EDITORIAL

# Methicillin-Resistant *Staphylococcus aureus* Decolonization: "Yes, We Can," But Will It Help?

Jan Kluytmans, MD, PhD; Stephan Harbarth, MD

(See the article by Robicsek et al. on pages 623–632)

Approximately 100,000 invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections occurred in 2005 in the United States, and the number of associated deaths was estimated at 19,000, which is more than the corresponding annual number of associated deaths for human immunodeficiency virus (HIV) and AIDS.[1] With the increasing number of community-onset MRSA infections,[2] prevention of staphylococcal infections is now more important than ever.

For more than 50 years, it has been known that carriage of *S. aureus* plays an important role in the pathogenesis of staphylococcal infections and represents a potential target for preventive interventions. One of the first reports (1952) that clearly demonstrated the relationship between *S. aureus* carriage and subsequent infection involved miners who experienced beat disorders of the knees and elbows.[3] A carefully performed microbiological survey showed that there were 24 "heavy" carriers of *S. aureus* among 45 beat case patients, compared with 5 heavy carriers among 45 matched control subjects without disease (odds ratio, 9.1 [95% confidence interval {CI}, 3.1–26.5]). Phagetyping showed that, in the majority of cases, the carriage strain matched the strain that caused disease. Hospital-based studies in the 1950s and 1960s confirmed this relationship, especially for surgical patients.[4] More recently, these studies have been repeated in various other patient populations—for example, dialysis patients, patients with HIV, organ transplant recipients, and critically ill patients with intravascular catheters—with similar results.[4]

It seems obvious that eradication of *S. aureus* carriage can reduce the risk for infection. This strategy has been studied in several groups of patients, and a recent Cochrane review aggregated the evidence with regard to the effect of eradication of carriage on the *S. aureus* infection rate.[5] Eight randomized controlled trials studied the effect of mupirocin nasal ointment in various groups of patients. The pooled estimate showed a significant reduction of the *S. aureus* infection rate (relative risk [RR], 0.55 [95% CI, 0.43–0.70]; $P < .001$). An analysis of subgroups showed a pronounced effect on surgical patients and on patients who were receiving dialysis, and this fact confirms results of a previously published systematic review.[6] Recently, a large trial was completed in which patients were screened on hospital admission for *S. aureus* nasal carriage by means of a 2-hour polymerase chain reaction–based assay, and carriers were subsequently randomly assigned to mupirocin nasal ointment and chlorhexidine skin washings or to placebo. The treated carriers had a significantly lower *S. aureus* infection rate (RR, 0.42 [95% CI, 0.23–0.75]).[7] In addition, the length of hospital stay was significantly shortened for the group of treated carriers (mean reduction of the length of stay, 1.8 days; $P = .04$). Despite the evidence that treatment of proven carriers lowers the *S. aureus* infection risk, there are several issues remaining. Patients who underwent elective surgery were probably the most important group to benefit from treatment of proven carriers. Because most studies of surgical patients have included both *S. aureus* carriers and *S. aureus* noncarriers, it is difficult to assess the overall effect of treatment of proven carriers. Moreover, some studies have found that the infection rate caused by microorganisms other than *S. aureus* was significantly higher among patients treated with mupirocin, compared with that for control subjects (RR, 1.38 [95% CI, 1.11–1.72]).[5] This finding was based mainly on one large study of dialysis patients who were treated repeatedly.

Compared with suppression or eradication of carriage of methicillin-susceptible *S. aureus*, suppression or eradication of MRSA carriage remains a more difficult task. Rather than being related to pathogen-associated factors that are not fundamentally different between most methicillin-susceptible *S. aureus* and MRSA clones, the frequent failure of eradication treatment is related to common characteristics of MRSA carriers, such as skin lesions, catheters, and comorbidities, that make MRSA

From the Department of Medical Microbiology and Infectious Diseases, University Medical Center, Amsterdam (J.K.), and the Laboratory for Microbiology and Infection Control, Amphia Hospital, Breda (J.K.), The Netherlands; and the Infection Control Program, University of Geneva Hospitals and Medical School, Geneva, Switzerland (S.H.).

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decolonization a daunting exercise. Additional complicating factors are extranasal MRSA carriage and simultaneous exposure to antibiotic agents selecting for MRSA.[8,9] Not surprisingly, the difficulty of eradication is reflected in the mixed experience and efficacy of MRSA decolonization treatment regimens reported in the literature.[9,10] Nevertheless, a recently performed systematic review of clinical trials to determine the effectiveness of different approaches for eradicating MRSA carriage concluded that, in uncomplicated cases, short-term nasal application of mupirocin remains the most effective treatment for eradicating MRSA carriage, with an estimated success rate of approximately 90% one week after treatment and of approximately 60% at longer follow-up.[11]

Clearly, the success of MRSA decolonization depends not only on the choice of topical and/or systemic agents used but also on the intensity, compliance, and supervision of the applied decolonization regimen. As shown by a Swiss study,[12] high rates of MRSA eradication are possible when a decolonization regimen is administered under direct supervision and includes hygiene measures for all body sites and for family members of the index patient, if necessary. A similar approach is used in The Netherlands. Uncomplicated carriers are initially treated with mupirocin nasal ointment and skin disinfection by means of chlorhexidin. If treatment fails, then a source in the family is considered. In complicated carriers (eg, those with skin lesions or invasive devices), the topical treatment is combined with 2 systemic agents.[11] However, MRSA decolonization is much less successful in endemic settings in which patients are commonly given the responsibility of careful application of topical decolonization treatments. Recently, the mother of a colleague in Geneva (Switzerland) and the father of a colleague in Cremona (Italy) were found to be MRSA carriers but were left alone with their MRSA decolonization regimens. In the absence of direct supervision and daily help, many elderly, bedridden patients are unable or simply too overwhelmed to handle the correct administration of topical decolonization treatment. Even if eradication treatment is judiciously applied, endogenous or exogenous MRSA recolonization remains common, as long as other MRSA sources are not properly controlled. Thus, many hurdles have to be overcome to achieve eradication of MRSA carriage in hospitalized patients who are persistently colonized.

Even if permanent eradication is not achieved, a secondary benefit of MRSA decolonization treatment is a decrease in bacterial load (suppression treatment), potentially contributing to reduced cross-transmission and nosocomial MRSA acquisition.[13] This concept has not yet been proven in a large cluster-randomized multicenter clinical trial. However, outbreak reports and recent modeling studies and MRSA screening trials provide some data that support this conclusion.[14,15]

In the present issue of the journal, Robicsek et al.[16] evaluated in a large observational cohort study whether topical decolonization with mupirocin was successful in reducing MRSA carriage and infection in colonized inpatients. This well-conducted real-life study complements recently reported data from the same group[14] and represents an interesting attempt to evaluate whether mupirocin use is beneficial to patients admitted mainly to medical services at their institution (less than 10% were surgical patients). Consistent with previously published evidence, decolonization treatment was temporarily effective but failed to permanently eradicate MRSA carriage in a large proportion of readmitted patients, who may have been recontaminated by MRSA via exogenous routes. Similarly, a clear trend was observed toward prevention of early-onset MRSA infection for patients who were receiving decolonization treatment, compared with patients not exposed to mupirocin and chlorhexidine body washing. This effect, however, disappeared once the brief decolonization treatment was discontinued. Wertheim et al.[17] observed a similar event in a large, placebo-controlled randomized study that involved nonsurgical patients. The temporary nature of the prevention raises a question: is one course of mupirocin administered on hospital admission sufficient to provide protection when patients are hospitalized for prolonged periods of time?

The study has several limitations that are appropriately discussed by the authors. Nevertheless, some issues warrant further comment. First, the inclusion of a larger proportion of surgical patients who are undergoing elective high-risk procedures could have been beneficial.[18,19] It would be interesting to know why the surgeons were so reluctant to apply topical decolonization treatment even when time permitted its use. Second, the lack of supervision and coordination of MRSA decolonization treatment inside the institution may have modified the effectiveness of the treatment. Likewise, although it would be difficult to coordinate, repeated decolonization treatments and concerted action in the affiliated long-term care facilities could have decreased the risk of exogenous recontamination.[20] Third, confounding by indication remains a substantial problem in this type of uncontrolled study, in addition to other sources of bias recognized by the authors. Fourth, a disturbing observation was the high proportion of mupirocin-resistant isolates in this unselected cohort of patients. This high proportion increases the likelihood of treatment failure and raises questions about the indiscriminate use of decolonization treatment in patients at low risk of MRSA infection.

In conclusion, this study raises important questions that still lack definitive answers.[18] At present, it is clear that staphylococcal carriage is an important risk factor for infection and that eradication of carriage has proven successful for patients who are undergoing elective surgery. For other groups of patients, it is still unclear what the benefits are. It is obvious that indiscriminate use of mupirocin is associated with development of resistance. Therefore, additional studies are warranted to define the optimal MRSA decolonization strategy, including what should be given, to whom, and at what moment and who should guide and supervise the regimen.

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Address reprint requests to Jan Kluytmans, MD, PhD, Laboratory for Microbiology and Infection Control, Amphia Hospital Breda, PO Box 90158, 4800 RK Breda, The Netherlands (jankluytmans@gmail.com).

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