**TRENDS IN METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) BLOODSTREAM INFECTIONS: EFFECT OF THE MRSA “SEARCH AND ISOLATE” STRATEGY IN A HOSPITAL IN ITALY WITH HYPERENDEMIC MRSA**

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**ABSTRACT**

**OBJECTIVE:** To evaluate the secular trends in MRSA BSIs after the introduction of a nosocomial MRSA control intervention.

**DESIGN:** Before–after study.

**SETTING:** An 850-bed community hospital with an ICU and vascular surgery, neurosurgery, bone marrow transplantation, and AIDS units. MRSA is endemic at this hospital; the prevalence of methicillin resistance among patients with *S. aureus* infection is greater than 50%.

**PATIENTS:** Among all inpatients, MRSA BSI was identified, its origin defined, and incidence rates calculated by ward and origin.

**INTERVENTION:** A MRSA control program was implemented based on active surveillance cultures to identify MRSA-colonized patients, followed by isolation using contact precautions. Incidence rates of MRSA BSI during the intervention (ie, January 1, 1997, to December 31, 2001) and preintervention (ie, January 1, 1996, to June 30, 1997) periods were compared.

**RESULTS:** Sixty-nine MRSA BSIs were identified. When compared with the preintervention period, the incidence rate of MRSA BSI was reduced from 0.64 to 0.30 per 1,000 admissions (RR, 0.46; CI, 0.25–0.87; *P* = .02) during the intervention period. The impact was greater in the ICU, with an 89% reduction (RR, 0.11; CI, 0.01–0.98; *P* = .03), and for CVC-associated MRSA BSIs, with an 82% decrease (RR, 0.17; CI, 0.05–0.55; *P* = .002). Methicillin resistance among *S. aureus* blood isolates decreased from 46% to 17% (RR, 0.36; CI, 0.22–0.62; *P* = .0002).

**CONCLUSION:** A reduction in MRSA bacteremia is achievable through use of the MRSA “search and isolate” intervention even in a hospital with high rates of endemic MRSA (*Infect Control Hosp Epidemiol* 2005;26:127-133).

*Methicillin-resistant Staphylococcus aureus* is the most common human pathogen, and infections caused by methicillin-resistant *S. aureus* (MRSA) are increasing in most hospitals throughout the world. MRSA is one of the most common nosocomial pathogens in Europe and North America. Recent data have revealed that hospitals in Italy have some of the highest MRSA incidence rates in Europe, ranging from 30% to 40%. The incidence rates of *S. aureus* bloodstream infection (BSI) have increased over the years, and MRSA BSIs are associated with increased mortality compared with methicillin-sensitive (MSSA) BSIs.

MRSA infections also are frequent in high-risk populations, such as patients in intensive care units (ICUs), patients with central venous catheters (CVCs), or liver transplant recipients. Patients colonized with MRSA are at higher risk for MRSA BSIs than are patients colonized with MSSA. Nosocomial infection control programs have been implemented in many countries, and several of these programs are based on the “search and isolate” strategy to control the nosocomial spread of MRSA. There are fewer data on the efficacy of these control interventions for MRSA BSIs, particularly where the prevalence of MRSA exceeds 50%.

We evaluated the incidence rate of MRSA BSIs by ward and possible origin, before and after the introduction of a control program at the hospital of Cremona, Italy. The prevalence of methicillin resistance among nosocomial isolates of *S. aureus* at the time of the intervention was greater than 50% in this hospital.

**METHODS**

**Study Design and Period**

This was an interventional before–after study. Data regarding MRSA or MSSA BSIs were collected from January 1, 1996, through December 31, 2001. From January 1, 1997, through December 31, 2001, identifica-
tion was prospective, whereas during 1996, identification was retrospective.

For the purpose of analysis, three periods were identified. The preintervention period (from January 1, 1996, through June 30, 1997) was the period before the introduction of the program to control nosocomial transmission of MRSA (Period “Pre”). Intervention period A (from July 1, 1997, through December 31, 1999) was the first part of the intervention period, when the program was progressively introduced on each ward and service. An educational program for healthcare workers regarding the new infection control measures was implemented. Intervention period B (from January 1, 2000, to December 31, 2001) was the final part of the study period, when the search and destroy protocols were fully implemented.

Setting

The study was conducted at the hospital of Cremona in Lombardy, Italy. The hospital is an 850-bed community hospital with medical and surgical wards, one general ICU, a neonatal ICU, a vascular surgery unit, a bone marrow transplantation unit, and an infectious diseases and acquired immunodeficiency syndrome (AIDS) unit. A neurosurgery unit was opened in 1999. The hospital’s computer system. Data regarding the number of surgical procedures were obtained from the hospital’s computer system.

Microbiology

All blood cultures were processed by the hospital’s microbiology laboratory using the Bactec 9240 System (Becton Dickinson, Milan, Italy). *Staphylococcus* species were identified using the API System (API Staph, bioMérieux, Rome, Italy). Antimicrobial susceptibility testing was performed using the Sceptor System (Becton Dickinson) with a 3-point breakpoint according to National Committee for Clinical Laboratory Standards guidelines. Mupicitin resistance was confirmed through growth identification using the Oxa Screen Agar System (Becton Dickinson).

Overall Hospital Population Data

The number of admissions per ward per month and the number of surgical procedures were obtained from the hospital’s computer system. Data regarding the number of CVCs were obtained from the registers of the wards where the CVCs were inserted, specifically the ICU, general surgical wards, and nephrology and dialysis wards.

Clinical Chart Analysis

An active surveillance system was established with the clinical microbiology laboratory. Three to five times a
week, a member of the infection control team visited the laboratory and entered any *S. aureus* isolated from blood cultures into the database.

Patients' medical records were reviewed after patient discharge, and the origin of MRSA BSI was defined. All data were entered in the database.

**Definitions: Origin of MRSA Bacteremia**

The definition of MRSA BSI was based on the Centers for Disease Control and Prevention definitions of nosocomial infection or the 1996 guidelines on CVC-related MRSA BSI, as appropriate. A final review of each CVC-associated MRSA BSI was performed using the definitions of CVC-related bacteremia as indicated by the 2001 guidelines. The differences between the 1996 and the 2001 guidelines are minimal: (1) the introduction of paired blood cultures with differential time to positivity and (2) the reduction of the colony-forming units from the 2001 guidelines.25 The differences between the 1996 and the 2001 guidelines are minimal: (1) the introduction of paired blood cultures with differential time to positivity and (2) the reduction of the colony-forming units from 10 to 10 obtained through quantitative culture of a segment of the catheter, for a catheter to be considered infected. The use of paired blood cultures was introduced in our hospital in June 2000. At the same time, the use of quantitative blood cultures was discontinued. Because CVC-associated MRSA BSIs were considered as a separate group, a BSI was considered as primary if no source, not even an intravascular catheter, was identified.

MRSA BSI was defined as secondary to surgical-site infection (SSI) when MRSA was isolated from a swab of the surgical site or in the absence of a microbiological sample obtained from the surgical site.

Isolates were identified as either nosocomial or community acquired. Isolates were defined as community acquired when cultures were performed less than 48 hours after admission. An isolate was defined as nosocomial if the culture was performed more than 48 hours after admission.

A patient was defined as MRSA positive when the pathogen was isolated from at least one site on at least one occasion. MRSA-positive patients could be either infected or colonized.

A wound was defined as colonized if no sign of local infection was present and MRSA was isolated from a wound swab.

**Statistical Analysis**

Results were expressed as incidence rate and relative risk (RR) with 95% confidence interval (CI). Statistical analyses were performed using the statistical process control method and quality control charts. Control charts compare a current performance with a past performance to indicate whether they are in statistical control. The analysis uses the mean score and ±3 standard deviations (SDs) to determine whether a change in the data is due to chance. With the use of the 2-band analysis it is assumed that if data are outside the bands, it is a statistically significant change or event at the .05 level.

Differences in frequencies were evaluated by means of chi-square or Fisher’s exact test, as appropriate.

A P value less than .05 was considered to indicate statistical significance; all tests were two-sided. Analyses were performed using STATA software (release 7.0; STATA Corp., College Station, TX).

**RESULTS**

During the 6-year study period, there were 156,871 admissions and 47,032 surgical procedures (surgical procedures increased progressively from approximately 6,000 in 1996 to approximately 9,000 in 2001). The number of CVCs inserted increased progressively during the study period from 13.9 per 1,000 admissions in the preintervention period to 16.9 in intervention period A and 26.6 in intervention period B.

During the study period, 251 episodes of *S. aureus* BSI were identified (1.6 cases per 1,000 admissions); 69 (27.5%) were due to MRSA (0.44 per 1,000 admissions). MRSA BSI developed in 7.8% of the 885 MRSA-positive patients. All MRSA BSIs identified were healthcare related; no community MRSA BSIs were identified.

The rate of methicillin resistance among blood isolates of *S. aureus* was 46% in the first 18 months (preintervention) and decreased to 17% in intervention period B ($P < .0001$). During intervention periods A and B, the proportion of *S. aureus* isolates with methicillin resistance was 21%; this was a significant reduction compared with the preintervention period ($P < .0003$).

The incidence rate of MRSA BSI decreased by 42%, from 0.64 case per 1,000 admissions in the preintervention period to 0.37 case per 1,000 admissions during the entire intervention period (RR, 0.57; CI: 0.35 to 0.92; $P < .03$). The secular trend had a bimodal form, with an initial decline in MRSA BSI during the first 2 years of the intervention (approximately 31%) and a smaller secondary decline (24%) in the last 2 years of the intervention. When the preintervention period and intervention period B were compared, the decrease in MRSA BSIs (to 0.46 case per 1,000 admissions) was statistically significant ($P < .02$) (Figure).

Next, we evaluated the impact by ward. Of the MRSA BSIs, 40 (58%) of 69 were identified in medical wards, 20 (29%) in surgical wards, and 9 (13%) in the ICU.

A significant decrease in the incidence rate of MRSA BSIs was obtained in all wards and units. The greatest impact was in the ICU, where there was a 56% reduction (RR, 0.44) between the preintervention period and intervention period A (from 6.07 to 2.66 cases per 1,000 admissions) and an 89% reduction between the preintervention period and intervention period B, when the MRSA BSI incidence rate decreased to 0.66 case per 1,000 admissions (RR, 0.11).

On the medical wards, the MRSA BSI rate decreased from 0.59 case per 1,000 admissions in the preintervention period to 0.43 case per 1,000 admissions in intervention period A (RR, 0.73) and subsequently to 0.36 MRSA BSI per 1,000 admissions (RR, 0.61) in inter-
infection rate of MSSA BSI rose from 0.81 case per 1,000 admissions (RR, 1.37; CI\(_{95}\), 0.91 to 2.05; \(P = .16\)). There was a further increase to 1.59 cases per 1,000 admissions (RR, 1.96; CI\(_{95}\), 1.32 to 2.93; \(P = .001\)) in intervention period B.

The percentage of all nosocomial \textit{S. aureus} isolates with methicillin resistance progressively decreased from approximately 50% in the preintervention period to 21% in intervention period B (\(P < .0001\)).

Finally, data regarding compliance with contact precautions were available for 370 of 741 patients positive for MRSA after the introduction of the control program. Contact precautions were correctly applied for 203 (55%) of 370 patients. In another 25 MRSA-positive patients (7%), the culture results were not available until the day of or after hospital discharge. Thus, the overall compliance rate for patients known to be MRSA positive during hospitalization was 62%.

**DISCUSSION**

The introduction of a search and isolate strategy to control nosocomial transmission of MRSA in a hospital with high endemic levels of MRSA led to a significant reduction in MRSA BSI. The control program was most effective in reducing MRSA BSIs among patients with CVCs and those in the ICU. The implications of these results are interesting for different reasons. A significant reduction in MRSA BSIs is feasible even in settings with high MRSA rates. Although partial control of MRSA in settings with high levels of MRSA has been previously achieved,\textsuperscript{27-29} there are few, if any, reports of a reduction in MRSA BSIs in hospitals with MRSA rates greater than 40%. Although complete eradication of MRSA BSIs from the hospital was not achieved, the results obtained were significant and impressive.

\textit{S. aureus} BSIs arise from the patients’ own flora in approximately 80% of episodes.\textsuperscript{30,31} There may be several explanations for our failure to fully eradicate MRSA BSIs, including failure to detect all MRSA-positive patients (unknown carriers pose a much higher risk of transmitting MRSA than known carriers\textsuperscript{32}); incomplete adherence to the isolation protocol, particularly to hand hygiene procedures (adherence to the protocol in our hospital was 62%); oversimplification of the isolation protocol (although gowns are an effective adjunctive means to control nosocomial transmission of MRSA,\textsuperscript{33} we recommend only for patients with purulent infections); delay in adherence to the MRSA protocol after patient admission; and changes in the patient population at the hospital, with an increase in the population at risk during the study period. Between 1996 and 2001, there was a significant increase in CVC insertions, a known risk factor for MRSA BSIs.\textsuperscript{13,34} Probably more than one of these factors played a role in the incomplete success of the program.

As per the origin, the most striking reduction was seen among CVC-associated MRSA BSIs. CVC-associated MRSA BSIs decreased by 82%. Because no other program for prevention of CVC-associated infection was implemented during the study period, which could have modified the incidence rate of CVC-associated BSIs (and MSSA BSIs due to SSI were reduced by 49%, from 0.73 during the preintervention period to 0.37 per 1,000 surgical procedures during the entire intervention period (ie, periods A and B) (RR = 0.51; CI\(_{95}\), 0.21 to 1.27; \(P = .17\)).

The incidence rate of primary MRSA BSI decreased 71% between the preintervention and the entire postintervention periods, from 0.12 to 0.03 case per 1,000 admissions (RR, 0.25; CI\(_{95}\), 0.08 to 1.09; \(P = .06\)).

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BSIs did increase), the reduction we observed was probably due to the MRSA intervention program itself.

Although a reduction in the number of MRSA-colonized patients could explain the reduction in CVC-associated MRSA BSIs, there is an alternative hypothesis: the decrease in the prevalence of MRSA-colonized patients, due to topical treatment with mupirocin and chlorhexidine, could reduce the risk of MRSA BSI. This hypothesis may be indirectly supported by the findings that SSIs are more frequently seen in heavily colonized patients (ie, nose and rectum) as compared with patients with only nasal colonization. Topical treatment is only partially effective in eliminating MRSA carriage, whereas it is probably very effective in reducing the overall body bacterial count, possibly reducing the risk of CVC-associated MRSA BSIs.

The reduction was most consistent in patients admitted to the ICU, where the incidence rate of MRSA BSIs decreased by 89%. CVCs were the most frequent site of origin of MRSA BSIs in the ICU both before (3 of 4; 75%) and after (5 of 5; 100%) the introduction of the intervention program. Although this could be due, at least partly, to the reduction in CVC-associated MRSA BSIs, we think that the reduction in the reservoir of MRSA-colonized patients, secondary to reduced cross-transmission rates of MRSA, had a central role in this result. The ICU was where our intervention was the most aggressive in searching for MRSA-colonized patients. Aggressive search and destroy systems are known to be successful in controlling nosocomial MRSA transmission in hospitals, and effective programs are generally characterized by the presence of an active surveillance culture program aimed at identifying MRSA carriers.

Approximately 24 months after the introduction of the program, a baseline level of MRSA BSI was reached (ie, 0.3 case per 1,000 admissions) and remained stable for the following 2 years. The reasons for this bimodal pattern may be that (1) such a control program shows a high efficiency in a hyperendemic setting, whereas in settings with lower incidences of transmission and infection a more aggressive approach is probably needed; and (2) the incomplete adherence to the isolation protocol (62%) did not permit a further reduction of the transmission of MRSA. It is possible that different levels of transmission need different approaches, such as the very aggressive “Dutch system” or a dedicated infection control nurse in high-risk units.

Finally, a significant reduction in methicillin resistance among blood isolates was seen: 46% during the first 18 months as compared with 17% in the last 2 years of the study period. The rate of methicillin resistance among blood isolates was similarly reduced from 50% in 1996 to 20% in 2001. Along with this decrease in methicillin resistance among blood isolates, the reduction of methicillin resistance among nosocomial S. aureus isolates continued: methicillin resistance decreased from 53% to 21% (P < .0001).

There are two main limitations of our study. First, it was not controlled. Second, the 1996 data were collected retrospectively unlike the data from 1997 onward, which were collected prospectively. Although we cannot exclude that the decrease in MRSA BSIs was just due to chance, we are relatively confident about the efficacy of the program for several reasons: (1) the incidence rate of methicillin resistance among nosocomial isolates of S. aureus in Italy, other European countries, and the United States has progressively increased during the past few years, opposite of what we observed; (2) the incidence rate of MRSA BSI decreased after the introduction of the intervention; and (3) the reduction in MRSA BSI was associated with a similar decline in methicillin resistance among S. aureus isolates, probably due to a reduction in the MRSA-colonized patient reservoir.

**TABLE 1**

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<tbody>
<tr>
<td>Overall</td>
<td>0.64</td>
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<td>ICU</td>
<td>6.07</td>
<td>2.66</td>
<td>0.66</td>
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<td>Medical wards</td>
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<td>0.43</td>
<td>0.36</td>
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<tr>
<td>Surgical wards</td>
<td>0.51</td>
<td>0.27</td>
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*Period Pre corresponds to the preintervention phase, period A represents the first period after the introduction of the control program, and period B represents the last 2 years of the study period, when the program was well known throughout the hospital. Comparisons between period Pre and periods A and B are reported as both reduction in percentage, with P value in parentheses, and RR.

RR = relative risk; CI95 = 95% confidence interval; ICU = intensive care unit.

*STAPHYLOCOCCUS AUREUS BACTEREMIA PER DEPARTMENT PER 1,000 ADMISSIONS*
When we compared our data with those from Luzzaro et al.,7 which were obtained from 16 hospitals in the same region and in the same period (1999 to 2000), the methicillin resistance that we achieved was statistically significantly greater: 17% in Cremona versus 34% in the other Lombardy hospitals (RR, 0.49; CI95, 0.30 to 0.81; P < .0001). Notably, the incidence reported by Luzzaro et al. was similar to, although slightly higher than, that seen in our hospital before the program (46%; RR, 1.34; CI95, 0.98 to 1.82; P = .11).

As per the data of 1996, which were retrospectively collected, BSI, per se, cannot be misdiagnosed because we used the same criteria during the entire period: isolation of MRSA from blood cultures. Furthermore, the reduction in MRSA BSI between intervention periods A and B was statistically significant even when only prospectively collected data were used.

Although a specific pharmacoeconomic analysis was not performed, we estimated that the cost of the program, including active surveillance cultures, patient isolation, and treatment of patients, was approximately 25,000 to 30,000 euros per year. This is similar to the cost of 1 to 3 patients with MRSA BSI, based on previous estimates.40-42 We estimate that the amount saved just in one from 3 patients with MRSA BSI, based on previous estimates, was approximately 25,000 euros per year. This is similar to the cost of 1 to 3 patients with MRSA BSI, based on previous estimates.40-42

To obtain eradication of MRSA, if feasible, we think that an aggressive approach is needed. Every hospital should seek to employ this strategy based on national and international guidelines, specific patient populations, local medical knowledge and relationships, and financial resources.

Because a significant reduction was seen in CVC-associated MRSA BSIs and in MRSA BSIs among ICU patients, a program of MRSA control should be mandatory in every hospital with a high rate of methicillin resistance or a high incidence rate of CVC-associated MRSA BSIs and in hospitals with MRSA BSIs in their ICU. More sophisticated, and probably more expensive, interventions may be necessary to eradicate MRSA from hospitals, although it is not yet known whether this target is feasible.

As outlined by Harbarth and Pittet,29 our hospital directors should give us the chance to further investigate this issue. Our patients deserve it.

**REFERENCES**

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