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ARTICLES

Attempts to eradicate methicillin-resistant *Staphylococcus aureus* colonization with the use of trimethoprim-sulfamethoxazole, rifampin, and bacitracin

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Retrospective review of 197 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) identified 47 in whom a regimen for eradication of MRSA colonization could be evaluated. The patients were elderly (mean age, 67.7 years), with 53% transferred from another institution and 53% treated in an intensive care unit. A mean of 47.1 days of hospitalization with an average of 4.9 antibiotics preceded the first MRSA culture. The usual regimen (mean, 6.0 days) was oral trimethoprim-sulfamethoxazole, 160/800 mg twice daily, oral rifampin, 600 mg once daily, and bacitracin ointment three times a day. Eradication succeeded in 40 patients, 9 relapsed, and MRSA persisted in 7. Twenty-four of 25 nares sites were cleared but only 16 of 22 other sites. MRSA infection eventually developed in 36%. No adverse reactions to the eradication regimen were noted. Although this treatment for MRSA carriage was safe and effective, decreased efficacy outside the nares and relapse limited its value. (AM J INFECT CONTROL 1988;16:141-6)

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Methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in Europe in 1961.[1] By the late 1960s MRSA constituted 30% to 50% of *S. aureus* isolates in some European hospitals.[2] Within 20 years, 55% to 81% of hospitals surveyed in the United States reported MRSA.[3-5] Underscoring the importance of this organism is the inability to eradicate it in 85% of the hospitals where it has caused infection.[6,7]

Vancomycin is the drug of choice for treating MRSA infections,[8] but it will not predictably eradicate the carrier state.[9] When used in attempts to eliminate colonization with MRSA, antiseptic baths, as well as local and systemic antibiotics, have produced varying results.[4, 9-18] Some promising regimens carry the demanding requirements of thrice-daily bathing[10] or the use of drugs not marketed in the United States.[18]

Although therapy with a combination of trimethoprim-sulfamethoxazole, rifampin, and bacitracin ointment (TS/R/B) frequently is used in attempts to eradicate colonization with MRSA,[4] the three published studies in the United States of patient treatment are uncontrolled, with the largest series limited to 26 patients.[12, 14, 15] Therefore a retrospective chart review of a larger group of patients was done to evaluate TS/R/B efficacy in the eradication of MRSA colonization. In addition, the patients who were successfully treated were compared with those in whom colonization persisted.

METHODS

In this study patients carrying MRSA were sought by review of the clinical microbiology laboratory records of the Veterans Administration Medical Center in Omaha. Hospital employees and hospitalized patients whose first positive MRSA cultures were obtained between August 1980 and March 1986 were identified. Of 197 MRSA patients found in this way, clinical records for 180 were available for review. Information sought in review of records included identifying information, age, admission and discharge dates, status at discharge, MRSA eradication therapy (drugs, dose, duration), use of other antimicrobial agents, presence of other illness, previous institutionalization, treatment in an intensive care unit, specialty service responsible for patient, results of cultures for MRSA, development of MRSA infection, and whether the patient remained alive. Sixty-nine patients whose cultures were positive for MRSA and who received at least 2 days of trimethoprim-sulfamethoxazole and rifampin therapy were identified. Culture sites and culture timing varied among the patients. In 47 (43 inpatients, 4 employees) efficacy could be analyzed by comparing a positive culture obtained immediately before therapy and a follow-up culture from the last day of therapy or within 4 days.

Colonization was defined as recovery of MRSA from a body site without evidence of invasive disease. Drug-attributable adverse experiences were determined by chart review.

Staphylococcus aureus was isolated from cultures done routinely or as part of screening programs. Screening programs included periodic cultures of intensive care unit patients and epidemiologically indicated cultures of employees. Screening cultures were streaked on mannitol salt agar plates (Regional Media Laboratories, Inc., Lenexa, Kan.), which were incubated at 35° C and read at 24 and 48 hours. Oxacillin susceptibility testing of the routine cultures was performed by Kirby-Bauer agar disk diffusion at 35° C with 48-hour incubation. Starting in December 1985 oxacillin susceptibility was tested both with an automated system (Vitek Automicrobic System, McDonnell Douglas Health Information Systems, Hazelwood, Mo.) using a 2 μg/ml breakpoint and with Mueller-Hinton agar containing 4% sodium chloride and 6 μg/ml oxacillin (Regional Media Laboratories), incubated for 24 hours at 35° C.

Proportions were compared with the Fisher's exact test (level of significance, $p = 0.05$).

RESULTS

The mean age of the 47 patients eligible for evaluation was 67.7 ± 13.4 (SD) years. Fifty-three percent (25 patients) had been admitted from a nursing home or transferred from another hospital. Fifty-three percent (25 patients) received part of their hospital care in an intensive care unit. Sixty-two percent (29 patients) were treated on the internal medicine service. The mean interval between the date of the first culture that was positive for MRSA and the start of TS/R/B was 19.4 ± 25.0 days. The mean interval from hospital admission to start of therapy was 47.1 ± 35.6 days. During that interval the patients received an average of 4.9 ± 2.9 antibiotics. The overall length of hospitalization was 88.0 ± 60.8 days.

The mean duration of TS/R/B therapy was 6.0 ± 2.4 (SD) days. Reflecting the variation in dosing schedules reported in the litera-

Table 1. Antimicrobial agents used in attempts to eradicate MRSA

Outcome (No. of patients)*	Trimethoprim-sulfamethoxazole		Rifampin		Bacitracin ointment			
	160/800 mg bid	80/400 mg bid	300 mg bid	600 mg qd	None	bid	tid	qid
Cleared	26	5	15	16	2	3	25	1
Relapsed	7	2	7	2	0	0	7	2
Failed	7	0	1	6	1	1	4	1

qd daily; *bid*, twice daily; *tid*, three times daily; *qid*, four times daily.

Table 2. Characteristics of care of patients in whom MRSA eradication was successful or unsuccessful

	Eradication outcome				
	Successful (N = 40)		Unsuccessful (N = 7)		p (Fisher's exact test)
	No.	%	No.	%	
Admitted from other hospital	7	17.5	2	28.6	0.4043
Admitted from nursing home	14	35	2	28.6	0.5533
Admitted from community	19	47.5	2	28.6	0.5745
Stayed in intensive care unit	22	55	3	42.9	0.4255
Received concomitant antimicrobial agents	19	47.5	3	42.9	0.5745
On medical service	23	57.5	6	85.7	0.1608
Eventual MRSA infection	14	35	3	42.9	0.4990
Survived hospitalization	22	55	5	71.4	0.3521

ture,[12, 14, 15] the doses of TS/R/B given to the patients whose charts were reviewed showed some variation (Table 1). Forty of the 47 patients eligible for evaluation received oral trimethoprim-sulfamethoxazole, 160/800 mg twice daily, with the others receiving 80/400 mg twice daily. Twenty-four patients received oral rifampin, 600 mg once daily, and 23 received 300 mg twice daily. Nearly all the patients (23/24) who took rifampin once daily received the 160/800 dose of trimethoprim-sulfamethoxazole, but only 17 of the 23 patients who took rifampin twice daily received the 160/800 dose (p = 0.0424). Bacitracin ointment was applied to affected sites three times a day in 36 patients, twice daily in 4, and four times daily in 4. No bacitracin was given to 3 patients, 2 of whom had a successful outcome.

Eradication treatment was successful in 40 of 47 patients eligible for evaluation. Later cultures, obtained at various times, showed relapse in 9 of 40 patients. For all four employees included in the group of 47, eradication treatment was successful and there were no relapses.

In 38 patients MRSA was detected with Kirby-Bauer methods (before December 1985); eradication was successful in 32, of whom 9 relapsed. Of the 9 patients whose MRSA was detected with Vitek or Mueller-Hinton agar with oxacillin (December 1985 and later), eradication was successful in 8, none of whom relapsed.

Twenty-four of 25 anterior nares sites were cleared, but only 16 of 22 other sites were cleared (p = 0.0324). During follow-up periods of up to 21 months, relapse was detected in 8 of the 24 patients from whom nasal carriage had cleared and in 1 of the 16 patients from whom carriage elsewhere had cleared. MRSA failed to clear in only 1 of 23 patients who received rifampin twice daily but failed in 6 of 24 patients on a once-daily regimen of rifampin (Table 1) (p = 0.0547). The choice of rifampin regimen, however, had no impact on patients' remaining free of relapse. Of the 23 patients who took rifampin twice daily, 15 remained clear of MRSA, as did 16 of the 24 patients on the once-daily regimen. Although MRSA cleared initially in all 7 patients who received the 80/400 mg

Table 3. Published studies of eradication by trimethoprim-sulfamethoxazole/rifampin of the carrier state of MRSA

Source	Antimicrobial agents used			Outcome of treatment courses				Follow-up in mo
				Extranasal sites		Nasal sites only		
	TMP/SMX (bid)	Rifampin	Bacitracin	Clear/total	Relapse/clear	Clear/total	Relapse/clear	
Winn et al.[12]	160/800	600 qd	tid	4/6	—	6/6	—	0.5-4.5
Ward et al.[14]	80/400	300 bid	tid	13/16	0/13	10/10	0/10	<3
Ellison et al.[15]	160/160	600 bid	No	8/12	2/8	0/0	0/0	<1 for 6
Current series	160/800*	600* qd	tid*	16/22	1/16	24/25	8/24	6,9 in 2 0-21

*Usual dose; see Table 1. *TMP/SMX*, Trimethoprim-sulfamethoxazole; *qd*, daily; *bid*, twice daily; *tid*, three times daily.

dose of trimethoprim-sulfamethoxazole, therapy with the 160/800-mg regimen failed initially in 7 of 40 patients ($p = 0.2964$). Eventually, patients receiving similar proportions of 160/800 mg and 80/400 mg, respectively, remained clear of relapse (Table 1).

Successfully treated patients were similar in several respects to those in whom the TS/R/B regimen failed. The two groups were similar in age (67.6 ± 14.2 years mean ± SD for successes, 68.4 ± 6.9 for failures), the interval between the first MRSA culture to the start of therapy (19.2 ± 25.4 days for successes, 20.3 ± 22.1 for failures), the interval from admission to start of therapy (48.3 ± 37.0 days for successes, 40.8 ± 26.1 for failures), the length of hospital stay (88.8 ± 60.3 days vs. 84.3 ± 62.8), the number of prior antibiotics (5.1 ± 3.0 vs. 3.6 ± 2.0), and the length of therapy (6.1 ± 2.5 days vs. 5.6 ± 1.8). No statistically significant differences were demonstrated in the proportions of patients in each group who were admitted from nursing homes, who stayed in an intensive care unit, and who were on the medical service (Table 2). MRSA infection ultimately developed in 36% of the patients. For 36% of the patients, hospitalization was terminated by death. No adverse reactions attributable to the TS/R/B regimen were noted.

DISCUSSION

In this study the efficacy of eradication of MRSA colonization with TS/R/B parallels that of previous reports (Table 3).[12, 14, 15] Winn et al.[12] reported a 5-day regimen of TS/R/B that cleared MRSA from all six patients with nasal carriage. Of six additional patients with extranasal colonization, the regimen was successful in only four. The latter six included four with both nasal and extranasal carriage; infection was cleared in two patients.[12] The same group of investigators published a 1981 report in which a lower trimethoprim-sulfamethoxazole dose was used.[14] Hexachlorophene baths were given during the initial 2 days of therapy. Although the regimen was uniformly successful in eradicating carriage confined to the nares, only 11 of the 14 patients with MRSA colonization of the nares plus a wound, or of a wound alone, were successfully treated. Rifampin resistance was not detected after treatment in those patients for whom the regimen failed. In an unspecified number of patients late follow-up cultures were performed as long as 3 months after the regimen was administered; none relapsed.

Ellison et al.[15] treated 13 patients and 1 employee with MRSA colonization with oral rifampin, 600 mg twice daily, and oral trimethoprim-sulfamethoxazole, 160/800 mg twice daily for 5 days. Of 12 initial treatment courses for which follow-up cultures were available, 8 posttherapy cultures were negative. However, 2 of the 8 patients relapsed 6 and 9 months later. Follow-up of the remaining 6 patients continued for up to 1 month. All of the researchers' patients showed at least one extranasal colonization site. Failure was partially predicted by

the presence of a foreign body at the colonized site. In both this and the report by Ward et al.,[14] there were no adverse drug reactions related to the regimen.

Although the earlier series[12, 14, 15] obtained similar results with both once-daily and twice-daily rifampin, the current study detected a trend toward greater initial success with twice-daily rifampin. Rifampin's 2- to 5-hour half-life[19] may make more frequent dosing more desirable in this setting.

Our patients were characteristic of those who have been at risk for infection or colonization with MRSA.[14, 20-22] Both the eradication-success and eradication-failure groups were dominated by elderly patients with prolonged hospital stays who had been exposed to multiple antimicrobial agents. The only factor distinguishing eradication failures was extranasal colonization.

The 85% efficacy of eradication of MRSA colonization with TS/R/B parallels that in previous reports of smaller numbers of patients. This regimen, however, is less effective for sites other than the anterior nares. No adverse reactions to the regimen were noted. Unfortunately, relapse after this regimen limits its value.

This series of patients is nearly as large as the three previous series combined. It thus provides an important endorsement of the regimen's safety and efficacy, particularly in the short term for patients with nasal colonization. Its conclusions, however, must be tempered by the realization that it is an uncontrolled, retrospective analysis, in which some variation in antimicrobial dosing was tolerated. Phage typing and plasmid analysis data are not available to determine how many of the patients shared staphylococcal strains and whether the treatment failures and relapses might represent, in some cases, reinfection with newly acquired strains. The current series provides a basis for the design of a prospective controlled study.

Studies of methicillin-susceptible *S. aureus* colonization in patients undergoing dialysis suggest that control of staphylococcal colonization could prevent invasive infection.[23] Thus, identifying a regimen effective in the long-term control of MRSA colonization holds promise not only for limiting the nosocomial transmission of MRSA but also for preventing serious infection.

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