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Randomized, Placebo-Controlled, Double-Blind Trial To Evaluate the Efficacy of Mupirocin for Eradicating Carriage of Methicillin-Resistant *Staphylococcus aureus*

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Mupirocin has been widely used for the clearance of nasal methicillin-resistant *Staphylococcus aureus* (MRSA) carriage during outbreaks, but no placebo-controlled trial has evaluated its value for eradicating MRSA carriage at multiple body sites in settings where MRSA is not epidemic. In a 1,500-bed teaching hospital with endemic MRSA, 102 patients colonized with MRSA were randomized into a double-blind, placebo-controlled trial and treated with either mupirocin (group M) or placebo (group P) applied to the anterior nares for 5 days; both groups used chlorhexidine soap for body washing. Follow-up screening, susceptibility testing, and genotyping were performed to evaluate treatment success, mupirocin or chlorhexidine resistance, and exogenous recolonization. At baseline, MRSA carriage was 60% in the nares, 38% in the groin, and 62% in other sites (skin lesions, urine). The MRSA eradication rate (all body sites) was 25% in group M (12 of 48 patients), compared to 18% in group P (9 of 50 patients; relative risk [RR], 0.72; 95% confidence interval [CI_{95}], 0.33 to 1.55). At the end of follow-up, 44% of patients (19 of 43) were free of nasal MRSA in group M, compared to 23% (11 of 44) in group P (RR, 0.57; CI_{95}, 0.31 to 1.04). Ten patients developed MRSA infections (three in group M and seven in group P). One mupirocin treatment failure was due to exogenous MRSA recolonization. No MRSA isolate showed chlorhexidine resistance or high-level mupirocin resistance; however, we observed an association ($P = 0.003$) between low-level mupirocin resistance at study entry (prevalence, 23%) and subsequent treatment failure in both study arms. These results suggest that nasal mupirocin is only marginally effective in the eradication of multisite MRSA carriage in a setting where MRSA is endemic.

The prevention and treatment of infections caused by *Staphylococcus aureus* has become a difficult task because of the worldwide emergence of multidrug-resistant strains (22). Nasal and extranasal carriage of methicillin-resistant *S. aureus* (MRSA) is an essential step in invasive MRSA infections and plays a decisive role in the dissemination of these microorganisms (18, 31). Topical mupirocin has been used widely for the clearance of nasal MRSA carriage during outbreaks (1). In guidelines recently issued by a British working group, this agent has been recommended for decolonization of all nasal MRSA carriers (4). Furthermore, mupirocin has been shown to eradicate carriage of *S. aureus* in health care workers (8) and to prevent staphylococcal infections in surgical and hemodialysis patients (19, 20).

Hitherto, there has not been a single placebo-controlled, randomized trial evaluating the value of mupirocin for eradicating multisite body carriage of MRSA in a setting where it is endemic. The aim of this investigation was to compare the efficacy of intranasal mupirocin and chlorhexidine body washing with that of chlorhexidine body washing alone in eliminating MRSA carriage at multiple body sites in hospitalized patients without signs of active MRSA infection.

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MATERIALS AND METHODS

Trial design and study objectives. This study was conducted in a double-blind, placebo-controlled fashion and was approved by the Institutional Review Committee at the University Hospitals of Geneva (HUG), Geneva, Switzerland. Treatment was allocated randomly in variable-length blocks. The primary study objective was the assessment of the clinical efficacy of mupirocin in eradicating overall MRSA carriage in patients who were MRSA carriers on admission to the hospital or became colonized during the hospital stay. Secondary study objectives were the assessment of the effect of mupirocin on MRSA nasal carriage, MRSA infection rates, resource use, and development of mupirocin or chlorhexidine resistance.

Setting and study population. HUG is a 1,500-bed health care center with 40,000 admissions per year, providing primary and tertiary acute care and geriatric long-term care. The annual rate of MRSA colonization or infection increased significantly ($r^2 = 0.88$, $P = 0.042$) from 0.05 cases per 100 admissions in 1989 to 0.57 cases per 100 admissions in 1994 (27). During the study period (October 1995 to September 1997), the number of newly identified MRSA patients decreased to a rate of 0.24 cases per 100 admissions following the implementation of various control measures previously described (12). On-site surveillance and molecular analysis showed that the spread of MRSA at HUG was mainly due to nosocomial transmission of several epidemic strains (12).

For the purpose of this study, patients were considered colonized with MRSA when one or more cultures from any body site yielded MRSA. MRSA infections were defined by the criteria set forth by the Centers for Disease Control and Prevention (CDC) (11). Patients older than 16 years who were admitted to HUG with a history of MRSA carriage during a previous stay or patients who acquired MRSA during their actual stay were eligible, provided that they were colonized and not infected with MRSA at the time of study inclusion. Exclusion criteria included a history of any of the following: pregnancy, hypersensitivity to the ointment, active staphylococcal infection and antimicrobial treatment directed against this infection, tracheal MRSA colonization or a tracheotomy tube colonized with MRSA, external osteosynthesis material colonized with MRSA, and previous enrollment.

Study medication and procedures. For patients receiving active treatment, calcium mupirocin 2% (Bactroban nasal; SmithKline Beecham) was applied

intranasally in a base of soft, white paraffin. Control patients applied a placebo ointment (soft, white paraffin base only) that was similar in appearance. Patients were instructed to apply a small amount of ointment (approximately 1 cm) with a cotton-tipped applicator to each of the anterior nares once in the morning and once again at night for 5 consecutive days. After each application, the nostrils were gently massaged to distribute the ointment. When necessary, a nurse administered the nasal ointment to ensure optimal compliance. Patients, investigators, and all health care workers involved were blinded as to the nature of the ointment. The tubes with the ointment bore the patient and study numbers without indicating the treatment. Concomitant infection control measures for all patients included consisted of the application of an antiseptic solution containing chlorhexidine for daily body cleansing and the contact isolation procedures routinely performed at HUG (12).

Microbiologic evaluation. Twelve, 19, and 26 days (each ±3 days) after the initiation of therapy, swabs were to be taken from different screening sites (the nose, the groin, pressure sores or other lacerated skin sites, and the urine if a catheter was present) and immediately introduced into Amies transport medium (Copan, Brescia, Italy). Semiquantitative cultures were performed on Columbia agar (Difco, Detroit, Mich.) supplemented with 5% sheep blood agar and on phenylethyl alcohol agar plates (Bacto Phenylethanol Agar; Difco) both incubated 48 h in 5% CO_2 at 35°C. Qualitative cultures were performed after enrichment in staphylococcal broth with 7.5% NaCl (Bacto m Staphylococcus Broth; Difco) during 24 h and subculturing on sheep blood agar plates. Identification of *S. aureus* was based on the morphology of colonies, a positive catalase test, the presence of clumping factor and protein A (Pastorex Staph-Plus; Sanofi Diagnostics Pasteur, Marnes-la-Coquette, France), and the production of heat-stable nuclease (Bacto DNase test agar [Difco] and toluidine blue O [E. Merck Suisse SA]) (17).

Antimicrobial susceptibility testing was performed according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) (25) by using disk diffusion methodology. Disks of mupirocin (Sanofi) were charged at 5 μg. The zone diameter breakpoints for isolates susceptible and resistant to mupirocin were at ≥14 and ≤13 mm, respectively (10). In addition, all *S. aureus* isolates were spot inoculated on Mueller-Hinton agar (Oxoid Ltd., Basingstoke, England) containing 6 mg of oxacillin (Sigma Chemical Co., St. Louis, Mo.)/liter and 4% NaCl according to NCCLS recommendations (25). MICs of chlorhexidine (Sigma Chemical Co.) were determined by the agar dilution method with an inoculum of 10^5 CFU/ml. MICs of mupirocin were determined by E-test methodology (AB Biodisk, Solna, Sweden). The MIC breakpoints of mupirocin were ≤4 mg/liter for susceptible isolates, 8 to 64 mg/liter for low-level resistance, 128 to 256 mg/liter for intermediate-level resistance, and ≥500 mg/liter for high-level resistance (21). *S. aureus* ATCC 29223 was used as a quality control strain for disk diffusion testing and for determination of MICs. Molecular typing of MRSA isolates was performed by contour-clamped homogenous electric field electrophoresis (CHEF), after digestion of chromosomal DNA as previously described (32). Clonal diversity was defined as proposed by Tenover et al. (30).

Efficacy analysis. The final outcome was determined without knowledge of which treatment had been given. Patients were withdrawn if they received antistaphylococcal agents other than the study drug or if they failed to receive two or more applications of the study ointment.

The results of bacteriologic cultures for MRSA provided the basis for evaluating treatment efficacy. If any of the screening cultures in the month following treatment with mupirocin or placebo were positive for MRSA, and if the strain was identical with the original strain, the case was counted as a failure.

Secondary outcome variables were MRSA nasal carriage, MRSA infection rates, development of mupirocin or chlorhexidine resistance, and resource utilization, which was measured by the length of the hospital stay after randomization, the duration of contact isolation, the number of visits by the infection control nurses, and the daily nursing workload. The latter was evaluated by the Project Research in Nursing (PRN) system, a validated system for managing nursing staff (13).

Sample size and statistical analysis. This study was designed to detect a difference of at least 30% in the overall MRSA eradication rate (60% in the mupirocin group [group M] compared to 30% in the placebo group [group P]) (15) with a power of 80% ($1 - \beta = 0.80$) and the overall α level set at 0.05. The minimal number of evaluable patients to be included in each study group was 48.

Analysis was performed by using the χ^2 test and the Fisher exact test for categorical variables and the *t* test or Wilcoxon test for continuous variables. Two-sided *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed with EpiInfo 6.0 (CDC, Atlanta, Ga.) and SPSS 8.0 (SPSS Inc., Chicago, Ill.).

RESULTS

Trial profile and study population. Between October 1995 and September 1997, a total of 275 patients were detected to be MRSA positive at HUG. Among these patients, 110 (40%) had MRSA infections and were not evaluated further. Sixty-three eligible patients (23%) were not enrolled because of varying exclusion criteria. Of the 102 randomized patients (51 to mupirocin and 51 to placebo), 4 were withdrawn at baseline because of concomitant systemic antistaphylococcal therapy. Ninety-eight patients (mupirocin, 48; placebo, 50) entered the intention-to-treat analysis.

TABLE 1. MRSA colonization sites of 98 patients assigned to receive mupirocin or placebo for topical decolonization

Group	No. (%) of patients with MRSA at the following site:				Total no. of colonized sites per patient (mean ± SD)
	Nares[a]	Groin	Skin[b]	Urine	
Mupirocin (n = 48)	26 (54)	18 (38)	26 (54)	9 (19)	1.8 ± 0.8
Placebo (n = 50)	31 (62)	19 (38)	19 (38)	11 (22)	1.7 ± 0.8

[a] Documented nasal MRSA carriage prior to randomization. Nasal screening was unavailable for 18 patients. Five patients were free of nasal MRSA carriage at baseline.

[b] Skin sites include pressure sores, chronic ulcers, and skin lacerations.

Ages averaged 74 ± 16 years; 59% of the patients were men. Sixty-three patients (64%) were newly detected MRSA carriers, and 35 (36%) had known MRSA carriage; among them, 22 had previously been exposed to mupirocin (median time interval, 155 days). Table 1 shows the different MRSA carriage sites at baseline: 58% of the patients (57 of 98) had microbiologically documented MRSA carriage in the anterior nares, 38% were colonized in the groin, and 62% were colonized at another site. Most patients (69 of 98; 70%) were colonized simultaneously at different body sites. There were no significant differences between the treatment groups with respect to other baseline characteristics (Table 2).

Efficacy. Table 3 shows the main results of this study. The overall MRSA eradication rate was 25% in group M (12 of 48 patients), and 18% in group P (9 of 50 patients; relative risk [RR], 1.39; 95% confidence interval [CI_{95}], 0.64 to 2.99; P = 0.40). The 21 patients who were free of MRSA throughout the follow-up period had a median of one MRSA-positive baseline culture (range, 1 to 3), with the following distribution: nose only, 4 patients; groin, 6; other skin sites, 11; urine, 4.

Among the total of 87 patients screened for nasal MRSA carriage at the end of follow-up, 19 of 43 (44%) were free of nasal MRSA carriage in group M, compared to 11 of 44 (23%) in group P (RR, 0.57; CI_{95}, 0.31 to 1.04; P = 0.06). For a subgroup of 51 patients, complete microbiologic documentation of nasal screening was available during at least 4 weeks of hospitalization. In this subgroup, nasal MRSA carriage was eradicated in 6 of 22 patients in group M and 5 of 29 patients in group P (RR, 0.63; CI_{95}, 0.22 to 1.81; P = 0.39). It is noteworthy that, of the 40 patients who were persistently colonized in the nose, 28 (12 in group M, 16 in group P) had concomitant groin colonization, 14 (6 in group M, 8 in group P) had skin lesions colonized with MRSA, and 8 (1 in group M, 7 in group P) had urinary-tract colonization. The noses of four patients in group M and two patients in group P who had negative nasal MRSA screening cultures after the end of the decolonization treatment were recolonized with genotypically identical MRSA strains during the follow-up period. In addition, treatment was associated with the eradication of previously documented MRSA skin carriage in 31% of patients in group M (8 of 26 previously colonized patients), compared to 21% (4 of 19) in group P (RR, 0.68; CI_{95}, 0.24 to 1.94; P = 0.47).

During follow-up, 10 patients developed MRSA infections (3 in group M and 7 in group P). All infections (four urinary-tract infections, five skin and wound infections, and one case of osteomyelitis) required systemic glycopeptide treatment for an average of 12 days (±10 days). Although it was not statistically

TABLE 2. Baseline characteristics of 98 patients assigned to receive mupirocin or placebo for topical decolonization of MRSA carriage

Characteristic	Value[a] for: Mupirocin group (n = 48)	Placebo group (n = 50)
Median age (range) (yr)	82 (38–105)	74 (28–94)
Sex (no. of males/no. of females)	27/21	31/19
Mean weight ± SD (kg)	67.2 ± 18.1	69.1 ± 19.6
Length of stay in hospital or institution prior to randomization (median no. of days [range])	42 (3–935)	33 (2–1,606)
No. (%) with previous hospitalization (within past 5 yr)	43 (90)	40 (80)
No. of previous hospitalizations (mean ± SD)	5.8 ± 5.5	6.1 ± 5.9
No. (%) with underlying conditions		
Coronary heart disease	12 (25)	10 (20)
Hypertension	18 (37)	17 (34)
Other cardiovascular disease	19 (40)	20 (40)
Diabetes mellitus (insulin dependent)	7 (15)	11 (22)
Diabetes mellitus (non-insulin dependent)	8 (17)	7 (14)
Liver cirrhosis	6 (13)	7 (14)
Other gastrointestinal disease	11 (24)	10 (20)
Rheumatologic disorder	3 (6)	4 (8)
COPD[b]	3 (6)	5 (10)
Other pulmonary conditions	5 (11)	11 (22)
Renal disease	6 (13)	7 (14)
Stroke	12 (25)	7 (14)
Other neurologic disease	9 (19)	8 (16)
Neoplasm	5 (11)	7 (14)
Mean no. of comorbidities[c] ± SD	3.3 ± 2.1	3.3 ± 2.1
Baseline workload score[d] (mean ± SD)	55.0 ± 27.3	55.0 ± 25.0
No. of infection control nurse visits (mean ± SD)	1.94 ± 2.8	1.98 ± 2.9
No. (%) with known MRSA status	20 (42)	15 (30)
No. (%) with prior mupirocin exposure	11 (23)	11 (22)
No. (%) who received previous antibiotic treatment for reasons other than MRSA infection	23 (48)	19 (38)

[a] No significant differences were found between the two groups of patients ($P > 0.10$ for all characteristics).
[b] COPD, chronic obstructive pulmonary disease.
[c] Summed up by using a composite index (28).
[d] Calculated by the PRN system (13).

significant, we observed a lower incidence density of MRSA infections in group M than in group P: 1.48 versus 2.82 infections per 1,000 patient-days, respectively (RR, 0.52; CI_{95}, 0.14 to 2.02; $P = 0.53$).

Further assessment showed no significant differences in resource utilization, length of stay, patient workload, and duration of isolation precautions between the two study groups (Table 3).

Genotyping and resistance patterns. A total of 183 isolates from 98 patients were available for molecular subtyping and determination of mupirocin and chlorhexidine resistance. The analysis of the chromosomal DNA of the MRSA isolates by CHEF showed identity of patient isolates at baseline and follow-up in all except two failure cases (one in each arm). All isolates were susceptible to chlorhexidine (MIC < 2 mg/liter).

No patient isolates showed intermediate or high-level resistance to mupirocin. Overall, 46 MRSA isolates with low-level mupirocin resistance (MICs, 8 to 64 mg/liter) were observed among 27 patients. At the time of study enrollment, strains with low-level resistance were documented in 23 patients (12 in group P and 11 in group M); strains in 4 patients acquired low-level resistance during mupirocin therapy. Mupirocin exposure prior to randomization was not a significant risk factor for low-level resistance (RR, 1.52; CI_{95}, 0.71 to 3.27; $P = 0.29$). In contrast, all 23 patients with strains exhibiting low-level resistance at the time of entry into the study had persistent MRSA carriage at the end of follow-up, compared to 54 of 75 patients without baseline low-level resistance (RR, 1.39; CI_{95}, 1.21 to 1.60). Thus, we noted an association between low-level mupirocin resistance at study entry and subsequent treatment failure ($P = 0.003$ by Fisher's exact test). It is noteworthy that this association was valid for both treatment arms, irrespective of the study therapy assigned: among 36 patients with persistent MRSA carriage in group M, 12 (33%) had strains with low-level mupirocin resistance at study entry, compared to 11 of 41 patients (27%) in group P (RR, 1.24; CI_{95}, 0.63 to 2.46; $P = 0.53$).

DISCUSSION

This is the first placebo-controlled, randomized trial to clarify the issue of mupirocin eradication treatment in hospitalized patients colonized with MRSA. Our results suggest that nasal mupirocin is only marginally effective in the eradication of multisite MRSA carriage in a setting where MRSA is endemic, even in combination with chlorhexidine body washing. Nasal MRSA carriage was reduced by mupirocin in some patients, but the elimination of MRSA from the anterior nares was not associated with an overall reduction at other body sites.

Our findings stand in contrast to those of studies in which mupirocin was given to health care workers (29) and to those of MRSA outbreak reports, in which it may have been over-

TABLE 3. Treatment results of 98 patients assigned to receive chlorhexidine body washing and mupirocin or placebo for decolonization of MRSA-positive body sites

Result	Value for: Mupirocin group (n = 48)	Placebo group (n = 50)	P
Primary outcome (no. of patients with MRSA decolonization of any positive body site/total no. of patients [%])	12/48 (25)	9/50 (18)	0.40
Secondary outcome			
No. of patients free of nasal MRSA carriage at the end of follow-up/total no. screened (%)[a]	19/43 (44)	11/44 (25)	0.06
No. of patients free of MRSA nasal carriage/no. of patients with complete nasal follow-up (%)[b]	6/22 (27)	5/29 (17)	0.39
Overall MRSA infection rate (no. [%] of infected patients)	3 (6)	7 (14)	0.32
Incidence density (no. of MRSA infections/1,000 days of follow-up)	1.48	2.82	0.53
Resource utilization			
Workload score[c] (mean ± SD)	36.1 ± 22.4	35.3 ± 22.5	0.71
Median no. of isolation days (range)	23 (2–168)	22 (3–98)	0.84
Length of hospital stay postrandomization (mean no. of days [range])	25 (1–249)	23 (2–447)	0.95
Median no. of postrandomization ICN[d] visits (range)	4 (0–19)	3 (0–53)	0.66

[a] Eleven patients were not screened at the end of follow-up.
[b] Refers only to patients with microbiologically proven baseline colonization and at least 4 weeks of complete in-hospital follow-up of nasal MRSA colonization.
[c] Calculated by the PRN system (13).
[d] ICN, infection control nurses.

looked that nasal carriage may have recurred after the end of mupirocin treatment (14). In addition, most outbreak studies did not evaluate carriage in the urinary tract or skin, which frequently provide sites for MRSA recolonization. Only one randomized trial from Spain compared mupirocin with oral cotrimoxazole plus topical fusidic acid and showed poor efficacy of mupirocin in eradicating extranasal MRSA carriage: MRSA eradication was achieved in 17 of 23 (74%) subjects treated with cotrimoxazole plus topical fusidic acid versus 3 of 13 (23%) patients treated with mupirocin ($P = 0.003$) (26). As in our patient cohort, many extranasal body sites (skin or urinary tract) existed where MRSA persisted and maintained itself.

The effect of mupirocin, considered the most effective agent available for elimination of MRSA carriage, may be overestimated and needs to be reconsidered in settings where MRSA is endemic. In fact, most studies of the use of mupirocin to eliminate MRSA carriage have been conducted during outbreaks, by using an observational study design, where mupirocin use was uncontrolled and multiple control measures were carried out in an effort to contain the epidemics quickly (1). Thus, it is difficult to evaluate whether the development of negative MRSA cultures in those outbreaks could be attributed to mupirocin therapy alone or to other infection control strategies as well.

In our study, the possibility that successfully decontaminated subjects were recolonized from external sources could be excluded in all but two cases. Although the development of high-level resistance has been reported in the literature (5), we observed no treatment failure related to this resistance mechanism. Thus, exogenous recolonization or high-level resistance cannot explain the results of our trial.

Hitherto, it has been postulated that low-level resistance to mupirocin (MIC $\leq$ 64 mg/liter) has no major clinical significance. This concept is based on the finding that strains with low-level resistance can be eradicated with mupirocin, given a local drug concentration of 20,000 μg/liter, the increased activity of the drug at acid pHs, and the rarity of clinical failures observed in the treatment of isolates demonstrating low-level resistance (3, 5, 9). Surprisingly, we observed in our study that low-level resistance at baseline was significantly associated with persistence of MRSA carriage, independent of the study drug assigned. Thus, even in placebo-treated patients, MRSA eradication was achieved only if low-level resistance was absent at study enrollment. Given the potential for specious associations when multiple statistical comparisons are performed, circumspection is required in dealing with these results. Further research in this direction is clearly needed, but our finding of a potential relation between baseline low-level resistance and subsequent treatment failure should reinforce heightened vigilance about mupirocin resistance and its clinical impact.

Several aspects of our study deserve careful analysis. First, despite the fact that we included all patients with a strong presumption of nasal MRSA carriage, only two-thirds (58%) of our study subjects had documented nasal carriage at baseline. In further studies, investigators should perform at least two pretreatment nasal swabs yielding MRSA in order to focus mupirocin treatment on patients who may better benefit from this eradication treatment. Second, we included a great variety of MRSA patients, including surgical and geriatric patients with multiple comorbidities and multiple MRSA colonization sites. We assume that by selecting less severely ill patients with nasal MRSA carriage only, we may have improved the efficacy rate of the mupirocin eradication treatment. Unlike other placebo-controlled mupirocin studies (8, 19, 20), in which the highly selected nature of the study population forced physicians to extrapolate results to the broader range of heavily colonized MRSA patients seen in most settings, our "real-life trial" was designed so that the circumstances of treatment closely resembled those of clinical practice. Third, we did not apply mupirocin ointment on skin lesions colonized with MRSA due to resistance concerns (16). Whether the combination of nasal and cutaneous mupirocin ointment could lead to improved outcomes needs further research. Finally, our results cannot be generalized to all settings. Mupirocin may still be a valuable element in stopping localized MRSA outbreaks, such as those occurring in critical-care units (6, 7, 24). But once MRSA has become endemic in a hospital, mupirocin is probably of less value, despite the common practice (23) and current recommendations (4) to apply mupirocin to all MRSA patients.

As stated by Boyce (2), more than 50 different treatment regimens have been tested for the eradication of nasal MRSA colonization, but the results have generally been unsatisfactory. Of all the topical treatments used, mupirocin has had the most encouraging results and is widely recommended for eradication of the MRSA carrier state. Based on our study results, we suggest that mupirocin should still be used with caution and may be targeted only at patients without chronic extranasal MRSA colonization.

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