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REVIEW

The significance of nasal carriage of *Staphylococcus aureus* and the incidence of postoperative wound infection

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Summary: *Staphylococcus aureus* infections are associated with considerable morbidity and, in certain situations, mortality. The association between the nasal carriage of *S. aureus* and subsequent infection has been comprehensively established in a variety of clinical settings, in particular, patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis (CAPD), and in patients undergoing surgery. Postoperative wound infections are associated with a high degree of morbidity and represent an important medical issue. Until recently, eradication of *S. aureus* nasal carriage by various topical and systemic agents had proved unsuccessful. Mupirocin is a novel topical antibiotic with excellent antibacterial activity against staphylococci. Recent studies have demonstrated that intranasal administration of mupirocin is effective in eradicating the nasal carriage of *S. aureus* and in reducing the incidence of *S. aureus* infections in haemodialysis and CAPD patients. It has been suggested that sufficient evidence now exists to test the hypothesis that eradication of the carrier state in surgical patients preoperatively may reduce the incidence of *S. aureus* postoperative wound infections.

Keywords: *Staphylococcus aureus*: surgery; wound infection; mupirocin.

Introduction

Staphylococcus aureus is one of the most important causes of nosocomial- and community-acquired infections. Although staphylococci are common inhabitants of the skin and the mucous membranes, the anterior nares provide the principal reservoir for these organisms. The general population, health care workers and patients can become intermittent or persistent nasal carriers of *S. aureus*, although the prevalence of nasal carriage varies widely depending upon the population.[1] Studies have shown that 10–15% of

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healthy adults carry *S. aureus* in their nares; this figure rises to approximately 20–35% in hospital personnel.[2] Many patient groups have higher rates of *S. aureus* nasal carriage in comparison to the general population and health care workers, such as patients infected with HIV and those treated by haemodialysis and continuous ambulatory peritoneal dialysis (CAPD).[3–6]

The postulated sequence of events which leads to infection is initiated with *S. aureus* nasal carriage. The organisms are then disseminated via hand carriage to other body sites where infection can occur when breaks in the dermal surfaces, by vascular catheterization or surgical incisions, have occurred. *S. aureus* is the most common organism responsible for postoperative wound infections and a leading cause of septicaemia, intravenous catheter-related infections and skin and soft-tissue infections.

Auto-infection of surgical wounds by *S. aureus* is common, and is associated with considerable morbidity and represents an important medical and economic problem. To date, no comprehensive studies have been undertaken to demonstrate whether the eradication of the carrier state would reduce the rate of wound infections by *S. aureus*. However, recent studies in patients undergoing haemodialysis[6] and CAPD[7] have shown that eradication of nasal carriage of *S. aureus* significantly reduces the incidence of infection in these patients. The evidence, therefore, suggests that eradication of the carrier state in patients preoperatively may reduce the rate of postoperative wound infections with *S. aureus*.[8] Indeed, this idea has been supported by a study, with historical controls, recently carried out by Kluytmans *et al.*[9]

Staphylococcus aureus nasal carriage and infection

The significance of nasal carriage of staphylococci in the epidemiology of staphyloccocal infection has been recognized for 40 years.[1] Tulloch[10] reported that staphylococci isolated from skin lesions in patients with chronic staphylococcal skin infection were of the same phage-type as staphylococci isolated from the anterior nares of patients in 88% of instances in which staphylococci were typable.

Infection in patients undergoing haemodialysis

Infection in haemodialysis patients is associated with considerable morbidity and is the second leading cause of mortality in this group of patients. The most common site of infection is that related to the vascular access site, and studies have shown that *S. aureus* accounts for 70–92% of these infections.[11] *S. aureus* nasal carriage in haemodialysis patients is relatively high, with up to 70% of patients carrying *S. aureus* in their anterior nares.[6] A direct link between nasal carriage of *S. aureus* and subsequent infections by the same organism was demonstrated in a five year prospective study of haemodialysis patients.[6] Yu *et al.*[6] found that of 16 dialysis patients with *S. aureus* infections, 14 were nasal carriers of staphylococci. Moreover, 93%

(13/14) of *S. aureus* infected carriers were found to be infected with the same phage-type as that carried in their nares. Importantly, patients who were nasal carriers of *S. aureus* had a significantly higher incidence of staphylococci infections than non-carriers. Similarly, in a study carried out by Ena *et al.*[12] patients who developed staphylococcal infections while undergoing haemodialysis were found to be infected by strains persistently carried in their nares.

Infection in patients undergoing CAPD

Studies evaluating patients on long-term CAPD have demonstrated the association between nasal carriage of *S. aureus* and subsequent infection in CAPD patients.[13] Peritonitis and exit-site infections are major complications of CAPD and are a leading cause of mortality in this group of patients. Sewell *et al.*[13] studied 30 patients, of which four were chronic *S. aureus* carriers, six intermittent carriers and 20 non-carriers. Of the chronic carriers, three patients developed five episodes of exit-site infections and six episodes of peritonitis, whereas three of the intermittent carriers developed three episodes of exit-site infections and one episode of peritonitis. In contrast, only four of the 20 non-carriers developed four episodes of exit-site infections and one of peritonitis. Chronic carriers, therefore, appear to be at a higher risk of developing *S. aureus*-related infections. In a subsequent study by Kim *et al.*[14] 10 of 12 CAPD patients were found to have isolates of the same phage-type in cultures of the exit-site and peritoneal fluid. Furthermore, of the 12 patients, seven had isolates with the same phage-type in cultures from the nares, hands and peritoneal fluid.

In a study in which the number of exit-site infections in 87 CAPD patients was recorded over eight months, patients who were nasal carriers were found to have a 6·7-fold increase in the incidence of exit-site infections compared with patients with negative cultures of the nares.[5] In a similar study in which 43 patients, 16 chronic carriers and 12 intermittent carriers, underwent CAPD prospectively for 15 months, 16 episodes of peritonitis occurred in the carrier group compared with none in the non-carrier group. Moreover, of those patients evaluated, 100% of strains isolated from the nares and the peritoneum were found to be of identical plasmid pattern.[15]

In a study carried out by Luzar *et al.*,[4] the relationship between the nasal carriage of *S. aureus* and subsequent catheter exit-site infection or peritonitis was assessed in 140 consecutive patients who were new to CAPD. Of these patients 63 were nasal carriers at the initiation of treatment. Luzar *et al.*[4] found a fourfold higher incidence of exit-site infections in nasal carriers in comparison with non-carriers. The probability of remaining free of an exit-site infection after 18 months on CAPD was 92% among non-carriers and 54% in carriers ($P=0{\cdot}012$). Furthermore, among nasal carriers, 11 of 31 episodes of peritonitis were caused by *S. aureus*, compared with none of 36 episodes in the non-carriers.

Methicillin-resistant *S. aureus* (MRSA) nasal carriage in patients undergoing CAPD is associated with an increased risk of CAPD-related infections in comparison with methicillin-susceptible *S. aureus* (MSSA) nasal carriers and non-carriers.[16] In a recent study, patients who were MRSA carriers were found to have an increased rate of exit-site infections and peritonitis. The risk of being free from MRSA peritonitis after one year on CAPD in the carrier group was 65 vs. 96% in the non-carrier group ($P<0{\cdot}01$). Similarly, the risk of being free from an exit-site infection after one year on CAPD was 67% in the carrier group in comparison with 96% in the non-carrier group ($P<0{\cdot}01$).[16] The number of patients who had a combination of CAPD-related infections or multiple episodes of peritonitis was also significantly higher in the carrier group than in the non-carrier group ($P<0{\cdot}001$). Moreover, MRSA nasal carriers suffered an increased number of catheter losses and CAPD drop-outs in comparison to MSSA carriers and non-carriers.[16]

Infection in HIV-infected and AIDS patients

Recent studies have demonstrated an increased prevalence of *S. aureus* carriage among HIV-infected patients[3,17] and patients with AIDS.[18] In a study by Weinke *et al*,[3] the frequency of nasopharyngeal *S. aureus* carriage in HIV patients and its relationship to the incidence of *S. aureus* septicaemia was examined. The study, conducted over eight months, found that 44% (60/136) of HIV-infected patients were nasal carriers of *S. aureus*. In comparison only 31% (12/39) patients with chronic disease and 23% (11/47) healthy hospital staff demonstrated *S. aureus* nasal carriage. Of eight HIV-infected patients with *S. aureus* septicaemia all were found to be nasal carriers. In contrast, no episodes of septicaemia occurred in non-colonized patients ($P<0{\cdot}01$).

Postoperative wound infections

Postoperative wound infections affect at least 920 000 of the 23 million patients who undergo surgery each year in the USA.[19] Surgical site infections are associated with high degree of morbidity and have important medical consequences in terms of prevention and treatment. *S. aureus* can account for up to 19% of postoperative wound infections in patients who are nasal carriers of *S. aureus*[20] (Table I). For several decades, it has been known that *S. aureus* nasal carriage by patients predisposes to postoperative wound auto-infection. Auto-infection of surgical wounds by *S. aureus* was first documented in 1959[21,22] and the early 1960s.[20,23–27] In a study of 125 patients undergoing major surgery, patients with positive preoperative *S. aureus* nasal cultures demonstrated a postoperative wound infection rate of 37%. In comparison, those patients with negative preoperative nasal cultures demonstrated an 11% infection rate.[21] Moreover, of those patients who were staphylococcal nasal carriers, *S. aureus* was the organism isolated from 94% of postoperative wound cultures. In contrast, a variety of organisms were

Table I. *Incidence of postoperative wound infection in nasal carriers and non-carriers of* Staphylococcus aureus

First author	Year of report	Incidence of wound infection: No. infected/ no. colonized	Incidence of wound infection: No. infected/ no. not colonized	% Endogenous*
White[20]	1964	20/106 (19%)	28/345 (8%)	66
Williams[22]	1959	20/276 (7%)	7/342 (2%)	55
Public Health Laboratory[23]	1960	73/821 (9%)	158/2235 (7%)	33
McNeill[24]	1961	12/74 (16%)	11/113 (10%)	42
Henderson[25]	1961	22/264 (8%)	18/569 (3%)	30
Bassett[26]	1963	24/442 (5%)	6/78 (8%)	58
Calia[27]	1969	16/96 (17%)	16/173 (9%)	100

* By phage-typing—showing same strains in preoperative nasal culture as identified in postoperative wound infection.

isolated from postoperative wound cultures in non-carriers. Furthermore, 92% of nasal carriers with postoperative staphylococcal wound infections demonstrated identical *S. aureus* phage-types from both nose and wound cultures.

Subsequent studies have shown the incidence of surgical wound sepsis in nasal carriers of *S. aureus* ranges from 5–19% (Table I). Moreover, 30–100% of wounds were infected with phage-types that were indistinguishable from those in the patient's nose. In comparison, the postoperative infection rate in non-carriers was between 2–10% (Table I).

Eradication of *Staphylococcus aureus* nasal carriage and the reduction in the incidence of infections

The link between nasal carriage of *S. aureus* and the aetiology of subsequent infections caused by this organism is well established in both haemodialysis/CAPD patients and surgical patients. However, eradication of the carrier state in patients prior to surgery, and the concomitant reduction in postoperative wound infections with *S. aureus*, have yet to be fully evaluated.[8] Mupirocin (pseudomonic acid) has been shown to have good in-vitro activity against clinical isolates of *S. aureus*,[28] and the efficacy of mupirocin in eradicating nasal *S. aureus* carriage in haemodialysis patients and healthy control volunteers has been comprehensively evaluated in several studies.[29–33] The use of mupirocin has also been advocated to eradicate MRSA nasal colonization in hospital staff and patients in the control of epidemic MRSA.[34,35] Moreover, recent studies have demonstrated the efficacy of mupirocin, in reducing both the carriage and the incidence of *S. aureus* infection among patients undergoing haemodialysis and CAPD.[7,36]

Haemodialysis and CAPD patients

Several studies carried out by Boelaert *et al.*[36,37] and Holton *et al.*[38] have evaluated the efficacy of mupirocin in eradicating *S. aureus* nasal carriage and reducing the incidence of *S. aureus* infections in haemodialysis patients. In a prospective, double-blind, placebo-controlled trial of 34 nasal carriers, intranasal application of 2% mupirocin ointment three times daily for two weeks followed by three times weekly applications for nine months, significantly reduced the incidence of *S. aureus* nasal carriage. Indeed, only 6% of nasal cultures in the mupirocin arm of the study were positive for *S. aureus* in comparison with 58% in the placebo arm of the study. There was also a significant reduction in the incidence of *S. aureus* infections, with one episode in the mupirocin group in comparison with six in the placebo group.[36] A subsequent study by Boelaert *et al.*[39] demonstrated that continuous therapy with mupirocin was superior to intermittent therapy.

The efficacy of mupirocin in reducing the incidence of *S. aureus*-associated bacteraemias was also evaluated by Boelaert *et al.*[37] in patients undergoing haemodialysis. In a prospective study, Boelaert *et al.*[37] applied 2% calcium mupirocin to stable *S. aureus* nasal carriers in the haemodialysis unit, three times daily for five days then three times weekly for six months and thereafter once weekly for the subsequent 18 months of the study. This regimen eradicated nasal *S. aureus* carriage in 96·3% of surveillance cultures and reduced fourfold the incidence of *S. aureus* bacteraemia per patient year among all dialysis patients. *S. aureus* was responsible for four out of 23 episodes of bacteraemia (17·4%) following mupirocin treatment. In comparison, the incidence of *S. aureus* bacteraemia assessed from historical controls was reported to be 18 out of 33 bacteraemia episodes (54·5%). Eradication of *S. aureus* from the nares did not lead to overgrowth by other organisms and the authors concluded that nasal mupirocin was effective in eradicating nasal carriage of *S. aureus* and decreasing the incidence of bacteraemias caused by this pathogen.

The findings of Boelaert *et al.*[36,37] were supported in a study carried out by Holton *et al.*[38] in which nasal mupirocin was applied to the anterior nares of patients undergoing haemodialysis. Holton *et al.*[38] treated 22 haemodialysis patients who were identified as *S. aureus* nasal carriers. The eradication rate immediately following the completion of therapy was 77% (17/22). Of the 17 patients who were culture-negative at completion of therapy, all remained free from *S. aureus* infections at three months follow-up. In contrast, two out of five patients (40%) who remained nasal culture-positive following mupirocin treatment suffered a *S. aureus* infection. Ten out of 46 patients (22%) not enrolled in the study but followed concurrently had a significantly higher incidence of *S. aureus* infection ($P=0·03$).

In a recent study, the efficacy of mupirocin in the eradication of nasal *S. aureus* in CAPD patients and the reduction in the incidence of CAPD-related infections was evaluated.[7] Ninety-four CAPD patients were enrolled in the study and of these 47·5% were *S. aureus* nasal carriers. A retrospective

assessment of 74 CAPD patients served as historical controls. Two percent mupirocin ointment, applied three times a day for seven days to the patients' nares, eradicated nasal *S. aureus* carriage in 100% of patients. The incidence of *S. aureus*-related peritonitis and exit-site infections was also significantly reduced following mupirocin treatment. Only two episodes of peritonitis occurred in CAPD patients, in contrast to 18 episodes in historical controls. Exit-site infections accounted for eight and 19 episodes in CAPD patients and historical controls, respectively.

Surgical patients

The efficacy of mupirocin in the reduction of both *S. aureus* nasal carriage and subsequent infection in patients undergoing haemodialysis and CAPD has prompted Wenzel[8] to suggest that sufficient evidence now exists to test the hypothesis that eradication of the carrier state would reduce the incidence of postoperative wound infections with *S. aureus*. Indeed, this has been reported recently in a historically controlled study conducted by Kluytmans *et al.*[9] In this study, mupirocin nasal ointment was applied to the nose twice daily for five days, commencing one day prior to the operation, in 629 patients undergoing cardiothoracic surgery during a 12 month period. The overall postoperative rate of infection assessed from 983 historical controls was 8·9%, and of these 3·5% were caused by *S. aureus*. In comparison, the incidence of all postoperative wound infections, and in particular those caused by *S. aureus* were significantly reduced during the period of mupirocin treatment, with figures of 1·8% ($P<0·0001$) and 0·6% ($P<0·0005$), respectively. *S. aureus* was isolated from four patients with postoperative wound infections following mupirocin treatment. However, the preoperative nasal cultures from these four patients did not grow *S. aureus*. Phage-typing showed that two of the isolates were identical to the type isolated previously from the nose of one of the nurses on the ward. Possibly, the infection was acquired postoperatively in the ward. Results, therefore, suggest that preoperative application of mupirocin reduces nasal carriage and reduces the incidence of postoperative wound infections by *S. aureus*. However, it must be remembered that this conclusion is based on only one historically controlled study. Large randomized, placebo-controlled clinical trials are required to assess more fully the efficacy of applying mupirocin preoperatively to reduce the incidence of postoperative wound infections. One such clinical trial is underway at the College of Medicine, University of Iowa, USA.

Resistance

The topical use of any antibiotic is invariably associated with concerns about the emergence of resistance.[39] Mupirocin-resistant *S. aureus* have rarely, however, been encountered in patients treated with mupirocin to prevent haemodialysis or peritoneal dialysis-associated infections. In a nine

month study by Boelaert *et al.*,[36] mupirocin was applied to the anterior nares of stable *S. aureus* nasal carriers undergoing haemodialysis; three times a day for two weeks followed by three times a week for the remaining nine months. Throughout the study all *S. aureus* isolates remained mupirocin sensitive [minimum inhibitory concentration (MIC) ≤ 1 mg/L]. In a subsequent study of haemodialysis patients with stable *S. aureus* nasal carriage, mupirocin was applied to the anterior nares three times a day for five days, then three times weekly for six months and thereafter once weekly for the subsequent 18 months of the study. Among the 29 *S. aureus* strains recovered from subsequent surveillance cultures of the nares, only one mupirocin-resistant strain was found (MIC>512 μg/mL),[37] i.e. one resistant isolate over 108 patient years. Further studies by Boelaert *et al.*[40,41] on the application of mupirocin to haemodialysis patients who were *S. aureus* nasal carriers have not demonstrated the development of mupirocin resistance.

Low- and high-level resistance by *S. aureus* to mupirocin has, however, been reported in the UK and is well documented in several letters to journals[42–45] and in the general literature.[46,47] Despite this, resistance among *S. aureus* to mupirocin remains uncommon. A multi-centre UK survey found only 0·3% of 7137 *S. aureus* isolates to be resistant to mupirocin (MIC >4 mg/L) and only four of these 23 isolates (17%) were highly resistant (MIC >512 mg/L).[44] In a separate study, during a MRSA outbreak in a Spanish hospital, an extensive screening programme combined with the use of intranasal mupirocin brought a two-year MRSA outbreak under control, 53 of 530 patients (10%) carried MRSA with low-level resistance to mupirocin (MICs 8–32 mg/L), of which 38 (72%) had previously had mupirocin-sensitive strains.[48]

The overall incidence of *S. aureus* strains showing high-level resistance to mupirocin (MICs >512 mg/L) remains extremely low, despite increasing worldwide usage of mupirocin. Where high level resistance to mupirocin has been encountered, such strains have generally been associated with patients on dermatology wards[42,43,45] or others receiving long-term mupirocin therapy of several weeks in duration.[44] In this setting, it has been suggested that there may be an environmental reservoir contributing to the spread of mupirocin-resistant isolates.[49]

Since the development of resistance to mupirocin is a cause for concern and the use of mupirocin preoperatively may encourage the emergence of mupirocin-resistant MRSA, alternative topical and systemic agents are available which can be used to eradicate the nasal carriage of *S. aureus* with varying degrees of success. Since it is not the intention of this paper to review alternative agents, readers are referred to a review of the subject by Hudson.[50]

Dosing regimen for intranasal mupirocin

The duration and frequency of mupirocin dosing have varied between studies. Overall the clinical data support twice daily use of intranasal

mupirocin for five days. Minimal dose requirements, to reduce the emergence of mupirocin resistance, have been investigated by Casewell and Hill[51] in 44 stable nasal carriers of MSSA. A single dose of mupirocin, or a regimen of four times daily for two days, eliminated nasal carriage of *S. aureus* within 24 h. Seven days after the single dose and the two day course, 92 and 96% of subjects, respectively, remained free of nasal *S. aureus* carriage. Recently, data from a one year prospective cohort study of *S. aureus* nasal carriers given treatment with mupirocin or placebo were reported.[52] All subjects received only five days of active drug or placebo. At six months, nasal carriage for *S. aureus* was 48% in the treatment group vs. 72% in controls ($P=0{\cdot}054$). At one year, nasal carriage was 53 vs. 76%, respectively ($P=0{\cdot}056$). Thus, a single brief treatment course of topical nasal mupirocin reduced nasal carriage for up to one year. Therefore, it would seem appropriate to recommend the use of mupirocin for five days, particularly in cases of MRSA.

Conclusion

Staphylococcus aureus remains a leading cause of infection in several clinical areas. In particular, *S. aureus* is responsible for a large proportion of postoperative wound infections and infections in patients undergoing haemodialysis or peritoneal dialysis. The significance of nasal carriage of *S. aureus* in the epidemiology of infection has been comprehensively established. Indeed, nasal carriage of *S. aureus* predisposes patients to auto-infection. Postoperative wound infections are associated with considerable morbidity and place a substantial medical and economic burden on both the patient and hospital. Between 30 and 100% of postoperative wound sepsis can be the result of endogenous strains of *S. aureus*. The reduction or prevention of postoperative wound infection by *S. aureus* is, therefore, an important medical goal. Elimination of nasal carriage of *S. aureus* can be achieved by various systemic and topical antibodies: however, topical mupirocin has been shown to be particularly effective. The eradication of the nasal carriage of *S. aureus* in haemodialysis and CAPD patients is associated with a significant reduction in the incidence of infections. Extrapolation from these results would suggest that elimination of nasal carriage of *S. aureus* in patients undergoing surgical procedures might reduce the incidence of postoperative wound infections due to this organism. This hypothesis has been examined in a historically controlled clinical trial carried out by Kluytmans *et al.*[9] in the Netherlands, and the results suggested a reduction in postoperative wound infections following eradication of *S. aureus* nasal carriage preoperatively. To corroborate these results, a large, randomized, placebo-controlled clinical trial is underway at the College of Medicine, University of Iowa, USA.

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