National guidelines for decolonization of methicillin-resistant *Staphylococcus aureus* carriers: the implications of recent experience in the Netherlands

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Screening of patients for carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) coupled with interventions such as contact isolation is widely regarded as a means of reducing rates of MRSA infection and inter-patient transmission. Recent studies in the Netherlands have shown that introduction of a national guideline in which uncomplicated carriage is treated with mupirocin nasal ointment and chlorhexidine soap solution, and complicated carriage is treated using the same regimen supplemented with two oral antibiotics, was successful, with up to 80% of patients being decolonized. Increased success was seen in patients, particularly those with complicated carriage, whose treatment adhered closely to the guideline. As the Netherlands has a low level of MRSA, further work is required to see if this regimen will be as effective at reducing carriage in countries with higher rates of endemic MRSA, where re-colonization may be expected to occur more often.

**Keywords:** MRSA, carriage, infection control, nosocomial infections

**Introduction**

Patients and the public increasingly regard methicillin-resistant *Staphylococcus aureus* (MRSA) and rates of MRSA infections as indicators of the quality of patient care. Detection and eradication of MRSA therefore represent a public health priority worldwide.\(^1\) An indirect but significant marker of public interest is the sustained level of media interest in MRSA. In the USA and the UK media, >350 news articles were published between 1990 and 2004, with members of the public and politicians representing 60% of the sources quoted. Although healthcare workers, experts and professional bodies have criticized the nature of media reporting, the sustained interest in the media is an indirect but significant marker of public interest.\(^2\)

With regard to efforts to control the spread of MRSA, an issue of major interest has been the screening of patients at the time of hospitalization. National and regional guidelines for MRSA prevention and control in all 13 European countries participating in a recent survey\(^3\) as well as many national societies for clinical microbiology, infectious diseases and public health\(^4,5\) recommend active surveillance or screening for the mucocutaneous carriage of MRSA, particularly in high-risk patients. Documented risk factors for carriage of MRSA include prior hospitalization in countries with high rates of MRSA, a history of colonization or infection with MRSA and transfer from long-term care facilities or high-risk wards such as intensive care units (ICUs).

The strategy of active surveillance is based on the finding that microbiological cultures performed for clinical reasons fail to detect MRSA carriage on admission in 69%–85% of colonized patients.\(^6\) Hence, screening patients for carriage of MRSA and isolation of those who test positive seems likely to have a significant role in reducing the pool of colonized individuals and the prevention of cross-transmission in hospitalized patients. This is important, as two systematic reviews\(^7,8\) showed a significant increase in the risk of infection after MRSA colonization as compared with methicillin-susceptible *S. aureus* (MSSA) colonization. Colonization with community-acquired (CA) MRSA also seems to increase the risk of infection, as shown in a prospective observational study of US army soldiers, where colonization with Panton–Valentine leucocidin-positive strains of CA-MRSA was correlated with a significant risk of developing pyogenic soft tissue infection.\(^9\)

Some countries have maintained low endemic levels of MRSA by implementing nationwide control measures targeting MRSA, such as the search and destroy (S&D) strategy. S&D measures include contact isolation for MRSA-positive patients, pre-emptive isolation and screening for high-risk patients, screening patients and personnel when an unexpected MRSA-positive patient is found, screening all healthcare workers and keeping carriers away from work until decontamination is achieved, and closing wards to new admissions when there is more than one carrier among hospitalized patients. Bootsma et al.\(^10\) defined a stochastic three-hospital model and an analytical one-hospital model to quantify the effectiveness of this strategy. The authors suggested that a combined approach of screening and isolation...
confers efficacy and that MRSA prevalence might be reduced to <1% in high-endemicity settings by an S&D strategy and stepwise interventions.

In 2009, EARS-Net, a European network that connects 900 public health laboratories serving >1400 hospitals in Europe and providing services to an estimated population of 100 million European citizens, reported that, even though the rate of methicillin resistance among *S. aureus* was still >25% in 10 of 28 countries, the occurrence of MRSA is stabilizing or decreasing in some countries and a sustained decrease in MRSA was observed in Austria, France, Ireland, Latvia and the UK.11 It should be noted that the English experience (where MRSA rates fell >50% over a 2 year period) has been exhaustively debated12,13 Implementation of hand hygiene, contact precautions and wide screening at hospital admission have surely played a role. Nonetheless, as Edgeworth12 recently noted, in France (where similar control measures were applied) only a gradual reduction of MRSA was observed. Edgeworth12 particularly underscored the importance of decolonization, arguing that available evidence, derived predominantly from ICU studies, combined with the introduction of national guidelines endorsing its implementation, support the view that widespread uptake of decolonization made the key additional contribution.

Recent experience from the Netherlands

In this issue of *JAC*, two articles from the same group of authors report on the efficacy of a national guideline for MRSA eradication in the Netherlands and determinants of treatment failure.14,15 Over a 2 year period (October 2006–October 2008) Ammerlaan et al.14 prospectively evaluated a cohort of 613 MRSA carriers in 18 Dutch centres who underwent one or more decolonization treatments, mostly after hospital discharge. Decolonization was achieved in 60% of patients at the first attempt and ultimately 80% of patients were decolonized, with a median time to decolonization of 10 days. The majority of patients (62%) were treated according to the guideline, which was associated with increased treatment success. Major points of interest in the Dutch guideline are the classification of colonization as complicated (defined as the presence of MRSA infection, skin lesions, foreign-body material, mupirocin resistance and/or exclusive extranasal carriage) or uncomplicated (not meeting these criteria) and a proposal for two different protocols of decolonization (with or without oral antibiotic therapy) for the two respective conditions. In their second article, Ammerlaan et al.15 show that adherence to the guideline increased the success of decolonization by 20%. Among those with uncomplicated carriage, the presence of chronic pulmonary disease, extranasal carriage and lack of decolonization of household contacts were associated with treatment failure. Among those with complicated carriage, throat carriage and dependence in activities of daily living were associated with failure.15

Are the Netherlands guidelines applicable to other countries?

Although the findings from the Netherlands are significant, a number of questions as to the applicability of the protocols outside the Netherlands need to be addressed. These questions may be summarized as follows:

**Is the classification of carriers transferable to other countries?**

The classification of carriers into complicated and uncomplicated cases should be easily applicable to different countries. However, acceptance of those definitions has practical and financial implications, in that the screening procedures must include extranasal sites (at least throat and perineum) and determination of the antibiotic susceptibility pattern of MRSA carriage isolates. From a hospital administrator’s point of view (unfortunately, a critical issue in the current economic climate), undertaking additional screening and antibiotic susceptibility testing and reporting have significant cost implications, which ideally require a cost-effectiveness analysis. Recently Nelson et al.16 compared the cost-effectiveness of a programme of active surveillance plus decolonization with the current Veterans Health Administration (VHA) strategy of active surveillance alone, as well as the common practice of not undertaking surveillance. A decision-analytical model was developed for an inpatient stay time horizon, using the VHA’s perspective. In the base-case analysis, the strategy of active surveillance plus decolonization outperformed both active surveillance alone and no surveillance. In addition, active surveillance alone proved more cost-effective than a policy of no surveillance. However, one-way and two-way sensitivity analyses demonstrated that at low levels of direct benefit of decolonization (1%–4%), the strategy of active surveillance plus decolonization would no longer be dominant.16

**How does a country’s MRSA endemicity level impact on the generalizability of the Netherlands’ experience?**

A major issue of the generalizability of the efficacy of the proposed protocols in countries with medium or high levels of MRSA relates to the risk of re-colonization. In the Netherlands trial, treatment failure might indeed reflect cases of re-colonization. In countries where the rate of MRSA is high both in the community and in healthcare facilities, the risk of re-colonization might be high and may need to be re-assessed with a different clinical trial design including molecular characterization of strains in patients who failed decolonization.

The second issue for generalizability is strictly related to the fact that the majority of the decolonization in the Netherlands study was undertaken in outpatients after hospital discharge. This implies that MRSA-positive hospitalized patients stay under contact precautions during their hospital stay. This, again, in a high endemicity situation, might represent a significant problem for organization of the hospital workload, as well as having economic implications.

**Does decolonization of hospitalized patients reduce CA-MRSA?**

Whether widespread decolonization proposed for hospital MRSA is also effective for containing CA-MRSA is still an open issue. A mathematical model aimed at quantifying the effectiveness of interventions to limit the spread of CA-MRSA in healthcare settings has revealed that in a setting where MRSA is highly endemic and is
frequently introduced in healthcare facilities, hand hygiene, screening and decolonization of CA-MRSA carriers are effective control strategies in the hospital setting. However, this hypothesis needs to be further verified in settings with different rates of CA-MRSA and according to healthcare system structures.

**Does decolonization of household contacts reduce MRSA rates?**

A significant finding from the Dutch study was the association between lack of decolonization of household contacts and treatment failure. Other evidence that public health facilities for case-tracking of CA-MRSA patients are effective in European countries is available. In a population-based observational survey performed in Denmark, a cluster of CA-MRSA infections occurred among 46 individuals in 26 households. Case-tracking revealed that likely routes of transmission were mostly intra-familial spread (57%), and contact in kindergarten, school and the workplace (each 9%).

**Which antibiotic regimens need to be considered when attempting to eradicate MRSA from hospitalized patients (or staff)?**

According to a systematic review, combination therapy including rifampicin has the greatest efficacy. However, the review was biased by a significant between-studies heterogeneity. Therefore the possibility for a single antibiotic, such as co-trimoxazole, at least in countries where MRSA retains susceptibility to that antibiotic, needs to be further investigated in a randomized clinical trial (RCT).

**Is the risk of resistance overestimated?**

In the Netherlands study, no case of mupirocin resistance was reported in a 2 year period. A very recent nested case–control study showed, by multivariate analysis, that carriage of combined low-level mupirocin and genotypic chlorhexidine resistance before decolonization independently predicted persistent MRSA carriage. These results seem to suggest that institutions with widespread use of these agents should monitor for mupirocin resistance and loss of clinical effectiveness.

**Conclusions**

Preventing MRSA transmission is important since MRSA infections are associated with considerable mortality and excess hospital costs. Current evidence, further supported by the first trial on mupirocin efficacy, suggests that a decolonization protocol including local and oral antibiotic therapy and decolonization of household contacts of complicated MRSA carriers, combined with the introduction of national guidelines endorsing decolonization, is highly efficacious in populations with a low endemic level of MRSA. However, the measures required to control MRSA in hospitals, including decolonization protocols, where MRSA is highly endemic may be different from those required in other institutions. Future research should focus on the impact of the proposed protocols in countries with different levels of MRSA endemicity. An economic and modelling study to assess the cost-effectiveness of such protocols and RCTs comparing single and combined antibiotic therapy might provide a definitive answer.

**Transparency declarations**

None to declare.

**References**


