Combined topical and oral antimicrobial therapy for the eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in hospitalized patients

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OBJECTIVE: How to eradicate methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in hospitalized patients is uncertain. We reviewed our experience with MRSA decolonization therapy in hospitalized patients.
SETTING: An 1100-bed, university-affiliated tertiary care teaching hospital in Toronto, Ontario.
DESIGN: Retrospective chart review of 207 adult inpatients with MRSA colonization hospitalized between February 1996 and March 1999.
INTERVENTIONS: All patients with MRSA colonization were assessed for possible decolonization therapy with a combination of 4% chlorhexidine soap for bathing and washing, 2% mupirocin ointment applied to the anterior nares three times/day, rifampin (300 mg twice daily) and either trimethoprim/sulfamethoxazole (160 mg/800 mg twice daily) or doxycycline (100 mg twice daily). This treatment was given for seven days.
RESULTS: A total of 207 hospitalized patients with MRSA colonization were identified and 103 (50%) received decolonization therapy. Patients who received decolonization therapy were less likely than untreated patients to have intravenous (P=0.004) or urinary catheters (P<0.001), or extranasal sites of colonization (P=0.001). Successful decolonization was achieved in 90% of the 43 patients who were available for at least three months of follow-up.
CONCLUSIONS: Combined topical and oral antimicrobial therapy was found to be effective in eradicating MRSA colonization in selected hospitalized patients, especially those without indwelling medical devices or extranasal sites of colonization.

Résumé à la page suivante

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Polythérapie antimicrobienne orale et topique pour l'éradication de colonies de staphylocoques dorés résistants à la méthicilline chez des patients hospitalisés

OBJECTIF : On ne sait pas très bien comment éradiquer les colonies de staphylocoques dorés résistants à la méthicilline (SARM) chez les patients hospitalisés. Voici donc notre expérience de décolonisation de SARM par la polythérapie chez des patients hospitalisés.
LIEU : Hôpital universitaire de soins tertiaires, comptant 1100 lits, situé à Toronto.
TYPE D'ÉTUDE : Étude rétrospective de dossiers de 207 patients adultes porteurs de SARM, hospitalisés entre février 1996 et mars 1999.
INTERVENTIONS : Tous les patients porteurs de SARM ont été évalués en vue d'un traitement possible de décolonisation comprenant un savon à base de chlorhexidine à 4 % pour le bain et le lavage, de la mupirocine à 2 % en onguent à appliquer sur les narines trois fois par jour (f.p.j.), de la rifampine (300 mg, 2 f.p.j.) ainsi que du triméthoprime-sulfaméthoxazole (160 mg-800 mg, 2 f.p.j.) ou de l'hyclate de doxycycline (100 mg, 2 f.p.j.), et ce, pour une durée de sept jours.
RÉSULTATS : Nous avons dénombré au total 207 patients hospitalisés, porteurs de SARM et 103 d'entre eux (50 %) ont été soumis au traitement de décolonisation. Les patients traités se sont montrés moins susceptibles d'avoir des cathéters intraveineux (P=0,004) ou des sondes urinaires (P<0,001) ou encore de présenter des foyers extranasaux de colonisation (P=0,001). Résultats : la décolonisation a été observée chez 90 % des 43 patients suivis sur une période d'au moins trois mois.
CONCLUSION : La polythérapie antimicrobienne orale et topique s'est avérée efficace pour éradiquer les colonies de SARM chez certains patients hospitalisés, notamment chez ceux non porteurs de dispositifs médicaux à demeure ou de foyers extranasaux de colonisation.

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasing in many Canadian hospitals over the past few years (1). The organism is as virulent as susceptible strains of *S aureus*, and is capable of causing serious infections including pneumonia, and surgical site and bloodstream infections. Although community-acquired MRSA in patients without recognized risk factors has been reported recently (2), MRSA is most often recognized to be a hospital-acquired organism, and nosocomial cross-infection occurs frequently (3). One strategy that has been recommended to reduce the risk of transmission of MRSA in hospitals has been the attempt to eradicate MRSA carriage ('decolonization therapy') (3,4). This approach is controversial, largely because its effectiveness is uncertain, and it is not known what antimicrobial agent or combination of agents would be most efficacious. Topical 2% mupirocin ointment, applied to the anterior nares, has been shown to be effective in eradicating staphylococcal nasal carriage in health care providers (5-7). However, the use of mupirocin ointment alone appears to be much less effective for eradicating MRSA in hospitalized patients and long term care facility residents, with high rates of relapse following the completion of therapy (8,9). Treatment failure has been attributed to extranasal sites of colonization with MRSA that would not be expected to resolve with the intranasal application of a topical agent. For this reason, the combination of topical with oral systemic therapy has been investigated (10-12). Few of these studies involved large numbers of high risk hospitalized patients. The objective of the present study was to describe the experience with the use of combined topical and systemic antimicrobial therapy for the eradication of MRSA colonization in patients at a tertiary care hospital and an affiliated long term care facility.

PATIENTS AND METHODS

Setting

Sunnybrook and Women's College Health Sciences Centre is a tertiary care teaching hospital affiliated with the University of Toronto, Ontario, operating out of three sites in the city. The present study was conducted at the Sunnybrook campus, which has approximately 480 acute care beds and 520 long term care beds. The priority clinical programs of the hospital include trauma, oncology, cardiac disease, musculoskeletal disease, perinatal care and gynecology. Inpatients colonized with MRSA at the Sunnybrook campus of Sunnybrook and Women's College Health Sciences Centre between February 1996 and March 1999 were identified by the review of microbiology laboratory culture reports and the Infection Prevention and Control service records. The hospital records were reviewed retrospectively to determine the demographic and clinical characteristics of these patients, antimicrobial therapy and outcome. Patients with MRSA had not been identified or treated as part of an outbreak investigation or management.

Interventions

Most MRSA colonized patients had been assessed by one of three infectious diseases physicians to determine whether an attempt to eradicate MRSA colonization would be appropriate. Criteria for decolonization therapy included an expected survival of greater than three months and the absence of multiple indwelling medical devices. Patients with MRSA or another infection were not considered for decolonization therapy until their infection had resolved and the use of all other antibiotics had been discontinued.

In general, the recommended decolonization therapy at the hospital consisted of 4% chlorhexidine gluconate aqueous soap for daily bathing and washing, 2% mupirocin ointment applied to the anterior nares three times/day, rifampin (300 mg twice daily) and trimethoprim-sulfamethoxazole (TMP/SMX) (160 mg/800 mg twice daily) for a total of seven days. If the isolate was resistant to TMP/SMX, or if the patient was allergic to sulfonamides, doxycycline (100 mg twice daily) was used instead of TMP/SMX. The final decision regarding decolonization therapy was made at the discretion of the attending physician.

TABLE 1
Baseline characteristics of patients who were and were not treated for methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization

Characteristic	Number treated (%)	Number not treated (%)	P
Number of patients	103 (50)	104 (50)	–
Male	70 (68)	52 (50)	0.007
Mean age (years)	73.9	68.2	0.02
Patient in long term care	50 (49)	9 (9)	0.02
Confined to bed or chair	36 (35)	38 (37)	0.81
Urinary incontinence	12 (12)	25 (24)	0.02
Indwelling urinary catheter	37 (40)	66 (64)	<0.001
Intravenous catheter	51 (55)	83 (81)	0.004
Gastrostomy tube	28 (30)	38 (37)	0.34
Two or more medical devices*	35 (39)	62 (60)	0.005
MRSA nasal colonization only	87 (84)	67 (64)	0.002
Extranasal MRSA colonization	17 (16)	37 (36)	0.001
Mean number of sites colonized with MRSA	2.3	2.6	0.36
Two or more sites colonized with MRSA	62 (60)	64 (62)	0.89

**Indwelling medical devices include urinary catheter, intravascular catheter, dialysis catheter, tracheostomy, gastrostomy or other feeding tube*

Baseline and follow-up cultures for MRSA were obtained from the anterior nares, perineum, cutaneous wounds or skin lesions, catheter exit sites and any other previously positive sites, following the completion of decolonization therapy. These cultures were obtained weekly for up to three months, and then monthly for up to 12 months. Successful decolonization was defined as persistently negative follow-up cultures for at least three months following the completion of therapy.

Laboratory methods

Specimens were planted onto mannitol salt agar (Quelab Laboratories Inc, Canada) with oxacillin (2 µg/mL) incubated at 35°C for up to 48 h. Resistance to methicillin was confirmed using oxacillin agar screen plates as recommended by the National Committee for Clinical Laboratory Standards guidelines (13), and by polymerase chain reaction assay for detection of *mec*A and *nuc*A genes (14). Mupirocin susceptibility was determined by E test (AB Biodisk, Sweden). Susceptibility testing of the isolates for other antimicrobial agents was done using the Vitek GPS-107 card (BioMérieux Inc, USA).

When MRSA was recovered again after decolonization therapy, the pre- and post-treatment isolates were typed by pulsed-field gel electrophoresis (PFGE) following DNA extraction and digestion with SmaI (15).

Statistical methods

Data were entered and analyzed using EpiInfo software version 6.1 (Centers for Disease Control and Prevention, USA). Differences in proportions were compared using Fisher's exact test, and continuous variables were compared using Student's *t*-test.

RESULTS

A total of 207 patients colonized with MRSA were identified. There were 122 males and 85 females, with a mean age of 71 years (range 16 to 96 years). Most (72%) of the patients were admitted to an acute care service in the hospital, whereas 58 (28%) patients were in long term care units. One hundred and four (50%) patients did not receive decolonization therapy. Reasons for not being treated included poor short term prognosis, the presence of multiple indwelling medical devices or discharge from hospital before culture results became available.

The remaining 103 patients received decolonization therapy. Ten patients (10%) received topical therapy only (nine patients received treatment with 2% mupirocin and one patient was treated with topical fusidic acid). The maximum length of follow-up for these 10 patients was two months. Six (6%) patients received oral antimicrobial therapy only (four patients received rifampin only and two patients received rifampin and doxycycline). The remaining 87 patients received a combination of topical and oral antimicrobial therapy. Fifty-nine (57%) patients were treated with 2% mupirocin, rifampin and TMP/SMX; 26 (25%) patients were treated with 2% mupirocin, rifampin and doxycycline; and two (2%) patients were treated with 2% mupirocin, TMP/SMX and doxycycline. Follow-up cultures for MRSA were available at one, three, six and 12 months following the completion of therapy for 69 (67%), 43 (42%), 34 (33%) and 23 (22%) patients, respectively.

The characteristics of the 103 treated patients and the 104 untreated patients are summarized in Table 1. Patients who received treatment were older (74 years of age compared with 68 years of age; P=0.02), less likely to be incontinent (12% versus 24%; P=0.02), less likely to have an

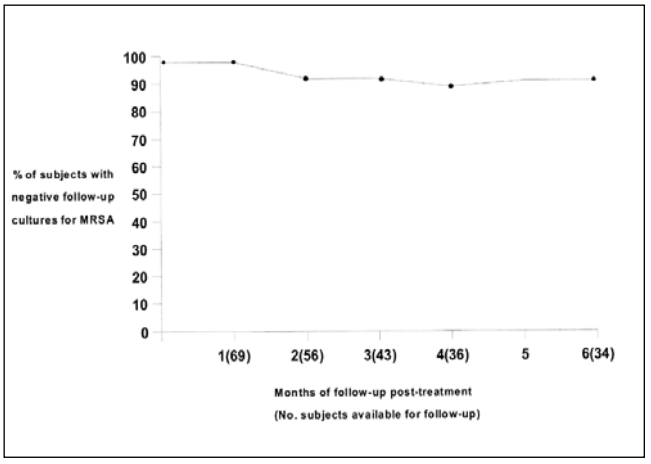

Figure 1) *Proportion of patients with negative follow-up cultures for methicillin-resistant* Staphylococcus aureus *(MRSA) one to six months following decolonization therapy*

indwelling urinary catheter (40% versus 64%; P<0.001), less likely to have an intravenous catheter (55% versus 81%; P=0.004) and less likely to have two or more indwelling medical devices (39% versus 60%; P=0.005). Although there was no difference in the mean number of sites colonized with MRSA, those patients who were offered decolonization therapy were less likely to have extranasal sites of MRSA colonization (16% compared with 36%; P=0.001). There were no apparent differences between those who were and were not offered treatment in admitting diagnosis, comorbidities or earlier receipt of antimicrobial therapy.

Cultures were negative for MRSA in 98%, 94% and 90% of patients at one, three and six months after the completion of decolonization therapy (Figure 1). High rates of successful decolonization (88%) persisted up to 12 months after the completion of therapy, although the number of patients in whom follow-up cultures were available declined substantially with increased length of follow-up. No adverse reactions attributed to decolonization therapy were noted in the medical records of these patients.

Susceptibility testing of MRSA isolates obtained at baseline (ie, before beginning decolonization therapy) revealed that only 1% of the isolates were resistant to rifampin and 2% were resistant to mupirocin (minimal inhibitory concentration of 128 µg/mL or higher). Resistance to TMP/SMX was detected in 35% of the isolates and resistance to tetracycline occurred in 8% of the isolates. Susceptibility test results of follow-up isolates (ie, after the receipt of decolonization therapy) were not available.

The most common strains of MRSA identified were CMRSA-1 and CMRSA-2, which were also the most prevalent strains in Ontario during the study period (15). Baseline (pretreatment) and follow-up (post-treatment) isolates from patients who failed decolonization therapy demonstrated identical PFGE DNA profiles.

DISCUSSION

Potential indications for attempting to eradicate MRSA colonization in hospitalized patients include the prevention of serious infections in an individual, and the interruption of transmission within a health care facility. Although this approach has been used successfully in the management and control of MRSA outbreaks, occasionally, when other measures appear to have failed (6-8,11,16-23), decolonization therapy is controversial. There are concerns regarding the effectiveness of the strategy and the emergence of antimicrobial resistance to the agents used (4,24-27). Moreover, should a decision be made to use this strategy, the optimal antimicrobial agent(s) for decolonization therapy has not been determined. A summary of studies examining the use of topical agents alone or in combination with systemic oral drugs is presented in Table 2. The results are mixed, with some studies suggesting efficacy and others indicating that decolonization therapy is ineffective. Most of these studies involved relatively small numbers of study subjects, often young and healthy health care providers (6,12,16,26,28-32). Many of the studies were observational; only four were randomized controlled trials. In some of the studies, follow-up was short (fewer than two months).

Topical agents, such as mupirocin ointment, have the advantage of achieving high drug concentrations at the site of colonization (eg, the anterior nares), with minimal risk of adverse reactions. However, with topical therapy, the eradication of MRSA from multiple extranasal sites of colonization is often difficult (8). The presence of MRSA at multiple body sites has been identified as an important risk factor for the persistent carriage of the organism following treatment with mupirocin (33). This may provide a rationale for using a combination of topical and systemic agents for MRSA decolonization therapy. In this study, we found that combined topical and oral decolonization therapy with 2% mupirocin ointment, rifampin and either TMP/SMX or doxycycline appeared to be effective in eradicating MRSA colonization for at least three months in a selected group of patients. Patients who were most likely to respond to treatment, with prolonged eradication of MRSA, included those who were not acutely ill, who were not being treated for another active infection, who did not have multiple indwelling medical devices, and who were less likely to have extranasal sites of colonization.

There are several important limitations of our study. Because this was a retrospective review, there was no control group available for comparison, although a rate of elimination of MRSA colonization as high as 94% at three months of follow-up without treatment has not previously been reported in hospitalized patients. The number of patients available for follow-up cultures beyond one month was relatively low, primarily because of discharge from hospital. Therefore, we cannot make any conclusions regarding the long term effect of decolonization therapy. However, if the goal of decolonization is to prevent nosocomial transmission (rather than a requirement for permanent eradication of the organism), the results suggest that this approach

TABLE 2
Summary of studies of methicillin-resistant *Staphylococcus aureus* decolonization therapy with follow-up of at least two weeks

Reference	Study population	Number of subjects	Type of study	Treatment	Duration of follow-up (weeks)	Eradication rate (%)
Topical therapy alone						
6	Hospital patients	40	Cohort	Mupirocin	2	65
9	LTCF residents	19	Cohort	Mupirocin	8	53
28	LTCF residents	65	Cohort	Mupirocin	16	60
8	Hospital patients	102	RCT	Mupirocin vs	4	25
				Placebo		18
29	Hospital patients	11	Cohort	Polysporin	8	82
Combination antimicrobial therapy						
16	Health care workers and hospital patients	20	Cohort	Rifampin+fusidic acid	10	80
30	Health care workers	13	Cohort	Rifampin+TMP/SMX	16	75
10	Health care workers and hospital patients	47	Cohort	Rifampin+TMP/SMX +bacitracin	4	68
31	Health care workers and LTCF residents	36	Cohort	Rifampin+TMP/SMX	4	44
26	Health care workers and hospital patients	94	RCT	Rifampin+TMP/SMX vs	2	53
				Rifampin+novobiocin		67
32	LTCF residents	35	RCT	Rifampin+minocycline vs	12	50
				Rifampin vs		70
				Minocycline vs		38
				Placebo		14
12	Health care workers and hospital patients	84	RCT	Mupirocin vs	12	78
				TMP/SMX+fusidic acid		71

LTCF Long term care facility; RCT Randomized controlled trial; TMP/SMX Trimethoprim-sulfamethoxazole

may be effective. We were unable to determine risk factors that might predict the success or failure of decolonization therapy because the number of available subjects whose cultures became positive after treatment was too small.

In summary, the results of this study suggest that, in selected hospitalized patients without multiple indwelling medical devices and extranasal sites of colonization, it may be possible to eradicate MRSA carriage for at least three months by using a combination of topical mupirocin and oral antimicrobial agents. We believe that the results of this study provide support for conducting a randomized controlled trial to evaluate the efficacy of combined topical and systemic antimicrobial agents for MRSA decolonization in hospitalized patients. Studies to document the effectiveness of this strategy for limiting nosocomial transmission of MRSA in hospitals also need to be completed.

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