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Nasal and Hand Carriage of *Staphylococcus aureus* in Healthcare Workers

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Summary

Six double-blind, randomised placebo-controlled clinical trials in the United States have evaluated the elimination of *Staphylococcus aureus* carriage in healthcare workers with mupirocin ointment. Consistent data from the six centres demonstrated that calcium mupirocin ointment administered intranasally for five days is safe and effective in eliminating nasal carriage of *S. aureus*. Hand cultures were also performed at one centre, showing that hand carriage rates were significantly decreased 72 hours post-therapy and at six months. Additionally, molecular typing of all isolates obtained from the nares and hands found identical strains at both sites in the majority of subjects, implicating the nares as the primary reservoir of *S. aureus* colonisation.

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INTRODUCTION

Recent epidemiological studies have shown that *Staphylococcus aureus* remains an important cause of nosocomial infections.[1] Therapy for serious staphylococcal infections has become increasingly difficult with the emergence of strains resistant to multiple antibiotics. Many healthy adults are persistently or intermittently colonised with *S. aureus* in their anterior nares [2] and thus are at increased risk for certain staphylococcal infections. Although various topical and systemic antibiotics have been used to eliminate nasal carriage, recolonisation typically occurs after a brief period of time.

Mupirocin (pseudomonic acid A), obtained from *Pseudomonas fluorescens,* is a topical antibiotic with a unique chemical structure which exhibits excellent *in vitro* activity against a wide range of Gram-positive organisms, including methicillin-susceptible and methicillin-resistant strains of *S. aureus*.[3,4] Dacre and colleagues [5] used a formulation of mupirocin in polyethylene glycol to control successfully an outbreak of methicillin-resistant *S. aureus* (MRSA). However, irritation of the nasal mucosa was noted and a new formulation in a white soft paraffin base was developed to eliminate this side effect.

Studies at the University of Iowa on the carriage of *S. aureus* in healthcare workers were stimulated by the work of Casewell and Hill,[6] who performed the first clinical trial of mupirocin in eliminating nasal carriage. Using a 2% mupirocin ointment in white soft paraffin in healthy nasal carriers, administered four times a day for five days, all 32 carriers were cleared of nasal *S. aureus* after two days and remained negative for two weeks. Even

22 weeks later, 56% of the subjects were free of nasal colonisation. Furthermore, none of the carriers had *S. aureus* recovered from the wrist or perineal sites immediately post-therapy.

Subsequently, a series of six independently randomised double-blind, placebo-controlled clinical trials was performed in the United States to evaluate the elimination of *S. aureus* nasal carriage using calcium mupirocin ointment. This paper presents an overview of the pooled results,[7] as well as a review of the results obtained from our centre at the University of Iowa [8] which independently studied hand and nasal carriage. Finally, the prospective follow-up of the original study cohort from our centre is also reviewed [10,11] including an investigation of the long-term epidemiology of carriage among healthcare workers using molecular typing methods.[9,11]

STUDY METHODOLOGY

All six centres followed a common protocol.[7] Healthcare workers, aged 18 years and above, who were stable nasal carriers of *S. aureus* and without systemic illness, were enrolled in the trial. The entry criteria required two nasal cultures on two separate occasions, at least 24 hours apart and within a five day period. Minimal exclusion criteria included hypersensitivity to mupirocin or white paraffin, chronic cardiac, renal or hepatic disease or a history of any type of dermatitis; however, very few subjects were excluded.

Mupirocin and placebo ointments were distributed as identical 15 g tubes.[7] A 1 cm length of ointment (equivalent to 5 mg of mupirocin) was measured onto a sterile swab and applied to each of the anterior nares (1 cm per naris) and massaged backward for one minute to distribute the ointment fully. A total of 10 doses was applied (morning and evening for five days). Specimens for bacterial culture were obtained with a sterile rayon swab, one rotated five times in each nostril, and both swabs directly inoculated onto a single blood agar plate. Colonies of *S. aureus* were identified by morphology and slide latex coagulase tests. Antibiotic susceptibility tests were performed using disc-diffusion techniques, with or without replication by microbroth dilution according to National Committee for Clinical Laboratory Standards (NCCLS). In addition, all isolates underwent phage typing and/or plasmid analysis at a reference laboratory.

Therapy was considered successful if culture of the anterior nares 48-96 hours after the last dose was negative for *S. aureus*. Further follow-up cultures of the nares were also taken one, two and four weeks after therapy.

POOLED RESULTS FROM THE SIX TRIALS

The six clinical trials were performed at the University of Iowa, University of Cincinnati, Columbia University, University of California San Francisco, St Joseph's Hospital in Tampa and the Medical University of South Carolina.[7]

A total of 339 subjects was enrolled in the studies, 170 in the mupirocin group, 169 in the placebo group.[7] There were no significant differences between the groups in baseline characteristics such as age, gender and race *(Table 1)*. There was a similar frequency of reasons for discontinuation in both groups.[7] Overall, 24 subjects (14 mupirocin, 10 placebo) were unable to continue in the study. Of these, eight subjects were excluded because of negative pre-therapy cultures (five mupirocin and three placebo), i.e., subjects who did not meet the enrolment criteria. The only adverse event leading to discontinuation was an unpleasant after-taste experienced by one subject receiving mupirocin.

TABLE 1 - *Demographic data of the participants in the six clinical trials.*

Characteristic	Mupirocin (n=170)	Placebo (n=169)
Age: mean ± SD (range)	32.9 ± 9.2 (18-62)	32.7 ± 8.6 (21-60)
Gender: no. (%)		
Female	104 (61)	100 (59)
Male	66 (39)	69 (41)
Race: no. (%)		
Caucasian	128 (75)	120 (71)
Hispanic	14 (8)	14 (8)
African-American	10 (6)	11 (7)
Asian	12 (7)	19 (11)
Other	6 (4)	5 (3)

Note: results included here, with permission from: Doebbeling BN, Breneman DL, Neu HC et al. Elimination of *Staphylococcus aureus* nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. Clin Infect Dis 1993; 17: 466-474

The primary end-point in the study was elimination of *S. aureus* from the nares at 48 to 96 hours post-therapy.[7] *Table 2* shows the rate of eradication of *S. aureus* among the participants evaluable in the six centres. The overall rate of eradication was 91% in the mupirocin group versus 6% in the placebo group, giving a crude difference of 85% and an adjusted difference of 90%. The overall risk ratio for *S. aureus* carriage following treatment was 16. Thus, participants were 16 times more likely to have *S. aureus* in the nares after treatment if they had received placebo compared to mupirocin. This effect was consistent across centres (ranging from eight to 32).

TABLE 2 - *Nasal carriage elimination rates of Staphylococcus aureus among evaluable subjects from the six clinical trials.*

Centre	Mupirocin*	Placebo*	p value
All	130/143 (91)	8/142 (6)	<0.0001
1	31/32 (97)	1/33 (3)	<0.0001
2	21/23 (91)	1/20 (5)	<0.0001
3	19/28 (68)	1/30 (3)	<0.0001
4	6/7 (86)	0/5	<0.015
5	20/20 (100)	1/23 (4)	<0.0001
6	33/33 (100)	4/31 (13)	<0.0001

* Number of participants with eradication of *S. aureus*/total number (% with eradication)

Note: results included here, with permission from: Doebbeling BN, Breneman DL, Neu HC et al. Elimination of *Staphylococcus aureus* nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. Clin Infect Dis 1993; 17: 466-474

Rates of nasal carriage elimination for subjects at most centres ranged from 68% to 100%.[7] There was a highly significant difference ($p<0.001$) at all but one of the individual centres and overall for all centres combined. Although the protocol called for the enrolment of at least 50 subjects at each study site, only 12 subjects were enrolled at the sixth centre. Despite the small study sample, the results at this centre were also significant ($p<0.015$).

An intention to treat analysis which included all enrolled subjects, including those who did not meet all the pre-defined evaluable subject criteria, found similar results: 87% of the mupirocin group and 7% of the placebo group were free of *S. aureus* in the nares post-treatment ($p<0.001$).[7] A log linear model showed no evidence of any interactions between the treatment centre and outcome. This analysis demonstrates that there was a consistent effect in favour of mupirocin which was unaffected by any of the differences in patient populations or the method by which the protocol was implemented at each centre.

The proportion of subjects who were negative post-therapy and remained negative at the four week follow-up period is shown in *Table 3*.[7] Interestingly, 74% of the successfully treated mupirocin subjects (96/130) remained negative at four weeks, while only one of the eight subjects in the placebo group who had been negative post-therapy remained negative.

TABLE 3 - *Rates of nasal carriage elimination throughout the four week follow-up period from the six clinical trials.*

Centre	Mupirocin*	Placebo*
All	96/130 (74)	1/8 (13)
1	26/31 (84)	0/1
2	14/21 (67)	0/1
3	12/20 (60)	0/1
4	4/6 (67)	0/0
5	16/20 (80)	0/1
6	24/32 (75)	1/4 (25)

* Number of participants with negative nasal cultures one week, two weeks and four weeks after therapy/total number (% with negative cultures)

Note: results included here, with permission from: Doebbeling BN, Breneman DL, Neu HC et al. Elimination of *Staphylococcus aureus* nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. Clin Infect Dis 1993; 17: 466-474

Molecular typing was performed both by phage and plasmid pattern analysis.[7] Among the placebo subjects with post-treatment isolates, 97/106 (92%) had the same strain as was present at baseline. In the mupirocin groups, considerably fewer isolates were available after treatment; however, 5/7 (71%) had the same apparent strains as at baseline, whereas a new strain was found in the remainder (29%).

The study also tested for development of mupirocin resistance.[7] Although at the baseline there were five isolates which showed mupirocin resistance by disc-diffusion, when

the isolates were tested by broth microdilution, all the isolates had minimum inhibitory concentrations of less than 0.12 mg/l. At follow-up, two of the mupirocin and one of the placebo subjects who had resistant strains according to the disc-diffusion technique at baseline were negative for any *S. aureus* post-treatment. One of the placebo subjects was not evaluable for efficacy. The third placebo subject was positive at follow-up; however, the isolate was mupirocin-susceptible by both techniques. Following treatment, five isolates were considered mupirocin-resistant by the disc-diffusion technique, four in the mupirocin group and one in the placebo group. All of those isolates were mupirocin-susceptible by broth microdilution. The study demonstrated that the two susceptibility testing techniques do not agree. However, since there was no resistance according to the more reliable technique, we concluded that there was no evidence of development of mupirocin resistance.

Adverse experiences were reported by 57 subjects, 17% in each treatment group.[7] A similar frequency of respiratory or nasal signs and symptoms also occurred in each treatment group (14 mupirocin, 12 placebo), all of which were mild or moderate in severity. There were no serious adverse events.

UNIVERSITY OF IOWA STUDY

Our study at Iowa followed the same protocol as the other five centres; however we also evaluated hand carriage and performed enrichment cultures in addition to direct inoculation onto blood agar plates.[8] Additionally, we evaluated subjects in the original cohort at regular intervals over the year following therapy.[8,9]

A total of 311 healthcare workers was screened for nasal carriage using a pre-moistened rayon swab.[8] Of these, approximately one-third were nasal carriers with at least one positive culture, and 73 subjects (23%) had stable nasal carriage confirmed by a second positive culture. Five volunteers were judged incligible for enrolment by the pre-defined exclusion criteria, and the remaining 68 subjects were randomly assigned to receive mupirocin or placebo (34 to each group).

The baseline characteristics of the two study groups were quite similar *(Table 4)*.[8] Subjects in the mupirocin group were slightly older (p =0.20). Although not statistically significant, a trend towards older age could have biased the results against the mupirocin treatment and in favour of placebo. Nearly all of the 68 subjects completed the full three months of follow-up. The only subject not evaluable left town because of a death in the family and failed to take his medicine with him. All other cultures were obtained with the exception of one culture each in two different subjects (0.6% of the total).

TABLE 4 - *Characteristics of the participants in the University of Iowa study.*

Characteristic	Mupirocin (n=34)	Placebo (n=34)
Mean age (years)	34.9*	32.1
Gender: no. (%)		
Female	24 (71)	23 (68)
Male	10 (29)	11 (33)
Race: no. (%)		
Caucasian	33 (97)	32 (94)
Other	1 (3)	2 (6)
Involved in patient care: no. (%)	26 (77)	30 (88)
Early withdrawal from study: no.	0	1

* p=0.20. Note: all other comparisons not statistically significant (p>0.20)

Note: results included here, with permission from: Reagan DR, Doebbeling BN, Pfaller MA et al. Elimination of coincident *Staphylococcus aureus* nasal and hand carriage with intranasal application of mupirocin calcium ointment. Ann Intern Med 1991; 114: 101-106

Nasal cultures were obtained as described above with an additional culture into TLSO (5% Tween 80, 2% lecithin, 0.5% sodium oleate, 0.1% sodium sulphite, 0.1% proteous peptone and 0.1% tryptone) broth enrichment media, incubated for 24 hours, then subcultured onto blood agar.[8] Hand cultures were carried out by immersing each hand in a sterile plastic bag containing 30 ml of TLSO broth media and agitating for 30 seconds.[8] Aliquots of the broth were cultured onto blood agar plates and a further aliquot was incubated for 24 hours, then subcultured onto blood agar plates. Nasal and hand cultures were taken at

72-96 hours post-therapy, and nasal cultures were repeated one week, two weeks, one month and three months post-therapy. Long-term nasal and hand cultures were obtained at six months and one year (see "long-term follow-up" section below).

Figure 1 shows the rates of nasal carriage at each interval after treatment.[8] The upper line demonstrates that rates of nasal carriage in the placebo group declined over time from 100% at baseline to 82% after 12 weeks. In the mupirocin group at 12 weeks, 29% were positive for *S. aureus*. Thus there was a highly significant difference at three months in nasal carriage (p value <0.001; 95% confidence interval (CI_{95}) 26-80%). Thus, it is estimated that treatment resulted in a 53% difference in nasal carriage of *S. aureus* three months after therapy, although this difference could range from 26% to 80% in the overall population.

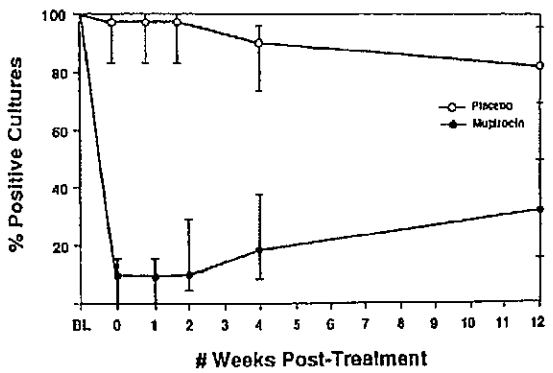

Figure 1 - Rates of nasal carriage at each time interval after treatment (University of Iowa study).

Note: results included here, with permission from: Reagan DR, Doebbeling BN, Pfaller MA et al. Elimination of coincident *Staphylococcus aureus* nasal and hand carriage with intranasal application of mupirocin calcium ointment. Ann Intern Med 1991; 114: 101-106.

Figure 2 demonstrates hand carriage rates at baseline and at 72 to 96 hours post-therapy. At baseline there was a slight difference in hand carriage, 29% in the mupirocin group compared with 50% in the placebo group (p=0.137). Only 3% of the mupirocin group as opposed to 58% of the placebo group carried *S. aureus* on the hands post-therapy, a significant decrease, even controlling for the baseline difference (p<0.001; CI_{95} 30-80%).[8]

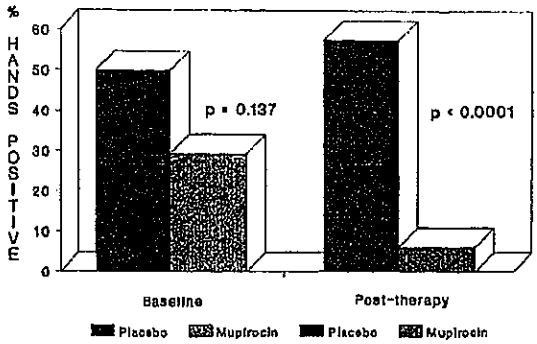

Figure 2 - Hand carriage rates at baseline and at 72-96 hours post-therapy (University of Iowa study).

Note: results included here, with permission from: Reagan DR, Doebbeling BN, Pfaller MA et al. Elimination of coincident *Staphylococcus aureus* nasal and hand carriage with intranasal application of mupirocin calcium ointment. Ann Intern Med 1991; 114: 101-106.

We also performed molecular typing using restriction endonuclease analysis of plasmid DNA, and some sample subjects are shown in *Figure 3*.[8] The first three columns show a placebo subject whose pre-treatment nasal (lane 1) and pre-treatment hand (lane 2) isolates appeared identical; at 12 weeks the same strain was isolated from the nose (lane 3). Lanes 4 and 5 show a mupirocin subject whose pre-treatment nose and hand strains were identical; subsequent cultures were negative until week 4 when a strain with the same pattern (lane 6) was isolated. Lane 7 is an isolate from another mupirocin-treated subject whose pre-treatment nasal isolate had one pattern and subsequently (following four negative nasal cultures) at the three month visit had a post-treatment nasal strain (lane 8) that had an obviously different plasmid type (i.e. re-colonisation by an apparently new strain).

Overall, the treatment group had significantly decreased nasal carriage at three months as well as significantly decreased hand carriage at 72 hours post-therapy. Molecular typing of the strains colonising the hands demonstrated that the isolates were almost uniformly of the same plasmid and antibiogram type as the strains colonising the nares. Side effects were mild, of brief duration and resolved with continued therapy. The frequency of any adverse experience was essentially identical in each group (22 mupirocin vs 23 placebo) and not significantly different. Thus, the study demonstrated that intranasal mupirocin calcium

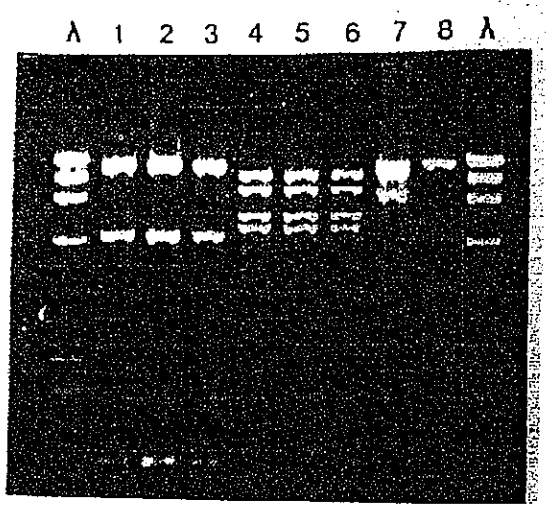

Figure 3 - Molecular typing using restriction endonuclease analysis of plasmid DNA (University of Iowa study).

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ointment was safe and effective in eliminating *S. aureus* hand carriage shortly after therapy, as well as nasal carriage for up to three months after a single brief treatment course. Importantly, the study results suggested that the anterior nares were the primary reservoir for *S. aureus* carriage in healthy adults.

LONG-TERM FOLLOW-UP STUDY

The original cohort of healthcare workers from the clinical trial at the University of Iowa was followed prospectively over a one year period.[9-11] The nares and hands of the subjects were cultured at six and 12 months, in addition to the cultures previously obtained. The isolates were typed by restriction endonuclease analysis of plasmid DNA and by antibiotic susceptibility testing.[10,11] Of the 68 healthcare workers in the initial group, 100% were cultured at six months and 93% at one year. The major outcome measure was the occurrence of any *S. aureus* cultured at either site (nares or hand) at six and 12 months, regardless of molecular type.[9,11] The similarity of nasal and hand isolate types at each time interval was compared with baseline isolates.

At six months, nasal carriage was 48% in the mupirocin group versus 72% in the controls, a relative risk for *S. aureus* of 0.68 in the treated group, with a difference that approached statistical significance (p=0.054).[10,11] At 12 months, nasal carriage was 53% in the mupirocin group versus 76% in the controls, giving a relative risk of 0.70, (p=0.056). Hand carriage at six months was significantly reduced in the mupirocin group, 15% versus 48% of controls (p=0.04), after adjusting for the baseline rate of hand carriage. Hand carriage was observed at least once in two-thirds of the subjects during the one year follow-up. Nearly all of the isolates (87%) matched the subject's current nasal plasmid and antibiogram type.[9,11] Typing of all the isolates showed that approximately one-third of the mupirocin-treated subjects were re-colonised in the nares with an entirely new strain, another third had re-isolation of the original strain after initially negative post-therapy cultures, and another third had negative cultures throughout.[9,11]

The overall results demonstrated that nasal carriage in the mupirocin group had returned to around 50% by six months, with a similar treatment effect persisting to one year. Nasal carriage in the treatment group was approximately 70% that of the control group at both time points. Hand carriage rates were significantly decreased at six months in the treatment group.

CONCLUSIONS

The results of these studies have important clinical implications for understanding the molecular epidemiology of staphylococcal infections. Typing of strains demonstrated that when *S. aureus* was recovered following intranasal treatment, isolation of the original strain occurred as commonly as did recovery of a new strain. Our study also found that *S. aureus* hand carriage was significantly decreased six months following a single course of intranasal therapy, which provides additional confirmation of the nares as the primary site for *S. aureus* colonisation in healthy volunteers. Healthcare workers who are nasal carriers of *S. aureus*, particularly those who have direct patient contact, represent an important hospital reservoir of *S. aureus*.

Additionally, the randomised, placebo-controlled studies demonstrate that a single five day course of intranasal mupirocin ointment is safe and well tolerated and effectively eliminates stable nasal carriage of *S. aureus* in healthy subjects. Long-term follow-up of the original cohort at one centre found that the majority of carriers were still clear after three months and that half were still negative after one year.

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