Screening and Decolonization: Does Methicillin-Susceptible Staphylococcus aureus Hold Lessons for Methicillin-Resistant S. aureus?

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Methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant S. aureus (MRSA) have few structural differences, but their epidemiologies differ profoundly in terms of colonization, infection, and transmission. We compare strategies for controlling hospital infection due to MSSA and MRSA. Despite the straightforward epidemiology of MSSA, the effectiveness of screening and decolonization was established only recently. The optimal strategy for controlling MRSA spread and infection remains debated. Many data need to be acquired, given the complexity of MRSA epidemiology, the entanglement between collective and individual objectives, and the challenges faced when adjusting for confounders. However, studies have consistently demonstrated that screening is useful in high-risk units to identify the reservoir and to initiate contact precautions. In an endemic setting, the contribution of MRSA decolonization to cross-transmission limitation is probably small in comparison to the impact of precautions. Screening and decolonization may be effective in decreasing the MRSA infection risk in carriers.

Methicillin-resistant Staphylococcus aureus (MRSA) is the most prevalent nosocomial bacterium [1]. In the area of health care-associated infection, few topics have generated as much debate in recent years as screening for MRSA [2]. Although the need for contact precautions for patients with MRSA colonization or infection is agreed on, the merits and optimal extent of screening for MRSA carriage remain controversial [3].

Many factors feed this controversy.

1. The epidemiology of MRSA varies across countries [4]. Control measures that work in countries or hospitals where MRSA cases occur sporadically or in small outbreaks may not be effective in large, prolonged epidemics.

2. The epidemiology of MRSA is changing at a fast pace. In some countries, measures for controlling nosocomial MRSA have recently met with success. In others, MRSA is increasing in the community and, in some cases, is replacing “nosocomial” MRSA in hospitals [5].

3. Measures used to control the spread of MRSA include screening, decolonization of carriers, patient isolation in a single room, hand decontamination, and protective clothing [6, 7]. No well-designed studies have assessed the effectiveness of any of these measures considered individually. In addition, the efficacy of several preventive measures has been established in epidemic settings and may not extend to endemic settings. Therefore, contact precautions are usually implemented as a bundle, the effectiveness of which is supported by numerous studies [8]. However, nearly all these studies were quasi-experimental studies, and many were performed over brief periods.

4. Adherence of health care workers to infection control guidelines is an important consideration. The degree to which health care workers follow standard and contact precautions influences the result. An intervention will be less effective in a unit where standard precautions are scrupulously followed than in a unit where lapses are common [9]. On the other hand, contact precautions are unlikely to help in a unit where compliance with hand hygiene is very low at baseline [10]. Studies evaluating the impact of isolation precautions should collect data on compliance with precautions. Even when such data are available, however, a major obstacle to interpreting observational studies is the lack of a standardized methodology.
5. One of the keys to a successful strategy is leadership, which encourages health care workers to adhere to recommendations. This factor probably makes a major contribution to the success of infection control interventions; however, it cannot be quantified [11].

These uncertainties fuel the current controversy. In contrast, for methicillin-susceptible S. aureus (MSSA), a well-established endemic organism, the strategies designed to decrease the risk of MSSA infection rest on a stronger scientific foundation. In this review, we will draw parallels between MRSA and MSSA, compare screening and decolonization interventions for these 2 organisms, and discuss the scientific facts that underlie these strategies (Table 1). To this end, we will cast our discussion in the setting of MRSA endemicity, because this is the situation in most countries. We will not discuss the recent increase in community MRSA strains that are acquired as nosocomial organisms, because this is a recent phenomenon about which epidemiological data are just starting to accumulate.

**CARRIAGE OF S. AUREUS**

**MSSA.** About 20%–30% of the general population are carriers of S. aureus. The anterior nasal cavity is the main site of S. aureus carriage. Among nasal S. aureus carriers, approximately one-half also carry the organism on their skin. Recent studies have established that S. aureus is often found at nonnasal sites, particularly the pharynx and the gastrointestinal tract, with some carriers having colonization confined to these sites [14, 15].

**MRSA.** The prevalence of MRSA carriage at hospital admission varies across departments. In intensive care units of large hospitals or university hospitals, 5%–15% of patients are MRSA carriers at admission [17, 30]. Prevalences of 3%–5% have been reported in acute-care wards [13]. Routine screening at hospital admission identifies about one-half of the carriers, with the other one-half being identified by positive clinical cultures or a history of MRSA [13, 17, 30]. Several studies have evaluated factors associated with MRSA carriage at hospital admission. The same factors were identified consistently in most studies. They include recent contact with the health care system, use of antibiotics, invasive procedures at hospital admission, chronic skin lesions, older age, and co-morbidities. However, these studies indicate that screening sensitivity is sufficient only when about two-thirds of admitted patients are screened [13]. In this situation, identifying patients at high risk for carriage may prove difficult and may lead to carriers being missed.

As with MSSA, MRSA may colonize the gastrointestinal tract and sites outside the usual reservoirs. MRSA may be found in association with chronic skin lesions or invasive procedures or in the urine [16]. Thus, the characteristics of carriage differ between MSSA and MRSA. Although identifying populations at high risk for MRSA carriage may be feasible, universal screening seems more accurate and easier to implement. The identification of MSSA carriers rests on nasal swabs and, perhaps, on pharyngeal and/or gastrointestinal swabs. MRSA, in contrast, may be found at other sites, such as skin breaks or sites of invasive procedures. Screening for MRSA is therefore more costly if it is designed to identify all sites of carriage.

### Table 1. Characteristics of Methicillin-Resistant Staphylococcus aureus (MRSA) and Methicillin-Susceptible S. aureus (MSSA) Carriage and Decontamination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MSSA</th>
<th>MRSA</th>
</tr>
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<tbody>
<tr>
<td>Carriage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence at hospital admission</td>
<td>20%–30% [12]</td>
<td>5% [13]</td>
</tr>
<tr>
<td>Sites of carriage</td>
<td>Nose (throat, digestive tract) [12, 14]</td>
<td>Nose (throat, digestive tract infected/colonized sites [14–16]</td>
</tr>
<tr>
<td>Risk factors for carriage</td>
<td>No</td>
<td>Yes [13, 17]</td>
</tr>
<tr>
<td>Targeted screening</td>
<td>Easy (ward/indication based)</td>
<td>Difficult (risk factor based)</td>
</tr>
<tr>
<td>Infectious risk in carriers</td>
<td>Usual</td>
<td>High [18]</td>
</tr>
<tr>
<td>Decolonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of decolonization</td>
<td>Demonstrated [22]</td>
<td>Usually effective (failure possible) [23]</td>
</tr>
<tr>
<td>Impact on the risk of infection</td>
<td>Demonstrated [20, 22]</td>
<td>Uncertain [24, 25]</td>
</tr>
<tr>
<td>Indication for decolonization</td>
<td>Defined</td>
<td>To be defined</td>
</tr>
<tr>
<td>Clearance of S. aureus</td>
<td>Stable over time [26]</td>
<td>Potential for recurrence [27]</td>
</tr>
<tr>
<td>Resistance to mupirocin</td>
<td>Rare</td>
<td>Possible [28, 29]</td>
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with ~5% for MRSA carriage in endemic situations. Thus, it may seem surprising that >50% of hospital-acquired S. aureus infections are related to MRSA in this setting. A study showed that the risk of MRSA bacteremia in an MRSA carrier was higher than the risk of MSSA bacteremia in an MSSA carrier [18]. The reasons for this difference are still poorly understood. The existence of an immunological adaptation between the carrier and the MSSA strain has been suggested [31]. This form of adaptation of MSSA may explain the decreased risk of MSSA infection in MSSA carriers, compared with the risk of MRSA infection in MRSA carriers. Intercurrent systemic antibiotic use may further decrease the risk of MSSA infection in MSSA carriers [32]. Indeed, most systemic antibiotics are effective against MSSA. Some antibiotics such as fluoroquinolones and rifampin, which diffuse well in tissues, can decontaminate sites of nasal or skin carriage [33]. In contrast, intercurrent use of most antibiotics increases the MRSA burden. Thus, antibiotics probably play a role in the conversion from MRSA carriage to MRSA infection [32] and increase the reservoir for cross-transmission. In addition, the presence of comorbidities, invasive procedures, or immune deficiency may predispose MRSA carriers to infection, compared with MSSA carriers [18].

**S. AUREUS DECOLONIZATION**

**MSSA.** Decolonization usually relies on intranasal mupirocin ointment, with or without chlorhexidine soap. In healthy volunteers, this intervention resulted in immediate decolonization of MSSA in >90% of cases, and decolonization persisted for several weeks [26]. Evidence indicating an association between nasal S. aureus carriage and subsequent S. aureus infection has led to the development of decolonization programs aimed at decreasing the S. aureus infection rate in dialysis or clean-surgery patients [19]. In contrast, in S. aureus carriers at lower risk of infection, decolonization did not decrease the infection rate, although the time to infection was increased [34].

However, until now most studies evaluating the decolonization of carriers found no conclusive evidence of efficacy. This result is ascribable in part to the quasi-experimental nature of these studies, which might fail to distinguish between the effects of decolonization and those of confounding factors. Some studies focused on populations where the association between nasal carriage and the risk of infection was not immediate [35]. Other studies were conducted in patients at low risk of S. aureus infection and, consequently, had limited statistical power despite the large number of patients [34].

Studies of pooled data in systematic reviews or meta-analyses, however, strongly support the efficacy of decolonization in patients at high risk of infection [20]. A recent multicenter, controlled, double-blind study confirmed this observation [22]. In sum, available data on MSSA screening and decolonization support screening of patients scheduled for procedures associated with a high risk of both S. aureus infection and severe consequences of such infection. Cardiac surgery is the best indication. On the basis of local data, decolonization of S. aureus carriers may be extended to patients undergoing clean surgery with implants or invasive procedures at high risk of S. aureus infection (eg, before insertion of a long-term vascular catheter). Thus, the target population for screening is easy to define. Furthermore, this strategy is cost-effective and is associated with a low risk of emergence of mupirocin resistance.

**MRSA.** Many studies have evaluated the efficacy of decolonization on MRSA carriage. A recent systematic review of 23 randomized, placebo-controlled trials was performed to assess the efficacy of decolonization in an overall population comprising both MRSA and MSSA carriers [36]. This population included healthy volunteers, health care workers, and patients. The intervention consisted in topical decolonization alone or in combination with systemic treatment. Decolonization eliminated nasal carriage in 90% of the study participants overall. However, efficacy was lowest in the 2 studies that assessed topical decolonization alone in patients admitted with MRSA carriage [37, 38]. In a randomized, placebo-controlled trial, decolonization failed to eradicate MRSA from all carriage sites and eradicated MRSA from the nasal cavity in only 44% of patients [37]. Persistent MRSA carriage was associated with intercurrent fluoroquinolone therapy and with colonization of >1 site [37]. In the other study of topical decolonization in MRSA carriers [38], decolonization was achieved in one-half of patients in the intervention group. In this study also, colonization of nonnasal sites was associated with failure of topical decolonization.

Higher success rates have been achieved with topical decolonization accompanied with, or followed by, systemic decolonization. In a multicenter, randomized, controlled trial, decolonization consisted of nasal mupirocin ointment, chlorhexidine soap, and a 7-day course of rifampin and doxycycline [23]. This carefully designed study included chronic carriers of MRSA who were free of infection and who underwent prolonged testing after decolonization. Important characteristics of the study patients were advanced age, dependency on health care, dementia, skin lesions, and multiple MRSA carriage sites. Although these features would be expected to decrease the chances of decolonization, 74% of patients were decolonized after 3 months of follow-up. It is worth pointing out that most patients in the intervention group adhered scrupulously to the decolonization regimen.

In another study, many patients had colonization of the usual sites (nose, pharynx, perineum, and groin), and 44% had colonization of skin wounds [39]. The decolonization regimen combined standard topical treatment; systemic antibiotics in patients with skin wound, urinary tract, or vaginal colonization; and gastrointestinal decolonization if needed. Systemic antimicrobials...
were used in two-thirds of patients. The success rate was 47% after 1 decolonization cycle and 76% after 2 cycles. In keeping with earlier data [37], colonization of multiple sites was associated with failure of decolonization.

Taken together, these studies suggest that MRSA decolonization may be achieved fairly easily in patients colonized at usual sites and with greater difficulty in patients with colonization of additional sites. In this last situation, combining topical decolonization and systemic antimicrobials may increase the success rate. These studies also suggest that close monitoring of and adherence with the decolonization regimen may be crucial [24].

**ARE MRSA SCREENING AND DECOLONIZATION PROGRAMS EFFECTIVE?**

The only objective of MSSA screening programs is the decolonization of carriers to decrease their individual risk of infection. For MRSA, carriers identified by screening can receive contact precautions and, if needed, decontamination, with the objective not only of decreasing their individual risk of infection but also of diminishing the reservoir and, consequently, the risk of cross-transmission. In addition, knowledge of MRSA carriage can be helpful for other preventive strategies, such as appropriate prophylactic antibiotic therapy in surgical patients.

Many studies have evaluated the usefulness of screening and decolonization as part of overall strategies for limiting the dissemination of MRSA. Most used a quasi-experimental design, with the implementation of several preventive measures [6]. Although most reports indicate that these strategies were effective, this fact may be ascribable in part to publication bias. The recent development of polymerase chain reaction–based rapid screening tests has prompted larger and better-designed studies, with no screening in the control group. The first study was performed in 3 hospitals over a 3.5-year period, and the rate of MRSA disease decreased significantly [25]. In a single-center, 6-month cluster cross-over study in 8 surgical units [21], screening was performed routinely at hospital admission, and MRSA carriers received contact precautions and were recommended for decolonization and prophylactic antibiotic therapy. The MRSA rate did not decrease significantly during the intervention period [21]. A meta-analysis included 3 additional studies, and a nearly significant 31% decrease in the infection rate was found [40]. The use of rapid screening tests, however, was not found to be effective, compared with conventional culture-based methods. This is not surprising, because the actual median time to results was 20–24 h [40].

Thus, the results of these studies are conflicting. Furthermore, it is unclear which measure or measures were effective. For example, some studies evaluated screening at admission to the intensive care unit followed by weekly screening with contact precautions but no decolonization [28, 41, 42]. This strategy was associated with a significant decrease in MRSA acquisition [41, 42]. The uncertainty about whether screening alone or screening plus decolonization is required to decrease infection rates is compounded by several sources of bias. In the above-mentioned study [21], nearly one-half the MRSA infections occurred in patients who were not identified as MRSA carriers at hospital admission. A similar proportion of non-carriers was found in a study of MSSA in surgical units [35]. These data suggest persistent cross-transmission of MRSA despite precautions and decolonization. Other confounding factors complicate the interpretation of these studies, particularly the degree of adherence to hand hygiene rules and to contact precautions, the workload, and local factors such as leadership and accountability.

Furthermore, the surgical-unit study [21] provided valuable information on the measures taken in identified MRSA carriers. MRSA carriage was known in 69% of patients scheduled for surgery, but only 30% of MRSA carriers who underwent surgery finally received appropriate prophylactic antibiotics. In another study, 933 patients were scheduled to receive decolonization for 5 days [27]. However, 23% of them received no mupirocin at all, and only 37% received decolonization for at least 4 days. Median follow-up was 9 months, during which 69 (7.4%) experienced MRSA infection. Neither the use nor the duration of mupirocin therapy seemed protective for MRSA infection. The only effect was a delayed time to MRSA infection. Furthermore, failure of decolonization or recolonization after decolonization was common. Taken together, these 2 studies show that knowledge of MRSA carriage should be used for action and that single-cycle decolonization, when effective, may be followed fairly promptly by recolonization. Additional cycles may be needed to prolong the effect, but the use of multiple cycles may increase the risk of MRSA resistance to mupirocin [23].

Rapid screening tests may be chiefly useful for implementing measures aimed at decreasing the individual risk of MRSA infection, similar to those used for MSSA. For instance, most patients scheduled for clean surgery who are not known to be MRSA carriers in countries with a low or intermediate prevalence of methicillin-resistant staphylococci receive conventional antibiotic prophylaxis that is not effective against MRSA [43]. This situation is akin to performing surgery without prophylactic antibiotics. In contrast, whether rapid screening tests improve the control of MRSA dissemination is less clear. With rapid screening tests, isolation methods could be instituted or lifted 24–48 h earlier than with cultures, which may not be crucial given the far greater impact of following contact precautions.
MUPIROCIN RESISTANCE

Mupirocin resistance of MRSA is of potential concern. The proportion of MRSA strains resistant to mupirocin is increasing. In Canada, this proportion increased from 1.6% in 1995–1999 to 7.0% in 2000–2004 [29]. High-level mupirocin resistance has been shown to be associated with decolonization failure [23, 25].

Although the mechanisms of mupirocin resistance are identical in MSSA and MRSA, mupirocin resistance is far less common among MSSA strains than among MRSA strains. The reasons are simple; mupirocin eradication rates are higher for MSSA, and the risk of emergent resistance is lower, because patients decolonized for MSSA are usually admitted to wards with lower health care procedure intensities and, consequently, lower transmission rates, compared with patients with MRSA. In addition, patients decolonized for MSSA spend less time in hospitals and have fewer readmissions. Finally, when mupirocin resistance emerges in MRSA, intercurrent antibiotic treatments contribute to select the resistant strain, relative to mupirocin-resistant MSSA strains.

CONCLUSIONS

MSSA screening and decolonization is intended only to decrease the risk of infection in the carrier. Despite the simple and direct epidemiology of this organism, the efficacy of screening and decolonization was established only recently and only in patients at high risk of infection. The situation for MRSA is different for the following reasons. First, the epidemiology of MRSA is complex and still poorly understood. Second, screening-decolonization is usually implemented as part of a broader infection-control strategy, and the individual impacts of screening, contact precautions, and decolonization are unclear. Third, several causes of screening failure and carrier decolonization failure have been identified. That the efficacy of screening-decolonization has not yet been convincingly demonstrated for MRSA is therefore not surprising. Multicenter, controlled studies are therefore urgently needed to separately assess the efficacy of screening, contact precautions, and decolonization.

Nevertheless, several results deserve attention. When there is an established MRSA outbreak, screening is probably useful in high-risk units to identify the reservoir and to initiate contact precautions; whether screening should be more extensive remains debated. The effectiveness of decolonization in decreasing the risk of infection in MRSA carriers and its effectiveness in decreasing the spread of MRSA should be assessed independently. In an endemic setting, however, MRSA decolonization to diminish the MRSA burden is probably of limited effectiveness, compared with precautions aimed at minimizing cross-transmission.

To date, rapid screening tests based on polymerase chain reaction assays have proved to be effective for MSSA in high-risk patients but not in MRSA carriers. However, screening, particularly rapid screening tests, will probably be useful if routine preventive measures, notably surgical antibiotic prophylaxis, are not effective in MRSA carriers. Standard and contact precautions, most notably hand hygiene, in a setting where leadership and behavioral strategies are used to enhance health care worker compliance are probably crucial to successful MRSA control.

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