Nasal Colonization with Methicillin-resistant *Staphylococcus aureus*: Clinical Implications and Treatment

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an increasingly important pathogen during the past 30 years, and infections due to MRSA are associated with substantial morbidity and mortality. Despite intensive infection control measures, the prevalence of MRSA has increased significantly, and the organism has become endemic in many hospitals worldwide. Asymptomatic nasal carriage of MRSA has been identified as a major risk factor for subsequent *S. aureus* infection in multiple settings and populations. As a result, considerable interest exists in developing decolonization strategies, with the ultimate goal of reducing the incidence of MRSA infection. Approaches to decolonization have included the use of systemic and inhalation antibiotics, antiseptic washes, and topical antimicrobials.

Introduction

Staphylococcus aureus is perhaps the greatest nosocomial pathogen of our time. As the primary agent responsible for bacteremia, wound infections, and nosocomial pneumonias, *S. aureus* is the leading cause of infectious complications within the hospital environment. The rise of *S. aureus* and specifically methicillin-resistant *S. aureus* (MRSA) as a significant nosocomial is attributed to its inherent virulence, resistance to multiple antibiotics, ease of spread within the hospital environment, and the prolonged nature of carriage among colonized patients [1]. A thorough understanding of the nature of *S. aureus* colonization, the risks of infectious complications following the development of colonization, and the effectiveness of available agents to eradicate colonization are an important foundation to establish approaches to reduce the incidence of MRSA within the hospital environment.

Epidemiology of MRSA Colonization

Colonization with *S. aureus* is a common event often beginning at the time of birth [2]. Detailed epidemiology of the extent of *S. aureus* colonization has emerged recently due to a number of large prospective surveys of nasal colonization among both outpatients and patients admitted to the hospital. In the largest population-based survey completed, Graham et al. [3] found that among 9622 National Health and Nutrition Examination Survey (NHANES) participants who underwent cultures of their nares, 31.6% were colonized with methicillin-susceptible *S. aureus* (MSSA), and 0.84% were colonized with MRSA. Generally between 30% and 50% of healthy adults have evidence of nasal colonization with MSSA, and up to 3% are colonized with MRSA [4]. Identified risk factors for colonization with MRSA have included advanced age, diabetes mellitus, admission to the hospital or long-term care facility in the past year, antibiotic exposure, and close contact with MRSA-colonized persons [1,3,4]. Transmission and acquisition of MRSA among military recruits, sports teams, day cares, and family members have demonstrated that MRSA is easily transmitted in situations associated with close contact. Family members of MRSA-colonized persons are 7.5 times more likely to acquire MRSA, and once colonized, they are often colonized for prolonged periods of time [5].

Although the nares are the major reservoir for *S. aureus* colonization in humans, several other body sites are often colonized including the throat, gastrointestinal tract, axilla, vagina, and perineum. The majority of patients are colonized with MRSA at more than two distinct sites. The sensitivity of nasal swabs for the detection of MRSA carriage ranges from 80% to 95% [6,7]. Due to the extent of extranasal MRSA colonization, inclusion of additional culture specimens to nasal culturing vastly improves the detection of MRSA. Nose, throat, and perineum swabs together increase the sensitivity to 98.3% with a negative predictive value of 99.8% [6]. In addition, cultures from infected wounds combined with those of

the nares also increase both the sensitivity and negative predictive value to 100% [7].

Even though culturing of multiple sites increases sensitivity, nasal culturing remains the standard screening technique, primarily because of the attendant costs of multiple-site culturing and the relatively high sensitivity of nasal culturing. Culturing multiple sites for evidence of extranasal colonization is often reserved to document the effectiveness of regimens aimed at eradicating MRSA colonization. The breadth of MRSA colonization also serves as a reminder that the most effective regimens used to eradicate MRSA colonization must target all areas of colonization beyond the nose.

Consequences of MRSA Colonization

The carriage of pathogenic organisms often precedes the development of serious infections for many opportunistic pathogens. This is especially true for *S. aureus* infections. Detailed epidemiologic data have now demonstrated that nasal colonization with MRSA is the single most important determinant of subsequent MRSA infection. Among patients with evidence of MRSA nasal colonization the risk of subsequent development of MRSA bacteremia ranges from 1.09% to 8.3% [8,9]. In the largest series to follow patients with *S. aureus* nasal colonization, von Eiff et al. [8] found that among 1278 patients, 14 (1.09%) subsequently developed *S. aureus* bacteremia. In addition, the authors demonstrated that 86% of subsequent bacteremic isolates were identical to isolates that colonized the nose, proving the endogenous origin of most infections. Nasal colonization with MRSA also increases the risk for the development of many infectious complications in hospitalized patients including surgical site infections, central venous catheter–associated bloodstream infections, dialysis catheter–associated infections, ventilator-associated pneumonias and urinary tract infections.

Unfortunately, the development of MRSA colonization among hospitalized patients is a grave prognostic risk factor. A high percentage of patients found to be colonized with MRSA subsequently develop MRSA infections with a high mortality rate. Huang and Platt [10] followed 209 newly identified MRSA-infected or colonized patients for up to 18 months following admission to intensive care units (ICUs). In all, 29% of newly identified patients developed MRSA infection within 18 months. Mortality was noted to be 25% among MRSA patients, with over half of the deaths during the initial hospitalization. MRSA infection is associated with excess mortality in numerous studies ranging between 22% and 35% [11,12].

Duration of MRSA Colonization

Unfortunately, most evidence would suggest that acquisition of MRSA is associated with a prolonged carriage state. Patients identified with MRSA during hospitalization demonstrate prolonged carriage after hospital discharge, with reported median durations of colonization of 8 to 40 months [7,13]. Colonization for individual patients may persist for years or decades. Patients with persistent carriage are most often colonized at multiple sites. Identified risk factors for persistent carriage include age, presence of skin lesions, and receipt of antibiotics [13,14]. The prolonged carriage state for patients after discharge greatly increases the chances that on subsequent hospital admission they will remain colonized with MRSA. Several studies have demonstrated that previously identified MRSA patients have persistent evidence of colonization on readmission 40% to 63% of the time [14,15].

The prolonged carriage state impacts care during hospitalizations as well. Among ICU patients, MRSA colonization is most often persistent and can be demonstrated throughout their ICU admission. Most patients (> 55%) have evidence of ongoing positive cultures for MRSA during their entire ICU stay [15]. The prolonged carriage state makes compliance with barrier precautions and proper hand hygiene the greatest concern among identified MRSA patients. Even small breaks in technique can increase the potential for nosocomial transmission of MRSA. A number of agents have been used in attempts to eradicate the prolonged staphylococcal carriage state including systemic antimicrobials, topical disinfectants, and topical antibiotics [16–36].

Eradication of MRSA Colonization

Systemic antimicrobials

Eradication of nasal MRSA carriage has been attempted with systemically administered antibiotics, used either alone or in combination with topical preparations. In his review of nasal decolonization strategies, Boyce [16] listed no fewer than 12 oral antibiotics that have been used for this purpose. The few available randomized controlled trials of oral agents have generally yielded disappointing results. Muder et al. [17] randomized MRSA-colonized residents of long-term care facilities to one of four treatment arms: rifampicin alone, minocycline alone, rifampicin and minocycline, and no treatment. They found no statistically significant differences in any of the arms. Two randomized controlled trials, one comparing ciprofloxacin and rifampin to trimethoprim-sulfamethoxazole (TMP/SMX) and rifampin and the other comparing novobiocin and rifampin to TMP/SMX and rifampin, demonstrated no significant differences in MRSA decolonization rates between treatment groups [18,19]. Notably, MRSA isolates from each of the above trials developed resistance to the intervention antibiotic, and both were terminated prematurely due to the development of resistance. Recent systematic reviews have concluded that there is insufficient evidence to support the sole use of oral antimicrobial therapy for the purposes of eradicating nasal or extranasal MRSA colonization [20].

Nebulized antibiotics

Eradication of *S. aureus* nasal colonization has been attempted using several nebulized solutions, including vancomycin, neomycin, kanamycin, bacitracin, chlorhexidine, and povidone-iodine [21]. Inhalation vancomycin is perhaps the best studied of these agents. Case reports and small, nonrandomized, prospective studies have suggested that aerosolized vancomycin can eliminate upper respiratory tract MRSA colonization [22]. The US Centers for Disease Control and Prevention has discouraged the use of vancomycin for this purpose, primarily due to concerns that inadvertently ingested drug could result in the selection of vancomycin-resistant enterococci [37].

Topical intranasal antimicrobials

Local therapy with intranasal topical antimicrobial preparations has emerged as the preferred strategy for elimination of the carrier state. More than 20 topical agents have been explored for *S. aureus* nasal decolonization [16], although relatively few of these antimicrobials have been studied in patients colonized solely with MRSA. A notable exception is mupirocin, which has emerged as the most effective topical therapy for MRSA nasal decolonization [16,24].

Bacitracin has been proposed as a decolonizing agent based on in vitro data demonstrating enhanced bactericidal effect against MRSA compared to mupirocin [23,24]. Evidence from clinical studies, however, has been less encouraging. In a retrospective review, Roccaforte et al. [23] used topical bacitracin along with systemic therapy to eliminate nasal colonization in 24 of 25 patients (96%) with MRSA. However, relapse rates were high, and the simultaneous use of potent oral therapy without appropriate controls prevented conclusions about the individual effectiveness of bacitracin. In a blinded, randomized controlled trial of 37 healthcare workers with *S. aureus* nasal carriage, bacitracin was found to be significantly less effective than mupirocin for decolonization at 72 to 96 hours (44% vs 94%) and at 30 days (23% vs 80%) [25].

Monotherapy with neomycin cream was demonstrated to effectively reduce *S. aureus* nasal carriage in the 1960s [26]. Due to the emergence of resistant strains, topical use of this agent has been largely abandoned. However, some authorities have suggested the use of neomycin-chlorhexidine cream for mupirocin-resistant MRSA isolates [24].

The efficacy of triple antibiotic ointment (gramicidin, polymyxin B, and bacitracin) for eradication of the MRSA carrier state was explored in an uncontrolled pilot study involving 11 medical patients, 10 (91%) of whom previously failed decolonization with mupirocin [26]. The majority of patients were colonized at multiple sites. Nine patients (82%) were successfully decolonized, including three of five patients with high-level mupirocin resistance, based on a mean follow-up period of 2.1 months. Four patients in the series received concurrent systemic antibiotics during decolonization, potentially confounding results. A different formulation of triple antibiotic ointment (neomycin, polymyxin B, and bacitracin) recently demonstrated 98% in vitro efficacy against MRSA isolates, though the clinical significance of this finding has not been confirmed [27].

Fusidic acid, derived from the fungus *Fusidium coccineum*, has excellent antistaphylococcal activity, including against MRSA. Topical and oral preparations are available, and both have been widely used throughout Europe and Australia to treat infections due to *S. aureus*. The drug is currently unavailable in the United States. Regardless, the evidence to support use of fusidic acid for nasal decolonization is limited. In a small, prospective, randomized trial, intranasal fusidic acid was equivalent to no antistaphylococcal therapy for nasal *S. aureus* eradication in peritoneal dialysis patients [28].

During a Swedish epidemic from 1969 to 1971, Ericson and Larsson [29] identified 40 patients colonized with MRSA, six (15%) of whom were treated with fusidic acid nasal cream and hexachlorophene 5% detergent. Decolonization was only successful in half these patients. Lastly, an open, randomized, controlled trial involving 84 stable MRSA nasal carriers compared topical fusidic acid plus TMP/SMX to topical mupirocin for decolonization. No statistically significant differences were observed between the two groups at 2, 7, 28, or 90 days [30]. Clinically significant rates of fusidic acid resistance have emerged in recent years, largely due to the inappropriate use of topical fusidic acid as monotherapy for chronic dermatologic conditions.

In vitro studies have demonstrated the effectiveness of povidone-iodine cream and solution against MRSA. Additionally, small, nonrandomized clinical trials have reported some success in decolonizing nasal MRSA carriers [31]. Masano et al. [31] decreased MRSA carriage in a cohort of neonatal ICU nurses and physicians from 13.3% to 0% by applying intranasal povidone-iodine. The significance of these results is unclear, however, because the study lacked a suitable control group and adequate follow-up.

Mupirocin

Mupirocin, an antibiotic produced by fermentation of *Pseudomonas fluorescens*, has a unique chemical structure and acts by reversible inhibition of bacterial isoleucyl transfer ribonucleic acid synthetase. The agent demonstrates excellent in-vitro activity against a broad range of gram-positive bacteria, including MSSA and MRSA. Since its introduction, mupirocin has emerged as the agent of choice for eradication of nasal carriage of *S. aureus*.

The first randomized, controlled trial to examine the effectiveness of intranasal mupirocin in eliminating nasal *S. aureus* carriage was conducted by Casewell and Hill [32]. Mupirocin 2% ointment eliminated staphylococcal carriage in 32 healthy volunteers within 48 hours, whereas placebo failed to eradicate nasal carriage in any subject. Despite the early success of mupirocin, long-term eradication of

S. aureus carriage was not seen in a majority of the treated subjects. Nasal cultures obtained at 14, 35, and 98 days post-treatment demonstrated recolonization in 0%, 19%, and 43% of patients, respectively.

In an open, noncomparative clinical study conducted at 102 hospitals in the United Kingdom and Ireland, mupirocin was administered to 1510 patients and staff with documented nasal carriage of *S. aureus* [33]. Concurrent extranasal colonization or staphylococcal infection was present in nearly 40% of the study population. Complete microbiologic data was available for 766 subjects, of whom 628 (82%) harbored MRSA. Eradication of MRSA was achieved in 609 of these 628 subjects (97%) after 4 to 8 days of treatment. Among those with nasal MRSA carriage but no extranasal site of colonization or infection, the eradication rate was 97.8%. Mupirocin therapy was generally well tolerated with an adverse event rate of 1.5%; mild, local reactions were the most commonly reported reaction.

Unfortunately, the increased use of mupirocin has been associated with increasing reports of mupirocin resistance. General surveys of mupirocin resistance among staphylococcal isolates have indicated that resistance rates range between 1.9% and 5.6% [34]. Geographic variation in resistance rates vary widely, though, with reported rates of mupirocin resistance as high as 28% in New Zealand; highlighting the need for continuous monitoring of regional susceptibility rates [35]. Fortunately, some recent studies have indicated that judicious, targeted use of mupirocin for limited indications such as perioperative prophylaxis can be associated with persistently low rates of mupirocin resistance [36].

In summary, a wide variety of studies conducted in varied populations have demonstrated that mupirocin applied to the anterior nares for 2 to 14 days is highly effective compared to placebo for short-term MRSA decolonization. Sustained decolonization has generally not been observed beyond 90 days. Most long-term follow-up studies have been conducted in MSSA nasal carriers, in whom recolonization rates at 12 months post-therapy approach 50% for healthcare workers and 75% for peritoneal dialysis patients.

Novel Agents for Nasal Decolonization

Tea tree oil (TTO), derived from the Australian native plant *Melaleuca alternifolia*, has recently received attention as a potential alternative to more conventional topical agents. The oil is a complex mixture of substances, but the main active ingredient is terpinen-4-ol, which has antimicrobial activity against MRSA. Only two randomized controlled trials of TTO for MRSA decolonization have been conducted. Both trials included the use of topical skin disinfectants and demonstrated efficacies similar to mupirocin-based regimens [38,39]. The safety profile of TTO has not been fully determined, although irritant and hypersensitivity reactions have been described.

Lysostaphin, a 27 kD endopeptidase produced by *Staphylococcus simulans*, has potent antistaphylococcal activity, and clinical studies conducted during the 1960s and 1970s confirmed that topical lysostaphin was effective in eradicating nasal *S. aureus* carriage [40]. Although a clinical trial specifically designed to evaluate the efficacy of lysostaphin in MRSA decolonization has not been conducted, a resurgence of interest in this agent has occurred given the rising incidence of resistance to conventional antibiotics.

Another nontraditional strategy for MRSA nasal eradication is the use of fatty acid formulations, which have long been recognized to have antimicrobial properties. Recently, lauric acid monoesters have been tested against several MRSA isolates in vitro and in vivo using a murine model with promising results.

Combined Approaches to Decolonization

Although mupirocin has been demonstrated to be an effective short-term agent to eradicate nasal carriage of MRSA, attempts to provide longer term eradication of MRSA have often relied on using a combination of topical skin disinfectants, nasal application of mupirocin, and systemic antibiotics. The addition of simple chlorhexidine bathing to nasal mupirocin improves the chances of eradicating long-term nasal carriage of MRSA [41]. Long-term success (> 3 months) of the use of just nasal mupirocin in the eradication of MRSA from all sites is generally low (25%–61%) in published reports. However, the addition of chlorhexidine bathing to nasal mupirocin increases long-term clearance rates of MRSA from all sites [42].

More aggressive decolonization regimens have included the addition of systemic antibiotics. In a recent placebo-controlled trial, the use of chlorhexidine bathing, nasal mupirocin, and oral doxycycline and rifampin eradicated carriage of MRSA in 74% of patients treated compared to 32% of patients who received placebo [43••]. Rates of mupirocin resistance following treatment were low (< 5%), and 54% of treated patients remained culture-negative for MRSA after 8 months. Parras et al. [44] examined the use of cotrimoxazole, topical fusidic acid, and chlorhexidine bathing, and they demonstrated an eradication rate of 69% at 3 months [44]. The addition of systemic antibiotics (cotrimoxazole) increased the long-term eradication rate compared to nasal mupirocin and chlorhexidine baths, which only had a 45% eradication rate at 3 months.

One of the most aggressive decontamination regimens reported to date involved the use of intravenous linezolid, rifampin, endotracheal vancomycin, oral and topical chlorhexidine solution, intranasal mupirocin, and povidone-iodine spray for wound care for the treatment of intubated patients diagnosed with MRSA pneumonia [45]. The authors reported clinical cures of MRSA pneumonia and elimination of MRSA colonization in all treated patients. Although the results of this uncontrolled obser-

vational study cannot be recommended for wide-scale use, the study is provocative for two main reasons. First, it emphasizes the broad range of agents potentially available to treat MRSA colonization, and second, it highlights the growing trend to treat MRSA colonization with a combination of agents.

Reductions in MRSA Infections Following Decolonization

Given the established risk factors for MRSA infections following the detection of MRSA colonization, it is no surprise that attempts to eradicate MRSA colonization as a strategy to prevent infections would emerge. Eradication of MRSA carriage as a strategy to prevent subsequent MRSA infections has been most studied in three populations: dialysis patients, surgical patients, and ICU patients.

One of the first wide-scale uses of mupirocin was in the prevention of continuous peritoneal catheter-associated infections and hemodialysis catheter infections. Mupirocin applied at the exit site of these two catheter types is an effective means to prevent subsequent MRSA line-associated infections, with reported reductions of up to 85% [46]. In addition, eradication of nasal carriage with mupirocin is also associated with a reduction in catheter-associated infections and exit-site infections in several trials. Additional agents with activity against *S. aureus* (eg, gentamicin cream, povidone-iodine, and chlorhexidine) have been shown to reduce the risk of exit-site infections. Proper exit-site care with an antiseptic or antibiotic cream and eradication of nasal MRSA colonization are now standard practices in many dialysis centers.

Surgical patients colonized with *S. aureus* are two to nine times as likely to develop surgical site infections compared to noncarriers. Several trials using historical controls have reported lower rates of *S. aureus* surgical-site infection among patients undergoing mupirocin nasal decolonization. The Mupirocin and the Risk of *Staphylococcus aureus* Study (MARS) was the largest trial evaluating the potential benefit of eradicating *S. aureus* nasal colonization in the perioperative period in order to prevent surgical site and nosocomial infections [47]. The study evaluated 4030 patients undergoing general, gynecologic, neurologic, or cardiothoracic surgery and randomized them to receive either intranasal mupirocin or placebo at the time of their surgery. Overall, 22% of patients were colonized with *S. aureus*, and those who received intranasal mupirocin had a 48% reduction in the rate of nosocomial *S. aureus* infections. Since then, several smaller randomized and observational studies have been completed and show an overall reduction in the rate of *S. aureus* surgical-site infections and nosocomial infections with the routine use of mupirocin in the perioperative period for orthopedic, cardiothoracic, and general surgery patients.

The use of mupirocin to prevent nosocomial *S. aureus* infections in nonsurgical patients has also been studied. Dupeyron et al. [48] conducted an unblinded, prospective intervention among 2242 patients (89% nonsurgical) admitted to a gastroenterology unit. Nasal MRSA carriers were identified by active surveillance and decolonized with mupirocin (> 96% efficacy), resulting in a significant reduction in the incidence of MRSA infection (1.41 infections/1000 hospital days preintervention vs 0.59/1000 hospital days postintervention; $P = 0.022$) [48]. A similar strategy decreased the mean number of MRSA bacteremia cases from 3.6 per month to 1.8 per month ($P < 0.001$) in a 700-bed community hospital [49•].

ICU patients have the highest reported prevalence rates of MRSA colonization and subsequently are at the highest risk for MRSA-associated infections. Although early identification of colonized patients and prompt institution of barrier precautions is becoming a standard practice among many ICUs, several trials have now emerged evaluating the potential added benefit of eradicating MRSA colonization. In a retrospective study involving 98 medical ICU patients with MRSA nasal carriage, decolonization with mupirocin alone resulted in a significant reduction in the number of endogenously acquired MRSA infections compared to historical controls ($P = 0.006$) [50]. Girou et al. [51] studied the use of chlorhexidine bathing and intranasal mupirocin among ICU patients identified with MRSA and found that after the introduction of this practice, the incidence of all ICU-acquired MRSA cases and of acquired colonization or infection decreased from 5.8% and 5.6% to 2.6% and 1.4% ($P = .002$ and $P < .001$), respectively.

Bathing ICU patients with chlorhexidine has also been used in conjunction with nasal application of mupirocin in the control of MRSA outbreaks in ICUs with great success [52]. Bathing with chlorhexidine is an essential component of many eradication regimens used for long-term control of MRSA-acquired infections in ICUs. Sandri et al. [53•] identified 364 nasal MRSA carriers among 2200 ICU patients and successfully decolonized 72.3% of these patients using intranasal mupirocin and chlorhexidine baths. During the 5-year study period, the cumulative incidence of nosocomial MRSA infections in the ICU decreased from 8.2% to 2.8% ($P = 0.001$). Larger clinical trials of routine bathing with chlorhexidine among ICU patients are currently underway and hopefully will more clearly delineate the potential for reducing MRSA acquisition and infection with this relatively simple procedure.

Conclusions

The prolonged carriage state seen among patients with MRSA has made eradication of colonization particularly difficult. The effectiveness of mupirocin in eradicating nasal colonization is often short lived and has spurred interest in more comprehensive regimens that aim to eradicate all

sites of staphylococcal carriage. Newer strategies are clearly needed. Additional novel agents that show in vitro activity against MRSA strains including probiotics, natural compounds like TTO, and lauric acid monoesters have recently begun evaluation for potential use. The use of combinations of antibiotics with activity against MRSA has also been investigated in vitro and shows some promise, as does the recent introduction of newer antimicrobials with potent MRSA activity including daptomycin. Initial success has been noted with several regimens that combine the use of mupirocin with topical skin disinfectants (chlorhexidine) and the possible addition of systemic antibiotics.

Long-term success with these regimens is still unrealized in many cases, which emphasizes the diligence that is required when attempting decolonization of patients and healthcare workers. Several studies among adult healthcare workers have demonstrated that up to three decolonization attempts are needed before full eradication of MRSA colonization can occur. Unfortunately, an ideal regimen for use in patients and healthcare workers cannot be recommended and must be crafted with attention to local resistance patterns, the targeted patient population, and the intended effect. Additional trials of potential eradication regimens are needed and will most likely include a combination of approaches.

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