ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1995, p. 175–179 Vol. 39, No. 1
0066-4804/95/$04.00+0

Comparative Study of Mupirocin and Oral Co-Trimoxazole plus Topical Fusidic Acid in Eradication of Nasal Carriage of Methicillin-Resistant *Staphylococcus aureus*

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Received 22 February 1994/Returned for modification 17 May 1994/Accepted 11 October 1994

Mupirocin is a topically applied drug that is very active in the eradication of nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA). However, studies designed to compare mupirocin treatment with other antimicrobial regimens are lacking. We therefore conducted an open, prospective, randomized, controlled trial to compare the efficacy and safety of mupirocin versus those of oral co-trimoxazole plus topical fusidic acid (both regimens with a clorhexidine scrub bath) for the eradication of MRSA from nasal and extranasal carriers of MRSA. The eradication rates with mupirocin and co-trimoxazole plus fusidic acid at 2, 7, 14, 21, 28, and 90 days were 93 and of 93, 100 and 100, 97 and 94, 100 and 92, 96 and 95, and 78 and 71%, respectively, for nasal carriage. At 7, 14, and 28 days the eradication rates for extranasal carriage by the two regimens were 23 and 74, 83 and 76, and 45 and 69%, respectively. The efficacies and safety of both regimens were similar. The MRSA isolates were not resistant to the study drugs either at the baseline or at follow-up. These results suggest that mupirocin and co-trimoxazole plus fusidic acid, both used in conjunction with a chlorhexidine soap bath, are equally effective and safe for the eradication of MRSA from nasal and extranasal MRSA carriers. Mupirocin was easier to use but was more expensive.

Nasal and extranasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) plays a decisive role as a reservoir of and in the dissemination of MRSA infections (1).

Eradication of MRSA from these reservoirs can be accomplished with only a few topical or systemic antimicrobial agents. Topical mupirocin (pseudomonic acid) is effective against both methicillin-susceptible *S. aureus* and MRSA carriage (3, 22, 24). Oral co-trimoxazole (13) and topical fusidic acid are antimicrobial agents commonly used either individually or in association to eradicate MRSA (8, 10, 15). We conducted an open, randomized, controlled trial in order to compare the efficacies and safety of two different regimens (mupirocin versus co-trimoxazole plus topical fusidic acid) to eradicate MRSA from nasal and extranasal carriers of MRSA during an extensive outbreak of MRSA in our hospital.

(This study was presented in part at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, Calif., 11 to 14 October 1992.)

MATERIALS AND METHODS

Hospital setting. Gregorio Marañón Hospital is a 2,200-bed university institution with an ongoing outbreak of MRSA representing 25% of all *S. aureus* isolated during 1991 (15). All of our MRSA strains are susceptible in vitro to co-trimoxazole, fusidic acid, and mupirocin (15).

Study sample. From September 1991 to July 1992 we carried out a prospective, open, randomized, comparative trial in order to compare the efficacy and safety of topical mupirocin versus those of the combination of oral co-trimoxazole plus topical fusidic acid in the eradication of MRSA from nasal carriers. Patients and health care workers from areas with high incidences of MRSA (two intensive care units and one surgical ward) were routinely screened for nasal carriage of MRSA. Rates of infection remained unchanged during the study period.

We included candidates who fulfilled the following criteria: adults (>18 years old), stable nasal carriers (at least two consecutive MRSA isolates from the nares in a 5-day period), and no clinical history of allergy or intolerance to any of the involved drugs. All patients consented to participate in the study. We excluded pregnant women or patients with biochemical evidence of renal or hepatic dysfunction.

Study design. A brief medical history and a medical examination were performed on all subjects. Samples from nasal and extranasal (axillae, groin, and perineum) areas were obtained for culture. A drug assignment list was prepared by a computer method with randomization of blocks of four. Patients belonging to the mupirocin group received topical 2% mupirocin calcium ointment in a paraffin base without polyethylene glycol (three times daily). The ointment was applied with the fingertip or a rayon swab; this was followed by a short nasal massage. Patients belonging to the other group received a combination of topical 2% sodium fusidate salt in paraffin ointment as described above plus oral (or nasogastric) co-trimoxazole in the form of a double-strength tablet (160 mg of trimethoprim plus 800 mg of sulfamethoxazole). Both therapeutic regimens were administered during a 5-day period and were combined with a daily or a twice-daily chlorhexidine soap bath.

While receiving treatment each subject was examined daily by one of the investigators. Repeated examinations were done and samples from the anterior nares, axillae, groin, and perineum of each subject for culture were obtained on the second day of therapy and between 48 and 72 h after the end of therapy (first week). Follow-up samples from nasal and extranasal areas for culture were obtained at 2 weeks, 3 weeks, 1 month, and 3 months after the end of therapy, when possible.

Microbiological evaluation. Culture specimens were obtained by firmly rotating a new, premoistened, rayon-tipped swab five times in both anterior nares. The swabs were cultured directly on mannitol salt agar (Becton Dickinson, BBL Microbiology Systems). The plates were incubated at 37°C in air and were examined at 24 and 48 h. All mannitol-positive colonies were subcultured onto blood agar plates and were then identified by standard procedures (12). All isolates of *S. aureus* for which oxacillin MICs were greater than or equal to 2 μg/ml were considered methicillin-resistant isolates according to the criteria of the National Committee for Clinical Laboratory Standards (14).

Antimicrobial agents and susceptibility tests. Mupirocin, in the form of lithium salt pellets, was provided by Beecham Laboratories, Spain. Dilution of the compound was performed on the day of use, in accordance with the manufacturer's instructions. Other antimicrobial agents were supplied in lyophilized form in MicroScan panels (Baxter Laboratories, West Sacramento, Calif.). Inoculation of the panels was performed according to the manufacturer's specifications.

Mupirocin MICs were determined by standard agar dilution technique in Mueller-Hinton agar (Oxoid, Unipath Ltd., Basingtoke, England) following the specifications of the National Committee for Clinical Laboratory Standards (14). All strains for which MICs were equal to or greater than 4 μg/ml were considered resistant. Determination of susceptibility to penicillin, ampicillin, oxacillin, co-trimoxazole, rifampin, ciprofloxacin, fusidic acid, and imipenem was performed

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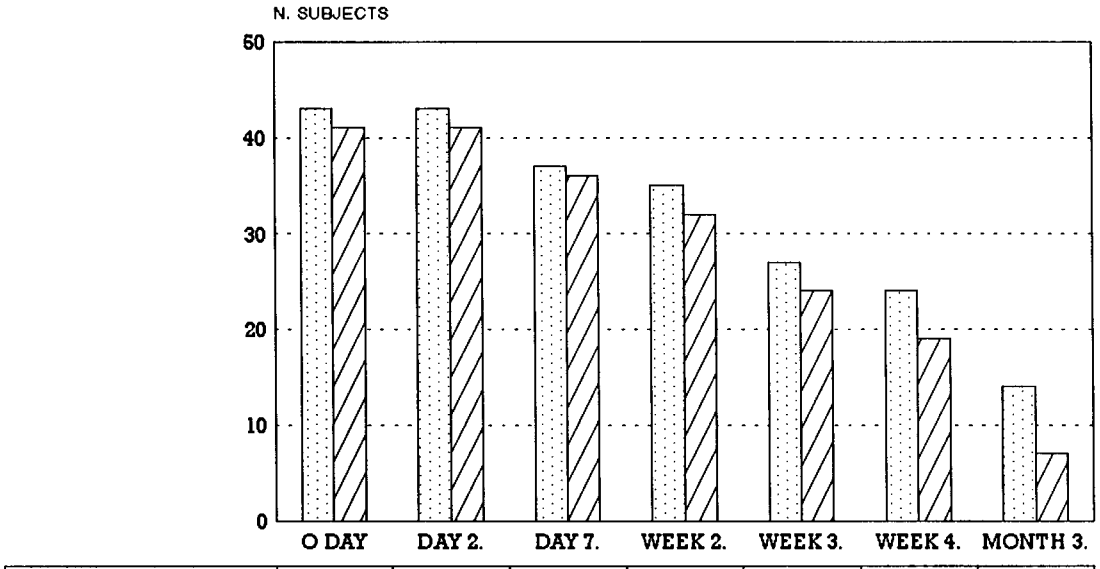


FIG. 1. Follow-up of the mupirocin (▤) and co-trimoxazole plus fusidic acid (▨) groups.

by automated microdilution methods with MicroScan AutoScan 4 panels. *S. aureus* ATCC 25923 was used as a control strain.

Analysis of efficacy. Results of bacteriological culture for *S. aureus* provided the basis for evaluating the efficacy of treatment. Strain identity was determined by antimicrobial susceptibility testing and biochemical pattern (MicroScan). In the evaluation of the efficacies of both regimens a negative response was defined as noneradication of the initial strain. Noneradication was defined either as isolation of the initial MRSA strain after treatment (failure) or as initially negative cultures after treatment with subsequent isolation of the initial strain (relapse). A positive response was defined as the absence of isolation of MRSA after therapy.

Statistical analysis. The demographic characteristics of both study groups as well as adverse events were evaluated by a two-sample *t* test for each continuous variable and either a chi-square or a Fisher exact test for categorical variables. Two-tailed tests were used for all analyses.

RESULTS

During the study period (September 1991 to July 1992), 1,056 subjects were screened for nasal carriage of MRSA. MRSA was isolated from the anterior nares of 156 (15%) subjects. Among them, 84 (8% of all study patients) were considered to be stable nasal carriers of MRSA and met all inclusion criteria for the study. Eleven subjects were health care workers and 73 subjects were patients.

Forty-three patients were assigned to the mupirocin group and 41 were assigned to the co-trimoxazole plus fusidic acid group. The demographic, clinical, and epidemiological characteristics of both groups (Table 1) were comparable with respect to age, sex, underlying diseases, days of hospitalization, concomitant use of vancomycin, clinical situation at the beginning of therapy, and mortality. Extranasal colonization was more frequent in the co-trimoxazole plus fusidic acid group, and this was statistically significant ($P = 0.009$; Fisher exact test). However, patients were randomly selected to enter each therapeutic regimen, independently of nasal or extranasal colonization. Eleven subjects in each group died during the first 4 weeks of follow-up. In addition, a number of subjects were lost, especially after the fourth week of follow-up, when they were discharged from the hospital, and when they did not return for the last examination. The number of patients remaining in each period of the study in both groups is shown in Fig. 1.

Mupirocin proved to be very effective in the nasal eradication of MRSA (Fig. 2). After 48 h of treatment, 40 of 43 patients (93%) were free of nasal MRSA. The three patients whose MRSA persisted into the second day of therapy were found to be clear of MRSA in the next control (seventh day). Consecutive percentages of nasal eradication with mupirocin are shown in Fig. 2 and were as follows: 37 of 37 (100%) at the seventh day, 34 of 35 (97%) at the second week, 27 of 27 (100%) at the third week, 23 of 24 (96%) at the fourth week, and 11 of 14 (78%) at the third month. In five subjects a probable relapse of MRSA colonization was documented. The strains were not typed genetically in order to determine if the relapses were actual relapses with the same strain or reinfection with a new and different strain. However, all strains were typed biochemically by means of the MicroScan panels as well

TABLE 1. Characteristics of the two study groups

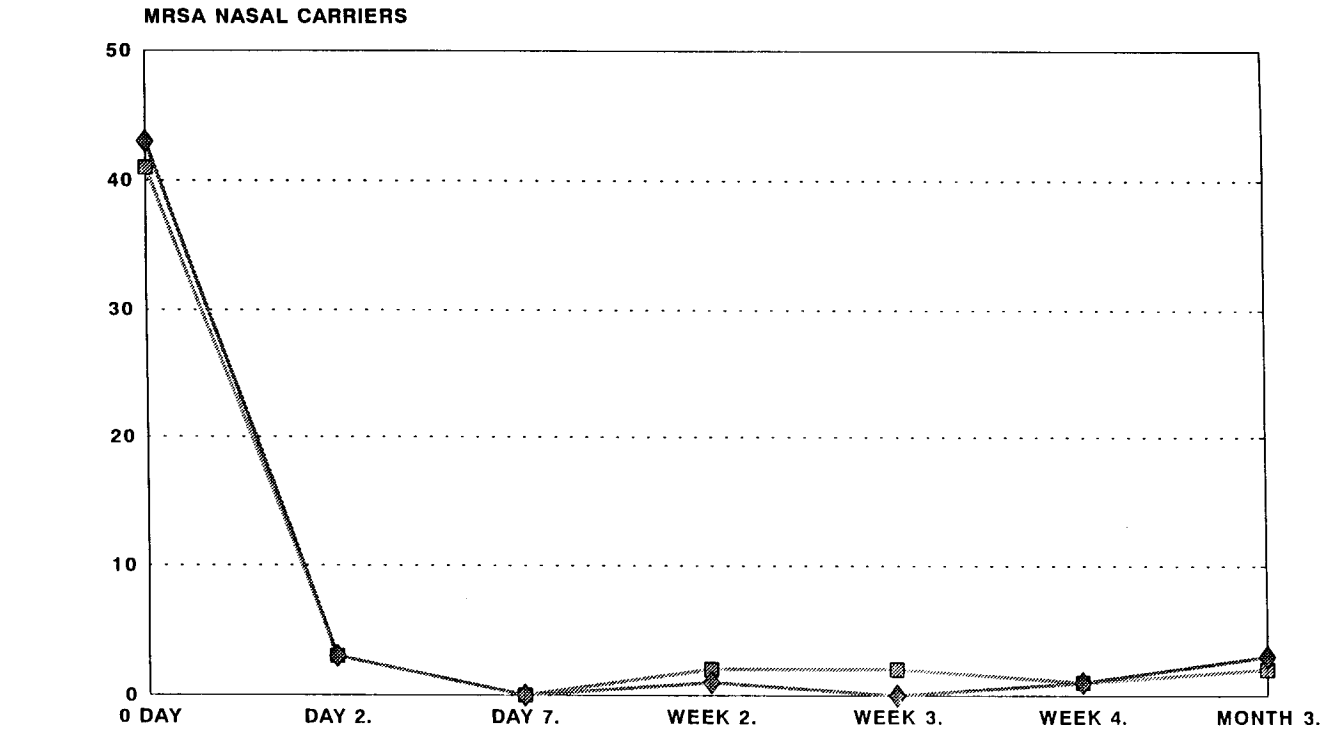
Characteristic	Mupirocin group	Co-trimoxazole + fusidic acid group
No. of patients	43	41
No. of health care workers	7	4
Mean time of hospitalization (days)	19.3	26.2
Mean age (yr)	52.3	55.8
No. of males/no. of females	29/14	28/13
Underlying disease[a]	1/10/26	1/7/27
Clinical status[b]	16/14/7	16/12/6
No. of subjects with MRSA infection	17	10
No. of subjects that used vancomycin	14	8
No. of subjects with extranasal colonization	17	28[c]
Mortality (no. of patients)	11	11

[a] Numbers indicate numbers of patients with rapidly fatal/ultimately fatal/nonfatal diseases, according to McCabe.

[b] Numbers indicate number of patients with stable/severe/critical clinical status, according to the modified Winston criterion.

[c] $P = 0.009$ by the Fisher exact test.

[d] $P > 0.10$ using the Student t test.



MUPIROCIN	43	43	37	35	27	24	14
SXT + FA	41	41	36	32	24	19	7

FIG. 2. Nasal eradication of MRSA in the mupirocin (◈) and co-trimoxazole plus fusidic acid (▤) groups.

as by their antibiotypes, and in all cases the biotypes and antibiotypes of the strains were the same. Moreover, the study was performed during an outbreak in our hospital caused by the same strain. None of the strains isolated from the patients with relapses were resistant to mupirocin, co-trimoxazole, or fusidic acid.

Of the 41 subjects who received co-trimoxazole plus fusidic acid, MRSA was eradicated from 38 (93%) after 48 h of therapy. MRSA persisted in three patients and was eradicated in the next control. Follow-up controls disclosed percentages of eradication similar to those in the mupirocin group (Fig. 2): 36 of 36 (100%) at the first week, 30 of 32 (91%) at the second week, 22 of 24 (91%) at the third week, 18 of 19 (95%) at the fourth week, and 5 of 7 (71%) at the third month. A total of seven subjects had MRSA colonization relapses. None of these strains were resistant either to co-trimoxazole or fusidic acid.

There were no significant differences between the two groups either in the initial or in the sequential efficacy in the nasal eradication of MRSA.

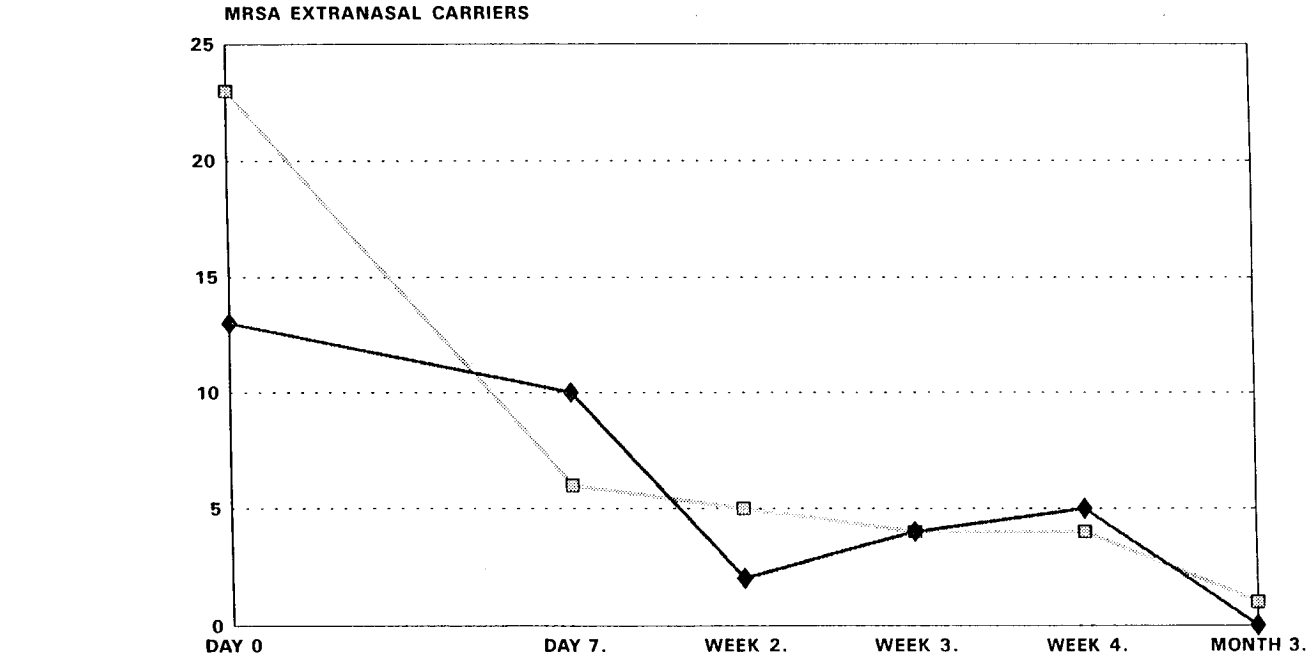
In addition to positive nasal cultures, MRSA was isolated from one or more extranasal sites (axillae, groin, or perineum) of 45 subjects. Of these subjects, 28 received co-trimoxazole plus fusidic acid and 17 received mupirocin. Figure 3 shows the eradication of extranasal carriage of MRSA by the two therapeutic regimens. Eradication of extranasal MRSA was registered for 17 of 23 (74%) evaluable subjects treated with co-trimoxazole at the end of therapy, while only 3 of 13 (23%) evaluable subjects treated with mupirocin manifested eradication at the end of therapy ($P = 0.003$). Surprisingly, 7 of the 10 patients treated with mupirocin in whom MRSA persisted cleared the organism without further intervention during the second week of follow-up. No significant differences in the percentages of eradication were found between the two groups in subsequent follow-up controls at 14 and 28 days: 83 and 76 and 45 and 69% for the two groups, respectively.

Twenty-six treated patients had surgical wounds; however, the presence of wounds did not influence the eradication of nasal and extranasal MRSA carriage after treatment. Six patients presented with surgical wound colonization by MRSA, in which eradication was more difficult with both regimens.

Both regimens were safe. No subjects were forced to stop therapy because of secondary events. A negligible number of those patients treated with the topical application of mupirocin or fusidic acid presented with minimal nasal discomfort. No systemic adverse effects directly attributable to the drug during the time that it was administered were observed in the co-trimoxazole group (only two patients suffered from co-trimoxazole-related nausea). The cost of the entire mupirocin treatment period ($15), was five times higher than that of co-trimoxazole plus fusidic acid ($3).

DISCUSSION

Traditionally, nasal MRSA eradication trials involving only one topical or systemic antimicrobial agent have met with limited success and have often led to the development of bacterial antimicrobial resistance (1, 6, 20). However combinations of topical and oral antibiotics such as co-trimoxazole, ciprofloxacin, or rifampin were found to be effective, with success rates ranging from 67 to 83% (5, 19). In our institution, we have been successfully using the combination of oral co-trimoxazole and topical fusidic acid for this purpose (15).



MUPIROCIN	17		13	13	11	10	6
SXT + FA	28		24	22	15	13	4

FIG. 3. Extranasal eradication of MRSA in the mupirocin (◈) and co-trimoxazole plus fusidic acid (▤) groups.

Mupirocin, a new topical agent, has been reported to be very effective in eradicating nasal and extranasal carriage of MRSA (2, 4, 7, 9, 17, 18). In spite of this high degree of efficacy there are no comparative studies between mupirocin and the other antimicrobial agents traditionally used to eradicate MRSA carriage.

The present study demonstrated that topical mupirocin is as effective as oral co-trimoxazole plus fusidic acid. Both regimens, in combination with a clorhexidine soap bath, were safe, well tolerated, and effective in eliminating the nasal carriage of MRSA. It could be argued that the number of patients included in the study was not enough to demonstrate that the two regimens are equally effective. The inclusion of more than 300 patients in each arm of the study would be necessary to establish such a conclusion.

Only three patients in each group suffered persistence of MRSA in their anterior nares 48 h after the beginning of therapy. At the end of treatment (5 days), 100% of patients in both groups presented with nasal eradication of MRSA.

Nasal eradication was stable in the majority of patients in both groups. A total of five patients in the mupirocin group had relapses after therapy: three patients at the first month and two patients at the third month. In the co-trimoxazole plus fusidic acid group, eight patients had relapses: six patients at the first month and two patients at the third month. There were no statistical differences between the groups. There is little experience described in the literature of MRSA carriage eradication from severely ill patients with mupirocin or co-trimoxazole plus fusidic acid. The majority of the studies are performed in healthy nasal carriers (3), health care workers (17), or patients located at long-term-care facilities (11). However, the results obtained in our study were similar to those described by other investigators in the eradication of carriage of MRSA from patients (11, 17). Walsh et al. (23) obtained MRSA eradication at all body sites, nasal and extranasal, in 67% of patients who received novobicin and rifampin and in 53% of patients who received co-trimoxazole plus rifampin. Our results are similar to those obtained in that study; however, the methodologies and therapeutic regimens used in both studies were different.

Additionally, both regimens were moderately effective in eradicating extranasal MRSA. The drugs eradicated extranasal MRSA from two-thirds of the treated patients. Nevertheless, we found differences in the speed of extranasal eradication. In patients who received mupirocin, the efficacy was observed after the fifth day of treatment, and in those treated with co-trimoxazole plus fusidic acid, the results were observed at 48 h. Eradication of extranasal MRSA was less stable. At 4 weeks of follow-up almost half of the patients probably presented with some relapse of extranasal carriage of MRSA, as stated above.

In contrast to other studies described in the literature (3, 11, 17), ours was designed to demonstrate the efficacies of both regimens among severely ill patients admitted to intensive care units and surgical wards. These factors add credibility to the study and to the efficacy of these regimens. Importantly, neither regimen completely or permanently eradicated MRSA from extranasal locations.

The emergence of mupirocin-resistant MRSA, either at low or at high levels, is infrequent (16, 21) and usually occurs after prolonged treatments for cutaneous infections (16, 21). In our experience with 5-day treatments, none of the strains isolated from the patients with relapses were resistant to mupirocin. We also did not find any strains resistant to co-trimoxazole and

fusidic acid, which is in contrast to the rapid induction of resistance reported after treatments with rifampin and ciprofloxacin (15).

Both regimens were equally safe. Nevertheless, the use of a topical drug has advantages over the use of a combination of systemic drugs. We continue using both regimens at our center, but for the reasons mentioned above, we prefer mupirocin in situations in which economic costs are not a determinant.

ACKNOWLEDGMENT

This work was supported by grant 93/1124 from the Fondo de Investigaciones Sanitarias de la Seguridad Social, Ministerio de Sanidad, Madrid.

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