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## DOES THE NOSE KNOW? AN UPDATE ON MRSA DECOLONIZATION STRATEGIES

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### Abstract

Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) is an important step in the pathogenesis of active infection and is a key factor in the epidemiology of MRSA infection. Decolonization of patients found to have MRSA carriage may be of value in certain patient populations, especially those undergoing elective surgery. However, the most commonly used agent for decolonization, mupirocin, comes with a considerable risk of resistance if widely employed. Recent studies of other novel agents for decolonization show promise but further research is necessary. This review focuses on the pathogenesis from MRSA colonization to infection, identifies the risk factors for colonization, and summarizes decolonization strategies, including novel approaches that may have a role in decreasing MRSA disease burden.

### Keywords

MRSA; decolonization; mupirocin; infection control

## INTRODUCTION

Methicillin resistant *Staphylococcal aureus* (MRSA) infection continues to be a leading cause of morbidity and mortality among hospitalized patients, especially in those who are critically ill. In the most recent National Healthcare Safety Network (NHSN) report spanning the years 2009–2010, among eight pathogen groups that accounted for 80% of all

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### Compliance with Ethics Guidelines

### Conflict of Interest

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### Human and Animal Rights and Informed Consent

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healthcare-associated infections (HAI), MRSA was the most commonly isolated (18%), and was the number one pathogen causing Ventilator-associated pneumonias (VAP) and surgical site infections (SSI). MRSA has become endemic in health care institutions worldwide, with up to 70% of invasive *S. aureus* infections caused by resistant strains 1,2.

Most patients who develop MRSA infection will have been colonized prior to infection. Approximately 20% of the general population is persistently colonized with *S. aureus*, most frequently in the anterior nares, although other body sites may also be colonized. Another 30% of the general population is intermittently colonized, and the remaining 50% appear not to be susceptible to *S. aureus* carriage for unclear reasons 3. As a result of the association between colonization and subsequent infection, researchers have focused on decolonization strategies as eradication of carriage may decrease the possibility of infection while also disrupting transmission of disease to others. The purpose of this paper is to review the pathophysiology of MRSA colonization and infection, provide a summary of risk factors for colonization, discuss evidence-based approaches regarding decolonization, including recent and novel antimicrobial therapeutic options.

## PATHOPHYSIOLOGY: COLONIZATION TO INFECTION

*S. aureus* is both a commensal organism and a pathogen. Studies have shown that the anterior nares are the main reservoir for colonization 4. However, emerging data suggests that extranasal carriage is frequent, including the axillae, groin, pharynx and gastrointestinal tract. Among emergency department patients undergoing a comprehensive *S. aureus* screening (anterior nares, oropharynx, palms, groin, perirectal area, wounds, and catheter insertion sites), 17 and 45% of patients had exclusive extranasal colonization for MSSA and MRSA, respectively. MRSA detected in the oropharynx represented 67% of the exclusive extranasal colonization cases 5. A population based study with a *S. aureus* colonization prevalence of 30% also observed high rates of exclusive oropharyngeal colonization (30%) 6. A recent meta-analysis of *S. aureus* screening studies concluded that extranasal screening increased yields by approximately one-third over nasal screening alone 7. However, when the nares are treated topically to eliminate nasal carriage, in most cases the organism also disappears from these other areas of the body 8,9.

Over time, three patterns of carriage can be distinguished -- *persistent carriers* are individuals who almost always carry one type of strain. This occurs in 20% of the population. In contrast, a large proportion of the population (66%) harbors *S. aureus* intermittently, and the strains change with varying frequency. Such persons are referred to as *intermittent carriers*. Finally, the remaining minority (+/-20%) almost never carry *S. aureus* and are called *non-carriers* 4. Interestingly, persistent carriage is more common in children than in adults, and in many people the pattern of carriage changes between the age of 10 and 20 years 10. Persistent carriage seems to have a protective effect on the acquisition of other strains, at least during hospitalization 11.

Colonization of the nares provides a niche where *S. aureus* can conceal itself from host defenses. It can later lead to infection when host defenses are breached, whether through trauma, injury, insertion of a foreign device or catheter, or a surgical procedure. The basis

for colonization by *S. aureus* remains incompletely understood but Wertheim, et al, in their excellent review of nasal carriage 3, propose that colonization is “the net result of repellent and attracting forces” and there are several pre-requisites to becoming a nasal carrier. These four pre-requisites, and the factors leading to them are beyond the scope of this review, but are diagrammatically represented in Figure 1.

Colonization, whether present on admission or hospital acquired, has been proven to increase the risk for subsequent HAI 12–14. In a multicenter study by Von Eiff 15, for example, swabs for culture were obtained from the anterior nares of 219 patients with *S. aureus* bacteremia. A total of 723 isolates were collected and genotyped. Results subsequently showed that the blood isolates were identical to those from the anterior nares in 180 of 219 patients (82.2%). In a second study by the same authors, 1640 *S. aureus* isolates from nasal swabs of 1278 patients were collected over a five year period and then compared with isolates from the blood of patients who subsequently had *S. aureus* bacteremia. In this study, 12 of the 14 patients (86%) who subsequently developed bacteremia also had clonally identical isolates from nares and blood. This underscores the fact that individuals with *S. aureus* infections are generally infected with their colonizing strain 16. Huang and Platt 17 followed MRSA colonized patients after hospital discharge and 30% of patients developed infections due to MRSA over an 18 month period. This indicates MRSA colonization may be a long term risk factor for serious bacterial infections.

The recurrent nature of skin and soft tissue infections (SSTIs) due to community-acquired - MRSA and the well-documented outbreaks among individuals in close proximity (sports teams, military) 18, indicates that a similar relationship between colonization and infection likely exists for community acquired infections. However, there is a paucity of data regarding this relationship. Stevens et al. 19 reported higher rates of subsequent skin and soft tissue infections among MRSA colonized subjects but the magnitude of this difference decreased with time. Nasal MRSA colonization was only positive on admission in 67% of patients admitted with confirmed MRSA infections in a study by Robicsek et al 20. It is feasible that high rates of exclusive extranasal colonization explain the discordance. We are unaware of any studies that utilized a comprehensive MRSA screening protocol to characterize the relationship between active colonization and community-acquired infections.

Interestingly, colonization with resistant *S. aureus* as opposed to susceptible strains (MSSA) confers a higher risk of infection. In a meta-analysis by Safdar and Bradley 21, which included ten studies that assessed both MSSA and MRSA colonization and infection and encompassed 1170 colonized patients (791 colonized by MSSA and 379 by MRSA), the authors found that MRSA colonization conferred a four-fold increased risk of infection (OR 4.081 95% CI, 2.09–7.94) compared to MSSA colonization. The authors suggested that severity of illness may have been the most important factor leading to infection in colonized patients, and that severely ill patients are more likely to acquire MRSA than MSSA because of prolonged hospital stays, greater antimicrobial use, and more invasive procedures.

There is little uncertainty regarding the relationship between colonization and infection. Although not all infections are necessarily causally related with persistent MRSA carriage,

there is sufficient data to show that colonization by MRSA may act as a reservoir which can subsequently develop into an infection once immunity wanes or immune defenses are breached.

## RISK FACTORS FOR COLONIZATION

Given the increased infection risk with colonization, studies have attempted to identify risk factors associated with nasal carriage of MRSA. Harbarth, et al. 22 for example, examined risk factors for persistent MRSA carriage in 98 patients with MRSA colonization who were enrolled in a double-blind, placebo-controlled trial of nasal mupirocin. The probability of persistent MRSA colonization was almost 2 times greater among patients with >1 colonized body site and among patients who had recently received fluoroquinolones. Low-level mupirocin resistance tended to increase the risk of persistent MRSA carriage, whereas nasal mupirocin treatment tended to confer protection.

More recently, Forster et al 23 performed a systematic review in an attempt to identify patient-level risk factors predicting MRSA colonization upon hospital admission. This review included 27 studies, published between 1994–2011 and included a total of 68,877 participants with 2,928 cases of confirmed MRSA carriage at hospital admission. The authors found a total of 36 patient-level risk factors associated with MRSA carriage. Previous admission to hospital was the most commonly reported risk factor, examined by almost all (25/27) studies. In addition, presence of chronic wounds or skin lesions, patient transfer to hospital from nursing home or long-term care facility, and use of urinary or intravenous catheters were also often examined by the included studies. Unfortunately, there was significant heterogeneity among all studies, including extensive variation in definitions, precluding a meta-analysis.

## DOES DECOLONIZATION WORK?

Controversy exists in trying to determine which patient populations, if not all patients, should be screened, who would benefit from decolonization, with which agents, and for how long.

Screening for MRSA is currently not universally employed because of its associated costs, and conflicting evidence regarding its benefit (e.g. decreased infection rates, lower morbidity / mortality). A recent prospective, interventional study using a crossover design, for example, was conducted to compare the effect of rapid screening and standard infection control measures versus standard measures alone on the development of nosocomial MRSA infections 24. The study involved 10,193 patients, of whom 515 were MRSA positive, including 337 previously unknown carriers. Results showed, however, that there was no reduction in MRSA infection rates between the control and intervention periods.

Once MRSA is identified, whether by clinical cultures or systematic screening, the very pertinent question arises of whether these patients should be decolonized. Rijen et al 25, undertook a meta-analysis to determine whether the use of mupirocin nasal ointment preoperatively in patients with identified *S. aureus* nasal carriage reduced post-operative *S. aureus* infection rates. In this analysis, which included 4 randomized controlled studies 26–

29, a total of 1372 nasal carriers were analyzed, which were equally divided into mupirocin and control groups. Three of the four studies showed statistically significant reduction in nasal carriage 27–29. However, only the study by Perl 29 showed a significant effect of mupirocin on *S. aureus* infection rate. Analysis of these four studies together in a forest plot showed a significant effect of mupirocin on the *S. aureus* infection rate after surgery in carriers (RR 0.55, 95% CI 0.34–0.89). In surgical patients who were not carrying *S. aureus*, however, there was no effect of treatment, with a slightly higher infection rate noted in the treated group (RR 1.09, 95% CI 0.52–2.28). The authors then concluded that mupirocin appears to be cost-effective only in those patients that are proven nasal carriers, as a significant and strong reduction on *S. aureus* infection was found. Thus, in patients undergoing elective surgery, particularly procedures where implants may be anticipated, preoperative screening for *S. aureus* and mupirocin for those found to be colonized is recommended.

Decolonization as a strategy for MRSA prevention has also been used in long-term care facilities 30–32. In a study by Mody et al.<sup>33</sup>, 127 patients were randomized to either mupirocin or placebo twice a day for 14 days. Immediately at the end of treatment, at day 15, 51 (93%) of 55 study participants who were randomized to receive mupirocin were no longer colonized with *S. aureus*, compared with 7 (15%) of 47 in the placebo group ( $P = .001$ ). At day 90, there was an appreciable decrease in the mupirocin effect, with only 14 (61%) of 23 remaining free of *S. aureus*, consistent with other studies. Ten (10%) of 102 residents who finished the 14-day treatment course developed laboratory-confirmed or probable infection with *S. aureus*. Three (5%) of 55 residents treated with mupirocin and 7 (15%) of 47 who received placebo developed infection ( $P=.10$ ). The authors concluded that mupirocin was effective in decolonizing *S. aureus* in persistent carriers living in LTCF, and showed a trend towards reduction in infections; however the effect is often not sustained, probably because the factors promoting acquisition of MRSA in the first place are largely immutable (chronic illness, functional status decline)

Decolonization as a strategy to help decrease the risk of infection has also shown some merit among hemodialysis patients 34,35, and those admitted to the ICU. 36 Recently, universal decolonization with mupirocin and daily chlorhexidine bathing was studied in the REDUCE MRSA trial, a large cluster randomized trial in 42 ICUs and was found to be the most effective strategy for reducing MRSA infection rates, compared with active screening followed by contact precautions or screening and targeted decolonization with mupirocin and chlorhexidine bathing.<sup>37</sup> Unfortunately the independent effect of mupirocin could not be distinguished from the combined mupirocin/chlorhexidine effect. The results of this trial are expected to have major implications for clinical practice, not least of which is the effect that widespread mupirocin use may have on the development and spread of mupirocin resistant strains of MRSA.

## DECOLONIZATION STRATEGIES

Since colonization is often cited as the initial step in the pathogenesis of infection, studies have looked at the most effective approach to eradicate MRSA carriage. In the Netherlands,

for example, a guideline regarding decolonization was published in 2006, and a recent study validates its usefulness in guiding clinical practice 38.

Topical mupirocin is the most commonly favored method of MRSA eradication given its low cost, proven efficacy, and short-term application. However, there is growing evidence of increasing mupirocin resistance and treatment failure, especially in those individuals colonized with MRSA in multiple sites, which has prompted a renewed interest in evaluating alternative methods of decolonization. The use of mupirocin, as well as other topical (Table 1) and systemic agents (Table 2) for decolonization are listed and/or described below.

## A. Topical therapies

**1. Mupirocin**—Mupirocin (pseudomonic acid A) is a topical antibacterial agent, which inhibits bacterial protein and RNA synthesis. It has excellent *in vitro* activity against staphylococci and most streptococci, but has less activity against other Gram-positive and most Gram-negative bacteria. It is rapidly metabolized, which precludes systemic use. Side effects are minimal, and commonly limited to local site reactions 39. Three categories of mupirocin susceptibility have been described for *S. aureus* 40. These categories are mupirocin susceptibility with minimum inhibitory concentrations (MICs) < 4 mg/mL, low-level mupirocin resistance with MICs from 8 to 64 mg/mL, and high-level mupirocin resistance with MICs >512 mg/mL 41. Most isolates that demonstrate high-level mupirocin resistance have acquired plasmid-mediated *mupA*, which encodes a novel isoleucyl RNA synthetase 42,43. The association between low-level mupirocin resistance and the outcome of mupirocin decolonization is not clear although high level resistance is independently associated with decolonization failure 44,45.

Several randomized controlled trials have examined the use of mupirocin for decolonization of MRSA in the nares. In a recent systematic review by Ammerlaan et al 46, which included 23 trials, mupirocin 2% ointment applied 2 or 3 times daily for 4–7 days on both anterior nares showed excellent efficacy in eradication of Staphylococcal carriage, with a success rate of 90% 1 week after treatment. In this analyses 12 studies focused on the use of mupirocin as a single agent for decolonization but only 4 studies involved patients exclusively with MRSA 33,45,47,48. Of these, the effect of mupirocin vs. placebo at end of the follow up period could only be quantifiable in two. The overall risk reduction with use of mupirocin was 0.71 (CI 0.55–0.90). Overall, however, including studies of MSSA, the risk reduction was 0.44 (0.39–0.5) at end of follow up. The acquisition of mupirocin resistance was reported in only a handful of studies 33,44,45 and was found in 6 (1%) of 714 total subjects evaluated in 12 studies.

The risk of growing mupirocin resistance has precluded its routine use for decolonization of MRSA. In a recent study by Caffrey et al 49 including 40 mupirocin resistant cases and 270 matched controls, three independent risk factors for the emergence of mupirocin resistance were identified -- (1) exposure to mupirocin in the year prior to the culture date [odds ratio (OR): 9.84; 95% confidence interval (CI): 2.93–33.09]; (2) *Pseudomonas aeruginosa* infection in the year before the culture-related admission (4.85; 1.20–19.61); and (3) cefepime use in the year prior to culture (2.80; 1.03–7.58). The increasing prevalence of



mupirocin resistance has important implications, especially in institutions where decolonization is the standard of care, as increased use may reduce effectiveness. In these institutions, monitoring of emergence of resistance is essential

**2. Bacitracin**—Bacitracin is derived from cultures of *Bacillus subtilis* and is effective against gram-positive bacteria, including MRSA 50. However, data concerning the use of bacitracin ointment, usually in combination with polymixin B and neosporin (e.g. polysporin) as a decolonization strategy for MRSA has not been as encouraging as that of mupirocin.

In a recent double blind randomized controlled trial by O Grady, et al 51, 49 individuals were treated with polysporin twice daily for seven days, compared to 54 patients given mupirocin. All patients were also given daily chlorhexidine washes. In both study groups, at least 50% of patients were colonized in multiple sites (e.g. nasal and extranasal). At 48 hours, only 15/49 patients (30.6%) on the polysporin arm were MRSA negative at all sites, compared with 35/54 (64.8%) of those given mupirocin (RR 2.12; 95% CI 1.33 to 3.37; P=0.001). At 3 months, more patients on the mupirocin arm remained uncolonized and MRSA free (12/16 (75)) compared to the polysporin arm (1/3 (33.3)) although there was no significant statistical difference (RR 2.25; 95% CI 0.44 to 11.43; P=0.22). Given the poor outcome in the bacitracin arm, the authors concluded that topical bacitracin cannot be recommended as a decolonization strategy.

**3. Tea Tree Oil**—Tea tree oil is obtained from the leaves of the *Melaleuca alternifolia* plant and exhibits a broad-spectrum antimicrobial effect. Its adverse effects are largely unknown, but the use of tea tree oil has been reported to cause gynecomastia, probably because of estrogenic and antiandrogenic properties 50. Dryden et al. 47 studied the use of a tea tree oil based regimen compared with standard treatment consisting of mupirocin, chlorhexidine, and sulfadiazine cream. They found that 56/114 (49%) patients who received standard treatment were cleared of MRSA carriage. In comparison, 46/110 patients (41%) who received the tea tree oil regimen were likewise cleared. There was no significant difference between treatment regimens (Fisher's exact test; P = 0.0286). The authors surmised that tea tree preparations were effective, safe and well tolerated and could be considered in regimens for eradication of MRSA carriage.

A more recent study 52 investigated the efficacy of 5% tea tree oil body wash in preventing MRSA colonization in critically ill adults. The authors hypothesized that MRSA colonization would be reduced by daily application of 5% tea tree oil body wash compared to Johnson's Body Solution. Results of the study was not encouraging as colonization rates among the 445 patients randomized into the trial were equivalent, and they concluded that tea tree oil was a poor choice to prevent MRSA colonization. Data concerning the efficacy of tea tree oil remains scarce, and further randomized studies are necessary to determine its applicability as a decolonization strategy for MRSA carriage.

**4. Retapamulin**—Retapamulin is a member of a new class of antibiotics, the pleuromutilins, and was approved in 2007 by the FDA for treatment of impetigo. Retapamulin exhibits activity against various skin bacteria by interacting at the 50S subunit

of the bacterial ribosome 53. In a recent study by Candel et al 54, retapamulin inhibited all isolates of MSSA and MRSA at 0.125mg/L, demonstrating excellent *in vitro* activity against MSSA and MRSA strains. However, among strains carrying the *cfr* gene, which conferred linezolid resistance, retapamulin was ineffective, with MIC of >32mg/mL. In 2008, preliminary findings of a clinical trial evaluating the safety, tolerability, and efficacy of retapamulin application in the nares were reported at the International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 55. In this randomized, double-blind, placebo-controlled study in 43 patients, a 3- and 5-day application of retapamulin applied to the anterior nares led to eradication of *S. aureus* nasal carriage in 92–94% of patients with persistent colonization at 7 days and 75–86% of patients at 28 days. The complete results of this study are awaited.

**5. Chlorhexidine gluconate**—Chlorhexidine gluconate (CHG) is a topical antimicrobial agent with broad-spectrum activity, including against *S. aureus*. It has received considerable attention for its demonstrated superiority over povidone-iodine and residual antimicrobial effects 56,57. Significant reductions in central line associated bloodstream infections have been observed when CHG is used for procedural skin preparation 58. The ability of daily CHG bathing to reduce bacterial skin burden among ICU patients, thus reducing ICU-acquired infection, is the focus of some recently published studies.

In a crossover trial, Bleasdale et al 56 observed a 60% reduction (95% confidence interval, 1.2–11.0) in BSIs among ICU patients who underwent daily bathing with 2% CHG-impregnated washcloths versus soap and water. Interestingly, this result only became apparent after 5 days in the ICU and they only observed one MRSA BSI. This single center study was followed by two similarly designed multiple center trials which collectively enrolled over 12,000 subjects. In an adult ICU population, Climo et al 57 observed a 23% overall reduction in VRE/MRSA acquisition and 28% reduction in BSIs with 2% CHG bathing. However, when analyzed by individual organism, there were no significant reductions in MRSA acquisition or *S. aureus* BSIs. A similar trial among pediatric ICU patients demonstrated a 36% reduction in bacteremia with 2% CHG bathing, which failed to achieve significance in the intention to treat analysis. Again no difference was observed in the rate of *S. aureus* bacteremia 59. Regarding the safety of CHG, none of these studies observed serious skin reactions with the bathing protocol.

**6. Sodium hypochlorite (bleach)**—First reported in 1915 by Dakin, bleach has since been used extensively as a topical antimicrobial for the treatment of wounds and burn.<sup>60</sup> This property resulted in the inclusion of dilute bleach baths as part of *S. aureus* decolonization protocols. The most recent IDSA guidelines recommend nasal mupirocin and dilute bleach baths, made with one-fourth cup per one-fourth bathtub, for 15 minutes twice weekly for three months as treatment for patients with refractory MRSA SSTIs 61. *In vitro* research has shown 99% MRSA eradication with one-half cup per one-fourth tub at 5 minutes, suggesting an alternative, more convenient regimen 62. Results of a trial comparing various decolonization regimens showed the highest rates of successful *S. aureus* carriage eradication (71%) in patients treated with a combination of nasal mupirocin and daily bleach baths 63.



## B. Oral

Oral therapy, has been used to decolonize individuals who carry MRSA in multiple, or extra nasal sites. Antimicrobials from the different classes with anti-MRSA activity, including tetracyclines, folate inhibitors, quinolones, rifamycins, and macrolides have all been utilized as decolonizing agents, usually in combination with topical therapy. A summary of these oral agents are outlined in Table 2.

Among the 23 studies included in a systematic review by Ammerlaan, et al, 6 studies 9,30,45,64–66 utilized systemic antibiotics for decolonization of MRSA. Of these, only 2 45,64 compared these with no treatment. The study by Chang 64 was a small prospective randomized study, with only 16 patients. Of the 6 patients given oral fusidic acid thrice daily for seven days, only two were decolonized and MRSA carriage was recurrent in one of them. Furthermore, highly resistant strains were subsequently recovered in two cases who received fusidic acid, despite initial susceptibility upon enrollment. The study by Simor 45 evaluated use of oral rifampin and doxycycline in addition to topical therapy. Of 146 patients enrolled in the study, 87 patients treated with a regimen were followed up for at least 3 months. At 3 months follow-up, 64 (74%) of those treated had culture results negative for MRSA, compared with 8 (32%) of those not treated ( $P=.0001$ ). This difference remained significant at 8 months of follow-up, at which time 54% of those treated had culture results negative for MRSA. The overall treatment failure risk reduction for both studies discussed above was modest -- at one week it was 0.57 (95% CI 0.38–0.85) compared to 0.63 (95% CI 0.41–0.96) at the end of follow-up.

The use of oral antimicrobials for decolonization of MRSA carriage may be considered in certain populations (e.g. multiple sites of colonization) or under specific circumstances (e.g. prior to surgery) although the risk of resistance to oral therapy or systemic side effects must be carefully weighed.

## C. Investigational agents

There are several other agents on the horizon that are under investigation and have potential for use as future agents for MRSA decolonization. Most of these have been recently reviewed by McConeghy et al 50, and are summarized below.

**1. Lauric acid monoester (LAM)**—Lauric acid is a surfactant with activity against *Staphylococcus* species, including MRSA, but its mechanism of action is not understood. To date, no clinical trials have evaluated lauric acid monoester for the decolonization of MRSA. However, results from in vitro assays showed that three different LAM formulations have lower effective MIC<sub>90</sub> against MRSA and MSSA than mupirocin (1–4 µg/ml). The use of LAM with 0.5% benzoic acid was also found to be more effective at eliminating nasal MRSA carriage when compared with mupirocin 67.

**2. Lysostaphin**—Lysostaphin is a glycylglycine endopeptidase which cleaves the cross-linking pentaglycine bridges in the cell walls of staphylococci. In an animal model, a single application of 0.5% lysostaphin cream eradicated MSSA, MRSA, and mupirocin-resistant *S. aureus* from the nares of animals more effectively than did mupirocin 68. Lysostaphin has

also been found superior to mupirocin ( $-2.05 \pm 0.12 \log_{10}$  cfu/ml) and tea tree oil ( $-0.52 \pm 0.23 \log_{10}$  cfu/ml,  $p < 0.05$ ) in 24-hour time kill studies 69. These results need to be validated by clinical trials before lysostaphin can be used for MRSA decolonization.

**3. Omiganan Pentahydrochloride**—Omiganan pentahydrochloride is a novel topical cationic peptide active against a broad spectrum of bacteria and yeast. The agent causes membrane depolarization in susceptible bacteria, leading to cell death 70. A recent study 50 of its *in-vitro* activity against staphylococcal resistant strains, including vancomycin-intermediate and vancomycin resistant strains was encouraging, as omiganan demonstrated potent activity against *S. aureus*, regardless of the underlying resistance mechanism. The observation that omiganan remains equally active against all isolates of this species at a level significantly below the clinical formulation concentration (1% gel; 10,000 microg/ml) is promising, and merits study in clinical trials.

**4. Photodynamic Therapy**—Photodynamic therapy involves treating microbes with a light-activated chemical, termed a photosensitizer, which when exposed to a specific ultraviolet or infrared wavelength generates free radicals that are highly reactive and damaging to bacterial cell walls and membranes 71. An investigation of photodynamic therapy against staphylococci resistant strains was published a few years ago 72. In this study, a  $>3$ -log 10 kill was achieved against *S. aureus*, with little or no effect on human epithelial cells. Although promising, this area is still in its infancy and much more preclinical work is needed to establish safety and potential areas of application before undertaking clinical trials for efficacy.

**5. Probiotics**—Probiotics, usually lactobacillus species may reduce colonization by pathogenic organisms by increasing colonization resistance in the gastrointestinal tract. The effect of MRSA is unknown. In a recent study by Roos 73, 7 patients who were persistent carriers of MRSA (throat and nasal sites) were given oral and nasal probiotics, comprised of 4 lactobacilli strains with *in vitro* activity against MRSA. Among the 7 patients, 5 were reported to be free of MRSA after a follow up spanning 10–37 months. This is promising preliminary data and suggests that probiotics deserve further study as potential agents for MRSA decolonization, and the choice of strains, dose and duration of treatment must be evaluated carefully.

**6. Bacteriophages and other agents**—Bacteriophage-encoded bacterial cell wall-degrading enzymes exhibit intrinsic bactericidal activity. A recent study by Vipra 74 found that P128, a chimeric protein that combines the lethal activity of two enzymes is effective against *S. aureus* clinical strains including MRSA. In addition, in time-kill assays, P128 reduced colony-forming units by 99.99% within 1 h and inhibited growth up to 24 h. P128 hydrogel was also lethal to staphylococci recovered from nares of healthy people and treated without any processing or culturing steps, indicating its *in situ* efficacy.

Another promising agent is ClyS, an engineered staphylococcus-specific phage lysin. In a recent study 75 ClyS was formulated into an ointment and applied it to a mouse model of skin colonized / infected with *S. aureus*. Unlike the topical antibacterial agent mupirocin, ClyS eradicated a significantly greater number of methicillin-susceptible *S. aureus* (MSSA)

and -resistant *S. aureus* (MRSA) bacteria causing a 3-log reduction with ClyS as opposed to a 2-log reduction with mupirocin. The use of ClyS also demonstrated a decreased potential for the development of resistance by MRSA and MSSA organisms compared to that from the use of mupirocin *in vitro*. *This is a promising area for future investigation.*

## CONCLUSION

Managing colonization with MRSA continues to be a dilemma especially in healthcare institutions. Colonization associated with an increased risk of infection and thereby increased morbidity and mortality. There have been many attempts to eradicate carriage, mostly with topical agents, but success rates have not been consistent or applicable to all populations, possibly due to host factors and extranasal carriage. In the efforts to eliminate MRSA carriage, other concerns have emerged, including increased risks of systemic toxicity, adverse drug reactions, and drug resistance.

The use of topical mupirocin as a decolonizing agent has been proven to be effective in the short-term, and helps decrease infection risk in select populations. It is safe, well tolerated, and not systemically absorbed, which makes it an ideal agent for decolonization. However, resistance to mupirocin develops predictably and rapidly when mupirocin-based decolonization regimens are used routinely as a strategy to control endemic *S. aureus* infection and transmission among general inpatient populations. Thus, this remains an important area for research to identify and study alternative agents to mupirocin for reducing MRSA colonization.

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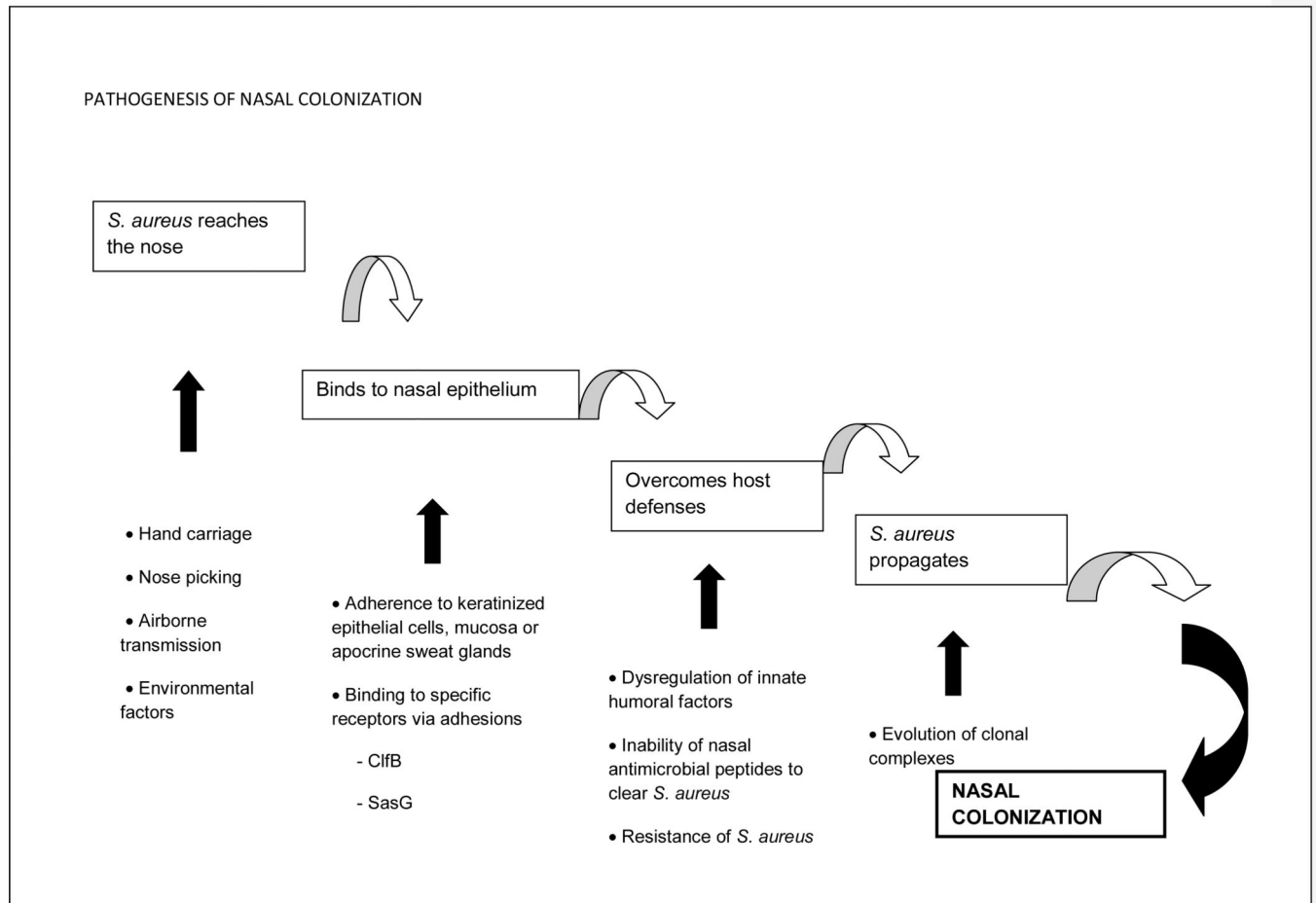
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**Figure 1.**

A schematic representation of the Pathogenesis of Nasal Colonization by *S. aureus* (Adapted from Wertheim et al )

**Table 1**

## A Summary of Topical Decolonization Strategies

TOPICAL AGENT	MECHANISM OF ACTION	ADVANTAGES	DISADVANTAGES
Mupirocin	Inhibits bacterial protein and RNA synthesis	Activity against MRSA Low cost Ease of use No systemic absorption	Local site reaction Increasing resistance
Bacitracin	Interferes with cell wall and phospholipids synthesis		Local site reaction Poor efficacy
Tea tree oil	Disrupts cell membrane		Gynecomastia
Retapamulin	Inhibits RNA synthesis of 50S ribosome	Activity against MRSA/ Ease of use No systemic absorption	Eczematous reaction Pruritus More Costly
Chlorhexidine gluconate	Disrupts cell membranes	Proven to reduce bacterial skin burden when given as baths	Hypersensitivity reaction Local site reaction
Sodium hypochlorite	Alters cellular metabolism and causes phospholipids destruction		

**Table 2**  
A Summary of Randomized Controlled Trials on Use of Oral Antimicrobials for MRSA Decolonization

AUTHOR, year	STUDY DESIGN	POPULATION	STUDY SIZE	ORAL ANTIMICROBIAL	COMPARATOR	OR (CI)
Peterson, 1990	SB-RCT	Hospitals	24	Rifampin + Ciprofloxacin	Rifampin + TMP/SFZ	0.57 (0.09–3.5)
Walsh, 1993	DB-RCT	Multi-center	94	Rifampin + Novobiocin	Rifampin + TMP/SFZ	1.76 (0.4–2.4)
Muder, 1994	RCT	LTCF	35	Minocycline alone Rifampin alone Minocycline and Rifampin	No treatment	3.6 (0.3–46) 14 (1.1–172) 6 (0.5 to 69)
Paras, 1995	O-RCT	University hospital	84	TMP/SFZ + Fusidic Acid	Mupirocin	0.69 (0.08 to 5.4)
Chang, 2000	O-RCT	ICU	16	Fusidic acid	No treatment	0.5 (0.06–4.1)
Simor, 2007	RCT	Acute care LTCF Rehabilitation hospital	146	Doxycycline and Rifampin	No treatment	5.91 (2.25–15)