

Prevention of Surgical Site Infections: Decontamination With Mupirocin Based on Preoperative Screening for *Staphylococcus aureus* Carriers or Universal Decontamination?

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Perioperative decolonization of *Staphylococcus aureus* nasal carriers with mupirocin together with chlorhexidine body washing reduces the incidence of *S. aureus* surgical site infection. A targeted strategy, applied in *S. aureus* carriers only, is costly, and implementation may reduce effectiveness. Universal decolonization is more cost-effective but increases exposure of noncarriers to mupirocin and the risk of resistance to mupirocin in staphylococci. High-level mupirocin resistance in *S. aureus* can emerge through horizontal gene transfer originating from coagulase-negative staphylococci (CoNS) and through clonal transmission. The current evidence on the occurrence of high-level mupirocin resistance in *S. aureus* and CoNS, in combination with the results of mathematical modeling, strongly suggests that the increased selection of high-level mupirocin resistance in CoNS does not constitute an important risk for high-level mupirocin resistance in *S. aureus*. Compared with a targeted strategy, universal decolonization seems associated with an equally low risk of mupirocin resistance in *S. aureus*.

Keywords. MRSA; mupirocin; decolonization; *mupA*; prophylaxis.

Nasal carriage with *Staphylococcus aureus* occurs persistently in 20% and intermittently in 30% of human subjects [1]. Nasal *S. aureus* carriage is associated with an estimated 5–10-fold risk of developing *S. aureus* surgical site infection (SSI) [2, 3], and >80% of all *S. aureus* SSIs are thought to be from endogenous origin (ie, caused by the same strain that previously colonized the nares [1]). Eradication of *S. aureus* carriage perioperatively reduces the incidence of *S. aureus* SSI. Although several studies failed to demonstrate significant reductions in *S. aureus* SSI when using universal perioperative intranasal application of mupirocin [4], the intervention seemed beneficial in patients who were carrying *S. aureus* preoperatively, as determined in a meta-analysis [5].

This preventive effect was subsequently confirmed in a randomized placebo-controlled multicenter trial of targeted decolonization of *S. aureus* carriers in the Netherlands [6]. In this study application of mupirocin nasal ointment twice daily and daily chlorhexidine body washing for a total of 5 days reduced the incidence of *S. aureus* SSI by 58% and even by 79% for deep SSI in nasal *S. aureus* carriers identified preoperatively

with polymerase chain reaction–based testing [6]. In a pragmatic multicenter study in the United States, implementation of a bundle consisting of *S. aureus* screening and decolonization and targeted prophylaxis reduced the number of postoperative complex *S. aureus* SSIs by 42% [7]. Bundle adherence in this study was 83% (full adherence in 39% and partial adherence in 44%). Incidences of complex *S. aureus* SSI rates did not decrease significantly in patients undergoing urgent or emergency surgery or in patient groups with only partial adherence or nonadherence to the bundle.

Implementing a screening and targeted decolonization strategy in daily practice, with either rapid molecular techniques or conventional cultures, is complicated. Only patients undergoing elective surgery can be screened in outpatient settings, and screening results need to be communicated in time, followed by allocation and administration of the appropriate therapy. This may be difficult, especially when the window of opportunity before surgery is small. A too long period between screening and surgery increases the risk of misclassification. Although successful screening and initializing treatment of all eligible patients has been reported to be as high as 85% [8, 9], others have reported logistical challenges and concerns about associated costs of rapid screening [8, 10].

Failure to obtain nasal samples, to report screening results in time, or to apply medication in time will all reduce the effectiveness of this intervention, because *S. aureus* carriers may not receive treatment. Moreover, reported sensitivities of polymerase

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chain reaction–based screening have ranged from 65% to 97%, which may also lead to missing *S. aureus* carriers [6, 11, 12]. However, negative screening results have been associated with lower colonization density [12], possibly reflecting lower infection risks [13, 14]. Finally, preoperative screening for *S. aureus* is usually based on nasal swab samples only, which may also lead to misclassification. Indeed, screening for nasal carriage has been consistently reported to detect only 65%–75% of methicillin-resistant *S. aureus* (MRSA) carriers [15], but whether this also applies to methicillin-sensitive *S. aureus* (MSSA) remains unknown.

The logistical challenges and costs of preoperative screening and the risk of not allocating a beneficial preventive measure to *S. aureus* carriers can be minimized by treating all patients with mupirocin and chlorhexidine body washing, irrespective of *S. aureus* carrier status, (Table 1). With this approach, all patients will be treated, including those with false-negative screening results. This also implies that all patients receive some form of protection against acquiring *S. aureus* after screening, for instance through cross-transmission during the first 5 days after surgery. However, decolonization of noncarriers will not contribute to the beneficial effects of decolonization, and though costs can be saved by avoiding screening, treatment costs will be higher. Nevertheless, in cost-effectiveness modeling studies, universal decolonization strategies had the highest cost savings compared with targeted decolonization strategies, mainly because of absent screenings costs and the more efficacious intervention [10]. Importantly, though, this cost-effectiveness analysis assumed persistent efficacy over time, neglecting the potential development of resistance against any of the components of the strategy with subsequent reduction in efficacy.

Concerns exist that widespread use of mupirocin, as used in universal decolonization, will increase the risk of resistance.

Table 1. Characteristics of Targeted and Universal Perioperative Decolonization Strategies

Characteristic	Universal Decolonization	Targeted Screening and Decolonization
Implementation of strategy	Easy prescription of medication	Logistics can and will be challenging for screening, reporting of results, and prescription of medication
Sensitivity of strategy	100% (<i>Staphylococcus aureus</i> carriers will not be missed)	Suboptimal (some patients may not be screened, test procedure may not have 100% sensitivity, and nonnasal <i>S. aureus</i> carriers may be missed)
Volume of mupirocin use	Approximately 5 times that in targeted strategy	Detected <i>S. aureus</i> carriers only
Volume of screening	Absent	All subjects
Cost components	Allocation of medication, mupirocin	Screening, reporting, allocation of medication, and mupirocin

Emergence of resistance against mupirocin has been associated with increased use, though not consistently, [16–18]. In particular, unrestricted, widespread use of mupirocin in the community and the use in wounds and pressure sores have been associated with the emergence of resistance [16, 19, 20]. Data are scarce on the emergence of mupirocin resistance among patients undergoing dialysis. In patients undergoing hemodialysis and receiving intranasal mupirocin, a single high-level mupirocin-resistant isolate was detected during 168 patient-years of follow-up [21]. In comparison, the emergence of mupirocin resistance has been described in patients undergoing long-term peritoneal dialysis and receiving prophylactic mupirocin applications to the catheter exit site [22, 23].

Here, we review the current evidence on the risks of developing mupirocin resistance for 2 perioperative decolonization strategies: targeted screening and decolonization of identified *S. aureus* carriers and universal decolonization irrespective of carrier status. We use a mathematical model and available epidemiological data to explore the dynamics of mupirocin resistance within a hospital setting and to identify the most important determinants for emergence of mupirocin resistance in *S. aureus*.

RESISTANCE TO MUPIROCIN

Mechanisms of Resistance

Mupirocin is a topical antibiotic that prevents bacterial protein synthesis by inhibiting the bacterial isoleucyl-tRNA synthetase (IleRS). It is the cornerstone for the decolonization of *S. aureus* including MRSA in both patients and healthcare workers. High-level mupirocin resistance is mediated through the plasmid based *mupA* gene encoding for an alternate *ileRS* gene, whereas low-level resistance results from point mutation in the native *ileRS* gene (Table 2).

Increasing resistance against mupirocin in *S. aureus* would greatly threaten the effectiveness of these decolonization strategies, because mupirocin resistance is associated with high failure rates. Successful decolonization of subjects carrying high-level

Table 2. Phenotypes of Mupirocin Resistance in *Staphylococcus aureus*, Associated Mechanisms, Breakpoints, and MRSA Carriage Eradication Rates

Phenotype	Mechanism	MIC, mg/L	Successful Eradication, %
Susceptible ^a	Wild type	≤4 ^a	90 ^b
Low-level resistance ^a	Point mutation in the native <i>ileRS</i> gene	8–64 ^a	29
High-level resistance	Plasmid-based <i>mupA</i> gene encoding for an alternate <i>ileRS</i> gene	>256	24

Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*.

^a Breakpoints for intermediate-resistant *S. aureus*, as defined by the European Committee for Antimicrobial Susceptibility Testing, are 2–256 mg/L, placing the susceptible threshold at the epidemiological cutoff value (1 mg/L).

^b Successful eradication of MRSA carriers 1 week after treatment. The success rate after a longer follow-up is approximately 60%.

mupirocin-resistant MRSA has been reported to be as low as 24% [24]. Isolates with low-level resistance seem to be initially cleared as effectively as susceptible strains, but recolonization seems to occur more frequently [25].

Emergence of Mupirocin Resistance

Several studies have quantified the development of mupirocin resistance in *S. aureus* following the implementation of decolonization strategies. In a Dutch multicenter trial, resistance against mupirocin was not detected in 917 patients carrying *S. aureus* before receiving mupirocin treatment, nor was it detected in any of the *S. aureus* isolates causing hospital-acquired infections [6]. Moreover, no infections (or carriage) caused by mupirocin-resistant *S. aureus* were detected among >20 000 patients treated perioperatively with mupirocin and chlorhexidine in a single Dutch hospital, not even in those with postoperative *S. aureus* SSIs [5]. In the United States only 1 of 36 isolates (2.8%) causing complex *S. aureus* SSI in *S. aureus* carriers receiving perioperative decolonization with mupirocin and chlorhexidine body washings showed high-level resistance to mupirocin [7].

In another randomized study comparing mupirocin with placebo in 871 patients in the United States, 6 of 1021 *S. aureus* isolates (0.6%), obtained from 6 patients, were resistant to mupirocin during the 4-year study period. It remained unknown whether resistance occurred after mupirocin exposure, but 3 of the 6 patients had not received mupirocin during the study period [4]. In a study of >7000 patients who had received nasal application of mupirocin in the United Kingdom, high-level mupirocin-resistant *S. aureus* isolates were not detected [26]. Low-level mupirocin resistance occurred in 1.8% and 5.1% of MSSA and MRSA isolates, respectively, and there was no discernible trend of increasing resistance during the 4-year study period.

Only 1 study, in the Netherlands, quantified the occurrence of mupirocin resistance in both *S. aureus* and coagulase-negative staphylococci (CoNS) after the implementation of universal perioperative decolonization [27]. Before treatment, 21% of all patients carried CoNS with *mupA*-mediated high-level resistance and of those patients without such bacteria 37% had *mupA*-mediated high-level resistance after completing decolonization treatment. No acquisition of high-level mupirocin resistance was detected in *S. aureus* in 939 patients who underwent decolonization therapy. Even though horizontal gene transfer of the *mupA* gene from *Staphylococcus epidermidis* to *S. aureus* has been described in vitro and in vivo [28], no such events were observed in this study. Next to interspecies transfer of *mupA*, clonal dissemination of mupirocin-resistant *S. aureus* and CoNS will increase the prevalence of resistance in hospitals [29].

Whether widespread use of chlorhexidine will increase the prevalence of chlorhexidine resistance in staphylococci is unclear [30], though clonal expansion of MRSA clones expressing chlorhexidine resistance genes has been described [31].

Moreover, the clinical impact of reduced susceptibility to chlorhexidine among *S. aureus* is yet to be determined [30]. We therefore restrict our analysis to mupirocin resistance.

TRANSMISSION DYNAMICS OF MUPIROCIN RESISTANCE

Model

We developed a deterministic mathematical model (see [Supplementary Material](#) for details) to compare the effects of targeted and universal decolonization on the future prevalence of mupirocin-resistant *S. aureus* in a hospital setting. High-level mupirocin resistance in *S. aureus* can emerge through clonal spread or through within-host horizontal transmission of *mupA* from CoNS to *S. aureus*.

Setting and Model Assumptions

For simplicity we used a single-ward model and parameterized the patient admission prevalence of mupirocin-resistant CoNS and *S. aureus*, decolonization rates for *S. aureus*, and patient length of stay ([Supplementary Table 1](#)). In the main analysis, the admission prevalence is 18.8% for *S. aureus* and 0.08% for mupirocin-resistant *S. aureus*. The patient-to-patient transmission rates of *S. aureus* and CoNS were derived from published transmissibility rates of MRSA in hospital settings and quantified as R_A , the single admission reproduction number, defined as the mean number of secondary cases generated by a single primary case patient (eg, a patient colonized with *S. aureus*) during a single hospital admission ([Supplementary Table 1](#)) [32, 33].

Dynamics of *S. aureus* and CoNS

Patients are either carriers or noncarriers for *S. aureus* with or without *mupA*. All patients carry CoNS, either *mupA* negative or positive. Only patients carrying *mupA*-positive *S. aureus* are not susceptible to acquisition of *mupA*-positive CoNS or *S. aureus*, and we ignore any protective effects of colonization with the other species. Application of mupirocin creates selective pressure for acquisition of *mupA*-positive staphylococci, which ceases immediately at day 5, when application is discontinued. Absent estimates of the in vivo horizontal gene transfer rates, we assume that these rates are similar for *S. aureus* and CoNS, both *mupA* positive and *mupA* negative. The effects of species-specific horizontal gene transfer rates are explored in sensitivity analyses.

Drivers of Mupirocin Resistance in *S. aureus*

Universal decolonization with mupirocin will increase the prevalence of *mupA*-based high-level resistance in CoNS, which increases the opportunities of horizontal gene transfer of *mupA*. However, because of the decolonizing effects of mupirocin on *S. aureus*, the prevalence of high-level resistance in this species increases only marginally, with no discernible difference in the prevalence of mupirocin resistance in *S. aureus* between targeted and universal decolonization strategies (Figure 1A). Increasing the interspecies conjugation rate of *mupA* between CoNS

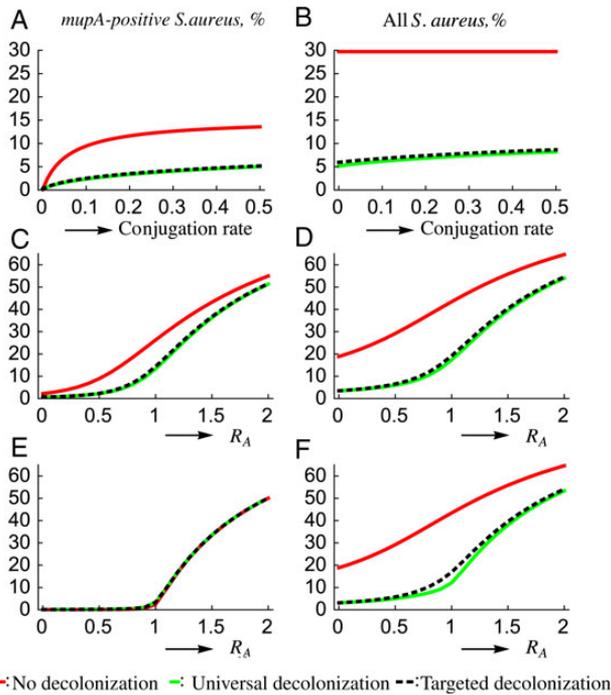


Figure 1. Results of model. *A, B*, Prevalence of *mupA*-positive and all *Staphylococcus aureus* with increasing conjugation rates of *mupA* between coagulase-negative staphylococci (CoNS) and *S. aureus*. *C, D*, Prevalence of *mupA*-positive and all *S. aureus* with increasing R_A and no horizontal gene transfer of *mupA* between CoNS and *S. aureus*. The following parameters were used: *A, B*, R_A , 0.52; *C, D*, conjugation rate, 0.1; *E, F*, conjugation rate, 0. For all figure parts, 18.8% of patients were colonized on admission with *S. aureus* and 0.06% with *mupA*-positive *S. aureus*, 81.2% had no colonization with *S. aureus*, 79% were colonized with CoNS, and 21% were colonized with *mupA*-positive CoNS.

and *S. aureus* hardly changes these dynamics. Of note, in the absence of decolonization (either targeted or universal), an increased interspecies conjugation rate, in combination with a high prevalence of patients carrying mupirocin-resistant CoNS on admission, would increase the rate of mupirocin-resistant *S. aureus* significantly, owing to the presence of more mupirocin-susceptible *S. aureus* recipients for *mupA* genes from CoNS (Figure 1A).

According to the model, the transmission capacity of *S. aureus*, quantified as R_A , is the main driver for an increase of high-level mupirocin-resistant *S. aureus* (Figure 1C). Without horizontal transfer of *mupA*, there will be no difference in the prevalence of mupirocin-resistant *S. aureus* between the 2 decolonization strategies and no decolonization (Figure 1E). Any increase in R_A leads to an increased prevalence of mupirocin-resistant *S. aureus*, but this is not influenced by the type of decolonization strategy.

Changing the admission prevalence of mupirocin-resistant CoNS and *S. aureus*, as well as of mupirocin-sensitive *S. aureus* did not change the results of the model (Supplementary Figures 4A–7A). In fact, the prevalence of mupirocin-resistant

S. aureus does not differ between decolonization strategies when the admission prevalence of mupirocin-resistant *S. aureus* increases. In such a scenario, decolonization will become increasingly less successful in both strategies, and because mupirocin-resistant *S. aureus* already contains the *mupA* gene, horizontal gene transfer of *mupA* genes does not occur effectively.

DISCUSSION

Perioperative decolonization of *S. aureus* carriage is associated with significant healthcare gains and cost savings due to prevention of *S. aureus* SSIs. Universal decolonization without screening for *S. aureus* carriage is more cost-effective than targeted decolonization based on preoperative screening. However, these benefits should be balanced against the risk of selecting mupirocin resistance in patients not carrying *S. aureus* on admission. The current evidence on the occurrence of high-level mupirocin resistance in *S. aureus* and CoNS, in combination with the results of mathematical modeling, strongly suggest that the increased selection of high-level mupirocin resistance in CoNS does not constitute an important risk for high-level mupirocin resistance in *S. aureus*.

Several assumptions made in the mathematic model should be discussed. First, we assumed the transmission capacities of *S. aureus* and CoNS, defined by R_A , to be identical, though little is known about transmission capacities of MSSA and CoNS in hospital settings. The R_A values used were derived from studies quantifying the transmission capacity of MRSA in low-endemicity settings [32, 33]. Nosocomial transmission of CoNS is rarely studied. In a Swedish intensive care unit (ICU), 14 of 20 patients were involved in ≥ 1 and up to 8 probable transmission events [34]. Second, the percentage of patients carrying mupirocin-resistant CoNS and *S. aureus* on admission were based on a setting in which mupirocin had been used in a universal decolonization strategy for 2 years. Although the question was not studied, this admission prevalence could have been influenced by the universal decolonization strategy, and prevalence might have been lower if less mupirocin had been used as part of a targeted strategy. However, modeling results were not sensitive to the prevalence of mupirocin resistance among CoNS before treatment (Supplementary Appendix). Third, the horizontal gene transfer rate from CoNS to *S. aureus* was based on a single study, with relatively short follow-up of patients. However, the observed prevalence of *mupA* high-level resistance in CoNS in that study and the absence of high-level mupirocin resistance in multiple *S. aureus* collections in the Netherlands provide further evidence that horizontal gene transfer does not occur frequently.

Feasibility and cost issues have prevented centers from implementing these measures. The same feasibility and costs issues favor the strategy of universal perioperative decolonization. Our findings, though partly based on modeling, strongly

suggest that the consequent use of mupirocin in those patients not carrying *S. aureus* does not extensively increase the risk that high-level mupirocin resistance will emerge in *S. aureus*. Quantifying the duration of carriage with high-level mupirocin-resistant CoNS and horizontal gene transfer rates in patients with longer follow-up would allow a more accurate assessment of the ecological safety of universal decolonization with mupirocin in surgical patients.

The impact of universal decolonization regimens with mupirocin in ICUs to limit transmission and infections caused by MRSA (as performed by Huang et al [35]), has yet to be determined. However, the dynamics of mupirocin resistance in the ICU setting do not differ substantially from those in surgical patients. Based on the observed low frequencies of within-host horizontal gene transfer of *mupA* from CoNS to *S. aureus* and the observation that dynamics hardly change with higher horizontal gene transfer rates, it is very likely that cross-transmission rates will also be the most relevant parameter in ICUs. Because of the higher frequency of healthcare worker patient contacts in ICUs, repeated introduction of mupirocin-resistant *S. aureus* may constitute a risk for the emergence of resistance through cross-transmission events. Therefore, an observed increase in the prevalence of such bacteria strongly suggests failing infection control procedures.

Alternatives for mupirocin nasal ointment include neomycin, fusidic acid, and chlorhexidine, but clinical trials comparing the effectiveness of these agents to mupirocin are lacking. Nasal povidone-iodine, however, was equally effective as mupirocin in preventing deep *S. aureus* SSI [36]. Newer therapies for decolonization include lysostaphin, ethanol, omiganan pentahydrochloride, tea tree oil, and specific bacteriophages, but, to our knowledge, none of these have yet been compared with mupirocin in clinical settings [37]. Even though the beneficial effects of eradicating *S. aureus* carriage before surgery are well established, survey results showed that only 37%–60% of hospitals in the United States have implemented decolonization strategies for *S. aureus* before surgical procedures and that current practices vary widely [38, 39]. Considering that universal screening for MRSA at hospital admission is already performed in many hospitals, it should be straightforward to also implement testing for MSSA carriage in patients scheduled for surgery. Universal perioperative decolonization without screening, however, is more feasible, more effective, and less costly. Considering the acceptable ecological risk profile for selection of mupirocin resistance in *S. aureus*, it should be a priority for hospitals to implement either of these strategies for surgical patients.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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