

REVIEW

The efficacy of intranasal mupirocin in the prevention of staphylococcal infections: a review of recent experience

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Summary: Staphylococcal infections remain an important cause of morbidity and mortality. Methicillin-resistant Staphylococcus aureus (MRSA) present a particular problem because of the costs of treatment and containing outbreaks. The role of nasal carriage of staphylococci in the epidemiology of staphylococcal infection has been recognized for over 30 years. Until recently, eradication of nasal carriage of S. aureus has proved difficult, with a variety of topical and systemic agents yielding poor results with either little discernible effect on nasal carriage or rapid recolonization. Mupirocin is a novel topical antibiotic with excellent antibacterial activity against staphylococci, including MRSA. Intranasal administration of calcium mupirocin has achieved excellent results in the eradication of nasal carriage of S. aureus and producing an associated reduction in S. aureus infection in a variety of clinical settings, including MRSA outbreaks, neonatal nurseries, haemodialysis, cardiothoracic surgery and familial staphylococcal infections. This article reviews the efficacy and safety of intranasal mupirocin in the prevention of staphylococcal infections.

Keywords: mupirocin; MRSA; staphylococcal infection; nasal carriage.

Introduction

Infections caused by staphylococci remain an important cause of morbidity and mortality. The costs of treating such infections can be high, and the increasingly frequent outbreaks of multiply resistant strains of staphylococci may cause significant disruption to hospital routine. In particular, methicillin-resistant Staphylococcus aureus (MRSA) epidemics have presented a challenge to hospitals worldwide and appear to be increasing in frequency. Prout et al., for example, detected an increase in MRSA bacteraemia from 4.4% in 1987 to 38.6% in 1990. Elsewhere, up to 40% of all clinical isolates of S. aureus have been reported as MRSA.

The containment of MRSA epidemics and the treatment of infected patients presents an ongoing challenge. MRSA strains are generally

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resistant to many antibiotics and the treatment of choice for serious infections remains vancomycin.⁴ Newer agents such as teicoplanin and ciprofloxacin have recently been introduced, but the use of quinolones to treat *S. aureus* infection has, unfortunately, been associated with the rapid and extensive emergence of resistance.⁵ The use of rifampicin has also been associated with the development of resistance even when combined with other agents.⁶

The economic implications of an MRSA outbreak are extensive. Not only are the antibiotics for infected patients expensive but also the intensive screening programme and extra cleaning and disinfection procedures add to the costs. Hospital stay becomes protracted and in some cases an isolation unit has been necessary.⁷

Nasal carriage of staphylococci

Nasal carriage of methicillin sensitive staphylococci.

The importance of nasal carriage of staphylococci in the epidemiology of hospital staphylococcal infection has been recognized for the past 30 years or more.⁸ Patients and health care workers can become intermittent or persistent carriers of either methicillin-sensitive or methicillin-resistant strains of *S. aureus*, although the prevalence of nasal carriage varies widely according to the population.⁸ The anterior nares provide the principal reservoir for staphylococci, with carriage at other sites generally being dependent on nasal carriage;⁹ the organisms being spread primarily on the hands of health care workers.¹

There is no doubt that intranasal carriage has been associated with the development of staphylococcal infections in a variety of clinical settings. Autoinfection of surgical wounds was documented in 1959 and the early 1960s; in their review of these studies, Casewell and Hill⁸ showed that the incidence of surgical wound sepsis in nasal carriers of *S. aureus* ranged from 5.6 to 16.5%. Between 47 and 89% of these wounds were infected with phage types that were indistinguishable from those in the patients' noses. The postoperative infection rate in non-carriers was only 1.1-7.6%. Similarly, Ena *et al.*¹⁰ reported that when haemodialysis patients become infected with staphylococci, the infections are caused by strains persistently carried in the patients' noses.

Yu and colleagues in a 5-year prospective study in a haemodialysis unit found that *S. aureus* infections occurred significantly more frequently in carriers than non-carriers.¹¹ In 93% of infected carriers the *S. aureus* infections were caused by the same phage type as that carried in the nares. A similar study was conducted by Luzar *et al.*¹² in patients beginning continuous ambulatory peritoneal dialysis. Nasal carriers of *S. aureus* had a four-fold higher incidence of exit-site infection than the non-carriers.

Two studies in France have investigated the link between the nasal carriage of *S. aureus* and infection among patients in intensive care units (ICU). Regnier and Decre¹³ found that 90% of patients with staphylococcal

infection were nasal carriers of the same strain whereas in patients without infection the carrier state rate was 25% ($P < 0.0001$). A similar result was reported from a survey¹⁴ of five medical ICUs: 91% of patients developing infection were persistent or transient carriers of *S. aureus* in comparison with 33% of those who were neither infected nor colonized.

Nasal carriage of methicillin-resistant staphylococci.

The problems associated with the emergence, during the 1970s and 1980s, of MRSA have already been outlined. Recognition of the increased prevalence and importance of MRSA has spawned many publications relating to its epidemic potential, outbreak control and role of the carrier state. These have been reviewed by others.^{6,8,15-17}

Eradication of nasal carriage

Many attempts have been made to eradicate nasal carriage of *S. aureus*, particularly MRSA, from patients and hospital personnel in order to reduce spread and prevent infection. A variety of topical and systemic agents have, in general, yielded poor results with either little discernible effect on nasal carriage or rapid recolonization. These studies, which are often difficult to interpret, have been reviewed by others.^{9,17,18}

Of the systemic agents, rifampicin has probably been the most successful but it is associated with frequent and rapid development of resistance.^{9,18} When oral rifampicin was combined with bacitracin to minimize this possibility, a significant reduction in *S. aureus* nasal carriage was observed in haemodialysis patients.¹¹ However, rifampicin-resistant strains were isolated from the anterior nares of four patients within one month of treatment. As a consequence of such resistance problems it is generally considered unwise to use systemic antibiotics topically for the eradication of staphylococcal nasal carriage. However, antiseptics and other non-systemic antimicrobials applied topically to the anterior nares such as chlorhexidine and 'Naseptin' cream (chlorhexidine hydrochloride 0.1%, neomycin sulphate 0.5%) have proved unsatisfactory.

Extensive investigations in many clinical environments have now been conducted using mupirocin, a non-systemic antibiotic available for intranasal use. The purpose of this paper is to review the worldwide experience with intranasal mupirocin and to discuss the place of mupirocin in the prevention and containment of staphylococcal infections.

Mupirocin

Mupirocin is produced by submerged fermentation of *Pseudomonas fluorescens*. It is active against staphylococci, including methicillin-resistant strains, streptococci and certain Gram-negative organisms. Mupirocin has a unique mode of action, inhibiting bacterial isoleucyl t-RNA synthetase and is structurally unrelated to other clinically used antibiotics.¹⁹ During

its early pharmacological evaluation when administered systemically, mupirocin was found to be rapidly metabolized to inactive monic acid and thus proved unsuitable as a systemic agent. With these characteristics, mupirocin is an ideal candidate for use as a topical antibiotic.

Mupirocin maintains its high anti-staphylococcal activity even in the presence of nasal secretions;²⁰ its activity is unaffected by the resistance profile for other topical or systemic antibiotics.²¹ Mupirocin was first formulated in a base of polyethylene glycol, for the treatment of superficial skin infections, however when this formulation was used intranasally, some subjects experienced local irritation,²² therefore a new formulation was developed specifically in a base of white soft paraffin and a glycerin ester (Bactroban Nasal, SmithKline Beecham) for intranasal use. This new formulation has been evaluated extensively in clinical trials and is now registered in over 15 countries worldwide, including the UK, France, Germany, Spain and Belgium.

Clinical experience with intranasal mupirocin

Eradication of nasal carriage of methicillin sensitive S. aureus. Clinical studies from around the world have demonstrated the efficacy of intranasal calcium mupirocin ointment in the elimination of nasal carriage of staphylococci. In the first such study, Casewell and Hill,²³ identified 36 hospital staff as stable carriers of *S. aureus* each having three consecutive positive nasal swabs. The subjects were randomly allocated to placebo or mupirocin, a 'match-head' sized quantity of ointment being applied with the finger to each nostril four times a day for 5 days. Any subject demonstrating nasal carriage within 30 days of completing treatment was crossed-over to the alternative therapy. Placebo failed to eliminate nasal carriage in any subject. In contrast, mupirocin eliminated the nasal carriage of persistent *S. aureus* within 2 days of commencing treatment in all 32 evaluable subjects. By 14 weeks post-treatment, 43% and by 22 weeks 50% of subjects followed-up had resumed nasal carriage of *S. aureus*. Thus, for a significant number of subjects, mupirocin resulted in clearance of nasal carriage over a clinically relevant time frame.

In a larger, multicentre, double-blind study,²⁴ 339 hospital staff who were stable carriers of *S. aureus* were randomized to receive either mupirocin or placebo intranasally bid for 5 days. Elimination of nasal carriage was achieved immediately post-treatment in 91% of evaluable subjects receiving mupirocin vs. 6% receiving placebo ($P < 0.001$). At 4 weeks post-treatment 82% of mupirocin treated subjects remained free of *S. aureus* in the nares in comparison with just 12% in the placebo group. As part of this placebo controlled study, Reagan *et al.*²⁵ enrolled 68 stable nasal carriers of *S. aureus* and demonstrated that intranasal mupirocin was also effective in significantly reducing hand carriage of *S. aureus*. One third of the 68 carriers had initial hand cultures that were positive for *S. aureus*. Two to 3 days post-treatment this proportion was significantly lower in the

mupirocin group (2.9%) than in the placebo group (57.6%). Hand carriage remained significantly lower in the mupirocin group at 6 months. Epidemiological typing of all *S. aureus* isolates revealed that the vast majority of hand isolates (87%) exactly matched the subject's current nasal plasmid type.²⁶ The authors conclude that their data implicate the nares as the primary reservoir site for *S. aureus* hand carriage.

MRSA outbreak control. In their comprehensive review on local treatment of MRSA carriage, Hill and Casewell pose the question "Why should MRSA carriage and colonization be eliminated?"¹⁹ They argue that uncontrolled colonization by MRSA is a prelude to serious sepsis and support the view that carriage of MRSA by hospital personnel provides an important source of organisms for nasal acquisition by patients, and for subsequent auto-infection and dissemination. It is for this reason that many workers have evaluated mupirocin in clinical trials.

The first documented intranasal use of mupirocin in the control of hospital outbreaks of MRSA^{7,27} involved the polyethylene glycol based formulation licensed to treat various superficial dermatological infections. Subsequently, the efficacy of the preferable calcium mupirocin intranasal ointment (formulated in a white soft paraffin base) in eliminating nasal carriage of MRSA during outbreaks has been confirmed in many clinical settings. One publication reports the treatment of 1510 subjects in MRSA outbreaks in over 100 hospitals in the UK. Eradication was found to be 97.1%.²⁸ Other studies include a veterans' nursing home,²⁹ ICUs,^{30,31} neonatal nurseries^{32,33} and an orthopaedic unit.³⁴ In the latter study, Barrett described how standard control measures were not sufficient to control an MRSA epidemic, but following the addition of nasal mupirocin the outbreak ended.

This wealth of clinical evidence indicates that mupirocin can make a significant contribution during an MRSA outbreak. Treatment of infected or colonized patients and known carriers alone may not be sufficient to control an MRSA outbreak. In such an outbreak in Spain lasting more than 2 years,³⁵ the outbreak was only brought under control when an active screening programme for the detection of all nasal carriers was added to the use of intranasal mupirocin.

The clinical implications of an MRSA outbreak in the absence of appropriate control measures, are illustrated by experience in South Africa, where a limited budget in a 3000 bed tertiary care hospital could not support extensive MRSA carriage surveillance.³¹ However eradication procedures, including treatment of MRSA carriers with twice daily intranasal mupirocin for 5 days, instituted in two high risk areas of the hospital, significantly reduced the incidence of MRSA bacteraemia. Over a 1-year period bacteraemia decreased from 1.3 to 0% in the paediatric oncology unit ($P = 0.0007$) and from 1 to 0.25% in the ICU ($P = 0.016$) while in the rest of the hospital the incidence increased.

Treatment of the carrier state in health care workers and patients is just

one of three measures for MRSA control outlined by Wenzel *et al.*¹ who recommend the use of intranasal mupirocin. This view is supported in the 'Guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus*' drawn up, and revised in 1990, by the combined working party of the Hospital Infection Society and the British Society for Antimicrobial Chemotherapy⁶ which state "the most effective treatment for nasal carriage is mupirocin". These guidelines support the view that the costs of ignoring strains of epidemic MRSA are higher than those of controlling them, since the annual recurrent costs for hospitals badly affected by MRSA were estimated at £250000.

Adoption of these guidelines resulted in the recognition and containment of all strains of epidemic MRSA introduced into a ward of highly immunocompromised liver-transplant patients, over a 5-year period. No infections occurred,³⁶ indicating the clinical value of using mupirocin in this way.

As intranasal mupirocin becomes established as the agent of choice in eradication of MRSA, comparative studies against other presently available agents may become increasingly difficult to justify or perform. Cookson and Phillips³⁷ cite several reasons why: the economic implications, the morbidity and mortality associated with continued MRSA acquisition and the problems of resistance to other agents. Nevertheless, some comparative studies have been conducted: in a prospective, randomized study, Guerrero *et al.*³⁸ compared intranasal mupirocin tid for 5 days with a combination of cotrimoxazole (160 mg trimethoprim) bd orally plus topical fusidic acid tid, both for 5 days, in similar groups each of 31 patients with two positive nasal cultures for MRSA. In addition both groups used chlorhexidine soap. Similar results were obtained for each group; at the end of treatment nasal eradication rates were 100% throughout while extranasal eradication rates were 60% and 62% for mupirocin and the cotrimoxazole/fusidic acid combination, respectively. One month after treatment, well over 90% of patients in each group remained free from MRSA nasal carriage.

Time to recolonization following eradication of S. aureus with intranasal mupirocin

Time to recolonization has been addressed in a number of studies. In contrast to other antimicrobials where generally carriage is quickly re-established,⁹ treatment with mupirocin renders subjects free from recolonization for protracted periods. In Casewell and Hill's original study²³ 50% of the subjects available for sampling remained free from recolonization 22 weeks post-treatment. Of the 14 who ultimately resumed carriage, phage typing and antibiograms identified that only 29% of subjects had relapsed with colonization by their pre-treatment strain, while 57% had acquired a different phage type.

A 1-year period of follow-up has been described in two studies. Bulanda *et al.*³⁹ reported that mupirocin eradicated *S. aureus* from the nares from all

but two of 69 volunteers immediately post-treatment. During the subsequent 6 months, 43% became stably recolonized; by 1 year 60% of subjects were positive for intranasal *S. aureus*, 42% of these being relapses while 58% were re-acquisitions (based on phage typing). In subjects recolonized after therapy the density of *S. aureus* was much lower than in the same subjects before therapy.

In the follow-up of 68 volunteers from the study by Reagan *et al.*, 71% in the mupirocin group vs. 18% in the placebo group remained free from nasal carriage 3 months after treatment;²⁵ this difference was highly significant. At 6 months and 1 year post-treatment, 48 and 53% of mupirocin treated patients, respectively, vs. 72 and 76% of controls demonstrated *S. aureus* nasal carriage.⁴⁰

Hill *et al.*⁴¹ evaluated mupirocin during an MRSA outbreak. Forty patients and 32 hospital personnel were all cleared of nasal MRSA with intranasal mupirocin tid for 5 days. At 8 and 10 weeks after the course, there were 22 and 17 staff still available for sampling and all were still negative. By 18 and 20 weeks, the corresponding figures were three negative of four available for testing at 18 weeks, and four of four at 20 weeks. In total, five of the staff recolonized at 2, 5, 5, 11 and 12 weeks and repeat application again eliminated carriage. Of the 40 patients treated, 36 remained clear of nasal MRSA for the duration of this follow up (1 day to 9 weeks, mean of 2 weeks). The anterior nares of four became recolonized 1 to 5 weeks after the course. This contrasts with the failure of chlorhexidine treatment used previously in 20 of the study subjects.

Comparison of these data with those reported for methicillin-sensitive strains of *S. aureus* suggests the time to recolonization following mupirocin treatment is equally prolonged whatever the resistance pattern of the strain. In fact, when recolonization occurs, it is often with a phage type different from the original colonizing strain. This appreciable carriage-free period has proved to be valuable in the management of MRSA outbreaks.

High risk patient groups

Haemodialysis patients. In this population at increased risk of infection the link between nasal carriage and infection has been clearly established. *S. aureus* is the most frequently isolated pathogen⁴² and infections are caused by strains persistently carried in the patient's nose.⁹ In evaluating the effects of several prophylactic regimens for a haemodialysis patients, Yu *et al.*¹¹ detected no discernible effect on nasal carriage of *S. aureus* using intravenous vancomycin or topical bacitracin. The combination of oral rifampicin plus bacitracin significantly decreased carriage at 1 week and 1 month post-treatment; by 3 months there was no significant difference from untreated controls.

A number of studies conducted by Boelaert *et al.* have extensively evaluated mupirocin in haemodialysis patients. The initial double-blind placebo controlled study⁴² in 34 nasal carriers demonstrated that mupirocin

applied three times daily for 2 weeks followed by thrice weekly applications for 9 months significantly reduced carriage, with only 6% of nasal cultures in the mupirocin group vs. 58% in the placebo group growing *S. aureus*. There was also a significant reduction in *S. aureus* infection, with one episode in the mupirocin group contrasting with six episodes in the placebo group.

Subsequently these authors⁴³ compared different regimens of mupirocin therapy, over a period of 9 months in 42 nasal carriers. All patients received an initial 5-day course of intranasal mupirocin tid, following which they were randomly assigned either to continue mupirocin on a thrice weekly basis (continuous therapy) or to repeat the 5-day course only if nasal carriage of *S. aureus* recurred (intermittent therapy). None of the 21 patients (112 patient months) who received continuous mupirocin had either positive nasal cultures or developed *S. aureus* infection in the course of the study. In comparison, 23 out of 118 nasal swabs from the 21 patients (124 patient months) receiving intermittent therapy grew *S. aureus* and five *S. aureus* infections developed. Continuous treatment appeared superior.

To evaluate the impact of mupirocin use on the incidence of bacteraemia caused by *S. aureus* in the haemodialysis unit and to analyse its cost-effectiveness, Boelaert⁴⁴ prospectively treated all stable *S. aureus* carriers in the unit with mupirocin, three times daily for 5 days then thrice weekly for 6 months and thereafter once weekly for the subsequent 18 months of the study. This routine use of mupirocin led to eradication of nasal *S. aureus* carriage in 96.3% of surveillance cultures and to a greater than four-fold reduction in the total incidence of *S. aureus* bacteraemia among all the dialysis patients (four episodes in 168 patient-years) when compared to historical controls prior to the use of mupirocin (18 bacteraemias in 186 patient-years). Importantly, this resulted in a marked reduction in the mean treatment cost of *S. aureus* bacteraemias from \$896 per patient-year at risk in the historical control population compared to \$231 per patient-year at risk during mupirocin use.

The periods of thrice-weekly and once-weekly treatment with mupirocin were compared for effectiveness. None of the 60 surveillance cultures obtained during thrice-weekly treatment were positive for *S. aureus*, compared with 29 of 732 cultures positive during the once-weekly treatment period. The incidence of *S. aureus* bacteraemia using mupirocin three times per week (one episode in 44 patient-years) was the same as the incidence during mupirocin once a week (three episodes in 124 patient-years). The total incidence of bacteraemia during this 2-year study was significantly less than during a 2-year control period, prior to the use of mupirocin. No nasal overgrowth by enterobacteriaceae or yeast occurred and the authors concluded that once weekly dosing with nasal mupirocin was effective in eradicating nasal carriage of *S. aureus* and decreasing the incidence of bacteraemias caused by this pathogen.

Several other studies on the prophylactic use of nasal mupirocin in this

high risk group of patients⁴⁵⁻⁴⁸ support the findings of Boelaert. Hingst *et al.*⁴⁶ reported a prospective randomized, placebo controlled study which showed that eradication occurred in 76% of 33 haemodialysis patients treated with mupirocin tid for 10 days in comparison with 11% of 21 placebo treated controls ($P < 0.001$) and approximately half the patients were still free from nasal *S. aureus* 20 weeks after the end of mupirocin treatment. Sampling from other body sites revealed a reduction in colonization with *S. aureus* following intranasal mupirocin.

Watanakunakorn *et al.*⁴⁷ reported an uncontrolled study evaluating intranasal mupirocin together with a chlorhexidine body scrub in 22 haemodialysis patients. The authors suggested that the success rates of 83 and 69% eradication of *S. aureus* nasal carriage 1 day and 12 weeks post-treatment, respectively, were excellent in comparison with published reports of other oral or topical agents.

Holton *et al.*⁴⁵ also treated 22 haemodialysis patients who were nasal carriers of *S. aureus* with intranasal mupirocin; the eradication rate immediately post-therapy was 77%. In addition the incidence of *S. aureus* infection in the 3 months post-mupirocin treatment (two infections, both in patients who had remained nasal culture positive) was significantly reduced ($P = 0.03$) in comparison with concurrently followed controls (10 infections in 46 patients).

Rifampicin was chosen as the comparator against mupirocin in a placebo-controlled pilot study reported by Muro *et al.*⁴⁸ In 25 haemodialysis patients mupirocin achieved 100% eradication of *S. aureus* from nasal cultures, whereas the post-treatment cure rates for rifampicin (300 mg qd for 5 days) and placebo were 75 and 38%, respectively.

ICU patients. In a previously mentioned study which emphasized the strong relationship between nasal carriage and infection in ICU patients¹³ intranasal mupirocin successfully eradicated the carrier state from all 27 patients.

Surgery. Wenzel⁴⁹ has suggested there is now sufficient evidence to test the hypothesis that eradication of the carrier state would reduce the rate of postoperative wound infections with *S. aureus*. This has indeed been reported by Kluytmans *et al.*⁵⁰ Mupirocin nasal ointment was applied to the nose twice daily for 5 days, starting the day before the operation, in 389 patients undergoing thoracic surgery during an 8-month period. In comparison with 1009 historical controls where the incidence of post operative wound infection was 8.7% (3.5% due to *S. aureus*), the incidence of all postoperative wound infections, and of those caused by *S. aureus*, was significantly reduced during the period of mupirocin intervention (2.3% for all wound infections and 0.5% due to *S. aureus*). *S. aureus* was isolated from two of the nine patients who developed postoperative wound infection after intranasal mupirocin. The preoperative nasal cultures from these two

patients did not grow *S. aureus*. Phage typing showed that both isolates were identical to the type isolated previously from the nose of one of the nurses on the ward, therefore suggesting that these infections were most likely acquired on the ward postoperatively.

The authors conclude from this comprehensive study that 'elimination of nasal carriage of *S. aureus* reduced the postoperative wound infection rate significantly'. Although the infection rate in this study is relatively high, the significant reduction seen following the use of mupirocin offers the opportunity of improving prophylactic antibiotic regimens by reducing auto-infection caused by *S. aureus*. These results require confirmation in a prospective placebo-controlled study to ensure no other factors contributed to the reduction in wound infection rates compared to historical controls.

Paediatrics. Several authors report the use of mupirocin in neonatal nurseries. In an outbreak of scalded skin syndrome in a Polish nursery⁵¹ caused by an epidemic strain of *S. aureus* producing the exfoliative toxin, mupirocin nasal ointment eradicated the organism from all hospital personnel who were identified as carriers. No new cases of scalded skin syndrome occurred thereafter. In another report following an outbreak of MRSA,⁵² colonized babies were treated with mupirocin twice daily for 7 days; all eight babies were clear of MRSA within 3 days of treatment. The authors stated that two epidemic strains of MRSA were successfully eradicated from the Special Care Baby Unit by mupirocin and the unit remained free of MRSA for 36 weeks. Sanchez *et al.*⁵² conducted a randomized, double-blind placebo controlled evaluation of mupirocin for eradication of MRSA colonization in 37 preterm infants. Any infant with a positive MRSA culture during the 4-week follow-up was treated with open label mupirocin. At the end of 5 days of treatment the overall eradication rate with mupirocin was 98% from the nose and 87% from the umbilicus; 4 weeks post-treatment the rates were 50 and 59% respectively, by which time all the infants who received placebo had become recolonized.

These reports confirm that mupirocin can reduce or eradicate colonization with *S. aureus* in special care baby units. Its use may lead to a reduction in nosocomial infection and thus help to control MRSA outbreaks.

Familial staphylococcal infection. Leigh and Joy⁵³ conducted a study comparing the efficacy of intranasal mupirocin with intranasal chlorhexidine/neomycin (Naseptin) cream in eradication of nasal carriage in 26 families (99 subjects including, 32 index (infected) patients and 67 family members) with recurrent Staphylococcal infections. Both treatment regimens were combined with chlorhexidine soap for washing and chlorhexidine powder applied to other possible carriage site. Patients failing with chlorhexidine/neomycin were then treated with mupirocin. Treatment was given for 7 days and follow up swabs were collected 8, 14, 28 and 91

days after the start of treatment. Prior to treatment, the authors found that the carriage rate of *S. aureus* was 67% in the anterior nares, 22% in the axilla, 23% in the groin and 19% in the perineal region. Follow up (day 8) nasal eradication rates were 95% in the mupirocin treated group, 85% in the group who received mupirocin following failure of chlorhexidine/neomycin treatment, and 61% in the chlorhexidine/neomycin treated groups. By day 91, 57% of the mupirocin treatment compared with 42% of the mupirocin treated following chlorhexidine/neomycin treatment, and 8% of the chlorhexidine neomycin treated group, were again colonized, thus demonstrating a lower recolonization rate during the follow-up period in the mupirocin treated patients. No further infection occurred in 56% of the mupirocin treated families compared with 27% of those receiving Naseptin.

Long-term care facilities. Long-term care facilities may serve as a reservoir for MRSA and subsequently contribute to the spread of the organism when patients are transferred to acute-care hospitals.⁵⁴

A number of studies have evaluated the use of mupirocin in this setting. Cederna *et al.*⁵⁵ screened 102 patients in a Veterans' Administration Nursing Home and found 39 (38.2%) were colonized, 18 with MSSA and 21 with MRSA. Colonized patients were treated with mupirocin ointment and, following treatment, eradication was achieved in 91.4% of colonized patients. At 1 and 2 months follow-up 11 patients became transiently recolonized and three became persistently recolonized. Kauffman *et al.*⁵⁶ screened 321 residents of a Veterans' Administration Nursing Home, 65 were found to be colonized and received mupirocin, which rapidly eliminated MRSA in most patients by the end of 1 week. Weekly maintenance intranasal mupirocin was not sufficient to prevent recurrence in 40% of the patients, however when mupirocin was used in nares and wounds, overall MRSA colonization in the facility fell from 22.7% to 11.5%. The authors concluded that mupirocin was effective in decreasing colonization with MRSA, but constant surveillance was required to identify patients recolonizing or being newly admitted. It was also noted in this study that mupirocin-resistant MRSA were isolated in 10.8% of patients, (seven patients with eight resistant isolates, seven low level resistance and one high level). All patients with low level resistance were successfully treated and their organisms cleared with mupirocin.

These studies confirm that mupirocin is effective in this setting, however, it is important to consider the value of doing so. If a patient is about to be transferred to another facility without MRSA, vigorous attempts should be made to eradicate carriage. Similarly, where an epidemic strain of MRSA is causing clinical infection, attempts to control the organism should be made.

In his review of this subject, Marples⁵⁷ discusses the implications of colonization with *S. aureus* in geriatric medicine. He points out that many geriatric patients suffer from trauma requiring orthopaedic treatment, under those circumstances MRSA becomes significant. He also recognizes

that a geriatric unit with minimal morbidity may be a significant source of MRSA for the local acute services, and the number of infections arising in a geriatric facility may not predict the virulence of the same organism when introduced into an acute-care unit or ICU.

Role of intranasal mupirocin in eradication of methicillin-resistant Staphylococcus epidermidis

In contrast to other studies, Willems⁵⁸ assessed the impact of nasal mupirocin treatment of nurses on the subsequent nasal carriage of methicillin-resistant *Staphylococcus epidermidis* (MRSE) by both nurses and patients on a cardiosurgical ICU. Mupirocin decreased nasal MRSE carriage in nurses from 71 to 12%. Nasal MRSE in patients on the second and sixth postoperative days decreased from 85 to 25% and from 90 to 65%, respectively, during the 1 week period in which the nursing staff received mupirocin tid, compared with run-in period. The author concluded that nurses may play an important role in the colonization of their patients with MRSE and that topical treatment with intranasal mupirocin may be of benefit to patients in reducing colonization.

Resistance

The topical use of any antibiotic is invariably associated with concerns about the emergence of resistance. This is particularly important for systemic agents with life-saving potential. Calcium mupirocin, however, is not available for systemic use. Furthermore, as a consequence of its novel structure and unique mode of action, mupirocin lacks cross-resistance with other clinically used antibiotics. *In vitro* the selection of resistant strains of *S. aureus* is slow.¹⁹ These properties appear to be of benefit in clinical practice.

The biochemical mechanism of mupirocin resistance has been extensively studied. Farmer *et al.*⁵⁹ screened 21 strains of *S. aureus* of varying resistance to mupirocin (including sensitive strains with a minimum inhibitory concentration (MIC) of 0.12–1.0 mg l⁻¹, moderately resistant strains, MIC 8–256 mg l⁻¹ and highly resistant strains, MIC > 2048 mg l⁻¹). They concluded that production of modified isoleucyl-tRNA synthetase (IRS) enzyme was the major cause of mupirocin resistance in the strains studied. Gilbert *et al.*⁶⁰ subsequently studied a range of isolates including susceptible, intermediate and high level resistant strains, to determine their IRS and presence of a gene known to encode high level mupirocin resistance. Their results demonstrated that two different IRS enzymes were present in highly mupirocin-resistant *S. aureus* strains. In strains expressing intermediate levels of resistance, only a chromosomally encoded IRS was detected which was inhibited less by mupirocin than IRS from fully susceptible strains.

Resistance among staphylococci to mupirocin remains uncommon. A total lack of resistance to mupirocin was detected in 200 strains of *S. aureus* isolated in the survey of five medical ICUs in France.¹⁴ A multicentre survey in the UK⁶¹ found only 0.3% of 7137 *S. aureus* isolates to be resistant to mupirocin (MIC > 4 mg l⁻¹) and only four of these 23 isolates were highly resistant (MIC > 512 mg l⁻¹). Mupirocin resistance among coagulase-negative staphylococci was 3% of 1083 isolates. A survey conducted in Spain evaluated mupirocin sensitivity amongst 1500 clinical isolates of *S. aureus* from 94 Spanish hospitals collected between 1979 and 1992. These included 1400 sporadic cases (15% MRSA) and 100 from nosocomial outbreaks (65% MRSA). The survey demonstrated that mupirocin did not modify its susceptibility against any *S. aureus* strains from 1979–1992. The MIC₉₀ for mupirocin for both sporadic and outbreak strains was 0.12 µg ml⁻¹.⁶² A recent study from the USA⁶³ reported 1% of 1309 nasal isolates of *S. aureus* to be mupirocin resistant. The level of resistance was not specified although the MIC₉₀ for mupirocin was ≤ 0.12 mg l⁻¹.

Low level resistance may be amenable to topical treatment with mupirocin since such high concentrations are achieved (around 20 000 mg l⁻¹) with the 2% preparation. Clinical evidence for this comes from a study involving 1510 subjects in MRSA outbreaks in the UK.²⁸ In this study only seven of the 523 nasal isolates of *S. aureus* tested for susceptibility were resistant to mupirocin (MIC for all seven = 32 mg l⁻¹). Mupirocin treatment, however, eliminated *S. aureus* from the nares of all five patients with bacteriological follow-up. In a separate study during an MRSA outbreak in a Spanish hospital, an extensive screening program combined with the use of intranasal mupirocin brought a 2-year MRSA outbreak under control.³⁵ 53 of 530 patients carried MRSA with low level resistance to mupirocin (MICs 8–32 mg l⁻¹), of which 38 had previously had mupirocin-sensitive strains. In this study, resistance was not related to failure of nasal elimination. In a study in the US in a long-term care facility referred to above, 65 patients were colonized with MRSA and received mupirocin ointment. Mupirocin rapidly eliminated MRSA at the sites treated in most patients by the end of 1 week, however recolonization recurred in 40% of patients. When mupirocin was used on the colonized wound as well as on the nose, MRSA colonization in the whole unit decreased. So called mupirocin-resistant MRSA strains were isolated from 10.8% of patients, however the MICs of seven of the eight organisms were 3.1 to 6.25 µg ml⁻¹, with only one exhibiting high level resistance. All patients colonized with low level mupirocin-resistant strains cleared their organism with continued mupirocin treatment.⁵¹ Thus there is now reasonable evidence that *S. aureus* isolates exhibiting 'low level resistance' can be successfully eradicated following the use of mupirocin.

The overall incidence of *S. aureus* strains showing high-level resistance to mupirocin (MICs > 512 mg l⁻¹) remains extremely low despite the

increasingly widespread use of this agent. Where clinical information on the source of the resistant isolate is provided, such strains have generally been associated with patients on dermatology wards or others receiving prolonged mupirocin treatment for infected skin lesions, often for many months.^{61,64-67} In this setting, there may be an environmental reservoir contributing to the spread of mupirocin-resistant isolates. In one such outbreak, a blood pressure cuff and patients, communal shower were found to harbour the mupirocin strain colonizing patients. Eradication of the environmental reservoirs controlled the outbreak.⁶⁷

In the context of mupirocin use for the elimination of *S. aureus* nasal carriage there has been no evidence for the emergence of mupirocin resistance as a mechanism for the relapse of nasal carriage.⁶⁸ However, it would seem wise to heed the advice of others^{69,70} to avoid prolonged and irregular use and to ensure, through appropriate use, that mupirocin remains a valuable agent for MRSA outbreak control.

Dosing regimen for intranasal mupirocin

Inevitably, during the clinical investigation of mupirocin, the duration and frequency of dosing have varied between studies. The bulk of the clinical data support twice daily use of intranasal mupirocin for 5 days. Minimal dose requirements have been investigated by Casewell and Hill¹⁶ in 44 stable nasal carriers of methicillin-sensitive *S. aureus*. A single dose of mupirocin was compared with four times daily dosing over 2 days. After 7 days post-treatment with one or eight doses, 92 and 96% of the subjects, respectively, remained free of nasal *S. aureus*. At present there are no data on the time to recolonization following such short courses of mupirocin. Given that the majority of studies have evaluated longer treatment it would seem appropriate to continue to recommend a full 5-day course particularly in cases of MRSA. The rapid elimination of MRSA has considerable economic implications, since mupirocin-treated hospital personnel will be able to return to work within 24 h of starting treatment.

Tolerance

Intranasal calcium mupirocin has been found to be well tolerated. In a review of 2186 subjects who received mupirocin in clinical trials, local symptoms such as nasal irritation, sneezing, runny nose or nasal congestion occurred in 1.46% of subjects. An abnormal taste was reported in 1.10% and headache in 0.96%. A sensation in throat or sore throat was reported in 0.82%, local pruritus in 0.32% and burning or stinging in 0.23%. The vast majority of these experiences were mild in nature and patients were able to continue taking the study medication. Only two events, abnormal taste and sore throat/sensation in throat, were statistically significant and more common in mupirocin-treated patients compared with those receiving

placebo (vehicle alone). These two events may be specifically related to mupirocin rather than the vehicle base.

Conclusions

The now considerable clinical experience with intranasal calcium mupirocin indicates two distinct roles for this unique, well-tolerated topical antibiotic which has become the treatment of choice for the elimination of staphylococcal nasal carriage. Firstly, nasal mupirocin provides a cost-effective adjunct to routine infection control measures in the containment of MRSA epidemics. Secondly the prophylactic use of mupirocin in high risk patients significantly reduces the risk of *S. aureus* infection. The number of isolates resistant to mupirocin identified so far is remarkably low; with continued responsible use mupirocin should remain an invaluable agent for the elimination of *S. aureus* nasal carriage and the consequent reduction in *S. aureus* infections.

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