MUPIROCIN-RESISTANT, METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*: DOES MUPIROCIN REMAIN EFFECTIVE?

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ABSTRACT

OBJECTIVE: To determine the efficacy of mupirocin ointment in reducing nasal colonization with mupirocin-susceptible, methicillin-resistant *Staphylococcus aureus* (MS MRSA) as well as mupirocin-resistant MRSA (MR MRSA).

DESIGN: Prospective evaluation in which patients colonized with MRSA were treated twice daily with 2% topical mupirocin ointment for 5 days.

SETTING: James H. Quillen Veterans' Affairs Medical Center.

PATIENTS: Forty hospitalized patients with two anterior nares cultures positive for MRSA within a 7-day period.

METHODS: Treated patients had post-treatment cultures at day 3 and weeks 1, 2, and 4. Isolates underwent mupirocin-susceptibility testing and DNA typing. MRSA clearance and type turnover were assessed for isolates that were mupirocin-susceptible, low-level (LL) MR MRSA and high-level (HL) MR MRSA.

RESULTS: Post-treatment nares cultures on day 3 were negative for 78.5%, 80%, and 27.7% of patients with MS MRSA, LL-MR MRSA, and HL-MR MRSA, respectively. Sustained culture negativity at 1 to 4 weeks was more common in the MS MRSA group (91%) than in the LL-MR MRSA group (25%) or the HL-MR MRSA group (25%). Positive post-treatment cultures usually showed the same DNA pattern relative to baseline. Plasmid curing of 18 HL-MR MRSA resulted in 15 MS MRSA and 3 LL-MR MRSA.

CONCLUSIONS: Mupirocin was effective in eradicating MS MRSA, but strains of MR MRSA often persisted after treatment. This appeared to reflect treatment failure rather than exogenous recolonization. MR MRSA is now more prevalent and it is appropriate to sample MRSA populations for mupirocin susceptibility prior to incorporating mupirocin into infection control programs (*Infect Control Hosp Epidemiol* 2003;24:342-346).

In the biological arms race between pathogen and antibiotic, the effectiveness of any antimicrobial can be impaired by the pathogen's ability to acquire resistance traits. This phenomenon is well exemplified in *Staphylococcus aureus*, for which resistance can extend from penicillin and methicillin to mupirocin. Methicillin-resistant *S. aureus* (MRSA) remains a major cause of nosocomial infections[1-4] and an array of infection control measures, including patient isolation, cohorting, chlorhexidine bathing, and decolonization efforts using mupirocin ointment, have been employed to control the spread of these infections in hospitals and nursing homes.[5-10] Whereas some investigators have incorporated applications of mupirocin ointment in their response to well-defined MRSA outbreaks,[5,11] others have advocated a broader use of the agent in programs aimed at aggressively managing MRSA colonizations or infections[9] or in efforts to reduce certain types of surgical-site infections.[12,13] Clearly, it is important to recognize published data that support the benefits associated with mupirocin use and, at the same time, it is appropriate to acknowledge the results of other studies that describe the emergence of mupirocin-resistant MRSA (MR MRSA), particularly in conditions for which mupirocin use has been widespread.[14-20]

Our review of the literature showed that definitions used to describe various levels of mupirocin resistance (low level vs high level) can differ[15,16,21-23] and several authors have raised doubt about whether some levels of mupirocin resistance are relevant at all because local mupirocin levels are approximately 20,000 μg/mL.[14-16,18,23,24] The issue of whether mupirocin resistance in MRSA is clinically important is critical for infection control personnel who are engaged in MRSA control efforts. Therefore, in view of this debate, we conducted a study to evaluate the ability of mupirocin to eradicate a variety of MR MRSA strains.

METHODS

Forty patients at James H. Quillen Veterans' Affairs Hospital were enrolled in the study (Table). Each patient had two sequential anterior nares cultures that were positive for MRSA within a span of 7 days (baseline cultures) and none were actively infected with MRSA. Eligible patients were at least 18 years old, male or female, and

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sufficiently healthy to complete a course of therapy. Patients were categorized according to functional status (from 0 to 4), with 0 representing a totally dependent patient. Mupirocin ointment (2% mupirocin calcium cream; Bactroban Nasal, SmithKline Beecham, King of Prussia, PA) was applied intranasally with a swab by a nurse twice daily for 5 days. Subsequent anterior nares cultures were performed at post-treatment day 3, week 1, week 2, and week 4. No other body sites had cultures for MRSA. Chlorhexidine body washes were performed on an irregular basis during the course of the study. Patients who received an oral or parenteral antibiotic to which the MRSA isolate was susceptible at any time during their participation in the study were eliminated from further evaluation. The study was approved by the East Tennessee State University Institutional Review Board and by the James H. Quillen Veterans' Affairs Medical Center Research and Development Committee. All enrolled patients completed an approved informed consent form.

Organism identification and methicillin resistance (growth on Mueller–Hinton plates containing 6 µg/mL of oxacillin and 4% sodium chloride) were confirmed and isolates were saved in skim milk at -70°C. All MRSA isolates were initially screened for mupirocin resistance using Mueller–Hinton agar and a 5-µg mupirocin disk (Oxoid Ltd., Basingstoke, England) incubated at 35°C. A zone size of 13 mm or less was considered to represent mupirocin resistance.[25] Organisms identified as mupirocin resistant by disk testing subsequently underwent minimum inhibitory concentration (MIC) testing to mupirocin using the Etest (AB Biodisk, Solna, Sweden). Isolates showing mupirocin MICs in the range of 4 to 256 µg/mL were categorized as low-level MR MRSA and those with mupirocin MICs of 512 µg/mL or more were considered high-level MR MRSA. These MIC ranges for low-level and high-level mupirocin resistance are similar to those published elsewhere.[17,22]

DNA typing was conducted using pulsed-field gel electrophoresis. Staphylococcal DNA was purified according to the method of Maslow et al.[26] Restriction digestion with *Sma*I was performed according to the manufacturer's guidelines and restriction fragments were separated in a CHEF DR II PFGE system (Bio-Rad Laboratories, Hercules, CA). The following electrophoretic conditions were used: 200 V, 14°C, and ramp 5 to 50 seconds for 22 hours. Restriction patterns were visualized by ethidium bromide fluorescence. An analysis of fragments was conducted by both visual inspection and the Alpha Imager 2000 (Alpha Innotech Corp., San Leandro, CA) using Alpha-Ease and PRO-RFLP software (DNA ProScan, Inc., Nashville, TN). Pulsed-field gel electrophoresis patterns were considered different if seven or more bands differed.[27]

Eighteen different high-level MR MRSA isolates were subjected to plasmid curing and were retested for mupirocin susceptibility by Etest. Plasmid curing was achieved by passaging broth cultures daily for 5 to 12 days at 42°C in tryptic soy broth.[15,28]

TABLE
PATIENT CHARACTERISTICS AND MUPIROCIN SUSCEPTIBILITY

	MS MRSA (n = 16)	LL-MR MRSA (n= 5)	HL-MR MRSA (n= 19)
Age, y			
Range	43–84	81–84	49–85
Mean ± SD	70.2 ± 11.2	82.8 ± 1.3	73.4 ± 8.5
Length of stay			
Range	7 d–5.5 y	2 wk–4.25 y	3 d–11 y
Median	2 mo	8 mo	2 mo
Functional status (%)*			
Level 0	3 (19)	2 (40)	3 (16)
Level 1	1 (6)	-	1 (5)
Level 2	3 (19)	-	1 (5)
Level 3	6 (38)	1 (20)	9 (47)
Level 4	3 (19)	2 (40)	5 (26)
Location at enrollment (%)†			
Nursing home	8 (50)	4 (80)	11 (58)
Intermediate care	4 (25)	1 (20)	3 (16)
Acute care	4 (25)	-	5 (26)
Chlorhexidine body washes (%)	6 (38)	2 (40)	9 (47)
Clinical factors			
Feeding tube	2	-	4
Decubitus ulcer	1	-	2
Bladder catheter	1	2	3
Endotracheal tube	-	-	1
Surgery in past month	2	-	1
Patients with ± 1 factor	1	-	3

SD = standard deviation; MS MRSA = mupirocin-susceptible, methicillin-resistant *Staphylococcus aureus*; LL-MR MRSA = low-level mupirocin-resistant MRSA; HL-MR MRSA = high-level mupirocin-resistant MRSA.
*Chi-square analysis of functional status ≤ 2 vs ≥ 3 for MS MRSA and HL-MR MRSA not significant ($P > .05$).
†Chi-square analysis of location at enrollment for MS MRSA vs HL-MR MRSA not significant ($P > .05$).

A chi-square analysis was used to test for significant differences among sample sets.

RESULTS

Patient enrollment extended from October 18, 1996, to August 27,1999. Enrollment dates for the three groups (mupirocin-susceptible MRSA [MS MRSA], low-level MR MRSA, and high-level MR MRSA) were well distributed throughout the study period. The table lists the characteristics of the 40 patients. In general, the population consisted of older men (no women were enrolled) with significant underlying illnesses. Baseline anterior nares cultures showed 16 patients (40%) with MS MRSA, 5 (12.5%) with low-level MR MRSA, and 19 (47.5%) with high-level MR MRSA. Twenty-three of the patients were located in the nursing home, 8 on intermediate care wards, and 9 on acute care wards. Functional status for highly dependent patients (levels 0 and 1) was similar for the MS MRSA and

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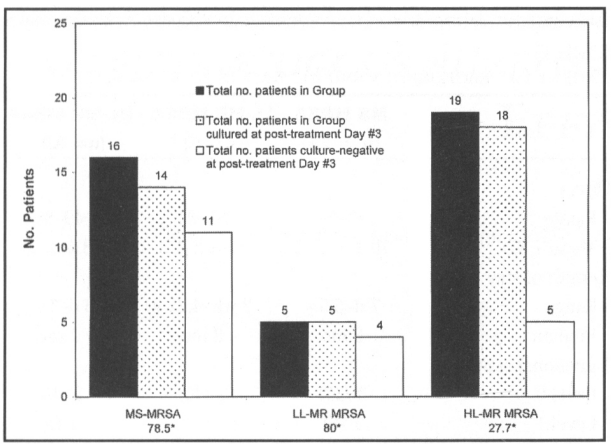

FIGURE. Clearance of methicillin-resistant *Staphylococcus aureus* (MRSA) by post-treatment day 3 according to baseline mupirocin susceptibility. MS-MRSA = mupirocin-susceptible MRSA; LL-MR MRSA = low-level mupirocin-resistant MRSA; HL-MR MRSA = high-level mupirocin-resistant MRSA; * = percentage MRSA culture negative at post-treatment day 3.

high-level MR MRSA groups (25% and 21%, respectively). Chlorhexidine body washes were performed for similar percentages of patients in each group and there were no major differences among clinical factors listed for the three groups.

For several years, mupirocin ointment was used on a regular basis on both acute care and long-term–care wards at our facility as part of a MRSA infection control program. During 1996 to 1999, a total of 864 inpatient prescriptions were written for mupirocin ointment.

Two time periods of post-treatment nares colonization were assessed: (1) the immediate post-treatment status (post-treatment day 3; Figure); and (2) for patients with at least two available subsequent nares swabs, colonization status during weeks 2 through 4. The two time periods provide different results. On the basis of day 3 cultures (Figure), MS MRSA and low-level MR MRSA were cleared at high and similar rates (78.5% and 80%, respectively) relative to high-level MR MRSA (27.7%). In contrast, sustained culture negativity was high for MS MRSA (91%), and much lower and equal for low-level MR MRSA and high-level MR MRSA (25%) ($P < .001$ for comparison between the MS MRSA and the high-level MR MRSA groups).

Post-treatment cultures tended to have the same genotype as the baseline culture, the same mupirocin resistance phenotype as the baseline culture, or both. Positive post-treatment cultures were recovered from 25% of MS MRSA, 80% of low-level MR MRSA, and 95% of high-level MR MRSA cases. In all but one case (a patient with high-level MR MRSA), the genotype found in post-treatment cultures matched the MRSA genotype recorded for the baseline culture. On rare occasion, the baseline genotype plus a new genotype or a completely new genotype was found. For the MS MRSA group, three of four post-baseline positive cultures were high-level MR MRSA. These isolates showed a genotype identical to that of the original MS MRSA isolate in each case and one patient showed the baseline genotype plus a new, unrelated genotype. All 4 low-level MR MRSA post-baseline positive cultures remained low-level MR MRSA and 17 of 18 of the high-level MR MRSA cultures remained high-level MR MRSA with one of these showing a mixed MS MRSA and high-level MR MRSA result.

Genetic diversity among MRSA isolates recovered in this study was limited. There were eight unrelated DNA types (designated 1 to 8). Four of these (types 1, 2, 3, and 6) included related subtypes. Similar genotypes were shared among the three groups (MS MRSA, low-level MR MRSA, and high-level MR MRSA) and no specific genotype predominated in a particular group.

Plasmid curing experiments were conducted on 18 high-level MR MRSA isolates that were recovered from 15 patients and that represented a variety of DNA types. Fifteen of these isolates (83%) converted to MS MRSA and 3 converted to low-level MR MRSA.

DISCUSSION

The occurrence of mupirocin resistance among strains of MRSA is now a well-defined phenomenon[14,15,17,19,20] that, in several reports, has resulted in the modification of infection control measures aimed at managing nosocomial MRSA infections.[9,17,23,28,29] Although most authors have categorized mupirocin resistance as either low level or high level, the respective levels of resistance associated with these terms have been inconsistent and have created difficulties when comparing the findings of one study against another.[15,16,23,24,30] For example, Watanabe et al.[16] define low-level resistance as correlating with a MIC range of 6.25 to 50 µg/mL, whereas others use the MIC range of greater than 4 to 256 µg/mL to define this population.[15,22] Clearly, it is desirable to standardize this terminology and accepting the MIC range of greater than 4 to 256 µg/mL for low-level mupirocin resistance and 512 µg/mL or greater for high-level mupirocin resistance as offered by Gilbart et al.[22] and Cookson[15] is a reasonable suggestion.

Most authors agree that low-level mupirocin resistance is the result of a chromosomally encoded altered isoleucyl-tRNA synthetase, whereas high-level resistance results from a plasmid-associated resistance element (mup A) that results in a novel isoleucyl-tRNA synthetase.[15,22,31] The clinical significance of any level of mupirocin resistance, and particularly low-level resistance, in *S. aureus* has been questioned because the local concentration of mupirocin can reach 20,000 µg/mL.[14-16,18,23,24,30] In this regard, Semret and Miller[24] have stated that the occurrence of low-level mupirocin resistance in MRSA is "probably of little or no clinical relevance." Interestingly, in certain reports in which the ability of mupirocin to eradicate strains of mupirocin-resistant MRSA has been described, mupirocin was applied to colonized patients for weeks or for the duration of their hospital stay.[23,24] In one study,[24] it appears that follow-up cultures to test for eradication were obtained while mupirocin applications were still under

way. In contrast, in a randomized, placebo-controlled, double-blind trial in which mupirocin was applied for 5 days, Harbarth et al.[21] found that the presence of low-level (MIC, 8 to 64 μg/mL) MR MRSA at the time of enrollment correlated with the persistence of MRSA carriage at the end of a follow-up period that extended to 26 days. Furthermore, their genotyping results showed the baseline and follow-up MRSA isolates to be identical in all but two cases and none of the treatment failures were associated with the recovery of high-level mupirocin-resistant isolates.

Data pertaining to the ability of mupirocin ointment to eradicate carriage of high-level MR MRSA are limited but the issue is of high importance because several outbreaks involving high-level MR MRSA have been reported in the literature.[17,19,20] Whereas Semret and Miller downplayed the clinical significance of low-level MR MRSA,[24] they also implied that mupirocin use may be beneficial even in the setting of high-level MR MRSA. Unfortunately, the specific mupirocin MICs for their study MRSA population were not stated, although 70% of their pre-study MR MRSA isolates were high-level MR MRSA. Furthermore, no genotype data were included to address the issue of exogenous recolonization versus relapse, mupirocin was applied to the nares four times daily for 2 weeks or until the patient's discharge, and it appeared that "follow-up" cultures were obtained while mupirocin applications were still under way. Others have expressed doubt about the ability of mupirocin to eradicate high-level MR MRSA isolates,[14,15,18,28,29,32,33] but to date a prospective study to assess this has not been conducted.

The current study was designed to include approximately equal numbers of patients in three study groups (MS MRSA, low-level MR MRSA, and high-level MR MRSA). However, there were only five patients with low-level MR MRSA and the number of patients in the other groups was also limited such that it is difficult to generalize our findings. When our data are interpreted, it is important to note that mupirocin ointment was applied to the anterior nares twice daily for 5 days and follow-up samples were obtained after the completion of treatment. There were no significant demographic or clinical differences between the MS MRSA group and the high-level MR MRSA group, but there was a trend favoring the use of various devices (eg, feeding tubes) in patients with high-level MR MRSA (Table). Although we found significant differences in the ability of mupirocin ointment to eradicate nasal MRSA carriage among the patients in these two groups, it is conceivable that the somewhat greater use of certain devices in the high-level MR MRSA group may have contributed to the high degree of persistent colonization in these patients by means of re-colonization from another body site.

As described by others,[34] our data show that mupirocin ointment can be highly effective in eradicating nasal carriage of MS MRSA. However, it does not appear effective in eradicating high-level MR MRSA strains and our limited experience with low-level MR MRSA supports the findings of Harbarth et al.[21]—the presence of low-level MR MRSA at study entry correlated with treatment failure.

Reasons for the recovery of MRSA in post-treatment anterior nares cultures vary and can involve re-inoculation from another colonized or infected body site or from a contaminated surface in the patient's environment, exogenous acquisition from other patients or staff, and treatment failure that might be associated with inappropriate application of the agent or with the presence of mupirocin-resistant organisms. We believe that it is the latter explanation that best accounts for the results found in our study, for the following reasons. MS MRSA showed sustained clearance at much higher rates than did cases with initially resistant MRSA (91% vs 25%), and for the four MS MRSA cases with post-treatment positive nares cultures, all were the same genotype as baseline and three were high-level MR MRSA. For the cases with mupirocin-resistant baseline cultures, all carried post-treatment MRSA with the same resistance phenotype and most had the same genotype (4 of 4 low-level MR MRSA and 17 of 18 high-level MR MRSA) as the baseline culture.

Regarding our MR MRSA population, plasmid curing experiments revealed that most of the high-level MR MRSA isolates converted to MS MRSA and a few became low-level MR MRSA. These findings are consistent with those of Cookson,[15] who noted that there are populations of MR MRSA that contain both plasmid-based (mup A gene) and chromosomally based mupirocin resistance determinants.

The following are worth noting:

1. There is considerable variation in design among studies that address the problem of MR MRSA. It is critical that investigators attempt to standardize definitions of low-level and high-level mupirocin resistance. The definitions of Cookson[15] and Gilbart et al.[22] could be adopted. Furthermore, readers must be cognizant of study design that might include prolonged use of mupirocin for individual patients and the obtaining of follow-up cultures while therapy is still under way.

2. Mupirocin use can be associated with the emergence of both low-level and high-level resistance in MRSA and it appears to be ineffective in eradicating the carriage of these organisms. Thus, both groups (low-level MR and high-level MR) should be viewed as clinically significant.

3. Suggestions for the appropriate use of mupirocin have been offered by several authors[9,15,35,36] and these should be considered prior to incorporating mupirocin into an infection control program.

4. In hospital settings in which mupirocin might be used on a broad basis, such as in the control of certain postoperative wound infections,[12,13] it would be essential to monitor for the emergence of mupirocin-resistant isolates. However, prolonged and widespread use of mupirocin in a healthcare facility should be discouraged.

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