Antimicrobial-Resistant, Gram-Positive Bacteria among Patients Undergoing Chronic Hemodialysis

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Numerous antimicrobial-resistant pathogens (ARPs) have emerged among patients who undergo chronic hemodialysis (CHD), including vancomycin-resistant enterococci, vancomycin-resistant coagulase-negative staphylococci, Staphylococcus aureus with reduced susceptibility to vancomycin, and linezolid-resistant S. aureus. In June 2002, the first isolate of vancomycin-resistant S. aureus (minimum inhibitory concentration of vancomycin, ≥32 μg/mL) was isolated in the United States from a patient who required CHD. Frequent administration of antibiotics and repeated exposure to settings conducive to cross-transmission contribute to a patient population at considerable risk of harboring ARPs. Dissemination of ARPs among patients who are undergoing CHD is facilitated by the requirement for regular hemodialysis in a closed setting in which health care workers provide concurrent care to multiple patients. Frequent hospitalizations in this patient population further contribute to acquisition of ARPs and to the spread of ARPs to other hospitalized patients. The epidemiology of antimicrobial-resistant, gram-positive pathogens in patients undergoing CHD is reviewed, and recommendations for limiting further dissemination are provided.

The population of patients who undergo chronic hemodialysis (CHD) has contributed substantially to the emergence and dissemination of antimicrobial-resistant pathogens (ARPs). The first reports of vancomycin-resistant enterococci (VRE) and vancomycin-resistant coagulase-negative staphylococci (CoNS) involved patients who required dialysis [1, 2]. In the past few years, Staphylococcus aureus isolates with reduced susceptibility to vancomycin and with high-level resistance to linezolid have been recovered from patients who were undergoing dialysis [3, 4]. In June 2002, the isolate that everyone feared would emerge was documented by the US Centers for Disease Control and Prevention (CDC): vancomycin-resistant S. aureus (VRSA) was isolated from a hemodialysis catheter–exit site infection [5].

Point prevalence data from the United States Renal Data System reported that, in 1999, 63% of patients with end-stage renal disease required CHD, and a 77% increase in this population by the year 2010 was projected. Presently, >200,000 patients require CHD in the United States [6]. The annual mortality rate among patients undergoing CHD is 23%. Infections are the second most common cause of death and contribute to >300 hospitalizations per 1000 patient-years. Bacteremia is the most common infectious cause of mortality, resulting in 10% of all deaths in this population [6, 7]. Given the rapid growth of this population, the frequency of infection, and the impact of antimicrobial resistance on morbidity and mortality rates, limiting the spread of ARPs among the CHD population is of paramount importance. This review will describe the factors that have led to the emergence and rapid dissemination of ARPs within the CHD population and will address measures to limit further spread.

MECHANISMS OF ARP ACQUISITION AND IMPLICATIONS FOR PATIENTS WHO UNDERGO CHD

Two essential factors contribute to the emergence and dissemination of ARPs, regardless of the population being studied: (1) patient-to-patient transmission of pathogens, and (2) the selective pressure from antibiotic exposure. Cross-transmission occurs either directly between patients in contact with each other or indirectly through the contaminated hands of health
care workers or environmental surfaces [8]. The dialysis unit and its population provide an ideal setting for cross-transmission of pathogens, because regular hemodialysis is required 3 times per week for 3–4-h shifts in a closed setting and because health care workers provide concurrent care to multiple patients. In addition to the potential for ARP acquisition in the outpatient dialysis unit, patients undergoing CHD require 1 or 2 hospital admissions per year [6]. During these hospitalizations, frequent exposure to antibiotics, intensive care unit settings, and inpatient hemodialysis units contribute further to ARP acquisition among patients who undergo CHD. The risk of acquiring ARPs may be even greater in the hospital setting than the outpatient hemodialysis setting because exposure to antibiotics and to other patients who harbor ARPs is more frequent and of longer duration during a hospital admission. The relative contribution of each setting to the prevalence of ARPs among patients undergoing CHD awaits quantification.

Coupled with repetitive exposures to settings conducive to cross-transmission, patients who undergo CHD are frequently administered antibiotics. For example, patients who undergo CHD have an 11-fold higher risk of receiving vancomycin during a hospital admission than do patients who do not require hemodialysis [9]. Antibiotics increase the risk of harboring and spreading ARPs in several ways. First, certain antibiotics can lead to the emergence of antimicrobial resistance among previously susceptible pathogens. Second, antibiotics can diminish the colonization resistance conferred by the normal gastrointestinal flora [10]. This concept refers to the protective effect of the indigenous gastrointestinal flora against colonization with ARPs. The eradication of normal flora by antibiotics may therefore increase the likelihood of colonization with ARPs when an exposure occurs. Another effect of eradicating the normal flora is to allow subpopulations of ARPs to overgrow and achieve higher stool densities, as has been demonstrated with VRE [11, 12]. Because skin and environmental contamination are more common with higher stool densities of VRE [11, 12], antibiotic exposure can also promote the spread of certain ARPs.

**VRE**

In 1988, one of the first patients with an infection caused by an *Enterococcus* species that was resistant to vancomycin was reported from a CHD unit in England [2]. Since then, the prevalence of VRE in patients who undergo CHD has increased rapidly. The National Surveillance of Dialysis-Associated Diseases, performed by the CDC, documented an increase in the percentage of dialysis centers reporting ≥1 patient harboring VRE from 11.5% in 1995 to 32.7% in 2000 [13].

The reasons for the widespread dissemination of VRE among patients who undergo CHD are numerous. These patients define the risk factors for harboring VRE: the majority of these patients will have multiple comorbid conditions, will be exposed to a substantial amount of antibiotics, and will require frequent hospitalization [6]. A prospective study performed at a tertiary care center detected VRE colonization at hospital admission among 6% of patients undergoing CHD. Acquisition of VRE during hospital admission occurred frequently: 19% of patients who were not colonized at admission and remained in the hospital for ≥4 days acquired VRE de novo [14]. Molecular typing by means of PFGE demonstrated that the acquired VRE strains were similar to VRE strains recovered from epidemiologically linked patients who were undergoing CHD. Previous hospitalization has also been identified as an independent risk factor for harboring VRE in an outpatient hemodialysis unit [15]. These findings strongly support cross-transmission between patients undergoing CHD in the hospital setting as a major contributor to VRE acquisition.

As a result of the high rate of VRE acquisition in the hospital setting, dialysis units should consider VRE screening cultures for patients who are undergoing CHD and who have recently been hospitalized at a health care institution with a high prevalence of VRE. For patients at high risk of disseminating VRE, enhanced infection-control precautions would then be instituted, which would limit the patients’ potential for spreading VRE to other patients who are undergoing CHD during a dialysis shift (table 1). Ideally, these surveillance cultures should be performed before discharge from the hospital for the results to be available before reinitiation of outpatient hemodialysis.

Curtailing the spread of VRE among patients undergoing CHD will require multiple concurrent interventions, including limiting inappropriate antibiotic exposure, improving compliance with infection-control measures, and providing VRE screening of high-risk patients. The impact of these various interventions on the endemic prevalence of VRE over time in an outpatient hemodialysis unit was quantified via mathematical modeling. This technique allows analysis of the numerous interrelated and dynamic interactions involved in the transmission dynamics of VRE between patients and health care workers. The parameter estimates for this model were obtained from a 120-bed hemodialysis unit affiliated with a tertiary care hospital, in which the ratio of health care workers to patients was 1:4 and compliance with hand hygiene was 40%, as determined by direct observation [16]. The model predicted that the endemic prevalence of VRE among patients undergoing CHD would reach 12% over time, irrespective of the number of patients who were colonized at baseline. Increasing compliance with hand hygiene measures to 100% or decreasing the ratio of health care workers to patients to 1:1 would decrease the overall prevalence of VRE to a minimum of 3%.

Interestingly, the model showed that the majority of the benefit would be achieved by improving compliance with hand
Table 1. Recommendations for preventing the spread of antimicrobial-resistant pathogens in the outpatient hemodialysis unit.

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Wear gloves when in contact with a patient or his or her dialysis station</td>
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<tr>
<td>Remove gloves and wash hands in between patients or dialysis stations</td>
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<tr>
<td>Avoid multiuse items</td>
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<tr>
<td>Do not use common medications carts</td>
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<tr>
<td>Enforce judicious antibiotic use; in particular, avoid use of vancomycin</td>
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<tr>
<td>for the treatment of (\beta)-lactam–susceptible infections in patients who</td>
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<tr>
<td>do not have a history of (\beta)-lactam allergy</td>
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<tr>
<td>Consider screening patients for VRE recently discharged from health care</td>
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<tr>
<td>institutions with a high prevalence of VRE(^a)</td>
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<tr>
<td>For patients at high risk of spreading antimicrobial-resistant pathogens</td>
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<tr>
<td>(including those with an infected skin wound with drainage not contained by</td>
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<tr>
<td>dressings, those with fecal incontinence, or those with diarrhea not</td>
</tr>
<tr>
<td>controlled by personal hygiene measures), use additional precautions,</td>
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<tr>
<td>including the following:</td>
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<tr>
<td>(1) wear both gloves and gowns while providing care, and (2) provide dialysis</td>
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<td>at stations with the minimal number of adjacent stations or during dialysis</td>
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<td>shifts with the fewest patients</td>
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</tbody>
</table>

**NOTE.** Data adapted from the Centers for Disease Control and Prevention recommendations for preventing transmission of infections among patients who are undergoing chronic hemodialysis [8]. VRE, vancomycin-resistant enterococci.

\(^a\) Not recommended by the Centers for Disease Control and Prevention.

Hygiene protocol to 60%, after which further improvement in compliance would have less effect on the number of patients harboring VRE in the dialysis unit over time. Duration of VRE colonization had the most impact on the prevalence of VRE. If colonization was prolonged to >50 weeks, as has been documented in some studies, the model predicted that the endemic prevalence of VRE would reach 70%. Although extreme, this simulation emphasizes the impact of colonized patients acting as reservoirs of VRE within the dialysis unit. It also indirectly emphasizes the importance of decreasing the duration of colonization by limiting antibiotic exposure. Finally, the model predicted that performing screening surveillance cultures for recently hospitalized patients before reinitiating outpatient hemodialysis was the only intervention that would eradicate VRE from the dialysis unit. Although this mathematical model awaits validation, it provides a theoretical framework with which to focus future interventions aimed at limiting further spread of VRE within hemodialysis units.

**METHICILLIN-RESISTANT S. AUREUS**

Staphylococci are implicated in >60% of the infections that occur in patients undergoing CHD. Although the rates of CoNS and S. aureus implicated in infections are equivalent in many studies, rates of morbidity and mortality associated with the latter are substantially higher [17]. Complications associated with S. aureus bacteremia, including osteomyelitis, septic arthritis, and endocarditis, are common, occurring in 15%–44% of patients. This wide range reflects varying treatment strategies, including duration of antimicrobial therapy and vascular access management. The range of attributed death rates is 8%–25% [17]. Infections caused by methicillin-resistant strains are associated with even higher rates of morbidity and mortality [18].

The percentage of dialysis units that reported \(\geq 1\) patient that had received treatment for a methicillin-resistant S. aureus (MRSA) infection increased from 40% in 1995 to 71% in 2000 [13]. Because colonization with MRSA increases the risk of subsequent infection, eradication of nasal carriage would be beneficial [19]. A short, 5–10-day course of treatment with mupirocin ointment is very effective and results in a mean elimination rate of 87%. Relapses are common, with rates ranging from 20% to 77% three months after discontinuation of therapy. Administration of mupirocin therapy at regular intervals is an effective strategy to prevent relapse, although emergence of mupirocin resistance is an inevitable consequence [20]. An alternative intervention to consider is periodic screening for nasal MRSA carriage with treatment of colonized patients. This strategy would target therapy and limit unnecessary exposure to mupirocin. Unfortunately, even these interventions have led to an increase in the prevalence of mupirocin-resistant S. aureus isolates [21]. Cost-effectiveness analysis demonstrates a tremendous benefit from both targeted screening strategies and intermittent treatment of all patients [22]. The optimal strategy that would achieve the highest rate of eradication of nasal colonization and result in the lowest rate of mupirocin resistance still needs to be determined. MRSA colonization at multiple sites can also decrease the efficacy of intranasal mupirocin [19].
EMERGENCE OF RESISTANCE TO VANCOMYCIN AND LINEZOLID AMONG S. AUREUS ISOLATES

*S. aureus* isolates with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]), have now been described throughout the world [23]. The first 5 isolates recovered from the United States were obtained from patients who required dialysis [3]. Four infections were from the bloodstream, and the remaining infection involved peritoneal fluid. Most of these VISA strains appear to have developed from preexisting MRSA infections, as determined by similar DNA patterns on PFGE. Prolonged exposure to vancomycin (up to 18 weeks in some patients) and the failure to remove the hemodialysis catheter promptly likely played an important role in the emergence of *S. aureus* isolates with reduced susceptibility to vancomycin. Therapy with a combination of vancomycin, aminoglycosides, rifampin, linezolid, or trimethoprim-sulfamethoxazole cleared the infection in most patients. Many of these isolates were susceptible to trimethoprim-sulfamethoxazole, linezolid, and quinupristin-dalfopristin. Monotherapy with vancomycin is probably inadequate [23]. Epidemiological investigations did not identify cross-transmission of VISA to other patients undergoing CHD or health care workers in these individual cases. However, the potential of cross-transmission of VISA to other patients who are undergoing CHD may rapidly increase if there is an increase in the number of patients harboring VISA who are undergoing CHD.

Widespread screening for VISA isolates is currently not recommended by the CDC because of the low prevalence of these isolates. However, authorities have suggested focusing attention on the population undergoing dialysis, given the high rate of MRSA infection and substantial exposure to vancomycin among this population [23]. Because MRSA is highly transmissible in the hospital setting, similar cross-transmission patterns are likely to apply to VISA isolates. CDC guidelines for the prevention of VISA dissemination in the hospital are available [24]. These recommendations include assigning patients to private rooms, wearing gloves and gowns before entering the room, and performing epidemiological and laboratory investigations with the assistance of the state health departments and the CDC. Similar principles should be applied to patients who are undergoing CHD. Although current recommendations for preventing the transmission of ARPs among patients undergoing CHD do not enforce use of private rooms for such patients with ARPs during outpatient hemodialysis shifts (table 1), isolation of patients who are undergoing CHD and who harbor VISA should be strongly considered, because dissemination of this ARP would have serious implications. If isolation rooms are not available, transfer to another facility may be necessary. Identification of VISA recovered from a patient who is undergoing CHD will also warrant extensive epidemiological investigations to identify VISA colonization among other patients who are undergoing CHD and health care workers in the dialysis unit.

Linezolid and quinupristin-dalfopristin are antimicrobial agents with activity against *S. aureus* isolates with reduced susceptibility to vancomycin. Although these antimicrobial agents have only recently been approved for clinical use by the US Food and Drug Administration, resistance has already been documented. The first report of linezolid-resistant *S. aureus* involved an 85-year-old man who was undergoing peritoneal dialysis and who was being treated with linezolid for MRSA peritonitis without replacement of the catheter [4]. Linezolid-resistant *S. aureus* strains were recovered intermittently from peritoneal fluid specimens during a 3-week period. The MRSA strains and linezolid-resistant *S. aureus* strains had different DNA patterns on PFGE, suggesting that the linezolid-resistant strains may have been acquired exogenously. Endogenous acquisition via the emergence of resistance in an undetected linezolid-susceptible MRSA strain, however, could not be excluded.

In June 2002, the CDC reported the first documented infection caused by VRSA, which involved a 40-year-old man from Michigan who was undergoing CHD [5]. The patient had received repeated courses of antibiotics, including vancomycin, for the treatment of a chronic foot ulcer. The patient developed MRSA bacteremia from an infected arteriovenous hemodialysis graft. After removal of the infected graft, an exit site infection developed at the site of the temporary hemodialysis catheter. VRSA and MRSA were isolated from the exit site. Subsequently, VRSA and VRE were recovered from the chronic foot ulcer. The VRSA isolate contained the *vanA* gene conferring resistance to vancomycin, implying that there was exchange of genetic material between the *S. aureus* isolate and the VRE isolate recovered from the ulcer site. The VRSA isolate was susceptible to several antibiotics, including linezolid, quinupristin-dalfopristin, minocycline, tetracycline, and trimethoprim-sulfamethoxazole. The patient was treated with aggressive wound care and trimethoprim-sulfamethoxazole. At the time of this publication, the patient was reported to be clinically stable, and preliminary epidemiological investigations had not documented cross-transmission to other health care workers or patients.

VANCOMYCIN RESISTANCE AMONG CoNS

CoNS are part of the normal skin flora. As a result of the requirement for vascular access with repeated puncture of the skin, CoNS are among the most common pathogens impli-
cated in bloodstream infections among patients who undergo CHD [17].

Recovery of CoNS isolates that are resistant to vancomycin has been reported in the literature for >2 decades. One of the earliest documentations was from George Washington University Medical Center in 1977, which involved a 77-year-old patient who was undergoing CHD and who was treated for *Staphylococcus epidermidis* bacteremia and presumed endocarditis. The reported MICs of vancomycin and penicillin were 20 μg/mL and 0.625 μg/mL, respectively [1]. Details of previous exposure to vancomycin were not provided. The patient was cured with intravenous nafcillin therapy. Other reports of CoNS with reduced susceptibility to vancomycin, isolates of which were recovered from patients who required peritoneal dialysis and who received prolonged courses of vancomycin therapy, have subsequently been published [25, 26]. Fortunately, reports of CoNS with reduced susceptibility to vancomycin remain sporadic, and cross-transmission has not been documented [27].

**RECOMMENDATIONS FOR PREVENTING THE DISSEMINATION OF ARP s**

The CDC has developed guidelines for the prevention of ARP transmission among patients undergoing CHD [8]. In the hospital setting, standard precautions for all patients, regardless of CHD status, are recommended. These include use of gloves, gowns, and masks if contact with body substances is anticipated. Contact precautions are recommended for patients harboring multidrug-resistant bacteria and, in particular, VRE. These precautions include providing single rooms, cohorting the patients, and donning gloves when entering the patient’s room. Gowns should be worn if there is potential for the health care worker’s clothes to be in contact with the patient or surrounding inanimate surfaces. If the patient has diarrhea or has had an ileostomy, a colostomy, or wound drainage not contained by a dressing, gowns should be worn by health care workers entering the patient’s room, regardless of the potential for contact.

In the outpatient hemodialysis unit, any contact with a patient undergoing CHD during a dialysis shift mandates health care workers to wear gloves and to change the gloves and wash their hands in between each patient station [8]. These recommendations reflect the added risk of transmitting bloodborne pathogens during a dialysis session and likely decrease the potential for ARP cross-transmission. As with many infection-control measures, however, compliance dictates its benefit. In one survey conducted in the outpatient dialysis setting, only 40% of dialysis nurses were compliant with hand hygiene practices [16]. Additional infection-control precautions are recommended for health care workers who interact with patients at high risk of disseminating ARPs. These patients include those who have an infected skin wound with drainage that is not contained by dressings and those with diarrhea or fecal incontinence uncontrolled by personal hygiene measure. Contact with these high-risk patients requires health care workers to wear gowns when treating the patient and to dialyze these patients adjacent to the minimum number of other dialysis stations—for example, corner units or during dialysis shifts with fewer CHD patients [8]. Specific precautions for preventing cross-transmission from contaminated items should be enforced, including prohibiting common medication carts and paying attention to proper disinfection or disposal of multiuse items. Finally, all surfaces of the dialysis station should be disinfected between patient uses (table 1) [8].

**ANTIMICROBIAL USE**

In the year 2000, the National Surveillance of Dialysis-Associated Diseases reported encouraging data regarding judicious use of antibiotics in dialysis units: 93% of dialysis centers reported having ≥1 measure aimed at limiting inappropriate use of antibiotics. These included recording the reason for antimicrobial administration (63% of dialysis centers), providing a written policy on antimicrobial use (36%), instituting automatic stop orders (31%), restricting the formulary (28%), and requiring approval (22%) [13]. The rate of compliance with these measures, however, is not known.

**VANCOMYCIN USE AMONG PATIENTS UNDERGOING CHD**

Vancomycin, which is derived from the word “vanquish,” was initially discovered in 1956 from a soil sample from Borneo [28]. This sample contained *Nocardia orientalis*, from which compound 05865, now known as “vancomycin,” was recovered. Because of its long dosing interval, vancomycin is frequently used among patients with renal insufficiency. As a result of the emergence of vancomycin resistance among several pathogens, and because, in many instances, alternative antibiotics can be used, guidelines for vancomycin use in the dialysis population have been developed [29]. The indications for vancomycin administration for patients who undergo CHD are similar to those outlined by the Hospital Infections Control Practices Advisory Committee of the CDC, with one major exception [30]: for patients undergoing CHD, vancomycin use is recommended for empirical therapy for patients with fever and an unclear site of infection, or for patients with a suspected hemodialysis access–site infection, pending culture or susceptibility data. These modified indications apply to patients who receive dialysis from facilities at which there is a high prevalence of methicillin-resistant pathogens or if the patient has a history of previous colonization or infection with methicillin-resistant.
pathogens. These guidelines were formulated from data obtained from a prospective study quantifying the appropriate and inappropriate indications for vancomycin administration among hospitalized patients who are undergoing CHD [9]. In this study, vancomycin administration was judged to have been appropriate for 80% of doses. The most common indication was for the empirical treatment of a febrile patient requiring CHD who did not have an obvious source of infection. Follow-up culture data for these patients revealed that a large proportion developed infections due to β-lactam–resistant pathogens, necessitating vancomycin use, and validated the indication for empirical vancomycin administration in febrile patients undergoing CHD. The main reason for inappropriate vancomycin administration among the 20% of doses was continued vancomycin therapy for β-lactam–susceptible pathogens without the patient having a history of β-lactam allergy. Intervention efforts aimed at improving vancomycin prescribing patterns should focus on these inappropriate indications.

**FUTURE DIRECTIONS**

Investigations into the epidemiology of ARPs among patients undergoing CHD have focused on MRSA and, more recently, on vancomycin-resistant pathogens. These studies have collectively demonstrated that overuse of vancomycin and cross-transmission between patients undergoing CHD have substantially contributed to the emergence and dissemination of these ARPs. Although to date there has been no evidence of spread of VISA or VRSA isolates to other patients undergoing CHD or to health care workers, if the number of patients harboring these ARPs continues to increase, as it has with other ARPs, cross-transmission and dissemination of VISA and VRSA may be inevitable.

Epidemiological studies defining the prevalence and transmission patterns of ARPs other than MRSA and vancomycin-resistant pathogens are needed, because it is more than likely that the prevalence of these ARPs is substantial in this high-risk population. Studies that address the utilization patterns for antibiotics other than vancomycin are also needed. Through these investigations, the extent of colonization or infection with ARPs among the CHD population can be assessed, and appropriate interventions can be developed. Limiting the emergence and spread of ARPs among this population will ultimately benefit all patients, regardless of whether they require hemodialysis.

**References**

24. Centers for Disease Control and Prevention. Interim guidelines for prevention and control of staphylococcal infections associated with