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 •
Author(s): Angelo Pan , MD; Giuseppe Carnevale , MD; Patrizia Catenazzi; Paolo Colombini , MD; Luciano Crema , MD; Lucia Dolcetti , MD; Lucio Ferrari , PhD; Placido Mondello , MD; Liana Signorini , MD; Carmine Tinelli , MD; Eugenia Quiros Roldan , MD; Giampiero Carosi , MD
Reviewed work(s):
Source: *Infection Control and Hospital Epidemiology*, Vol. 26, No. 2 (February 2005), pp. 127-133
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/10.1086/502515
Accessed: 09/05/2012 07:54

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

Angelo Pan, MD; Giuseppe Carnevale, MD; Patrizia Catenazzi; Paolo Colombini, MD; Luciano Crema, MD; Lucia Dolcetti, MD; Lucio Ferrari, PhD; Placido Mondello, MD; Liana Signorini, MD; Carmine Tinelli, MD; Eugenia Quiros Roldan, MD; Giampiero Carosi, MD

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, July 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_{95}, 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_{95}, 0.01–0.98; $P = .03$), and for CVC-associated MRSA BSIs, with an 82% decrease (RR, 0.17; CI_{95}, 0.05–0.55; $P = .002$). Methicillin resistance among *S. aureus* blood isolates decreased from 46% to 17% (RR, 0.36; CI_{95}, 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).

Staphylococcus aureus is the most common human pathogen,[1] and infections caused by methicillin-resistant *S. aureus* (MRSA) are increasing in most hospitals throughout the world.[2] MRSA is one of the most common nosocomial pathogens in Europe[3,4] and North America.[5] Recent data have revealed that hospitals in Italy have some of the highest MRSA incidence rates in Europe, ranging from 30% to 40%.[6,7]

The incidence rates of *S. aureus* bloodstream infection (BSI) have increased over the years,[8] and MRSA BSIs are associated with increased mortality compared with methicillin-sensitive (MSSA) BSIs.[9,10]

MRSA infections also are frequent in high-risk populations, such as patients in intensive care units (ICUs),[5] patients with central venous catheters (CVCs),[11] or liver transplant recipients.[12] Patients colonized with MRSA are at higher risk for MRSA BSIs than are patients colonized with MSSA.[13]

Nosocomial infection control programs have been implemented in many countries,[14] 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-

Drs. Pan, Carnevale, and Mondello are from the Divisione di Malattie Infettive; Dr. Ferrari is from the Laboratorio di Microbiologia; Dr. Crema is from the Servizio di Terapie Intensive; and Ms. Catenazzi and Dr. Dolcetti are from the Direzione Sanitaria, Istituti Ospitalieri di Cremona, Cremona, Italy. Drs. Pan, Colombini, Signorini, Roldan, and Carosi are from the Istituto di Malattie Infettive e Tropicali, Spedali Civili, Università di Brescia, Brescia, Italy. Dr. Tinelli is from the Servizio Biometria ed Epidemiologia Clinica, Direzione Scientifica, IRCCS Policlinico San Matteo, Università di Pavia, Pavia, Italy.

Address reprint requests to Angelo Pan, MD, Clinica di Malattie Infettive e Tropicali, Spedali Civili - Università degli Studi di Brescia, Piazzale Spedali Civili, 1, 20123 Brescia, Italy. ange.pan@tiscali.it

The authors thank Tomaso Ceruti, PhD, for his invaluable collaboration in the project, and Luisa Granata, RN, and Nadia Poli, RN, for their support in implementing this intervention within the hospital.

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 of Cremona admits approximately 25,000 patients each year.

When the intervention was initiated in the hospital of Cremona, like most Italian hospitals, it was characterized by (1) isolation of MRSA in the hospital for more than 10 years, (2) a high rate of transmission of MRSA (ie, more than 5 cases per 1,000 admissions[15]), and (3) a high rate of methicillin resistance among nosocomial isolates of *S. aureus* (> 50%).

Intervention

In July 1997, on the basis of the available literature,[16-20] we introduced a program to control nosocomial MRSA transmission within the hospital of Cremona using a multicomponent approach similar to the search and isolate system.[21] The key points of the program were:

1. Active Surveillance Cultures for MRSA: Obtaining Nasal Swabs From High-Risk Patients and Wards. An initial exploratory study was performed before the intervention to identify patients and wards at higher risk of MRSA colonization (unpublished data). High-risk patients were identified as those transferred from the intensive care, heart surgery, or neurosurgery units of other hospitals and nursing homes residents. High-risk wards were identified as ICUs, post-ICU rehabilitation units, and bone marrow transplantation units.

Nasal swabs were obtained on admission for these high-risk patients and wards. On high-risk wards, nasal swabs were performed periodically to identify MRSA-colonized patients. They were performed at different times on different wards, depending on the intensity of care: every 3 days in the ICU, every week in the bone marrow transplantation unit, and every 2 weeks in the rehabilitation unit. The different time points were based on the median time to MRSA positivity identified in these wards through a pilot study (unpublished data).

2. Isolation and Contact Precautions for All Identified MRSA-Positive (Colonized or Infected) Patients. Contact precautions included routine glove use and handwashing; gowns were used only when treating patients with infected wounds. The contact precautions protocol was simplified to save healthcare workers' time and possibly improve their compliance.

3. Treatment of MRSA-Positive Patients With Nasal Mupirocin Ointment. Mupirocin ointment (Bactroban pomata, GlaxoSmithKline, Verona, Italy), 2 to 3 mm in each nostril 3 times daily; chlorhexidine 4% soap solution (Neoxidina mani, Farmec, Settimo di Pescantino - VR, Italy) baths or showers, once a day for 5 days; and shampoos on the first and fifth day of treatment were administered to MRSA-positive patients. Colonized wounds were treated with polyethylenglycol mupirocin cream (Bactroban crema, GlaxoSmithKline) twice a day for 5 days.

4. Periodic Feedback of MRSA Data to Medical and Non-Medical Ward Staff. Data from MRSA-positive patients were entered into a database.

Other than MRSA control, no specific intervention to reduce BSIs caused by other pathogens was implemented during the study period.

Patients

The study included all inpatients from January 1, 1996, through December 31, 2001, who had at least one blood culture positive for MRSA or MSSA.

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.[22] Methicillin 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[23] or the 1996 guidelines on CVC-related MRSA BSI,[24] 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.[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 10^3 to 10^2, 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_{95}). Statistical analyses were performed using the statistical process control method and quality control charts.[26] 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 significantly 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_{95}, 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-

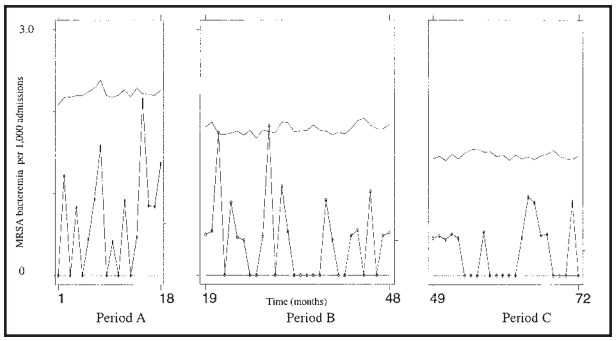

FIGURE. Quality control chart[26] demonstrating the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia per 1,000 admissions during the 3 phases of the study period. The solid line indicates the monthly incidence of MRSA bacteremia. The dotted line indicates the upper band of alarm of MRSA bacteremia, calculated with the mean incidence plus 3 standard deviations. The lower band of alarm, calculated with the mean incidence minus 3 standard deviations, corresponds to 0 during the entire period. 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. Period A corresponds to the preintervention phase. Period B represents the first period after the introduction of the control program, and period C the last 2 years of the study period, when the program was well known throughout the hospital.

vention period C (Table 1). In the surgical wards, the reduction observed between the preintervention and the entire postintervention period (ie, periods A and B) was approximately 50% (RR, 0.48; CI_{95}, 0.2 to 1.16; $P = .15$). The MRSA BSI incidence rate was 0.51 case per 1,000 admissions in the preintervention period and 0.21 in intervention period B (RR, 0.41) (Table 1).

Next, we evaluated the origin of MRSA BSI. Twenty-nine MRSA BSIs (42%) were CVC associated, 20 (29%) were secondary to SSI, and 10 (14%) were primary. Five MRSA BSIs (7%) originated from skin disease (namely, pressure sores, wounds, or abscesses), 3 (5%) originated from respiratory tract infections, and 2 (3%) were secondary to urinary tract infection.

Next, we evaluated the incidence rate of CVC-associated MRSA BSIs in patients who had a CVC inserted. A 31% decrease in MRSA BSI was detected from the preintervention period to intervention period B (1.71 to 1.18 MRSA BSIs per 100 CVCs). During intervention period B, there was an 82% reduction in CVC-associated MRSA BSIs, with the incidence rate decreasing to 0.3 case per 100 CVCs (RR, 0.17) (Table 2). No difference was identified in the diagnosis of CVC-associated MRSA BSIs using the 1996 or the 2001 definitions.

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, 0.29; CI_{95}, 0.08 to 1.09; $P = .06$).

MRSA 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 MSSA BSI rose from 0.81 case per 1,000 admissions in the preintervention period to 1.1 cases in intervention period A (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 *S. aureus* isolates with methicillin resistance progressively decreased from 53% 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,[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.

S. aureus BSIs arise from the patients' own flora in approximately 80% of episodes.[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[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,[33] we recommended them 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.[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

TABLE 1
INCIDENCE RATE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BACTEREMIA PER DEPARTMENT PER 1,000 ADMISSIONS*

Department	January 1996–June 1997 (Period Pre)	July 1997–December 1999 (Period A)	January 2000–December 2001 (Period B)	Decrease Pre vs A (*P*)	RR Pre to A (CI_{95})	Decrease Pre vs B (*P*)	RR Pre to B (CI_{95})
Overall	0.64	0.42	0.30	34% (.13)	0.66 (0.39–1.13)	53% (.02)	0.46 (0.25–0.87)
ICU	6.07	2.66	0.66	56% (.26)	0.44 (0.11–1.76)	89% (.03)	0.11 (0.01–0.98)
Medical wards	0.59	0.43	0.36	27% (.38)	0.73 (0.36–1.49)	39% (.32)	0.61 (0.27–1.37)
Surgical wards	0.51	0.27	0.21	47% (.31)	0.53 (0.2–1.43)	59% (.21)	0.41 (0.13–1.35)

RR = relative risk; CI_{95} = 95% confidence interval; ICU = intensive care unit.
*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.

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.[35] Topical treatment is only partially effective in eliminating MRSA carriage,[36] 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,[37] and effective programs are generally characterized by the presence of an active surveillance culture program aimed at identifying MRSA carriers.[33]

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"[37] or a dedicated infection control nurse in high-risk units.[38]

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 ($P = .0001$). In the ICU, 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, previously reported by our group, among all nosocomial *S. aureus* isolates[15] 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,[39] 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 2
INCIDENCE RATE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BACTEREMIA DEFINED AS PER THE ORIGIN, BASED ON THE EXPOSED POPULATION*

Group	January 1996–June 1997 (Period Pre)	July 1997–December 1999 (Period A)	January 2000–December 2001 (Period B)	Decrease Pre to A (*P*)	RR Pre to A (CI_{95})	Decrease Pre to B (*P*)	RR Pre to B (CI_{95})
Primary bacteremia†	0.12	0.05	0.02	60% (.28)	0.39 (0.09–1.64)	83% (.1)	0.17 (0.02–1.43)
CVC related‡	1.71	1.18	0.30	31% (.36)	0.69 (0.31–1.54)	82% (.002)	0.17 (0.05–0.55)
SSI related§	0.73	0.31	0.44	58% (.14)	0.42 (0.14–1.26)	40% (.48)	0.61 (0.22–1.67)

RR = relative risk; CI_{95} = 95% confidence interval; CVC = central venous catheter; SSI = surgical-site infection.
*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.
†Incidence rate of primary bacteremia per 1,000 admissions.
‡Incidence rate of CVC-related bacteremia per 100 CVCs inserted.
§Incidence rate of SSI-related bacteremia per 1,000 surgical procedures.

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; CI_{95}, 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; CI_{95}, 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 MRSA BSIs may be approximately 100,000 euros per year. The reduction in MRSA BSIs we obtained definitely paid for the entire MRSA intervention control program and probably the entire infection control program for our hospital.

Our study confirms the statement of the Society for Healthcare Epidemiology of America[33] guidelines for the control of MRSA and vancomycin-resistant *Enterococcus* that the search and isolate strategy represents the main way to control nosocomial MRSA transmission. This strategy is effective even in settings with endemic MRSA and high rates of methicillin resistance among *S. aureus* isolates.

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

1. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med* 1998;339:520-532.
2. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. *Crit Care Med* 2001;29:N64-N68.
3. Fluit AC, Wielders CL, Verhoef J, Schmitz FJ. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY study. *J Clin Microbiol* 2001;39:3727-3732.
4. Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I. Methicillin-resistant *Staphylococcus aureus* (MRSA) in Europe. *Eur J Clin Microbiol Infect Dis* 1994;13:50-55.
5. Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) System report: data summary from January 1992-June 2001. *Am J Infect Control* 2001;29:404-421.
6. Anonymous. Susceptibility of *Staphylococcus aureus*. EARSS Bulletin. Bilthoven, the Netherlands: European Antimicrobial Resistance Surveillance System; 2002:4. Available at www.earss.rivm.nl. Accessed April 6, 2004.
7. Luzzaro F, Viganò EF, Fossati D, et al. Prevalence and drug susceptibility of pathogens causing bloodstream infections in Northern Italy: a two-year study in 16 hospitals. *Eur J Microbiol Infect Dis* 2002;21:849-

855.
8. Steinberg JP, Clark CC, Hackman BO. Nosocomial and community-acquired *Staphylococcus aureus* MRSA bacteremias from 1980 to 1993: impact of intravascular devices and methicillin resistance. *Clin Infect Dis* 1996;23:255-259.
9. Cosgrove SE, Sakoulas G, Perencevich EN, Schuaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* MRSA bacteremia. *Clin Infect Dis* 2003;36:53-59.
10. Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and MRSA bacteremia. *Clin Infect Dis* 2003;37:1453-1460.
11. Pujol M, Pena C, Pallares R, et al. Nosocomial *Staphylococcus aureus* MRSA bacteremia among nasal carriers of methicillin-resistant and methicillin-susceptible strains. *Am J Med* 1996;100:509-516.
12. Singh N, Paterson DL, Chang FY, et al. Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis* 2000;30:322-327.
13. Pujol M, Pena C, Pallares R, Ayats J, Ariza J, Gudiol F. Risk factors for nosocomial MRSA bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis* 1994;13:96-102.
14. Richet H, Benbachir M, Brown DF, et al. Are there regional variations in the diagnosis, surveillance, and control of methicillin-resistant *Staphylococcus aureus*? *Infect Control Hosp Epidemiol* 2003;24:334-341.
15. Pan A, Catenazzi P, Ferrari L, et al. Evaluation of the efficacy of a program to control nosocomial spread of methicillin-resistant *Staphylococcus aureus* [in Italian]. *Infez Med* 2001;9:163-169.
16. Report of a combined working party of the Hospital Infection Society and British Society of Antimicrobial Chemotherapy. Guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 1986;7:193-201.
17. Boyce JM, Jackson MM, Pugliese G, et al. Methicillin-resistant *Staphylococcus aureus* (MRSA): a briefing for acute care hospitals and nursing facilities. *Infect Control Hosp Epidemiol* 1994;15:105-115.
18. Wenzel RP, Nettleman MD, Jones RN, Pfaller MA. Methicillin-resistant *Staphylococcus aureus*: implications for the 1990s and effective control measures. *Am J Med* 1991;91:S221-S227.
19. Guiguet M, Rekacewicz C, Leclerq B, Brun Y, Escudier B, Andremont A. Effectiveness of simple measures to control an outbreak of nosocomial methicillin-resistant *Staphylococcus aureus* infections in an intensive care unit. *Infect Control Hosp Epidemiol* 1990;11:23-26.
20. Murray-Leisure KA, Geib S, Graceley D, et al. Control of epidemic methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol* 1990;11:343-350.
21. Pan A, Tomasoni D, Calza A. Guidelines for the control of hospital diffusion of methicillin-resistant *Staphylococcus aureus*. *Italian Journal of Hospital Infection* 1999;6:29-42.
22. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically,* ed. 5. Villanova, PA: National Committee for Clinical Laboratory Standards; 2000. Approved standard M7-A5.
23. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128-140.
24. Pearson ML. Guideline for prevention of intravascular device-related infections: Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;17:438-473.
25. Mermel LA, Farr BM, Sheretz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001; 32:1249-1272.
26. Clark DE, Cushing BM, Bredenberg CE. Monitoring hospital trauma mortality using statistical process control methods. *J Am Coll Surg* 1998;186:630-635.
27. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982;97:309-317.
28. Harbarth S, Martin Y, Rohner P, Henry N, Auckenthaler R, Pittet D. Effect of delayed infection control measures on a hospital outbreak of methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2000;46:43-49.
29. Harbarth S, Pittet D. Control of nosocomial methicillin-resistant *Staphylococcus aureus*: where shall we send our hospital director next time? *Infect Control Hosp Epidemiol* 2003;24:314-316
30. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* MRSA bacteremia. *N Engl J Med* 2001;344:11-16.
31. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med* 2002; 346:1871-1877.
32. Vrien MR, Fluit AC, Foelstra, A, Verhoef J, Van Der Werken C. Are methicillin-resistant *Staphylococcus aureus* more contagious than methicillin sensitive *Staphylococcus aureus* in a surgical intensive care unit? *Infect Control Hosp Epidemiol* 2002;23:491-494.
33. Muto C, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus. Infect Control Hosp Epidemiol* 2003;24:362-386.
34. Roghmann MC, Siddiqui A, Plaisance K, Standiford H. MRSA colonization and the risk of MRSA bacteraemia in hospitalized patients with chronic ulcers. *J Hosp Infect* 2001;47:98-103.
35. Squier C, Rihs JD, Risa KJ, et al. *Staphylococcus aureus* rectal carriage and its association with infections in patients in a surgical intensive care unit and a liver transplant unit. *Infect Control Hosp Epidemiol* 2002;23:495-501.
36. Harbarth S, Dharan S, Lassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus. Antimicrob Agents Chemother* 1999;43:1412-1416.
37. Vandenbroucke-Grauls CM. Methicillin-resistant *Staphylococcus aureus* control in hospitals: the Dutch experience. *Infect Control Hosp Epidemiol* 1996;17:512-513.
38. Vandenberghe A, Laterre P-F, Goenen M, et al. Surveillance of hospital acquired infections in an intensive care department: the benefit of the full time presence of an infection control nurse. *J Hosp Infect* 2002;52:56-59.
39. Stefani S, Varaldo PE. Epidemiology of methicillin-resistant staphylococci in Europe. *Clin Microbiol Infect* 2003;9:1179-1186.
40. Abramson MA, Sexton DJ. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary MRSA bacteremia: at what costs? *Infect Control Hosp Epidemiol* 1999;20:408-411.
41. Stone PW, Larson E, Kamar LN. A systematic audit on economic evidence linking nosocomial infections and infection control intervention: 1999-2000. *Am J Infect Control* 2002;30:145-152.
42. Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. *Infect Control Hosp Epidemiol* 2002;23:190-197.