Nasal Carriage of *Staphylococcus aureus* and Prevention of Nosocomial Infections

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Abstract

This review summarizes the clinically relevant aspects of nasal carriage of *Staphylococcus aureus*. The epidemiology, associated risk, and the effects of eradication are discussed. The main conclusions are that nasal carriage of *S. aureus* is a well-defined risk factor for subsequent infection in nearly all categories of hospitalized patients that have been studied. However, studies that have been performed to evaluate the effect of eradication of carriage using mupirocin nasal ointment have been inconclusive so far in most subgroups. Only in patients on hemodialysis or chronic ambulatory peritoneal dialysis (CAPD) was a significant reduction of the infection rate found. But prolonged treatment in these groups carries a risk for the development of resistance. In surgical patients two randomized studies have found an effect on the surgical site infection rate in carriers that, when those studies are combined, was close to being statistically significant ($p = 0.06$). In non-surgical patients a significant delay in the onset of infection was found but the overall infection rate was not significantly different. When the results of all well-designed studies that have been performed are combined, a significant reduction of the nosocomial *S. aureus* infections in carriers is found (approximately 50% lower). Future studies should focus on treating carriers only and consider other treatment regimens.

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Introduction

Staphylococcus aureus continues to be one of the most important pathogens for mankind. Findings from a large population survey in Canada [1] show that invasive infections occur annually in approximately 30 people per 100,000 of the population. They arise for more or less half in the community and for an equal percentage in the hospital. The mortality associated with an invasive infection is 19%, resulting in an annual mortality rate of 5/100,000 people [1]. Historically, *S. aureus* is regarded as a true nosocomial pathogen because of its high incidence in nosocomial infections and because of its tendency to spread from patient to patient. In fact, modern infection control finds its roots in the pandemic of multiresistant *S. aureus* in the hospitals during the 1950s. Numerous studies were performed in those years, which provided insight into the reservoirs and routes of transmission of *S. aureus* within the hospital. Subsequently, preventive measures were developed to decrease the risk of cross-infection [2]. Nowadays, cross-infection can be largely prevented if the existing knowledge is implemented in the hospital setting. However, *S. aureus* continues to be one of the most important nosocomial pathogens. In part, this is because the measures to prevent cross-infections are often not implemented. But even if cross-infection is prevented, many patients are still infected by *S. aureus*. In such settings, typing studies have shown that most strains causing infections are unique [3–5]. The major source for these infections is the patient's own flora.

Epidemiology of *S. aureus* Nasal Carriage

S. aureus colonizes the skin and mucosal surfaces of humans and also of several animal species. Studies have shown that the anterior nares are the most consistent site from which this organism can be cultured [6]. In longitudinal studies, three types of *S. aureus* nasal carriers, can be distinguished: persistent carriers, intermittent carriers and noncarriers. Between 10 and 35% of healthy individuals almost always carry one strain and are called persistent carriers. A larger proportion (20 to 75%) of individuals harbor *S. aureus* intermittently, and are called intermittent carriers. Finally, between 5 and 50% almost never carry *S. aureus* and are called noncarriers [6] .

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Genotyping data reveal that persistent carriers usually carry only one identical *S. aureus* strain over time and that intermittent carriers commonly carry different strains over time [7]. The load of *S. aureus* is higher in persistent carriers compared to intermittent carriers, resulting in more dispersal and higher risk of infection [2]. Persistent carriage is more common in children than in adults and many people shift from persistent carriage to intermittent or noncarriage between the age of 10 and 20 years [8]. The reasons for these differences in colonization patterns are still unknown.

Cross-sectional studies yield a prevalence of approximately 35% in the general population, which is actually a mix of persistent and intermittent carriers at that time point [9, 10]. Subgroups of patients with significantly increased carriage rates include those with insulin-dependent diabetes mellitus, on hemodialysis or chronic ambulatory peritoneal dialysis (CAPD), intravenous drug use, S. *aureus* skin infections, liver dysfunction, and HIV [9,10]. The reasons for the higher carriage rates remain to be elucidated.

Clinical Impact of *S. aureus* Nasal Carriage

Carriage of *S. aureus* has been identified as a risk factor for the development of infections in various settings. This has been studied extensively in surgical patients (general, orthopedic, and thoracic surgery), in patients on hemodialysis, in patients on CAPD, HIV-infected patients, and in patients in intensive care units. Von *Eiff* et al. [3] elegantly illustrated in a prospective study that nasal strains and subsequent bacteremic strains have the same genotype in more than 80% of the cases. *Wertheim* et al. [4] studied the incidence of bacteremia in carriers as well as non-carriers in a nonsurgical patient population (n = 14,008). This study found a significantly increased risk for *S. aureus* nasal carriers to acquire a nosocomial *S. aureus* bacteremia, compared to noncarriers, relative risk of 3.0. (95% CI: 2.0–4.7) [14]. The bacteremic strain of the carriers had the same genotype as the nasal strain in again approximately 80% of the cases. On the other hand, *S. aureus*-related death was four times more likely in noncarriers who developed an infection [14].

In hemodialysis patients, *S. aureus* is the most frequently found pathogen in infections at the vascular access site and in bacteremia [11]. The infection rate is higher in carriers on hemodialysis, with relative risks varying from 1.8 to 4.7. *S. aureus* isolates are usually identical to the one previously isolated from the patient's nares. In patients treated with CAPD, *S. aureus* is the leading cause of exit site and tunnel infection, often leading to catheter loss. The observed relative risks for carriage are even higher than those in hemodialysis patients (range: 1.8 to 14.0) [9]. Also in CAPD patients, the nasal strain and the infectious strain are clonally related in most cases.

In HIV-positive patients, increased rates of *S. aureus* bacteremia and deep soft tissue infections have been observed, which frequently recur. Even higher rates are found in patients with AIDS compared with HIV-positive, asymptomatic patients. *Nguyen* et al. [12] found that nasal carriage is an important risk factor in this patient population (OR 5.1). It should be noted that nasal carriage was more common in patients who were not receiving trimethoprim-sulfamethoxazole prophylaxis.

After coagulase-negative staphylococci, *S. aureus* is the second most prevalent organism causing intravascular device-associated bacteremia [13]. However, few studies have been performed with the primary aim of establishing the role of *S. aureus* nasal carriage in this setting. *Pujol* et al. [15] looked at bacteremia in an intensive care unit. Most of the *S. aureus* bacteremias had an intravascular device as a source. In this study carriers of *S. aureus* had a relative risk of 12.4 for the development of *S. aureus* bacteremia [7].

Carriage of methicillin-resistant S. *aureus* (MRSA) constitutes a special problem with regard to prevention and treatment of infection. Studies show that nasal MRSA carriers have a higher risk of nosocomial infection with this microorganism, and more morbidity and mortality compared to carriers of susceptible strains [15, 16].

Prevention by Eradicating Nasal Carriage

To prevent *S. aureus* infection, elimination of *S. aureus* nasal carriage seems to be the most straightforward strategy. The introduction of mupirocin ointment in the late 1980s led to several intervention studies. One study compared cardiothoracic surgery patients who received mupirocin prophylaxis (n = 868) with a historical control group (n = 928) [17]. The surgical wound infection rate in the control group was 7.3% and was 60% lower (2.8%) in the treated group ($p < 0.001$).

Recently, two randomized controlled trials have been published, studying the efficacy of mupirocin in a general surgical and an orthopedic patient population [5, 18]. *Perl* [18] et al. included 3,864 patients in their study, both carriers and noncarriers, who were randomized to either mupirocin or placebo [18]. Overall, 2.3% of mupirocin recipients and 2.4% of placebo recipients had *S. aureus* infections at the surgical site. Nasal carriage of *S. aureus* was eliminated in 83.4% of patients who received mupirocin, versus 27.4% of those who received placebo. Among the *S. aureus* nasal carriers (n = 891), 4.0% of those who received mupirocin had overall nosocomial *S. aureus* infections, as compared with 7.7% of those who received placebo (OR for infection, 0.49 (0.25-0.92). *Kalmeijer* et al. [5] also included carriers and noncarriers, before an orthopedic surgical intervention. A total of 614 patients was randomized to receive mupirocin or placebo, respectively. The preoperative nasal carriage rate was approximately 30%. Eradication of nasal carriage was significantly more effective in the mupirocin group (eradication rate, 83.5% versus 27.8%). In this study, mupirocin nasal ointment did not reduce the *S. aureus* surgical site infection rate significantly (3.8% in the mupirocin group and 4.7% in the placebo group) nor the duration of hospital stay. In the mupirocin group, the

rate of endogenous *S. aureus* infections (i.e. the strain that causes the infection has the same genotype as the strain previously cultured from the nose) was five times lower than in the placebo group (not significant). Although both randomized clinical trials (RCTs) showed an effect of mupirocin it was not as strong as anticipated and the primary outcome variable was not statistically significant. When the results of these two studies are combined there is a nearly significant reduction of *S. aureus* surgical site infection rate in carriers (p = 0.06, pooled OR = 0.58, 95% CI: 0.33–1.02). However, if the outcome is expanded to all nosocomial infections caused by *S. aureus* in carriers, there is a significant reduction. In the carriers that received mupirocin 19 out of 525 developed a nosocomial *S. aureus* infection as compared to 39 out of 525 in the placebo groups (RR 0.49, 95% CI 0.29-0.83, p = 0.01). The number needed to treat to prevent one nosocomial S. *aureus* infection in surgery would be 26. Therefore, future studies should focus on inclusion of carriers only. A rapid diagnostic test to detect nasal carriage would be an important tool for this strategy.

Wertheim et al. performed a randomized placebo controlled study in a nonsurgical patient population of *S. aureus* carriers [4]. More than 17,500 patients were screened on admission and carriers were either assigned to a short course of mupirocin (n = 793) or placebo (n = 809) after a nasal culture grew *S. aureus*. No significant differences were observed in the rates of nosocomial *S. aureus* infections, in-hospital mortality, or in duration of hospitalization, between the mupirocin and the placebo group. Survival analysis showed that mupirocin prophylaxis significantly delayed the time to the occurrence of nosocomial *S. aureus* infection, from 13 to 32 days (p = 0.02) in the per-protocol group. This may indicate that one course of mupirocin at admittance may be insufficient in patients with prolonged exposure. In addition, it has to be questioned if topical treatment of the nose is sufficient to achieve the desired effect. Finally, it has to be noted that in this low-risk population the effect was less pronounced than anticipated when the trial started.

Several oral and topical antibiotics have been studied for eradication of *S. aureus* nasal carriage in hemodialysis patients and are summarized by *Chow* and *Yu* [19]. Rifampicin in conjunction with nasal bacitracin can result in a significant reduction of the *S. aureus* infection rate in hemodialysis patients. Emergence of rifampicin-resistant strains has been observed. Short course therapies and combination therapies may prevent the emergence of resistant isolates.

Mupirocin has also been evaluated extensively in hemodialysis patients [20]. In a randomized, double-blind placebo controlled trial, stable nasal carriers were treated with mupirocin for 2 weeks three times daily, and then thrice weekly for a total of 9 months [13]. A significant reduction in the *S. aureus* infection rate (1/104 patient-months among treated and 6/147 patient-months among untreated) was observed. The administration of mupirocin to nasal carriers was later adjusted to an initial course of 5 days, three times per day, and thereafter once a week during the remaining period on hemodialysis. Using this schedule a highly effective elimination of carriage was achieved and this was accompanied by a four- to sixfold reduction in the *S. aureus* bacteremia rate.

The effect of decolonizing the nares from *S. aureus* has also been studied in peritoneal dialysis patients. The effects of intermittent administration of rifampicin in patients on CAPD was studied in a randomized controlled trial [21]. No significant difference in the *S. aureus* peritonitis rates was found. Until now, two reports have been published studying the effects of mupirocin on the infection rate in CAPD patients. A case-control study in a CAPD patient population found that the *S. aureus* peritonitis rate was significantly reduced in *S. aureus* nasal carriers who were given mupirocin [22]. There was a significantly lower catheter loss due to exit-site infections in the treated group. The overall peritonitis rate was not reduced, mainly due to a significantly higher rate of peritonitis caused by gram-negative bacteria in the treated group compared to the not-treated group. Recolonization occurred frequently, especially after 3 months. Also a randomized controlled study was performed in this patient population. Nasal carriers were treated with mupirocin or placebo ointment twice daily for 5 days and this was repeated every 4 weeks. In 1,144 patients screened, 267 carriers were identified (23.3%). The *S. aureus* exit-site infection rate was significantly lower in the treated group (one in 99.3 patient-months versus one in 28.1 patient-months, p = 0.006). There was no significant increase in gram-negative infections and development of resistance to mupirocin was not observed. The possibility of development of resistance should be accounted for when using mupirocin for prolonged periods, such as in CAPD patients. It can be concluded that elimination of *S. aureus* nasal carriage in patients on CAPD decreases the exit-site infection rate. The effect on the peritonitis rates remains unclear.

Cost-Effectiveness of Prophylaxis

Cost-effectiveness studies have been performed for mupirocin prophylaxis in hemodialysis patients, peritoneal dialysis patients, and thoracic surgery patients [23–25]. *Bloom* et al. [24] evaluated three management strategies: (1) all patients are screened by a nasal culture every 3 months and those carrying *S. aureus* are treated with mupirocin, twice daily for 5 consecutive days, (2) all patients are treated, irrespective of their carrier state, with mupirocin weekly for 3 days, twice daily, or (3) no preventive measures are taken, only infections are treated. It was assumed that 75% of *S. aureus* infections are attributable to nasal carriage in hemodialysis patients and eliminating nasal carriage of *S. aureus* reduces the number of infections by 45% to 55%. The annual savings of the first strategy were USD 784,000 per thousand dialysis patients and of the second strategy the savings were USD 1,117,000 per thousand dialysis pa-

tients. Both strategies prevented death and improved the quality of life. Since the risk of development of resistance with widespread use of mupirocin is increased, the first strategy would be preferred.

Davey et al. also performed a cost-effectiveness study in peritoneal dialysis patients, on the basis of a randomized, placebo-controlled trial, described earlier [25, 26]. Patients in the mupirocin group had lower antibiotic and hospitalization costs. However, overall antibiotic costs, including mupirocin, were significantly higher in the mupirocin group. Mupirocin prophylaxis would have been cost neutral if the exit-site infection rate in the placebo group increased to 75%, or if the costs of screening was reduced from GBP 15 to GBP 3, or if the costs of mupirocin treatment was reduced from GBP 93 to GBP 40 per patient-year. This study did not take the patient's quality of life and the long-term effects of *S. aureus* infection into consideration. One may conclude that short-term savings of mupirocin prophylaxis in dialysis patients in healthcare costs are unlikely to be sufficiently great to offset the cost of mupirocin.

Vandenbergh et al. [23] assessed the cost-effectiveness of perioperative intranasal application of mupirocin calcium ointment in cardiothoracic surgery, based on results of an intervention study with historical controls. Postoperative costs were increased significantly in patients with a surgical-site infection, in comparison with uninfected patients. The mean attributable costs of these surgical site infections were estimated at USD 16,878. The incidence of surgical site infections was 7.3% in the control group and 2.8% in the mupirocin group. The costs of mupirocin were USD 11 per patient, which results in savings per surgical-site infection prevented of USD 16,633. A sensitivity analysis showed that of the four variables that could influence the resulting cost-effectiveness, being the cost of mupirocin, the effectiveness of the intervention, the cost of a surgical-site infection and the incidence of surgical-site infection without using mupirocin, only the costs of a surgical-site infection had a major influence on the model. Therefore, they conclude that, provided that perioperative mupirocin reduces the surgical-site infection rate, mupirocin prophylaxis in patients undergoing cardiothoracic surgery is cost-effective.

In conclusion, cost-effectiveness of prevention of nosocomial *S. aureus* infections will differ per patient category, depending most on the costs of these infections. Mupirocin only has proven effectivity in surgical and dialysis patient groups and cost-effectiveness data cannot be extrapolated to other patient categories.

Vaccination

During the past 100 years, many attempts have been made to develop a vaccine to control staphylococcal disease in humans and cattle. The fact that an infection with *S. aureus* does not protect against a new infection with *S. aureus* illustrates that vaccine development is not going to be easy. Some recent advances in vaccine development do show some protective action. Recently, a double-blind trial in patients receiving hemodialysis has evaluated the use of a conjugate vaccine with *S. aureus* type 5 and 8 capsular polysaccharides [27]. These two types account for approximately 85% of all clinical isolates and can induce a type-specific opsonophagocytic killing by neutrophils *in vitro* and confer protection in animals. The study has shown that this vaccine can confer partial immunity against *S. aureus* bacteremia for approximately 40 weeks, after which protection wanes as antibody levels decrease. Nearly 90% of the patients had a response to the vaccine and the decrease in vaccine efficacy paralleled the decrease in levels of specific antibodies. The effect was entirely caused by a reduction of the infection rate in carriers of *S. aureus*. It would be interesting to study the efficacy of this vaccine or an improved version of this vaccine in other patient populations at risk for *S. aureus* infections.

Conclusion

The increased risk of *S. aureus* nasal carriers for acquiring *S. aureus* infection and the introduction of mupirocin in the 1980s with reported high elimination rates of *S. aureus* nasal carriage has raised the hope that *S. aureus* nosocomial infections would be something of the past. Unfortunately, these hopes could not be met. *S. aureus* is at present still at the top of the list of causative organisms of nosocomial infections and has become even more resistant. Prevalence rates of MRSA strains in blood cultures have skyrocketed to prevalence rates of more than 50% in many countries. Also mupirocin resistance is on the rise due to increased usage, and the first vancomycin-resistant *S. aureus* strains were cultured from patients in the United States in 2002 and 2003.

The first trials studying the efficacy of mupirocin to prevent *S. aureus* nosocomial infection used historical controls. These studies may have resulted in an overestimation of the efficacy of mupirocin. In table 1 the randomized controlled trials that have been performed up to now are summarized. The randomized trial in general surgery showed a significant twofold decrease in overall nosocomial *S. aureus* infection in *S. aureus* nasal carriers. Two other studies in an orthopedic surgery and an internal medicine patient population, showed a twofold reduction rate in *S. aureus* infections, but the incidence of these infections was too low to show significance. Both the incidence of *S. aureus* infections and the effect of mupirocin on this incidence were lower than expected. The study in nonsurgical patients showed a significant delay in the onset of *S. aureus* infection in the treated group. There are several explanations for this phenomenon. The effect of the study itself on the incidence may have been stronger than the effect of the intervention studied. The fact that recolonization occurs, and that patients in the placebo arm also show a reduction in the carriage rate, contributes to this phenomenon.

Table 1
Summary of randomized controlled intervention studies.

Reference	Intervention	Population	Outcome
[18]	Mupirocin	Surgical	Twofold reduction in nosocomial *S. aureus* infections, in carriers.
[5]	Mupirocin	Orthopedic	Nonsignificant 1.7-fold reduction in surgical site infection rate. Fivefold reduction in endogenous *S. aureus* infection.
[27]	Vaccine	Hemodialysis	Twofold reduction for approximately 40 weeks in development of *S. aureus* bacteremia. Effect in carriers only.
[4]	Mupirocin	Medicine	Nonsignificant twofold reduction in nosocomial *S. aureus* bacteremia. Development of nosocomial *S. aureus* infection significantly delayed by 19 days.
[20]	Mupirocin	Hemodialysis	Fourfold reduction in *S. aureus* infection.
[26]	Mupirocin	CAPD	Threefold decrease in exit-site *S. aureus* infection.

CAPD: chronic ambulatory peritoneal dialysis

The randomized trials in hemo- and peritoneal dialysis patients show three- to fourfold reductions in *S. aureus* infections that are statistically significant. For hemodialysis patients mupirocin prophylaxis is cost-effective, but for peritoneal dialysis patients this may not be the case. Moreover, prolonged use in this population has caused resistance to mupirocin repeatedly.

From the combined results of all well-designed studies that have been performed up to now, it can be concluded that treatment of carriers with mupirocin results in a significant reduction of the nosocomial *S. aureus* infection rate. Future studies should target patients at risk for *S. aureus* infection, who may benefit from eliminating *S. aureus* from the nose. Further targeting of prophylaxis will lead to more cost-effectiveness and less resistance. Also the efficacy of strategies other than mupirocin on reducing the *S. aureus* carriage rates should be studied more carefully in different patient populations. Eliminating *S. aureus* carriage from extra-nasal sites may also contribute to more effective strategies in the future.

The ability to control *S. aureus* infections will depend on many factors, like development of new antibiotic agents, development of new prophylactic regimes (vaccines, topical agents), development of more rapid diagnostic tests to identify carriage and last but not least, optimization of infection control measures, especially handwashing. In conclusion, control of *S. aureus* remains a challenge to those interested in nosocomial infection control.

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