Comprehensive Strategy to Prevent Nosocomial Spread of Methicillin-Resistant *Staphylococcus aureus* in a Highly Endemic Setting

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**Background:** The effectiveness and feasibility of a comprehensive strategy to reduce nosocomial transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in a highly endemic setting have not yet been proved. Limited benefits and the high cost of such programs are the main concerns.

**Methods:** We prospectively evaluated the effect of an aggressive infection control program on transmission of MRSA in the University Clinic of Respiratory and Allergic Diseases. All patients with MRSA carriage during 5 years (January 1, 1998, through December 31, 2002) were included and categorized into imported or hospital-acquired cases.

**Results:** Methicillin-resistant *S aureus* was recovered from 223 hospitalized patients; 142 cases were imported and 81 were acquired at our institution. After introduction of the comprehensive infection control program in 1999, the annual incidence of MRSA carriage per 1000 admissions increased from 4.5 in 1998 to 8.0 in 1999 (*P* = .02), and remained stable thereafter. In this period, the proportion of MRSA cases acquired in our institution decreased from 50.0% in 1999 to 6.1% in 2002 (*P* < .001), whereas the proportion of MRSA cases transferred from other hospitals (*P* < .001) and nursing homes (*P* = .03) increased. All 19 MRSA carriers with 3 sets of follow-up cultures were successfully decolonized.

**Conclusions:** With a comprehensive infection control program, it was possible to reduce nosocomial transmission of MRSA in a highly endemic setting. With good hand hygiene using alcohol handrub, early detection, isolation, and a decolonization strategy, containment of MRSA was achievable, despite a high rate of transferred patients with MRSA.

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The first strain of methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in the United Kingdom in 1961. In subsequent decades, MRSA has rapidly spread throughout the world and has become highly endemic in many health care institutions. However, major variance in the ability to control MRSA has occurred with different strategies. In a laboratory-based survey conducted between 1990 and 1991 in 10 European countries, the proportion of MRSA among all *S aureus* isolates varied from less than 1% in Scandinavia to greater than 30% in France, Italy, and Spain. Similar results were found in a recent survey conducted in 15 European countries between 1997 and 1999, with prevalence rates ranging from 2% in the Netherlands and Switzerland to greater than 40% in Italy, Portugal, and Turkey. Interestingly, high variability in MRSA prevalence has also been found among different institutions in a given geographic area and even among different hospital wards of comparable size and patient case mix. These variations may reflect a combination of different management approaches and infection control guidelines, surveillance practices, awareness of the problem, legislative requirements, financial and personnel resources, and experience.

Some authors have reported their experience in successfully reducing the nosocomial spread of MRSA using a sustained and consistent infection control strategy. In their opinion, vigorous control efforts are justified, as MRSA does not replace methicillin-susceptible strains of *S aureus*, but adds to the overall rate of nosocomial *S aureus* infections. In addition, MRSA infections substantially increase morbidity and mortality in hospital and nosocomial transmission. In some institutions, complete eradication of MRSA was possible with an aggressive approach and strict infection control policy. Despite these encouraging re-
ports, aggressive infection control programs have not been universally accepted. In particular, hospitals with high rates of endemic MRSA carrier rates have concerns about high costs and limited benefits of such programs. Some health care professionals suggest that efforts to control MRSA in this setting are counterproductive and may cause more problems than they can solve.29

Like many other countries, Slovenia has a significant problem with MRSA. In October 2001, a nationwide prevalence study25 in 19 Slovene hospitals revealed a 62% prevalence rate of MRSA among all *Staphylococcus* isolates responsible for nosocomial infections. Two other epidemiologic investigations in Slovene intensive care units (ICUs) conducted in 1997 and 2001 showed MRSA prevalence rates between 60% and 75%.26 We prospectively evaluated the effectiveness and feasibility of an aggressive infection control strategy to reduce nosocomial transmission of MRSA during 5 years (from January 1, 1998, through December 31, 2002).

**METHODS**

**HOSPITAL SETTING**

The study was conducted at the University Clinic of Respiratory and Allergic Diseases, which provides secondary care for 100,000 inhabitants in the surrounding area and serves as a tertiary referral hospital for respiratory diseases for about 2 million inhabitants in Slovenia. This is a teaching facility with 237 beds, including 14 medical ICU beds. The patients are housed in rooms with 1 to 3 beds. The infection control team included 2 part-time clinicians (10% each) (D.T. and one other), 1 part-time clinical microbiologist (30%) (V.T.), and 1 part-time infection control nurse (50%).

**STUDY DESIGN AND DEFINITIONS**

We conducted a prospective cohort study during 5 years. All consecutive patients admitted from January 1, 1998, through December 31, 2002, constituted the study population. The institutional review board approved the study protocol. During the first year of the study, no active infection control program to improve hand hygiene, no screening for nasal carriage of MRSA, and no isolation and decolonization of MRSA carriers were performed. On January 1, 1999, the hospital implemented a rigorous infection control program for the next 4 years. The epidemiologic patterns of MRSA were observed during the study. On admission, we recorded whether patients were at risk for carriage of MRSA. These patients included those who were directly transferred from other hospitals, any ICU, or a nursing home; patients with a history of surgical treatment within the last year; patients with a history of hospitalization in the largest teaching hospital in Slovenia (University Medical Center in Ljubljana) within the last year; and patients previously infected or colonized with MRSA.

An MRSA case was defined as a patient from whom MRSA was recovered from any site. Each patient with MRSA was counted only once. The MRSA cases were classified as imported (when MRSA was recovered within 72 hours after admission or the patient was previously known to be an MRSA carrier) or acquired in our institution (when MRSA was recovered later than 72 hours after admission and the patient was previously not known to be an MRSA carrier). On admission, the following data were recorded on the case report form: transfer from another hospital or a nursing home or admission from a home environment, repeated hospitalizations in previous years, and surgical procedures in the previous year. In addition, MRSA cases were classified as being first detected by active surveillance cultures or by routine clinical diagnostic sampling.

**INTERVENTION PROGRAM**

On January 1, 1999, we implemented a rigorous infection control program, based on adapted Centers for Disease Control and Prevention (Atlanta, Ga) guidelines from University Hospitals Basel. The concept is based on a search-and-destroy strategy. It included (1) promotion of hand hygiene, (2) active surveillance cultures at admission to identify MRSA carriers, (3) strict application of barrier precautions for patients with MRSA, (4) eradication of MRSA carriage (decolonization), and (5) continuous education of health care workers (HCWs) on appropriate hygiene procedures. During the study, no significant changes in antimicrobial use were observed.

**Promotion of Hand Hygiene**

Compliance with hand hygiene was promoted by switching from conventional hand washing to the use of an alcohol handrub (hand disinfection) in all situations in which hands were not visibly dirty or visibly contaminated with body fluids (ie, in >90% of opportunities). Situations in which hand hygiene was considered necessary were consistent with published infection control guidelines27,28 and included all opportunities before and after each patient contact, after contact with body fluids and substances, and after removing gloves. One or 2 alcohol dispensers per room were installed at convenient locations between patients’ beds, near the entrance, and on carts. In the ICU and on medical wards where patients with tuberculosis are treated, every patient’s bed had an alcohol dispenser installed. Protective creams and lotions to prevent skin dryness and irritation were provided, and HCWs were encouraged to use them on a regular basis. Written guidelines for hand hygiene were distributed to all staff members, and friendly reminders were placed on the walls.

**Active Surveillance Cultures**

Selective screening for MRSA was routinely performed within 72 hours of hospital admission in all patients at risk for carriage of MRSA (see “Study Design and Definitions” subsection of this section). The samples were obtained by rotating a premoistened cotton-tip swab around the sampling site. Patients had initial surveillance cultures obtained always from the anterior vestibule of the nose and throat. If present, additional swabs from open wounds or skin breakdowns and respiratory secretions were obtained. If a urinary or vascular catheter was in place longer than 24 hours, urine or a swab from the vascular catheter insertion site was also sampled. Perirectal or rectal swabs were not obtained. If a hospitalized patient was found to carry MRSA, surveillance nasal cultures were obtained from all other patients in the same room and from HCWs who had contact with the MRSA carrier. Hospital records of MRSA carriers were routinely flagged until the patients were declared successfully decolonized.

**Barrier Precautions**

Patients who were known to be MRSA carriers at admission and patients from whom MRSA was recovered during their hospital stay were immediately placed in isolation in a private room; they were grouped with other MRSA carriers; or a distance of at least 1 m between patients’ beds was ensured. Gloves and gowns were required for all contacts with patients in isolation.
Eradication of MRSA Carriage

An attempt to eradicate MRSA colonization was performed in all carriers among HCWs and patients without open wounds, skin breakdowns, endotracheal tubes, and vascular or urinary catheters. Independent of the body site of MRSA recovery, a whole-body eradication treatment was performed. The decolonization procedure was performed for 5 consecutive days and involved nasal application of 2% mupirocin ointment (Bactroban nasal; Beecham Pharmaceuticals, Brentford, England) with a swab by a nurse twice daily, throat wash with 0.2% chlorhexidine digluconate (Skinsept mucosa; Henkel-Ecolab, Düsseldorf, Germany) 3 times daily, and washing or bathing with skin antiseptic containing 4.5% chlorhexidine digluconate (Pliva-sept penecl; Pliva, Zagreb, Croatia) once daily, including the scalp. All removable dentures were removed and soaked overnight in a solution containing 4.5% chlorhexidine. When MRSA was recovered in respiratory secretions or urine, oral combination of trimethoprim and sulfamethoxazole was also administered at a dosage of 160 mg trimethoprim and 800 mg sulfamethoxazole every 12 hours for 5 days. The patient was considered successfully decolonized when 3 sets of surveillance cultures (nose, throat, respiratory secretions, urine, wounds, or catheter insertion site) at intervals of 2 to 3 days obtained at least 3 days after completed decolonization showed no growth of MRSA and the patient did not receive systemic antimicrobial therapy at the time of culture sampling. When the eradication of MRSA carriage was not successful, the decolonization procedure was reviewed. Before the next decolonization procedure, possible reasons for decolonization failure were discussed, such as procedure violation or patient noncompliance.

MICROBIOLOGICAL PROCEDURES

Culture specimens were immediately transported to the clinical microbiology laboratory and usually processed on the same day. Regardless of the specimen quality, MRSA was searched for in the culture. Swabs were plated directly onto enriched sheep blood agar plates, and selective and differential medium oxacillin sodium–resistance screening agar base (ORSAB; Oxoid Ltd, Basingstoke, England) and an enriched trypticase soy broth were inoculated. *Staphylococcus aureus* was identified using standard laboratory procedures. Samples with inconclusive routine test results for identification of *S aureus* were further tested by a hybridization test (Accuprobe; GenProbe, San Diego, Calif). Methicillin resistance was determined using a salt agar screening plate containing 6 µg/mL of oxacillin and 4% sodium chloride, as recommended by National Committee for Clinical Laboratory Standards guidelines. Discordant results were confirmed by determining the minimal inhibitory concentration for oxacillin using the Etest (AB Biodisk, Solna, Sweden). All MRSA isolates were stored at −70°C. Genotyping of MRSA isolates was not performed.

Before each decolonization attempt, all MRSA strains were screened for mupirocin resistance using Mueller-Hinton agar and a 5-µg mupirocin disk (BD Diagnostic Systems, Sparks, Md) incubated at 35°C for 24 hours. An inhibition zone size of 13 mm or less was interpreted as mupirocin resistant. These strains were further tested for the minimal inhibitory concentration to mupirocin using the Etest. Isolates showing mupirocin minimal inhibitory concentrations between 4 and 256 µg/mL were categorized as low-level mupirocin resistance, and those with mupirocin concentrations of at least 512 µg/mL were considered as high-level resistance.

### TABLE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1998</th>
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<th>2001</th>
<th>2002</th>
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</thead>
<tbody>
<tr>
<td>No. of patients with <em>S aureus</em> carriage</td>
<td>29 (12.6)</td>
<td>52 (19.2)</td>
<td>53 (20.6)</td>
<td>40 (14.5)</td>
<td>49 (11.9)</td>
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<tr>
<td>No. (%) of imported cases</td>
<td>15 (51.7)</td>
<td>28 (50.0)</td>
<td>29 (54.7)</td>
<td>26 (65.0)</td>
<td>51 (93.9)</td>
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<tr>
<td>No. (%) of acquired cases at our institution</td>
<td>14 (48.3)</td>
<td>26 (50.0)</td>
<td>24 (45.3)</td>
<td>14 (35.0)</td>
<td>3 (6.1)</td>
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**Abbreviation:** MRSA, methicillin sodium–resistant *S aureus.*

**RESULTS**

During the 5 years, 33905 patients were admitted to the hospital. The annual number of hospital admissions increased steadily from 6351 in 1998 to 7186 in 2002 (mean, 6781 admissions). In the same period, the mean duration of hospital stay decreased from 12.5 to 9.8 days (mean, 11.1 days). The mean age of admitted patients increased from 63.3 years in 1998 to 72.3 years in 2002 (Table).

During the 5 years, 1445 patients showed growth of *S aureus* from at least 1 clinical specimen. Of these,
223 patients (15.4%) were infected or colonized with MRSA; 68.2% were men. One hundred forty-two MRSA cases (63.7%) were imported, and 81 (36.3%) were acquired in our hospital. The proportion of MRSA cases acquired in our institution steadily declined from 50.0% in 1999 to 6.1% in 2002 ($P < .001$ for trend), whereas the proportion of imported MRSA cases increased from 50.0% to 93.9% ($P < .001$ for trend) (Figure 1). In the ICU, 72 MRSA cases (32.3%) were detected. Of these, 43 (59.7%) were imported and 29 (40.3%) were acquired in our ICU (data not shown). The annual incidence of detected MRSA carriers per 1000 admissions statistically significantly increased in the first year after introduction of active surveillance cultures from 4.5 in 1998 to 8.0 in 1999 ($P = .02$), but remained stable thereafter ($P = .26$ for trend).

In 1998, no active surveillance cultures were obtained. In the following 4 years, the proportion of patients detected through active surveillance cultures progressively increased from 23.1% in 1999 to 83.7% in 2002 (Table). In this period, active surveillance cultures were obtained in 688 patients who were at risk for MRSA carriage, representing 2.5% of admitted patients. One hundred forty-four (64.6%) of 223 MRSA carriers were detected by routine clinical cultures and 79 (35.4%) by active surveillance cultures. Methicillin-resistant Staphylococcus aureus was first isolated from sputum (in 30.0% of cases), other respiratory secretions (in 27.4%), nose (in 19.3%), wound (in 10.8%), urine (in 6.3%), throat (in 4.0%), and blood (in 2.2%). Whereas sputum was the most common site for recovery of MRSA from 1998 through 2000, the nares had become the predominant site of recovery since 2001 (Figure 2).

Patients with imported MRSA carriage (142 cases) were transferred from other hospitals (75 cases), the community (50 cases), and nursing homes (17 cases). Twenty (40.0%) of 50 patients who were hospitalized from the community had at least 1 hospital stay in the previous 4 years in their history. Among 81 patients who acquired MRSA at our institution, 52 cases (64.2%) were detected on medical wards and 29 cases (35.8%) in the ICU. During the study, the number of patients who acquired MRSA at other hospitals ($P < .001$) and nursing homes ($P = .03$) increased, and the number of community-acquired MRSA cases remained stable ($P = .09$), while the number of patients with MRSA acquired at our hospital decreased significantly ($P < .001$) (Figure 3).

Among 26 patients who underwent a decolonization procedure for MRSA carriage, 19 were successfully decolonized based on 3 sets of surveillance cultures. For the remaining 7 patients, only 1 (6 patients) or 2 (1 patient) sets of surveillance cultures were obtained, and all were negative. Between 1998 and 2001, no mupirocin resistance in MRSA strains was detected. In 2002, however, 6 patients with mupirocin-resistant MRSA isolates were detected; 5 patients carried low-level strains, and 1 patient carried a high-level strain. All 6 patients with mupirocin-resistant MRSA isolates were transferred from other institutions. Of those 5 patients with low-level mupirocin-resistant strains, only 1 patient was decolonized and was subsequently free of MRSA in the surveillance cultures; the other 4 patients were not decolonized because of their poor general health. In the patient with high-level mupirocin resistance, the decolonization failed.
We evaluated the effect of an aggressive infection control program on the nosocomial spread of MRSA in a highly endemic setting. During the study, MRSA was recovered from 223 hospitalized patients. In the first year after the introduction of active surveillance cultures, the documented annual incidence of MRSA increased significantly (from 4.5 to 8.0 per 1000 admissions), indicating that approximately half of MRSA cases were probably missed before implementation of routine screening for MRSA at admission. This is also supported by the increasing proportion of patients detected through active surveillance cultures from 23.1% to 83.7%, and by replacement of sputum by the nares as the most common detection site of MRSA during the later study phase. Unrecognized MRSA cases may represent sources for recurring nosocomial outbreaks of MRSA or their endemic presence.

Despite implementation of an aggressive infection control program in 1999, the annual incidence of MRSA did not decline significantly. However, the acquisition of MRSA at our hospital was substantially reduced (from 50.0% to 6.1% of all MRSA cases), and most patients with MRSA were transferred from other hospitals or nursing homes. This observation suggests that the laboratory-based calculation, based on the proportion of MRSA among all *S. aureus* isolates, provides insufficient information about the effectiveness of an infection control program. Categorization of MRSA carriers into imported and acquired cases at an institution is a more appropriate epidemiologic indicator than the total number of cases. A substantial number (22.4%) of MRSA carriers had no previously identified contact with a health care institution, and we have no information about the possible source of MRSA acquisition in these patients. High percentages (30%-40%) of community-acquired MRSA among MRSA isolates from hospitalized patients were reported in some studies. Most of these patients had 1 or more health care–associated risks, emphasizing the importance of effective control of nosocomial transmission to prevent dissemination of MRSA throughout the community. Although we did not perform genotyping of MRSA isolates (eg, pulsed-field gel electrophoresis) to prove the clonality of MRSA in patients who acquired MRSA at our institution, the occurrence of these cases in clusters suggests nosocomial spread.

In this study, we were unable to determine the effect of each intervention in control of the nosocomial spread of MRSA, as all measures were introduced at the same time. However, we speculate that in a highly endemic setting, a combined multidisciplinary approach to controlling MRSA is essential. A significant improvement in compliance with hand hygiene was achieved, in most cases, simply by switching from conventional hand washing to a consistent use of an alcohol rub. The importance of early recognition of MRSA carriers by active surveillance cultures and application of strict barrier precautions was demonstrated in other studies. Successful decolonization of MRSA carriers eliminates the reservoir of MRSA and was shown to be important when eradication of MRSA is the ultimate goal. Another possible approach to preventing the spread of MRSA could be the reduction of antimicrobial selective pressure.

Conflicting data about the efficacy of decolonization exist. In our study, the decolonization procedure was successful after selection of appropriate patients (no skin lesions or presence of foreign bodies). All 19 patients for whom 3 sets of postdecolonization surveillance cultures were available showed no growth of MRSA. For evaluation of the efficacy of long-term decolonization, we plan to obtain surveillance cultures more than 1 year after completed decolonization (or earlier, if the patient is hospitalized). All MRSA cases with mupirocin resistance were imported and may reflect previous inconsistent decolonization attempts or transmission of a resistant strain from other patients.

Our study demonstrates that an active infection control program is effective in preventing nosocomial spread of MRSA even in highly endemic settings. A comprehensive approach is essential, including improved hand hygiene using alcohol handrub, education of HCWs, and early detection, isolation, and decolonization of MRSA carriers. This study confirms the effectiveness of the most recent Centers for Disease Control and Prevention guidelines on MRSA prevention.

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### REFERENCES


