Effect of Rifampin and Bacitracin on Nasal Carriers of *Staphylococcus aureus*†

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Anterior nares cultures from 664 hospital personnel identified 165 (24.8%) as carriers of *Staphylococcus aureus*. Persistent carriers (17.8%) were identified and randomly assigned to one of four treatment groups: rifampin (600 mg once a day for 5 days), bacitracin ointment (topically applied three times a day for 10 days), combined rifampin and bacitracin, and control (no treatment). Bacitracin ointment was ineffective in eliminating *S. aureus* from the anterior nares and had a posttreatment carrier rate equal to the control rate. Rifampin therapy caused a highly significant reduction (79%) in carriage; however, combined therapy was not as effective as treatment with rifampin alone. Of 132 strains of staphylococci isolated before and after treatment, all were susceptible to less than 0.016 μg of rifampin per ml. This study demonstrates that rifampin may be an effective antistaphylococcal antibiotic and could be used to control the carrier state in high-risk situations.

The anterior vestibule of the nose is an important reservoir of *Staphylococcus aureus*, and dissemination of this organism by carriers is important in the perpetuation and spread of staphylococcal disease (3, 12, 36). Staphylococci are responsible for more than 80% of the suppurative diseases found in medical practice (34) and are a major problem in newborn nurseries and neonatal intensive care units (11, 15). Additionally, the emergence of methicillin-resistant strains of staphylococci (6, 14, 17, 22) and strains with multiple resistance patterns (9, 10, 13, 21, 26, 28) heightened the importance of finding methods to treat staphylococcal disease, the staphylococcal carrier state, and associated nosocomial outbreaks (8, 19).

Bryan et al. (7) have reported that 70% of hospitals continue to obtain cultures from personnel during staphylococcal disease outbreaks, and about 40% prescribe topical antibiotic ointment for personnel with positive cultures. Although two studies performed in the 1950s (24, 32) reported that bacitracin ointment may be effective in controlling the carrier state and recent reports recommend use of topical antibiotics (23, 27, 29), there remains some question regarding the efficacy of bacitracin and other topical ointments (7, 19, 35). Recent studies (7, 8, 19) have suggested a need for further prospective controlled trials on the efficacy of topical bacitracin ointment and the establishment of more definitive guidelines relative to its use (7).

Several systemic antibiotic regimens also have been used to eradicate the staphylococcal carrier state (37, 38). In most cases, only a temporary suppression was achieved, persisting for a very short time after therapy was stopped. In a retrospective study, Sande and Mandell (25) have shown that rifampin may have considerable efficacy in eradicating nasal staphylococci. Most strains of *S. aureus* are exquisitely sensitive to low concentrations of rifampin (40). The drug penetrates well into nasopharyngeal secretions (16), and spread of rifampin-resistant strains appears to be minimal (25). Wheat et al. (33) have reported recently that they were able to eliminate nasal carriage of *S. aureus* among 80% of a group of male medical students given rifampin with or without cloxacillin. Their study also demonstrated that treatment with rifampin was effective in the eradication of coagulase-positive staphylococci in most subjects for 12 weeks after treatment (33).

The purpose of this study was to investigate the impact of systemic rifampin and topical bacitracin therapy, both alone and in combination, on nasal carriage of *S. aureus* among an occupationally diverse group of medical center personnel. We report the results of a randomized-controlled trial on persistent *S. aureus* nasal carriers.

**MATERIALS AND METHODS**

**Carrier identification.** Anterior nares cultures were obtained from asymptomatic personnel working in a large military medical center. The personnel cultured were divided into three major categories based on their job requirements. (i) Medical providers were defined as personnel who had frequent contact with patients (i.e., physicians, nurses, and health care technicians). (ii) Dental providers included only dentists and dental technicians. (iii) Nonproviders were personnel in the administrative and support sections of the medical center or technicians who had infrequent contact with patients. These categories are used for data presentation in Tables 1 and 2.

A sterile rayon-tipped swab (Marion Scientific Corp., Rockford, Ill.), preswabbed with transport medium, was used to obtain cultures by gentle rotation on both anterior nares. The cultures were plated on Trypticase soy agar (BBL Microbiology Systems) containing 5% defibrinated sheep blood, incubated at 37°C in 5% CO2, and examined at 24 h for staphylococcal colonies. Selected colonies were tested for coagulase (tube method) and DNase production. Coagulase-positive isolates were subcultured to check purity and transferred to slants for storage. Personnel identified as carriers of *S. aureus* were recultured 1 month later to determine persistent or transient carriage, and those with positive cultures on both occasions were contacted for entry into the study.

**Study design.** The purpose and nature of the study were explained to 95 subjects; 65 consented to enter by signing a
written informed consent. Each volunteer was randomly assigned to one of four groups. The three treatment groups were as follows: (i) 600 mg of rifampin taken once a day for 5 days, (ii) bacitracin ointment applied three times a day for 10 days, and (iii) a combination of both treatment regimens. The fourth group consisted of untreated controls. Fifty-nine subjects completed the study in full compliance with their assigned treatment regimen. There were no significant differences among the groups completing therapy based on age distribution, sex ratio, or occupational distribution (Table 1). No adverse side effects were reported from any of the subjects during the study.

Posttreatment nasal cultures from all groups were obtained 2 and 4 weeks after completion of the 10-day course of bacitracin therapy. This corresponded to 21 and 35 days after completion of rifampin therapy because rifampin was taken for only 5 days. Culturing and identification were performed as previously described; all coagulase-positive isolates were shipped for phage typing.

**MIC tests.** Rifampin MICs were performed on all 132 isolates obtained from the 59 subjects who completed the study. Bacitracin MICs were performed on 53 randomly selected isolates. The MICs were performed by the agar dilution method (1); rifampin was prepared at doubling dilutions from 0.004 through 2.0 μg/ml and bacitracin was prepared at doubling dilutions from 0.0625, through 32 μg/ml. These were prepared in Mueller-Hinton agar and poured to a depth of 4 mm in 150-mm plates. The plates were dried overnight and stored in the dark to avoid inactivation of the rifampin. After standardization of inoculum densities, each isolate was spotted onto the plates with 0.001-ml inoculating loop, and the plates were read after incubation at 35°C for 18 h.

Combination MICs were performed on 10 isolates; 5 were selected from pretreatment cultures and 5 were from posttreatment cultures. Bacitracin at levels of 0.5 and 1.0 μg/ml was combined with bacitracin at doubling dilutions from 0.001 through 2.0 μg/ml. The bacitracin levels were selected to be just below the previously determined MICs for these strains. These combination studies were performed by the agar dilution method described above.

**Phage typing.** Phage typing of all *S. aureus* strains was performed at the Epidemiology Laboratory, U.S. Air Force School of Aerospace Medicine, Brooks Air Force Base, Tex. Each strain was typed by the currently accepted international basic set (1974) of phages for routine typing of *S. aureus*. Additionally, *S. aureus* phage 292 was used for further subdivision of the type 94/96 and type 96 strains (5). Phage typing was performed at the routine test dilution and 100× the routine test dilution as described by Blair and Williams (4).

### RESULTS

Table 2 shows the distribution of nasal *S. aureus* carriers among the three major categories of medical center personnel. Initial cultures showed that the medical and dental provider rates (36.1 and 26.1%, respectively) were significantly higher than the rate among administrative personnel (19.1%). However, when persistent carriage was calculated from 1-month follow-up cultures, there were no significant differences among the three groups. A significant reduction in carriers among dental providers (*P* < 0.02 versus medical providers) at the 1-month follow-up culture indicated that there was a high level of transient colonization among the dental providers.

Culture results from 59 subjects who completed antibiotic treatment are shown in Table 3. Rifampin-treated subjects showed the highest reduction in carriage (79%) at the first posttreatment culture. A reduction of only 13% was observed among the bacitracin-treated group, which was virtually equal to that observed in the untreated group (control). Combination antibiotic therapy yielded a 42% reduction in carriers, which was less effective than rifampin therapy alone but more effective than bacitracin therapy. The highly significant reduction in carriers among rifampin-treated subjects (*P* < 0.001 versus control and bacitracin groups) was

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Age (yr) (Mean ± SD)</th>
<th>Occupation</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Medical providers</td>
<td>Dental providers</td>
</tr>
<tr>
<td>Rifampin</td>
<td>31 ± 6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>27 ± 6</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Combination</td>
<td>24 ± 4</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Control*</td>
<td>28 ± 7</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

* No significant difference among groups due to age (analysis of variance).

### Table 2. Distribution of *S. aureus* nasal carriers among medical center personnel

<table>
<thead>
<tr>
<th>Occupational group</th>
<th>Initial culture</th>
<th>Follow-up culture (1 mo)*</th>
<th>Persistent carriers*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. positive/</td>
<td>Carrier rate † (%)</td>
<td>No. positive/</td>
</tr>
<tr>
<td></td>
<td>no. cultured</td>
<td>(%)</td>
<td>no. cultured</td>
</tr>
<tr>
<td>Medical providers</td>
<td>103/394</td>
<td>26.1</td>
<td>78/103</td>
</tr>
<tr>
<td>Dental providers</td>
<td>22/61</td>
<td>36.1</td>
<td>11/22</td>
</tr>
<tr>
<td>Nonproviders</td>
<td>40/209</td>
<td>19.1</td>
<td>29/40</td>
</tr>
</tbody>
</table>

* Initial carrier rates among the medical and dental providers were significantly higher (*P* < 0.05 and *P* < 0.02, respectively) than the rate among nonproviders (chi-square analysis). The percent total carrier rate was 24.8.

† The percent total carrier rate was 71.5.

‡ Persistent carrier rates are calculated as the number of subjects with positive cultures at 1 month follow-up divided by the total number of subjects cultured in that group. The percent total carrier rate was 17.8.
TABLE 3. Results of nasal cultures for S. aureus after treatment

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>First posttreatment culturea</th>
<th>Second posttreatment culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. negative/total no. of cultures</td>
<td>Reduction</td>
</tr>
<tr>
<td>Rifampin</td>
<td>11/14d</td>
<td>79%</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>2/16</td>
<td>13%</td>
</tr>
<tr>
<td>Combination</td>
<td>5/12</td>
<td>42%</td>
</tr>
<tr>
<td>Control</td>
<td>2/17</td>
<td>12%</td>
</tr>
</tbody>
</table>

a Cultures in all groups were obtained 2 and 4 weeks after the 10-day course of bacitracin therapy was complete in the two groups receiving it; this corresponded to 21 and 35 days after completion of the 5-day course of rifampin therapy.

b Statistically significant at the P < 0.001 level when compared with the bacitracin and control groups; all other comparisons at the first posttreatment were not significant (chi-square test; Yate's correction for continuity).

c Statistically significant at the P < 0.05 level when compared with the bacitracin group and at the P < 0.02 level when compared with the control group. All other comparisons were not significant.

DISCUSSION

This study demonstrates that rifampin is an effective antibiotic for eradicating nasal carriage of S. aureus. A significant proportion of nasal carriers were free of S. aureus for more than 1 month after completing a 5-day course of rifampin therapy, and some subjects were negative when tested as much as a year later. Our results support previous observations of the carrier state during use of rifampin in antituberculous therapy (25) and also closely parallel results obtained in a similar study in which a 10-day course of rifampin was used to eliminate the carrier state (33). Recent reports of nosocomial outbreaks caused by multiply antibiotic-resistant staphylococci have demonstrated that these strains are difficult to eliminate from the hospital environment (6, 14, 19, 22). Although it has been shown that these resistant strains exhibit poor carrier colonizing potential (21, 22), only a small number of colonized personnel are necessary to perpetuate an outbreak (17, 19). Reporting on a large outbreak of multiply antibiotic-resistant S. aureus, Locksley et al. (19) have found that the outbreak was controlled only

TABLE 4. Phage typing analysis of S. aureus strains

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Initial isolates</th>
<th>% Typeable between initial and follow-up isolates</th>
<th>Posttreatment cultures</th>
<th>No. of isolates (% agreement with pretreatment isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. typeable/no. total</td>
<td>% Typeable</td>
<td>No. typeable isolates</td>
<td>Total no. of isolates</td>
</tr>
<tr>
<td>Rifampin</td>
<td>6/14</td>
<td>43%</td>
<td>100 100</td>
<td>100 100</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>7/16</td>
<td>44%</td>
<td>86 94</td>
<td>94 94</td>
</tr>
<tr>
<td>Combination</td>
<td>8/12</td>
<td>67%</td>
<td>88 92</td>
<td>92 92</td>
</tr>
<tr>
<td>Control</td>
<td>3/17</td>
<td>76%</td>
<td>92 94</td>
<td>94 94</td>
</tr>
</tbody>
</table>

a The phage lysis patterns of the first and second posttreatment isolates were compared with the lysis pattern of the second (follow-up) pretreatment isolate.

b Among typeable isolates, if there was a difference in lysis by less than two phages at the routine test dilution and less than three phages at 100× the routine test dilution, the initial and follow-up isolates were considered to be in agreement. Any changes in phage group or changes to nontypeable were considered to be not in agreement.

c Because of the high percentage of nontypeable isolates, they are included as part of the total no. of strains in this column; they were considered in agreement if paired isolates remained nontypeable.

d A single isolate in this group was unavailable for phage typing.
after rifampin was added to vancomycin treatment of infected patients, which correlated with eradication of the carrier state. In the same study, topical antibiotic therapy (polymyxin B-bacitracin ointment) was found to be uniformly ineffective in eradicating \textit{S. aureus} from nine patients. These authors have suggested that use of rifampin should be limited to high-risk situations (19, 31) and then only in combination with an additional antibiotic to prevent emergence of rifampin-resistant organisms (20, 39).

Use of bacitracin ointment to control or eradicate the carrier state during staphylococcal disease outbreaks still appears to be widespread (7, 8, 17, 19); however, its efficacy in this application has been questioned (7, 8, 19). Our results indicate that bacitracin ointment is not effective when used for this purpose, and because use of topical antibiotic ointments does have associated risk (13, 30), we agree that its empirical usage is questionable (7). In addition, we found that the group receiving a combination of topical bacitracin and systemic rifampin therapy actually had a higher post-treatment carrier rate than did the group receiving rifampin alone. In vitro studies did not indicate that antibiotic antagonism accounted for these results.

Phage type lysis studies showed that in the bacitracin and control groups the original strain of \textit{S. aureus} was, with few exceptions, carried throughout the study. The number of typeable isolates available for comparison in the combination and rifampin treatment groups was extremely small; however, there was a comparatively higher number of typing changes observed in the group receiving combination therapy. Subsequently, we considered these typing changes as treatment successes and found that combination therapy was approximately equal in effectiveness to treatment with rifampin alone. This observation led to the suggestion that the relatively high posttreatment carrier rate in the group receiving combination therapy might be due to rapid reacquisition of new strains after eradication of the initial organisms. This proposal offers a tenable explanation for the unexpectedly high number of carriers in the combination therapy group, although it does not indicate that bacitracin ointment contributed to eradication of the original colonizing strain. Alternatively, it is possible that continued use of the bacitracin ointment for 5 days after completion of rifampin therapy may have actually facilitated reacquisition of new strains. Wheat et al. (33) have reported that changes in phage type lysis occurred in 50% of their subjects who received rifampin with or without cloxacillin. Although we did not observe a high percentage of typing changes in our rifampin-treated subjects, these changes may have been evident with a larger number of typeable isolates.

In summary, our results lend support to the use of rifampin against the \textit{S. aureus} carrier state. Topical bacitracin therapy has little usefulness in this setting. Although we did not observe the emergence of rifampin-resistant organisms in this study, rapid development of resistance is well documented (2, 18, 20, 25, 39). For this reason, in addition to the potential renal and hepatotoxic problems associated with use of rifampin, it is generally recommended that it be used to eradicate colonization only in high-risk situations, and then only in combination with an additional antistaphylococcal antibiotic (19, 20, 39). Rifampin in combination with trimethoprim-sulfamethoxazole has been used successfully to eradicate the carrier state in patients colonized at both nasal and extranasal sites (31). Evaluation of such combinations in clinical studies resulting from the carrier state, such as recurrent furunculosis, is clearly warranted.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


