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Effect of Mupirocin Treatment on Nasal, Pharyngeal, and Perineal Carriage of *Staphylococcus aureus* in Healthy Adults

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Nasal carriage of *Staphylococcus aureus* is an important risk factor for *S. aureus* infections. Mupirocin nasal ointment is presently the treatment of choice for decolonizing the anterior nares. However, recent clinical trials show limited benefit from mupirocin prophylaxis in preventing nosocomial *S. aureus* infections, probably due to (re)colonization from extranasal carriage sites. Therefore, we studied the effectiveness of mupirocin nasal ointment treatment on the dynamics of *S. aureus* nasal and extranasal carriage. Twenty noncarriers, 26 intermittent carriers, and 16 persistent carriers had nasal, throat, and perineum samples taken 1 day before and 5 weeks after mupirocin treatment (twice daily for 5 days) and assessed for growth of *S. aureus*. The identities of cultured strains were assessed by restriction fragment length polymorphisms of the coagulase and protein A genes. The overall carriage rate (either nasal, pharyngeal, or perineal carrier or a combination) was significantly reduced after mupirocin treatment from 30 to 17 carriers ($P = 0.003$). Of the 17 carriers, 10 (60%) were still colonized with their old strain, 6 (35%) were colonized with an exogenous strain, and 1 (5%) was colonized with both. Two noncarriers became carriers after treatment. The acquisition of exogenous strains after mupirocin treatment is a common phenomenon. The finding warrants the use of mupirocin only in proven carriers for decolonization purposes. Mupirocin is effective overall in decolonizing nasal carriers but less effective in decolonizing extranasal sites.

In humans, the nose is the primary reservoir of *S. aureus* (6, 7). Approximately 30% of the healthy population carry *S. aureus* in the nose, which is an important risk factor for *S. aureus* infections (6). *S. aureus* nasal carriers have a threefold-increased risk for nosocomial *S. aureus* bacteremia compared to noncarriers (16). Approximately 80% of invasive nosocomial *S. aureus* infections are of endogenous origin in nasal carriers (14, 16).

Mupirocin nasal ointment is effective in temporarily eradicating *S. aureus* from the nose. When mupirocin is applied to the nose twice daily for 5 consecutive days, it has been reported to result in elimination rates of 91% directly after therapy, 87% after 4 weeks, and 48% after 6 months (2). However, despite these high elimination rates, three recent clinical studies found little or no efficacy of mupirocin in preventing nosocomial *S. aureus* infections (5, 9, 18).

In order to determine the effect of mupirocin treatment on *S. aureus* carriage at extranasal sites, we studied the effects of mupirocin treatment on different carrier types: persistent, intermittent, and nonnasal carriers of *S. aureus.* Pharyngeal carriage of *S. aureus* was assessed as well, since nasal application of mupirocin results in low concentrations of the drug in the pharynx (13, 15). Furthermore, perineal carriage was assessed, since perineal carriers are known to disperse more *S. aureus* organisms into the environment (10). Noncarriers were also included, in order to be able to identify whether mupirocin application in noncarriers may lead to carriage due to loss of colonization resistance (12). To assess the role of extranasal carriage sites in recolonization of the nose after mupirocin treatment, all strains were genotyped.

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MATERIALS AND METHODS

Study population and general study design. Healthy adult volunteers (n = 165) were screened for nasal carriage of *S. aureus* on at least five separate occasions, 1 week apart. A participant was labeled a persistent carrier if at least 80% of the cultures were *S. aureus* positive, as a noncarrier if all nasal cultures were *S. aureus* negative, and as an intermittent carrier in all other cases. Only participants who attended all culture occasions were included in the study.

Treatment and follow-up. Participants, who gave informed consent, self administered mupirocin 2% nasal ointment (SmithKline Beecham, Rijswijk, The Netherlands) twice daily for 5 days, according to the manufacturer's guidelines. Nasal, pharyngeal, and perineal samples were taken just before mupirocin treatment and once 5 weeks after treatment. Therapy failure was defined as having a positive nasal culture with *S. aureus* 5 weeks after the end of treatment. A nasal culture was taken by rotating a sterile swab four times in the anterior nares (Transwab; Medical Wire and Equipment Co. Ltd., Corsham, England). All swabs were processed on the same day. The swab was plated on Columbia blood agar plate medium (Becton-Dickinson, Etten-Leur, The Netherlands) and submerged in phenol red mannitol broth. The plates were read after 1 and 2 days of incubation, and the broths were read after 3 days of incubation at 35°C. Broths with a color change from red to orange-yellow were subcultured on blood agar plates. Identification of *S. aureus* was based on colony morphology, gram stain, a catalase test, and a latex agglutination test (Staphaurex Plus; Murex, Dartford, United Kingdom).

Genotyping. Genotyping was performed on the last *S. aureus* strain cultured before mupirocin treatment and on those strains cultured after mupirocin treatment. *S. aureus* DNA was obtained according to the method of Boom et al. (1). Restriction fragment length polymorphisms (RFLP) of the coagulase and protein A genes were determined for typing of all cultured *S. aureus* strains, as described previously (3, 4). Pulsed-field gel electrophoresis was performed to confirm the results obtained by RFLP, when appropriate, according to previously described methods (8). Strains were considered to be unrelated if the RFLP pattern of either the coagulase gene or the protein A gene differed from that of the other strain. Pulsed-field gel electrophoresis patterns were compared using the criteria of Tenover et al. (11).

TABLE 1. Change in carriage sites just before and 5 weeks after mupirocin treatment

Carriage site	No. positive					
	Persistent carrier (n = 16)		Intermittent carrier (n = 26)		Noncarrier (n = 20)	
	Before treatment[a]	After treatment	Before treatment[b]	After treatment	Before treatment	After treatment
Nose alone	6	3	5	1	0	1
Nose-throat	6	1	5	3	0	1
Nose-throat-perineum	0	1	1	1	0	0
Nose-perineum	3	0	0	0	0	0
Throat alone	0	2	2	0	1	1
Throat-perineum	0	0	1	0	0	0
Perineum alone	0	0	0	1	0	0
Total	15	7	14	6	1	3

[a] One persistent carrier had a negative nasal culture just before mupirocin treatment.
[b] Fifteen intermittent carriers had negative culture results just before mupirocin treatment.

Statistical analysis. Volunteers were classified, as described above, as persistent, intermittent, and nonnasal carriers using the results of at least five screening cultures. For each carriage type, the efficacy of mupirocin was assessed by comparing the culture results of the samples taken just before mupirocin treatment with the culture results of the samples taken 5 weeks after mupirocin treatment. Mupirocin therapy was considered to have failed if an individual carried *S. aureus* in the nose 5 weeks after treatment, irrespective of extranasal carriage. Nonparametric paired tests were used where appropriate. P values, two-sided, of <0.05 were considered significant.

RESULTS

At least five serial cultures each were obtained from 62 individuals from the initial cohort of 165 volunteers. Twenty volunteers were noncarriers (32%), 26 were intermittent carriers (42%), and 16 were persistent carriers (26%) (Table 1), and all participated in the mupirocin intervention. No serious side effects were observed, and all volunteers completed the treatment. The overall carriage rate (either nasal, pharyngeal, or perineal carrier or a combination) was significantly reduced after treatment, from 30 to 16 carriers ($P = 0.003$) (Table 1).

Mupirocin significantly reduces nasal carriage in persistent carriers. Of the 16 persistent carriers, 1 carrier had a negative nasal culture just before mupirocin treatment. Five carriers (31%) had therapy failure 5 weeks after mupirocin treatment (Table 1). Four remained colonized with the same strain, all of whom had at least one extranasal carriage site (three throat; one perineum). One volunteer acquired a new strain and never carried *S. aureus* in extranasal sites. In persistent carriers, mupirocin was effective in decolonizing *S. aureus* from the nose 5 weeks after treatment ($P = 0.002$) but was not effective in decolonizing throat and perineal carriage ($P = 0.69$ and $P = 0.5$, respectively).

No significant reduction of nasal carriage in intermittent nasal carriers after mupirocin treatment. Of the 26 intermittent carriers, 11 (42%) carried *S. aureus* just before treatment. Three of these (27%) had therapy failure. Two remained colonized with the same strain, one of whom was a perineal carrier before treatment. Of those who did not carry *S. aureus* just before treatment, two became colonized after treatment, one of whom was a combined pharyngeal and perineal carrier just before treatment. Overall, mupirocin treatment did not significantly reduce nasal ($P = 0.11$), throat ($P = 0.29$), and perineal ($P = 1.0$) carriage in this subgroup of intermittent carriers.

Rare acquisition of exogenous *S. aureus* after mupirocin treatment in nonnasal carriers. Within the noncarrier group ($n = 20$), there was one apparent throat carrier before mupirocin treatment. After treatment, two noncarriers became colonized with *S. aureus* (10%), one of whom carried *S. aureus* in extranasal sites before treatment. The pharyngeal carrier remained a pharyngeal carrier with the same strain.

Special emphasis on pharyngeal carriage ($n = 16$) and perineal carriage ($n = 5$). In general, there were 16 pharyngeal carriers before treatment, irrespective of carriage at other sites (12 were also nasal carriers). In 5 of the 12 nasal carriers (42%), the throat strain was different from the nasal strain. After treatment, six (38%) remained throat carriers, one of whom acquired a new strain, a significant reduction in throat carriage after mupirocin treatment ($P = 0.002$). Interestingly, of those who were nonthroat carriers before treatment ($n = 46$), five (11%) became colonized in the throat with *S. aureus*. Four of these new throat carriers were nasal carriers before treatment, and one was a noncarrier.

There were five perineal carriers (four were also nasal carriers) before treatment and three after treatment (a nonsignificant reduction). Only one perineal carrier remained a carrier after mupirocin treatment, with an identical strain. Two nonperineal carriers became perineal carriers after treatment, one of them with an endogenous strain.

DISCUSSION

Our results showed mupirocin efficacy on nasal decolonization 5 weeks posttreatment similar to that reported in previous studies (2). We found *S. aureus* nasal carriage elimination rates of 69% in persistent carriers and 58% in intermittent carriers. Therapy failure is not likely to be due to mupirocin resistance, since the prevalence of mupirocin-resistant strains is very low in The Netherlands: none was found in >1,000 strains (18). Only one strain was found to be mupirocin resistant after therapy in our study (data not shown). Though the prevalence of methicillin-resistant *S. aureus* is very low in The Netherlands, the findings of this study may be extrapolated to an

endemic methicillin-resistant *S. aureus* setting, as long as the strains are mupirocin sensitive (17).

Mupirocin nasal ointment also had a significant effect on pharyngeal *S. aureus* carriage decolonization, but not on perineal carriage. The effectiveness of mupirocin in reducing the occurrence of perineal carriage in this cohort was low, due to new acquisition of *S. aureus* at this site. Unlike in nasal carriage, where the effectiveness is much higher, mupirocin does not seem to have a preventive effect on *S. aureus* perineal carriage. Though the nose is the primary reservoir for *S. aureus*, the perineum itself is not directly affected by local application of mupirocin to the nose, as we saw in our study. Application of a local antibiotic or disinfectant on the perineum could be an option for optimal decolonization.

Interestingly, 10 volunteers became colonized at new sites 5 weeks after mupirocin treatment, 5 of them with exogenous strains (2 were noncarriers). Furthermore, two carriers became colonized with exogenous strains at their old sites after treatment. Overall, we can state that of the 17 carriers at any site after treatment, 10 (60%) were colonized with their old strains, 6 (35%) were colonized with an exogenous strain, and 1 (5%) was colonized with both old and exogenous strains. Therefore, the acquisition of exogenous strains after mupirocin treatment is a common phenomenon. The finding that two noncarriers became carriers after treatment (17% of all therapy failures) warrants the use of mupirocin only in proven carriers for decolonization purposes. Mupirocin also eradicates coagulase-negative staphylococci and corynebacteria, which may be present in noncarriers, and this change in the nasal flora may facilitate colonization with *S. aureus* by eliminating bacterial interference (12).

We conclude that mupirocin is effective overall in decolonizing nasal carriers but less effective in decolonizing extranasal sites. These extranasal sites may be sources for *S. aureus* infections. The majority of the *S. aureus* strains in those who remain colonized 5 weeks after treatment were endogenous, but acquisition of exogenous *S. aureus* strains occurs and warrants the performance of decolonization only in proven carriers. Furthermore, patients treated with mupirocin should receive follow-up cultures to determine treatment failure, which has already been introduced for dialysis patients.

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