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Methicillin-resistant *Staphylococcus Aureus* Colonization, Its Relationship to Nosocomial Infection, and Efficacy of Control Methods

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ANY particular healthy individual is thought to have approximately 100–200 species of bacteria colonizing their oral cavity, although more than 700 species of bacteria have been identified.[1] Although the relationship between the host and bacterium is often mutualistic and of no consequence to the host, it can have serious consequences in the perioperative patient. As organisms become B-lactam-resistant, colonization has received increasing attention as a risk factor for development of infection. The objective of this review is to discuss the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA)–related hospital infections with a focus on perioperative infections and to discuss methods that attempt to limit colonization and spread of MRSA.

Epidemiology and Overview of MRSA Infections

Nosocomial infections are responsible for significant patient morbidity and mortality and pose an enormous fiscal burden on the healthcare system. In 2002, nosocomial infections were responsible for 100,000 deaths,[2] which is greater than the number of cases of any other notifiable disease. Although organisms most commonly responsible for nosocomial infection vary, *S. aureus* is responsible for the highest number of these infections (30%).[3] Unfortunately, although the organisms responsible for nosocomial infections have remained relatively stable, their antibiotic profile has not, with an increase in several resistant organisms.[4] The national Nosocomial Infections Surveillance system demonstrated a prevalence of vancomycin-resistant *Enterococcus* of 27.5%, MRSA of 57%, and quinolone-resistant *Pseudomonas* of 33%, representing an increase of 11%, 13%, and 37%, respectively, over 5 yr.[5] Specifically, MRSA was responsible for 55% of nosocomial infections in the intensive care unit (ICU) in 2002, representing a 13% increase over a 5-yr period.[5]

MRSA has also increasingly been found in the community as well as in hospitals (fig. 1), rising to become the most frequent cause of skin and soft tissue infection presenting to the emergency department[6] and responsible for a plethora of invasive diseases in both the hospital and the community.[7] Figure 2 shows trends in MRSA prevalence.[8] In 2005, the Centers for Disease Control found that 94,000 invasive infections were attributed to MRSA alone, corresponding to an incidence of 31.8 per 100,000 persons and 18,600 deaths.[6]

MRSA infections are diverse. They continue to be one of the leading causes of nosocomial pneumonia, surgical site infection, and bloodstream infections[9] and are associated with 10–20% of bacteremia in the hospital.[6,10] Although *S. aureus* continues to be the most common cause of surgical site infection,[11] there has been a shift to antibiotic-resistant bacteria such as MRSA.

MRSA infections result in higher mortality, greater lengths of hospital stay, and increased cost compared with methicillin-sensitive *S. aureus* (MSSA) infections.[6,9,11,12] Methicillin resistance is an important independent prognostic factor in infections. Patients with MRSA bacteremia have a mortality 1.78–3-times higher than with MSSA bacteremia.[13,14] Likewise, another study found that methicillin resistance was independently associated with a 3-fold increase in mortality and increased hospital charges of $14,000 per infection in patients with *S. aureus* surgical site infection (in 2000).[11] Risk factors that have been associated with developing a methicillin-resistant bacteremia include: age, prolonged hospitalization, prior antimicrobial treatment, urinary catheterization, nasogastric tube placement, and previous surgery.[14] Because of the increasing role that MRSA

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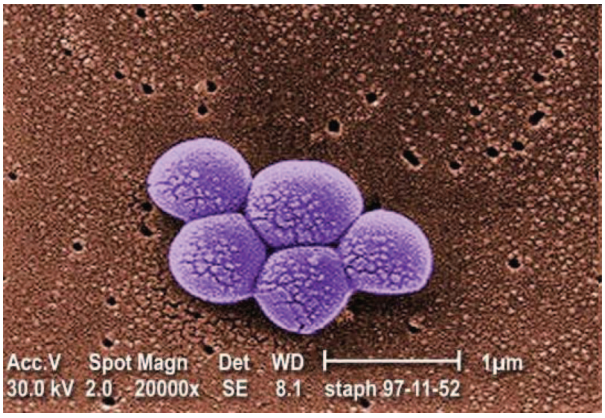

Fig. 1. Magnification: ×20,000. This colorized scanning electron micrograph (SEM) depicts a grouping of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria. These *S. aureus* bacteria are methicillin-resistant and are from one of the first isolates in the U.S. that showed increased resistance to vancomycin as well. Note the increase in cell wall material seen as clumps on the organisms' surface. Photo by Janice Carr, courtesy of the Centers for Disease Control and Prevention.

plays in infection, attention has been turned to detection of those at risk for MRSA infection.

Screening: Who Should Be Screened for MRSA Colonization?

Importance of MRSA Colonization. Nosocomial infection classically has been attributed to new microbes acquired as a consequence of exposure to the hospital environment. It is difficult to determine whether the cause of nosocomial infection is the result of a change in the patient's immune status or a change in the patient's endogenous MRSA. Molecular studies using DNA fingerprinting have allowed detection of the origin of microorganisms responsible for nosocomial infections. Although transmission-associated nosocomial infection is a significant contributor to patient mortality and morbidity,[15] only a minority (less than 40%) of nosocomial infections can be attributed to cross-transmission.[16,17] The majority of nosocomial infections bear no epidemiologic relation to organisms isolated from other patients in the same ICU,[16] suggesting that endogenous bacteria play a key role in infections.

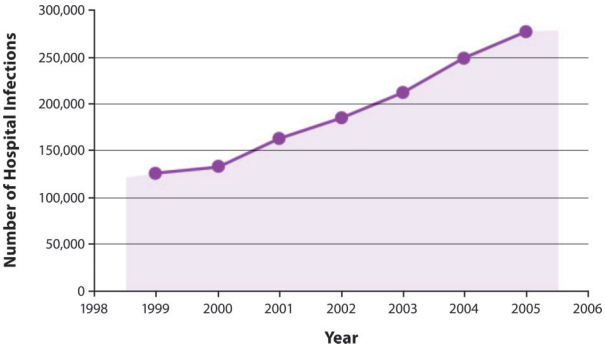

Fig. 2. Graphic trend of MRSA (methicillin-resistant *Staphylococcus aureus*) prevalence based on reported MRSA-related discharge diagnosis from 1999 to 2003. Data for figure obtained from Reference.[8]

MRSA colonization is increasing. A nationally representative survey of nasal colonization with *S. aureus* was conducted from 2001 to 2004 as part of the National Health and Nutrition Examination Survey. Colonization with *S. aureus* decreased in 2003–2004 to 28.6% from a previous level of 32.4% in 2001–2002. During this same time period, the prevalence of MRSA colonization rose from 0.8% to 1.5%. This is consistent with other studies showing a rise in MRSA colonization.[9,18,19] A possible reason for this is the effect of increased antimicrobial use, such as fluoroquinolones, on suppression of MSSA more than MRSA, subsequently promoting colonization of MRSA.[7] Multivariate analysis demonstrated that risk of MRSA nasal colonization differed by sex but was generally related to hospital exposure. However, the precise factors determining MRSA colonization are still not known. Other factors that have been suggested are: anatomic variation in nares, percutaneous disruption of nares, receiving prior antibiotics,[20] presence of foreign bodies, dialysis, liver disease, and severity of underlying disease.[21]

MRSA colonization has been shown to result in 10 times the number of nosocomial infections when compared with MSSA colonization.[7,10,13,18,22] This relationship is well established in surgical patients. Several studies have shown that *S. aureus* carriers have a 2- to 10-fold increased risk of developing a *S. aureus* surgical site infection, with a significant proportion of infections resulting from the patient's endogenous flora.[20,23,24] Nasal carriage of *S. aureus* is an independent risk factor for developing sternal wound infection in cardiothoracic patients[23] and postoperative abdominal infection.[25] A prospective study of 500 surgical ICU patients found that colonization was a risk factor for postoperative MRSA infection, with all clinical isolates matching isolates from the nares, and that those with MRSA developed infections almost twice as quickly as those not colonized.[21] This has also been described in bacteremia.[20,21,23,25–27] At any given time, approximately 1.5% of the United States population is colonized with MRSA, yet only a small minority of these people actually develop a clinical infection. The factors that determine why only a few colonized patients develop an infection have yet to be clarified. Host immune factors and interbacterial influences of the bacterial nasal community possibly play a role.

Evidence that Screening Improves Outcomes. Traditional strategies for controlling MRSA spread have focused on the prevention of cross-transmission and include hand hygiene practices, environmental cleaning and disinfection, timely identification of MRSA-infected or MRSA-colonized patients, and management of those harboring MRSA with isolation and barrier precautions.[28] One method that has been tested with mixed results is the nasal swabbing of all patients admitted to the hospital to detect those asymptomatically colonized, a process called active surveillance culturing (ASC). This method is intended to detect MRSA carriers so

that appropriate contact precautions can be instituted in a timely manner to reduce the frequency of cross-transmission events to other patients. Several large hospital organizations now screen all hospital admissions for MRSA, and several states have passed legislation mandating that all patients at risk for MRSA on hospital admission be cultured. The current Centers for Disease Control guidelines and recent infection control position statement recommend against routine or mandated use of ASC for MRSA control.[29]

Two large, recently published studies assessed the efficacy of ASC. The first study by Harbarth *et al.*[30] assessed the efficacy of ASC in an environment endemic for MRSA.[28] They divided 22,000 surgical patients into an intervention and a control group. In the intervention group, rapid screening was performed on all admitted surgical patients and standard infection control measures practiced when these patients were found to be MRSA-positive (including isolation, contact precautions, and topical decolonization applied for 5 days), in addition to changing perioperative antibiotics. Despite the identification of more than 300 patients who were asymptomatic carriers of MRSA, the incidence of MRSA infections did not decrease in the intervention group. The authors point out that 57% of infected patients were MRSA-free on admission but acquired the bacteria during hospitalization, demonstrating the limits of a screening system that only cultures patients on admission, rather than performing weekly surveillance cultures.[30]

Another large-scale 2008 study by Robicsek *et al.* found a significant reduction in infection with the institution of universal surveillance of all hospitalized patients.[12] This observational study compared rates of MRSA infection during and after hospital admission in three different types of surveillance intervention: baseline (standard surveillance procedures serving as a control group), surveillance of all admissions to the ICU, and universal surveillance of all hospital admissions. Patients found to be positive for MRSA were isolated, and decolonization with topical antibiotics was suggested; however, this decolonization procedure was not standard policy, and adherence to the regimen was not monitored. Robicsek *et al.* found a reduction by more than half of healthcare-associated MRSA bloodstream, respiratory, urinary tract infection, and surgical site infections during universal surveillance, although no significant benefit was observed in the ICU-only surveillance group.[12]

Other studies have demonstrated efficacy in reducing MRSA infection rates when ASC is initiated in the ICU setting. In another recent study by Harbarth *et al.*, a benefit of surveillance was observed only in the medical ICU, whereas no effect was observed in the surgical ICU.[31] Thus, two recent large-scale studies have demonstrated mixed results with the institution of ASC.[12,30] It should also be noted that ASC is not free of any unintended adverse consequences. A major issue is cost. Cost analysis was not performed in recent studies, but there is the added cost of infection control practitioners' time, laboratory material, and the need for additional isolation beds.[30] ASC has been estimated to result in a 2- to 5-fold increase in the number of patients placed on contact precautions in isolation. This could subject those patients to reduced attention from healthcare workers and might lead to an increase in depression and anxiety among other adverse effects.[28]

A prohibitive factor in effective screening strategies is the ability to detect those at highest risk for MRSA colonization efficiently. This process begins with the ability to recognize risk factors for colonization. One study looked at the utility of a dedicated critical care consult team to assess whether it could better identify those at higher risk for MRSA colonization.[26] They found that the team was able to identify those at higher risk more quickly, suggesting that institution of such a team might lead to more targeted screening, greater efficacy of existent isolation, and decolonization.

In addition to recent hospitalizations and nursing home residence, a recent study has demonstrated the importance of previous colonization as an integral independent predictor of MRSA colonization. Although the rate of colonization initially showed rapid decrease over the first year after detection (50%), rates remained high and never decreased below 20%, even in patients without other frequently described risk factors.[32] In addition, a time gap between recognition of colonization and confirmatory testing through routine culture creates a time delay for infections to develop and colonization to spread to other patients. Use of rapid polymerase chain reaction to determine MRSA colonization within hours, as opposed to traditional culture which takes days, could improve detection. This technique has been demonstrated to show success in earlier detection, resulting in lower infection rates, and has also been found to decrease costs.[33]

Traditional attempts to control infection have continued to lack efficacy. The use of surveillance continues to be debated. These shortcomings in MRSA infection control may be a reflection of data, suggesting that the majority of nosocomial infections are endogenous in origin.[34] Traditional methods of infection control and ASC focus on cross-contamination and thus address only exogenous sources of infection. One suggested mechanism of controlling nosocomial infection that is directed at the endogenous origin of infection is decontamination of potentially harmful nasal colonizers.

Selective Antibiotic Decontamination. Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination are infection control measures in critically ill patients aimed at the prevention of nosocomial infection due to endogenous flora. The goal of these prophylactic measures is to reduce or eliminate potentially pathogenic colonizing bacteria responsible for infection while preserving flora that offer protection against invasive infections and overgrowth of resistant bacteria and yeasts.[35] A common antibiotic regimen consists of polymyxin E (colistin) and tobramycin, which are directed against aerobic Gram-negative bacteria, and amphotericin B, directed against yeast, applied four times a day to the stomach *via* a nasogastric tube and oropharynx *via* a paste. In addition, a cephalosporin,

usually cefotaxime, is administered parenterally in SDD.[35–37] Although most studies support a reduction of infection rates with the use of decontamination, especially when investigating pneumonia in the ICU, expert opinion is mixed as to whether this reduction affects mortality rate, length of stay, and cost efficacy.[35–37] Previously, mortality in several randomized controlled trials demonstrated a trend toward improved survival; however, most studies were too small to show a significant effect,[35,36] and significant reductions in mortality were observed only in meta-analyses.[36,38] One such 2004 meta-analysis found a significant reduction in mortality in SDD-treated patients with an odds ratio of 0.75 (95% CI, 0.65–0.87).[39] This reduction in mortality is confirmed by other recent studies,[37] which found the prophylactic regimen to be active against *S. aureus* colonization.

The major concern with the use of SDD/selective oropharyngeal decontamination is development of antimicrobial resistance. Because antibacterial activity of SDD is directed at Gram-negative organisms, there is a shift in flora to Gram-positive organisms, most concerning of which is high-virulence MRSA.[36] Surprisingly, several studies investigating the effects of decontamination on patterns of bacterial resistance actually indicate a reduction in antimicrobial resistance with the use of decontamination.[35] However, the data showed no change in the incidence of MRSA in ICUs with low prevalence of MRSA. There was a significant and worrisome increase in MRSA in some studies that had been performed in areas of high MRSA prevalence.[35–37] The addition of vancomycin to the regimen was very effective in preventing an increase in MRSA prevalence; however, use of vancomycin may have an effect on the incidence of other resistant bacteria, such as vancomycin-resistant *Enterococcus*.[35,36] As a result of this concern for the use of SDD in areas endemic for MRSA, universal application of selective decontamination cannot be recommended.[40] Other resistant bacteria, including Gram negatives, are also a concern with SDD/selective oropharyngeal decontamination because of suppression, rather than eradication, with a cephalosporin. A recent study demonstrated a significant increase in antibiotic-resistant Gram-negative bacteria in the intestinal and respiratory tract after discontinuation of antibiotic therapy.[41] Decontamination with antiseptics, such as chlorhexidine, has been suggested as a potential solution in areas with a high prevalence of multidrug-resistant bacteria.[35,37,42]

Antiseptic Decontamination. In contrast to antibiotics, antiseptics, such as chlorhexidine and povidone iodine, act rapidly at the target site and consequently may be less susceptible to the development of antibiotic resistance. Several studies support a beneficial effect of antiseptic use in reducing nosocomial infection,[12,42,43] although its effect on mortality is less clear.[42] Beneficial effects of antiseptic use have been shown in surgical patients. A marked reduction in nosocomial infection in cardiac surgery patients was demonstrated with nasal and oral decontamination with chlorhexidine.[44] A study randomizing MRSA-colonized surgical patients to a topical antibiotic (mupirocin) and a topical antiseptic (chlorhexidine) bath *versus* routine care found a 60% reduction in staphylococcal infections in the intervention group compared with the patients who received routine care. The most significant differences were found between deep surgical site infections in the two groups.[45] The authors speculated that the addition of chlorhexidine baths was necessary to attain the high level of prophylaxis measured because topical mupirocin itself would not affect colonizing sites other than the nares.

Use of antiseptics has also been shown to work in critically ill patients. Comparison of bathing with routine soap to chlorhexidine baths in the ICU setting found that chlorhexidine baths resulted in the reduction of acquisition of resistant bacteria (MRSA and vancomycin-resistant *Enterococcus*), in addition to reductions in infections as a result of some of these bacteria.[46]

Perioperative Antibiotic Choice

It is noteworthy that although there is convincing evidence for the relationship between MRSA colonization and the development of nosocomial MRSA infection, there is no large-scale study, to our knowledge, that has been sufficiently powered to evaluate preoperative surveillance of surgical patients to identify MRSA colonization and use perioperative antibiotic prophylaxis specifically active against MRSA. There are two smaller randomized trials aimed at addressing this problem. In patients undergoing cardiac surgery in a center with high prevalence of MRSA infections, prophylaxis with vancomycin compared with cefazolin did not decrease the incidence of surgical wound infections.[47] In contrast, another study done in a MRSA endemic environment in patients receiving cerebrospinal shunts showed a significant reduction in shunt infections and mortality when the patients received vancomycin instead of cefazolin as prophylaxis.[48] Both studies were limited in that the patients were not screened preoperatively, and preoperative MRSA colonization was not known. Currently, it is not standard of care to screen and cover for MRSA colonization perioperatively, although national guidelines by the Hospital Infection Control Practices Advisory Committee suggest that a high frequency of MRSA infection in an institution should influence the use of vancomycin for prophylaxis.[24] It is still not clear from the data whether the use of vancomycin in MRSA carriers is beneficial.

Conclusion

Although the organisms resulting in nosocomial infection have remained relatively constant in the past decade, a dramatic change has been the increase in prevalence of resistant organisms, particularly MRSA, in specific geographic locations. There are strong data to support a causal relationship between MRSA colonization and MRSA nosocomial infection, resulting in a call from experts to institute universal screening procedures to detect asymptomatic MRSA colonization as early as possible to reduce transmission events.

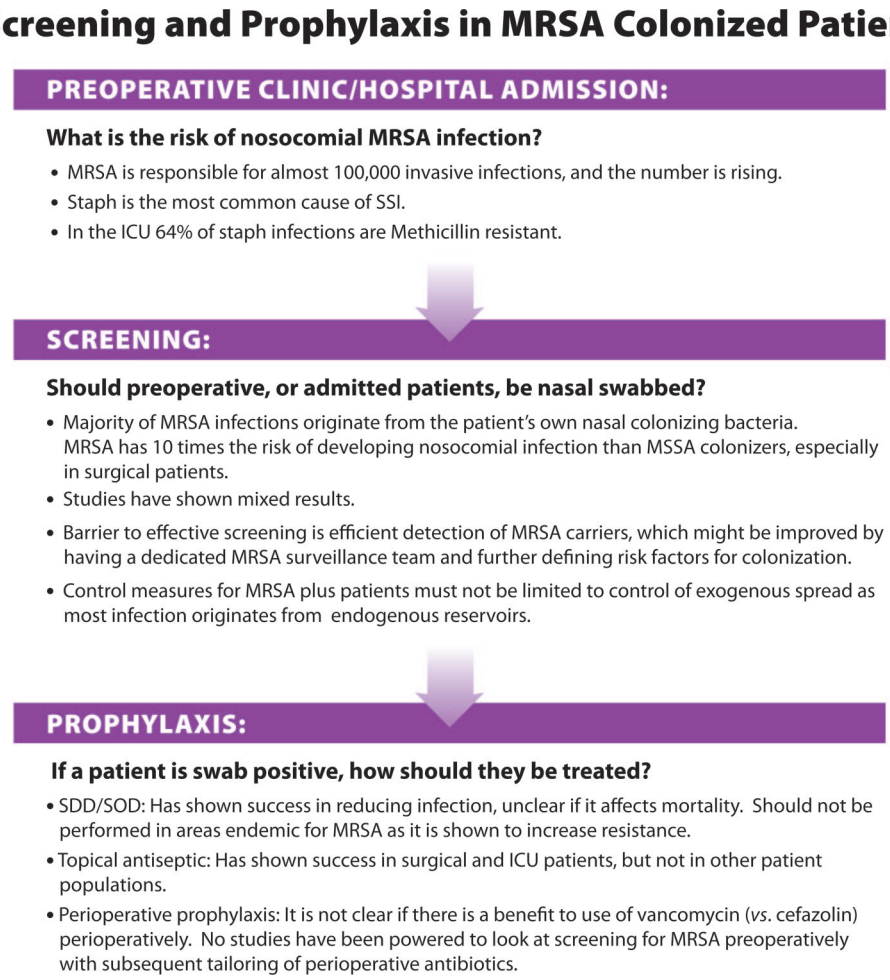

Fig. 3. Summary of data regarding MRSA infections, and the benefit of screening and prophylaxis. ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*; SDD = selective digestive tract decontamination; SOD = selective oropharyngeal decontamination; SSI = surgical site infection.

Studies evaluating the efficacy of ASC have demonstrated mixed results, finding a reduction in infection rates with hospital-wide ASC but no change in incidence rates when screening is limited to surgical patients. Surveillance efforts may have shown mixed results because eradication techniques were not uniform once the MRSA is detected. Traditional healthcare worker hygiene and isolation precautions address only exogenous forms of transmission. Most infections have been linked to endogenous sources. It is therefore important to include eradication of exogenous and endogenous sources in surveillance/prophylaxis programs to achieve success.

Success has been obtained with selective antibiotic decontamination of the nasopharynx, although its use is cautioned against in areas of high MRSA prevalence because an increase in rates of resistant infections has been observed in these areas. Studies on topical antiseptics have shown good efficacy in focused patient populations, particularly in cardiac surgery patients, and are currently part of their perioperative care. Topical antiseptics use is not without side effects, and broader studies are needed to determine efficacy before recommending widespread use (fig. 3).

MRSA colonization is associated with the development of infection both inside and outside of the hospitals. Despite this well-established relationship between colonization and infections, inadequate data exist regarding whether screening all patients for MRSA preoperatively with subsequent tailoring of perioperative antibiotic prophylaxis offers benefit; however, benefit was shown in empiric vancomycin treatment in a small study of neurosurgical patients. Further investigations are needed to determine the benefit of specific anti-MRSA antibiotic therapy in perioperative MRSA-colonized patients.

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