Screening for methicillin-resistant *Staphylococcus aureus* . . . all doors closed?

*Kalisvar Marimuthu*<sup>a,b</sup> and *Stephan Harbarth*<sup>b</sup>

**Purpose of review**
To describe the latest evidence for methicillin-resistant *Staphylococcus aureus* (MRSA) infection control strategies, with particular emphasis on active surveillance cultures with contact precautions and targeted decolonization, and their impact.

**Recent findings**
Several major trials published last year questioned the effectiveness of universal screening and contact precautions in controlling MRSA. These trials generally recommend universal decolonization as part of bundles to control MRSA, especially in ICUs, with some even concluding that universal decolonization should replace active screening and contact precautions. However, emerging resistance to agents used for decolonization, such as mupirocin and chlorhexidine, is a major concern. Several other studies confirmed a combination of hand hygiene enhancement, screening, contact precaution and targeted decolonization as a more viable MRSA infection control strategy for specific population groups.

**Summary**
Universal decolonization is an acceptable MRSA control strategy for intensive care units; however, close monitoring of chlorhexidine and mupirocin resistance is warranted. As a strategy, screening and contact precautions are suitable for hospital-wide MRSA control. Targeted decolonization is a proven measure for patients undergoing clean surgery. Enhancement of hand hygiene is a core measure regardless of the strategy.

**Keywords**
decolonization, horizontal interventions, methicillin-resistant *Staphylococcus aureus*, screening, vertical interventions

**INTRODUCTION**
Since its discovery in 1961 [1], methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major cause of healthcare-associated infections globally with significant morbidity and mortality [2,3]. Admittedly, copious amounts of studies, position papers and guidelines have been published over the years towards controlling MRSA, precipitating a declining trend globally [4]. The last couple of years have been exciting and interesting with top researchers publishing high-quality studies on prevention and control of multidrug-resistant organisms (MDROs), especially MRSA (Table 1). These meticulously designed studies took on the monumental task of assessing effectiveness of different measures in controlling MRSA of both horizontal interventions such as hand hygiene and universal decolonization, as well as vertical interventions such as screening and contact isolation (Fig. 1).

MRSA screening and contact isolation strategy’s primary aim is to prevent transmission of MRSA from carriers to noncarriers. Even though this may not necessarily prevent infection in colonized patients, a reduction in new MRSA carriers could produce a net reduction in infections [10]. Decolonization, however, aims to directly eradicate MRSA from carriers, at least temporarily, thus preventing transmissions to noncarriers and infections in carriers [11]. Hence, it is reasonable to expect this strategy to reduce MRSA infections quicker with the additional benefit of significantly reducing dermal colonization and systemic infections from other
MDROs. Although some experts argue that decolonization should be the only strategy, others contend that it should be a supplement to screening and contact isolation [7**, 12]. A recent editorial in the New England Journal of Medicine (NEJM) [13] suggested closing all doors on screening and contact precautions as a viable strategy for control of MRSA.

In this review, we aim to analyse recent studies published on control of MRSA to decide whether MRSA screening and contact isolation remains a viable strategy or whether it has reached the end of the road.

**KEY POINTS**

- Universal decolonization is an acceptable short-term MRSA control strategy for ICUs with high MRSA transmission rates.
- Targeted screening and contact precautions remain a viable strategy for hospital-wide MRSA control.
- Centres practising universal decolonization should actively monitor for chlorhexidine-resistant MRSA strains.

**METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CONTROL IN ICUS**

Bloodstream infections (BSIs) related to multidrug-resistant or extensively drug-resistant organisms are common in ICUs and are associated with a high mortality [14]. Consequently, prevention of acquisition and infection with these pathogens are of paramount importance. MRSA has been studied extensively in this respect, with arguments mounting from both sides of the aisle on value of universal screening, and infection with these pathogens are of paramount importance. MRSA has been studied extensively in this respect, with arguments mounting from both sides of the aisle on value of universal screening, and contact precautions as a viable strategy for control of MRSA.

In this review, we aim to analyse recent studies published on control of MRSA to decide whether MRSA screening and contact isolation remains a viable strategy or whether it has reached the end of the road.

In February 2013, a multicentre cluster-cross-over trial was published by Climo et al. [5*] in NEJM in which investigators compared the effectiveness of 2% chlorhexidine-impregnated washcloths against nonantimicrobial washcloths in reducing acquisition of and bacteraemia from MDROs, especially MRSA and VRE, although maintaining active surveillance cultures and contact precautions for VRE and MRSA. Nine ICUs and bone marrow transplant units from seven hospitals, most with MRSA prevalence above 10%, enrolled more than 7000 patients. Hospital-acquired BSI was 28% lower with chlorhexidine bathing with 4.78 cases per 1000 patient-days versus 6.60 cases per 1000 patient-days with nonantimicrobial washcloths. However, it should be noted that the reduction in bacteraemia was contributed mainly by reduction in coagulase-negative S. aureus, and it failed to reduce MRSA acquisition. Furthermore, several letters raised methodological concerns about this study [19]. Milstone et al. [6**], in a cluster-randomized crossover trial (SCRUB trial) of paediatric ICUs involving more than 4900 patients, studied the effect of daily bathing with 2% chlorhexidine-impregnated cloth against routine bathing practices without screening for MDROs in either group. The chlorhexidine treatment group showed, in per protocol analysis, an impressive 36% reduction in BSI mostly due to skin commensals. Although the finding was not corroborated by an intention to treat analysis, this study is significant in being one of the first cluster-randomized trials to assess the effect of universal decolonization in paediatric patients.

Although most interventions focused on various combinations of decolonization and screening modalities, Derde et al. [9**] from the Mastering Hospital Antimicrobial Resistance in Europe (MOSAR) study team creatively investigated the baseline rate (Phase 1) against the combined effect of enhanced hand hygiene and universal decolonization (Phase 2), as well as the additional impact of screening and contact precautions (Phase 3) on MRSA, VRE and highly resistant Enterobacteriaceae (HRE) in 13 European ICUs. The baseline rates of MRSA, VRE and HRE at admission to ICUs were 3.6, 4.7 and 12.8%, respectively. In Phase 2 with 100% of patients undergoing universal decolonization with chlorhexidine, the MDROs rate declined gradually [weekly incidence rate ratio (IRR) 0.92, 95% confidence interval (CI) 0.89–0.96] with an increase in...
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Design</th>
<th>Hand hygiene enhancement</th>
<th>Screening and contact isolation</th>
<th>Decolonization</th>
<th>MRSA rates</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Climo et al. [5**]</td>
<td>Adult ICUs and BMTUs</td>
<td>Cluster-randomized, two-period, cross-over trial</td>
<td>No</td>
<td>Yes: MRSA and VRE</td>
<td>Yes: 2% chlorhexidine washcloths</td>
<td>Intervention period: 13.8%; Control period: 12.8%</td>
<td>There was significant reduction in overall hospital-acquired BSI.</td>
</tr>
<tr>
<td>Milstone et al. [6**]</td>
<td>Paediatric ICUs</td>
<td>Cluster-randomized, two-period, cross-over trial</td>
<td>No</td>
<td>No</td>
<td>Yes: 2% chlorhexidine washcloths</td>
<td>Not available</td>
<td>For MRSA and VRE, there was significant reduction in acquisition, but not in BSI.</td>
</tr>
<tr>
<td>Huang et al. [7**]</td>
<td>Adult ICUs and BMTUs</td>
<td>Cluster-randomized, pragmatic, comparative effectiveness trial</td>
<td>No</td>
<td>Yes: Group 1: Screening and contact isolation</td>
<td>Yes: Groups 2 and 3: mupirocin and 2% chlorhexidine washcloths</td>
<td>Baseline period: Group 1: 10.2%, Group 2: 11.1%, Group 3: 10.6%; Intervention period: Group 1: 9.7%, Group 2: 11.1%, Group 3: 3.7%</td>
<td>Universal decolonization is more effective than universal screening and contact precautions with or without targeted decolonization in reducing MRSA clinical cultures and BSI due to any pathogens.</td>
</tr>
<tr>
<td>Lee et al. [8**]</td>
<td>Surgical wards</td>
<td>Controlled, interventional cohort study</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes: Targeted decolonization of MRSA carriers with mupirocin and 2% chlorhexidine bathing</td>
<td>Baseline phase: 0.8% Intervention phase: 1.1% Washout phase: 0.8%</td>
<td>A combination of enhanced hand hygiene, universal screening with targeted decolonization of MRSA carriers is superior to either strategies alone in reducing MRSA rates in surgical wards.</td>
</tr>
<tr>
<td>Derde et al. [9**]</td>
<td>Adult ICUs</td>
<td>Combination of interrupted time series and cluster-randomized study</td>
<td>Yes: Phase 2</td>
<td>Yes: Phase 3: ICUs were randomly assigned to either rapid or conventional screening for MRSA, VRE and HRE</td>
<td>Yes: Phase 2: Chlorhexidine body wash</td>
<td>Phase 1: 3.1% Phase 2: 3.1% Phase 3: Conventional screening arm: 2.8%; rapid screening arm: 4.5%</td>
<td>Hand hygiene enhancement with chlorhexidine body washing reduced MRSA acquisition.</td>
</tr>
</tbody>
</table>

BMTU, bone marrow transplant unit; BSI, bloodstream infections; CHG, chlorhexidine gluconate; HRE, highly resistant Enterobacteriaceae; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus; ICU, intensive care unit.
hand hygiene compliance from 52% during Phase 1 to 69% during Phase 2. Interestingly, with hand hygiene compliance rate increasing to 77% in Phase 3, the study did not note any additional benefit after introduction of screening and isolation. Although they were unable to decouple the effect of hand hygiene enhancement from universal skin decolonization (without nasal mupirocin application), this probably was the first cluster-randomized study to methodically confirm the positive role of increased hand hygiene compliance in prevention of MDRO transmission in ICUs.

Huang et al. [7**] ‘took the bull by the horns’ in their REDUCE-MRSA trial published in NEJM. In this pragmatic cluster-randomized trial involving 74 ICUs from 43 hospitals, investigators compared active surveillance and contact precautions (Group 1); active surveillance, contact precautions and targeted decolonization (Group 2) and universal decolonization regardless of MRSA status (Group 3). MRSA rates ranged between 10.0 and 11.5% between the three groups during a baseline period of 12 months. The 18-month study concluded that universal decolonization showed greater reduction in the hazard of MRSA-positive clinical cultures than did screening and isolation (hazard ratio in Group 3, 0.63; 95% CI, 0.52–0.75; hazard ratio in Group 1, 0.92; 95% CI, 0.77–1.10; \( P = 0.003 \)). The ICU-attributable BSI due to any pathogen was significantly lower in Group 3 with number of decolonization needed to prevent one BSI being 54. However, the reduction was mostly due to skin commensals as seen in other decolonization studies, and it did not demonstrate a significant reduction in ICU-attributable MRSA BSI. This study was done at centres in which universal screening and isolation had already been in place for more than 30 months resulting in an unfair comparison with newly implemented universal decolonization strategies [20,21]. Hence, a fourth comparison group with universal screening and isolation as a novel strategy would have been informative. Having said that, these data suggest that decolonization (whether universal or targeted) can provide at least an incremental benefit in controlling MRSA cross-infections in ICUs. Although this study cemented universal decolonization strategy’s position in discussions around MRSA control in ICUs, it falls short of obviating screening and isolation strategy at the present moment [13]. Furthermore, this approach may increase the clinical impact of mupirocin resistance, as previously observed [22].

**METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CONTROL OUTSIDE INTENSIVE CARE UNITS**

MRSA poses continued challenge for surgical patients with limited evidence-based preventive measures [23]. Randomized control trials in the past have failed to show unequivocal benefit of nasal decolonization with mupirocin or chlorhexidine in reducing \( S. \) aureus surgical site infections (SSI) although some benefit was seen in reducing nosocomial \( S. \) aureus infection [24]. A recent meta-analysis evaluated 16 clinical trials involving 9980 patients and concluded against whole-body chlorhexidine bathing [25]. However, in a systematic review published in the *British Medical Journal* (BMJ), Schweizer et al. [26*] conducted a pooled analysis comparing seven studies which used bundled intervention with nasal decolonization
and glycopeptide prophylaxis, 37 studies which implemented nasal decolonization and 15 studies investigating glycopeptide prophylaxis only. They concluded that although nasal decolonization and glycopeptide prophylaxis protected against S. aureus and MRSA SSI respectively, the bundled intervention reduced SSI due to all Gram-positive bacteria, but stressed on the need for randomized control trials to confirm these findings.

These strategies and their interaction with horizontal interventions were investigated by another MOSAR study group. Lee et al. [8**] in their controlled trial compared enhanced hand hygiene against universal MRSA screening with contact precautions and targeted decolonization (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers in 33 surgical wards of 10 hospitals in Europe. Interestingly, an unplanned third arm in the study employed a combination of enhanced hand hygiene, targeted MRSA screening based on risk factors, contact precaution and decolonization as per physician preference, thus replicating real-life situations. This combined intervention arm, with a baseline MRSA rate of less than 2.1%, experienced an increase in hand hygiene compliance from 49.3% (95% CI 47.2–51.4%) to 63.8% (95% CI 63.2–64.4%) from baseline to intervention phases. During the intervention phase, 22.3% were screened for MRSA, 35.9% were decolonized and compliance to contact precautions exceeded 90%. This strategy produced a significant reduction in the rate of MRSA-positive clinical cultures of 12% per month (adjusted incidence rate ratios of 0.88; 95% CI 0.79–0.98). A significant reduction of MRSA rates was also observed amongst patients undergoing clean surgery in the study group ascertained to universal MRSA screening with contact precautions and decolonization. The authors logically concluded that a strategy for effective control of MRSA in low-prevalence settings should be multimodal with a combination of horizontal and vertical interventions, with the exception of elective clean surgery in which universal screening and targeted decolonization could be applied successfully, in contrast to the previously cited claim in the editorial by Wenzel et al. [13].

COSTS AND CONSEQUENCES

Patients on isolation and contact precautions, be it cohort wards, single rooms or shared rooms, receive less attention from healthcare workers. In a retrospective study in 2003, Stelfox et al. [27] showed that patients isolated for infection control precautions suffered from more preventable adverse events and were dissatisfied with their treatment. This purported disadvantage of screening and isolation policy was called into question in 2013 when Harris et al. [28*] demonstrated, as a secondary outcome, no significant difference in preventable and unpreventable adverse events between the two study groups in a large cluster-randomized trial. Increased awareness amongst healthcare providers and advances in patient safety monitoring systems available now compared to 10 years ago might be possible explanations for the difference, but further controlled studies are needed to verify these findings.

Another disadvantage of screening and isolation policy is the lack of an evidence-based end point as the duration of colonization with MRSA varies, influenced by various factors including age, race, number of colonizing body sites, skin integrity, decolonization treatment, antibiotics exposure and frequency of contact with the healthcare system [29,30]. In one study, about 50% of patients were cleared of MRSA at 1 year and close to 80% were MRSA-free at 4 years [31]; however, high-quality evidence and standardized criteria for discontinuation of contact precautions are lacking. Shenoy et al. [32] documented that in a setting with an MRSA prevalence of 8%, a single nasal PCR performs well against three nasal swab cultures for identifying MRSA carriers with positive and negative predictive values of 86.1 and 96.6%, respectively. Although this study did not address the clinical effectiveness of discontinuation of MRSA contact precautions, it supports the use of a single nasal PCR for identifying MRSA-negative patients because of its rapidity, simplicity and efficiency despite a higher capital and per-test cost.

Decolonization involves applications of topical antibiotics to anterior nares and bathing with an antiseptic solution usually with mupirocin and chlorhexidine. Chlorhexidine has been in clinical use for more than 5 decades and is generally considered the choice biocide for skin decontamination because of its broad spectrum of activity, acceptable tolerability and residual antibacterial activity. Unfortunately, as with all antimicrobials, reports of phenotypic and genotypic resistance to chlorhexidine have been on the rise following its increased usage [33,34]. MRSA strains carrying qac A/B resistant genes are not only protected from bactericidal activity of chlorhexidine, but could potentially spread more rapidly [35]. In a recent study, investigators showed that the presence of these genes in combination with low-level mupirocin resistance is an independent risk factor for persistence of MRSA carriage after decolonization [22]. Prevalence of mupirocin-resistant MRSA has mirrored the increase and decrease in mupirocin consumption, suggesting an association between the two [36–38].
A research gap in good quality empirical studies dedicated to assess the economic impact of MRSA control strategies has resulted in diverse national policies and local strategies. A recent dynamic transmission modelling study in an ICU population concluded that universal decolonization with chlorhexidine had about 70% chance of being the most cost-effective approach, and if universal decolonization is not an acceptable strategy in a centre then universal MRSA PCR screening of all patients with targeted decolonization was the next best alternative [39]. This outcome was persistent regardless of the size of ICU, prevalence of MRSA on admission and proportion of high-risk patients admitted. Outside the ICUs, universal or targeted screening and isolation are widely used to control MRSA. Cost-effectiveness of these strategies, alone or in various combinations, is rather murky with modelling studies showing conflicting results [40–44]. A systematic review of 36 studies published between 1987 and 2011 showed that savings from infection control initiatives aimed at preventing MRSA transmission was approximately seven times higher than their cost [45]. The benefits seen were more pronounced in the intermediate (1–10%) and high (>10%) MRSA prevalence settings. However, this review was not powered to compare the efficacy of targeted versus universal screening.

CONCLUSION

Several recent high-quality studies are endorsing the idea of universal decolonization with or without screening and isolation of MRSA carriers for critically ill ICU patients; however, careful monitoring of mupirocin and chlorhexidine resistance is warranted. Screening and targeted decolonization of MRSA is an acceptable strategy to prevent infection in clean surgery patients. Screening and isolation remains a suitable measure for a hospital-wide MRSA control strategy, especially at centres with moderate to high MRSA rates and low hand hygiene compliance. Even as the doors to ICU begin to close, MRSA screening, targeted decolonization and isolation remains a welcome strategy in specific nonICU settings.

Acknowledgements

None.

Conflicts of interest

Stephan Harbarth: Member of the scientific advisory board of Destiny Pharma, DaVolterra and bioMérieux. He has received financial support for MRSA research activities from Geneva University Hospitals, B. Braun and the European Commission (MOSAR network contract LSHP-CT-2007-037941).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
■ of outstanding interest


This systematic review concluded that nasal decolonization and glycopeptide prophylaxis protected against S. aureus and MRSA SSI respectively.
