days at risk to 10.40 cases per 1000 patient-days at risk by period 4 of the study. Increased environmental cleaning was also associated with reduced growth of VRE from environmental
cultures. At baseline, weekly contamination rates were 0.15 and 0.1 for samples obtained before and after cleaning, respectively. Culture positivity decreased to 0.07 and 0.04 for before and after cleaning in period 2 and then remained at low levels during the remainder of the study. It is important to note that the method for disinfecting used in this study was the “bucket method” as promoted by Byers [127]. This study provides further support for the importance of an environmental reservoir and of environmental decontamination to prevent endemic cross-transmission of VRE [126].

Goodman et al [128] used similar interventions but added a feedback tool using a black-light monitoring system (ie, use of an invisible, nontoxic marker to delineate areas that are adequately or inadequately cleaned) to reduce the likelihood of isolating either MRSA or VRE from an ICU environment. This study also showed favorable results, and notably, the use of the black-light monitoring system identified specific areas that were typically inadequately disinfected. Results showed that flat, horizontal surfaces (eg, countertoops, bedside tray tables, and hamper tops) were adequately cleaned more often than small, vertical surfaces (eg, doorknobs, toilet handles, light switches, and electronics).

Part of the controversy surrounding the impact of environmental cleaning is the difficulty in determining its individual value as part of an overall infection control bundle [129]. A proposed area of demonstrable impact for environmental cleaning are frequently touched sites which are more likely to be contaminated with pathogens. Focusing on these “hot-bed” areas of the care environment may offer a useful adjunct to other infection control measures [129].

Active Surveillance

Active surveillance refers to periodic screening for asymptomatic carriers followed by placement of colonized patients in contact isolation. This practice is highly variable across institutions, as the evidence supporting this practice is conflicting and there are concerns about the cost of implementing this approach without solid evidence [70,130,131]. Despite lack of randomized controlled trials to guide this practice for MRSA prevention, many hospitals utilize MRSA surveillance and it is mandated by law in 9 states [132,133].

A prospective, interventional cohort study of universal MRSA screening on admission to surgical wards failed to reduce nosocomial MRSA infections [134]. Most recently, a pragmatic, cluster-randomized ICU trial reported that universal decolonization with chlorhexidine wipes and mupirocin use was more effective than screening and isolation in reducing rates of MRSA clinical isolates [65]. However, concerns regarding the risk of mupirocin resistance have been expressed [135,136]. The only randomized trial that compared active surveillance for MRSA and VRE followed by contact precautions to usual care did not find a benefit to active surveillance.

Huskins et al [137], in a large, cluster-randomized trial of 19 ICUs from different hospitals, determined the utility of using a culture-based active surveillance and contact isolation, compared with usual care (contact isolation for patients colonized with MRSA or VRE) as identified by existing hospital protocols, to reduce the incidence of colonization or infection with MRSA or VRE. In this trial, which spanned 6 months and involved 3488 participants, the authors found no significant difference between the intervention and control ICUs in terms of MRSA and VRE colonization or infection rates.

Conflicting with these findings is an observational study comparing MRSA infection rates before and after institution of a universal screening protocol, which demonstrated a 69.6% (CI, –89.2% to –19.6%; P = 0.03) reduction in hospital wide MRSA prevalence density with screening [138]. The “MRSA bundle” implemented in 2007 at VA hospitals nationwide, which included universal screening, produced a 62% (P < 0.001) reduction in MRSA ICU infections; the relative contribution of the various bundle components is uncertain [139,140].

A proposed cost-saving alternative to universal screening is selective screening based on risk factor assessment [141]. The effectiveness of this type of program depends on creating a clinical decision-making tool capable of accurately identifying high-risk individuals while also accounting for the different risk factor profiles between HA-MRSA and CA-MRSA [142]. It has been proposed that targeted screening protocols may be more cost-effective in settings with <5% prevalence of MRSA colonization on admission [143].

Many studies [61,144–149] have shown that active surveillance against VRE is cost-effective. For example, Calfee et al [144] showed that an established active surveillance program results in control of endemic VRE in high-risk patients. The infection control program was established in response to a hospital-wide VRE outbreak, and was sustained after the outbreak was controlled. The study by Calfee et al spanned 5 years and was performed...
at a tertiary-level university hospital, where cultures from perirectal areas were used to identify high-risk patients who were asymptomatically colonized with VRE. During the latter 2 years, 768 new cases of VRE colonization were detected among 69,672 admissions (1.1% of admissions), of which 730 (95.1%) were identified by active surveillance methods. This implies that routine clinical cultures would probably have missed the majority of colonized patients. During this period, the incidence of VRE infection was likewise extremely low at 0.12/1000 patient days (ie, 90 nosocomial VRE infections were identified in 83 patients during 743,956 days of patient care). Sixty-nine of the 83 patients (83%) who developed nosocomial VRE infections were found to be colonized with VRE by surveillance culture before the onset of infection.

**Patient Decolonization**

Chlorhexidine gluconate has been used in several settings to control outbreaks and infections related to MRSA and VRE due to its broad-spectrum activity against these pathogens. Chlorhexidine-based solutions reduce the density of skin colonization with pathogens such as MRSA and VRE (skin asepsis), thus lowering the risk for horizontal transmission between health care workers and patients.

Decolonization with chlorhexidine as an MRSA infection reduction technique has demonstrated benefit in the ICU setting [150]. The previously mentioned large, cluster-randomized ICU trial by Huang and colleagues found universal decolonization with twice-daily intranasal mupirocin for 5 days and daily bathing with chlorhexidine-impregnated cloths for the entire ICU stay was superior to targeted decolonization of known MRSA carriers in preventing overall MRSA isolates. However, universal decolonization failed to show a reduction in MRSA bacteremia [151], and concerns about mupirocin resistance may limit the applicability of this approach.

There are now several studies [152–154] that show decreased acquisition of VRE with use of daily chlorhexidine bathing. In a study including 1787 ICU patients, Vernon et al found [154] that the reducing microbial density of VRE on patient’s skin by using chlorhexidine led to decreased transmission. In another study by Climo et al [153] that involved 6 ICUs at 4 academic centers and measured the incidence of MRSA and VRE colonization and blood stream infections (BSI) during a period of bathing with routine soap for 6 months compared with a 6-month period where all admitted patients received daily bathing with a chlorhexidine solution, results found decreased acquisition of VRE by 50% (4.35 vs. 2.19 cases/1000 patient days, *P* < 0.008) following the introduction of daily chlorhexidine bathing. Furthermore, compared with 16 of 270 patients colonized with VRE who subsequently developed VRE bacteremia at baseline, only 4 of 226 VRE-colonized patients bathed with chlorhexidine in the intervention period developed a BSI, translating into a relative risk reduction of 3.35 (95% CI, 1.13–9.87; *P* < 0.035). Patients colonized with VRE were 3 times less likely to develop VRE bacteremia when bathed with chlorhexidine compared with regular bathing. Despite the success of this protocol for VRE, when analyzed by individual organism no significant reductions in MRSA acquisition or BSI were reported. This finding is similarly corroborated by a trial conducted in the pediatric ICU setting which found an overall reduction in bacteremia with daily chlorhexidine washes but no significant decrease in cases due to *S. aureus* [155].

The results of these studies suggest that daily bathing with chlorhexidine should be part of routine practice in health care, especially in ICUs where endemic MRSA or VRE rates are high. Whether there is benefit in other settings needs to be studied.

In addition to chlorhexidine washes, other decolonization techniques have been proposed to reduce colonization and the spread of HAIs in the ICU setting. A randomized controlled trial of daily 5% tea tree oil body washes for the prevention of MRSA colonization failed to significantly reduce rates compared to standard soap body washes [156]. Another proposed decolonization intervention that has not been widely adopted in the United States due to concerns related to development of resistant organisms is selective digestive decontamination (SDD) or selective oropharyngeal decontamination (SOD) with antimicrobial agents [157,158]. In terms of clinical benefit, SDD/SOD have been found to decrease MDRO infection rate [159] and mortality [160].

**Cohorting**

There is insufficient evidence to conclude that cohorting isolated patients is of benefit for routine use in the endemic ICU setting. A few studies, mainly in the outbreak setting, have examined this approach and the results are conflicting [161,162]. Pending further studies in this area, it is reasonable to cohort patients colonized with the same microorganisms, especially if patients cannot be placed in single rooms.
CONCLUSION

The emergence of MRSA and VRE has led to a resurgence of interest and emphasis on infection control practices and prevention. CDC guidelines to help health care practitioners manage these MDROs in the hospital and ICU-setting exist; however, many questions remain regarding best practice.

Prevention of MRSA and VRE needs to be a 2-pronged approach—antimicrobial stewardship [163] and infection control. A robust antimicrobial stewardship program to optimize and minimize inappropriate antibiotic use is necessary in every institution. From the infection prevention standpoint, it is unclear if systematic identification of MRSA and VRE colonization followed by contact precautions is useful in reducing transmission. It is clear that a strong institutional climate of promoting patient safety and a culture of infection prevention will help in reducing MRSA and VRE facility-wide. It also appears that universal gowning and gloving may be useful for reducing MRSA, but not VRE, transmission. While universal decolonization with mupirocin is efficacious in reducing MRSA, this strategy is not recommended because of promoting mupirocin resistance. However, the use of daily bathing with chlorhexidine represents a relatively low-cost, high-yield intervention that should be adopted. Pending further data, patients known to be colonized or infected with MRSA should be placed in contact precautions as is current practice in most institutions. Finally, in this era of MDROs, hand hygiene remains our best defense against the spread of pathogens in the health care environment.

Note: This article does not represent the views of the Department of Veterans Affairs.

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