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## Long-Term Efficacy of a Program to Control Methicillin-Resistant *Staphylococcus aureus*

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**The long-term efficacy of a program to control methicillin-resistant *Staphylococcus aureus* (MRSA) was evaluated in a 350-bed university hospital. Three periods were monitored: pre-epidemic (January 1989–November 1989), outbreak (December 1989–June 1990) and control program (July 1990–December 1992) periods. Control measures included cohort isolation, patient care measures and therapy (oral cotrimoxazole plus fusidic acid ointment) of MRSA carriage in patients, roommates and personnel. A total of 117 MRSA-infected patients were detected. For each period respectively, MRSA incidence (number of cases per 1,000 patient-days) was 3.2, 8.2 and 2.0 in the intensive care unit (ICU) and 0.08, 0.23 and 0.26 in the general wards. During the outbreak there was a 2.7-fold overall increase of baseline MRSA incidence ( $p < 0.02$ ). The crude mortality was 68 % and the attributable mortality was estimated to be 50 %. The program was estimated to have prevented 76 % (CI95 28–91,  $p < 0.0001$ ) of expected MRSA cases and 85 % (CI95 62–94,  $p < 0.0001$ ) of expected fatalities due to MRSA in the ICU, but it had no significant effect in the general wards. The program did not control vancomycin consumption.**

During the last decade outbreaks due to methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported with increasing frequency (1–5). Although some authors argue that MRSA infections create little impact in the hospital (6), others have demonstrated the ability of these microorganisms to cause severe infection (7). In fact, in some institutions MRSA has become the leading cause of nosocomial bloodstream infections (8). This has led to changes in routine empirical and culture-directed therapies, resulting in an increased consumption of vancomycin. Infection control programs ameliorated the impact of MRSA epidemics, even in institutions with limited resources (1, 2). However, the benefits of major programs to control MRSA are still debated (9).

In June 1990 we detected an MRSA outbreak that mainly affected patients in the intensive care unit. A series of approaches to control the infections was implemented. The present study evalu-

ates the efficacy of the program based on MRSA incidence, crude and attributable mortality from MRSA infections and vancomycin consumption before and after the control measures were implemented.

### Materials and Methods

**Hospital.** Hospital Príncipe de Asturias is a 350-bed teaching institution located in the northeastern area of Madrid, Spain, with approximately 1,200 admissions per month. The hospital opened in November 1987. The medical intensive care unit contains seven individual patient cubicles open to the nursing facilities and one isolation room. The post-surgical care unit is a large open area with 14 beds. The medical and surgical departments have two-bed rooms in units of 15 rooms. There are no special units for immunocompromised or burn patients. Hospital-wide surveillance of multiple-antibiotic-resistant organisms began in January 1988. Vancomycin consumption is routinely monitored by the Department of Pharmacy.

**Microbiological Methods.** Standard methods used to identify *Staphylococcus aureus* included the Gram stain, colonial and microscopic morphology and the catalase and tube coagulase tests (10). Susceptibility testing was performed by the microtiter dilution technique using an automated method (Pasco, USA). Antibiotics tested were penicillin, ampicillin, amoxicillin plus clavulanic

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acid, oxacillin, cefazolin, cefotaxime, imipenem, gentamicin, tobramycin, clindamycin, erythromycin, rifampin, norfloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole, fosfomicin and vancomycin. Resistance to methicillin was defined by an oxacillin minimal inhibitory concentration of 6.0 µg/ml or greater. Determination of susceptibility to mupirocin and fusidic acid was performed by disk diffusion tests (11). The epidemic strain was identified by antibiogram and phage typing (12). Phage typing was done at the National Reference Center (Centro Nacional de Microbiología, Virología e Inmunología Sanitarias de Majadahonda, Madrid, Spain).

**Definitions and Rates.** We reviewed the charts of all patients with MRSA isolation in clinical samples. A patient was considered to have an infection due to MRSA based on the Centers for Disease Control definitions for nosocomial infection (13). Otherwise, isolations of MRSA from clinical samples were considered to be colonizations. MRSA infection rates were determined by the number of patients infected with MRSA per 1,000 patient-days. All deaths in patients with MRSA were noted. Death was considered to be related to an MRSA infection when no other cause of death could be identified and, at the time of fatality, the patient had symptoms or signs of infection caused by MRSA or a clinical complication of the infection. MRSA crude mortality rates were determined by the overall number of deaths observed in MRSA-infected patients per 1,000 patient-days. MRSA attributable mortality was estimated by the number of deaths thought to be related to an MRSA infection per 1,000 patient-days. The number of MRSA cases and fatalities prevented was estimated by means of the etiologic fraction parameter, which represents the expected reduction in disease load following implementation of the program (14). To estimate the etiologic fraction, the difference between incidence rate of the program period and the epidemic period was divided by the incidence rate of the epidemic period. Vancomycin consumption

rates were defined by the number of grams of vancomycin used per 1,000 patient-days.

**MRSA Control Program.** The program to control MRSA was based mainly on the measures recommended by the Hospital Infection Society and the British Society for Antimicrobial Chemotherapy (15). The infection control procedures used are summarized in Table 1.

**Statistical Analysis.** Comparisons of incidence rates were performed by chi-square for patient-days estimations (16). Ninety-five percent confidence intervals (CI95) were calculated. For etiologic fractions, the CI95s were estimated using the approximate standard error derived from the Taylor series method (17). Two-tailed *p* values < 0.05 were considered significant.

## Results

**Pre-Epidemic and Outbreak Period.** From January 1989 to June 1990, before the control program began, a single strain of MRSA caused 49 infections in 43 patients. The epidemic strain was resistant to methicillin, ampicillin, amoxicillin plus clavulanic acid, aminoglycosides, macrolide-lincosamine group, rifampin, quinolones and imipenem. It was susceptible to vancomycin, trimethoprim-sulfamethoxazole, fosfomicin, fusidic acid and mupirocin. Organisms were lysed by phages belonging to group III.

Fifteen patients were diagnosed during the pre-epidemic period (January 1989 to November

**Table 1:** Measures used to control MRSA.

Patient care	Single room and cohort isolation for infected/colonized patients; Gowns, gloves and masks for every person entering the room; Chlorhexidine soap for personnel hand washing.		
Screening for carriers	Group	Sites sampled	When sampled
	MRSA infected or colonized patients	nose, axilla, cutaneous lesions, infection sites	weekly until discharge
	Roommates of MRSA infected or colonized patients	nose, axilla, cutaneous lesions, infection sites	baseline and weekly until discharge, if isolation was not feasible
	Health care workers	nose, hands, cutaneous lesions	if 3 or more cases of MRSA infection were detected in the same ward within a 15-day period
Treatment of carriers	Daily bath with chlorhexidine soap; Topical fusidic acid (t.i.d., 5 days) in nose and cutaneous lesions; Oral trimethoprim-sulfamethoxazole (160-800 mg b.i.d., 5 days).		

**Table 2:** Crude data and rates of MRSA-infected patients and vancomycin consumption.

	Pre-epidemic period (Jan. 1989–Nov. 1989)	Outbreak period (Dec. 1989–June 1990)	Program period (July 1990–Dec. 1992)
<b>Intensive care unit</b>			
No. of MRSA-infected patients	9	15	12
MRSA crude mortality	55.5 %	86.6 %	58.3 %
MRSA attributable mortality	33.3 %	66.6 %	41.6 %
Vancomycin consumption	215 g	191 g	646 g
No. of patient-days	2,794	1,833	5,997
MRSA infection rate (no./1000 patient-days)	3.2	8.2 (p < 0.0001) <sup>a</sup>	2.0 (p < 0.0001) <sup>b</sup>
MRSA crude mortality rate (no./1000 patient-days)	1.78	7.09 (p = 0.0050) <sup>a</sup>	1.17 (p < 0.0001) <sup>b</sup>
MRSA attributable mortality rate (no./1000 patient-days)	1.07	5.45 (p = 0.0067) <sup>a</sup>	0.83 (p < 0.0001) <sup>b</sup>
Vancomycin consumption rate (grams/1000 patient-days)	76.9	104.2 (p = 0.0016) <sup>a</sup>	107.7 (p = 0.34) <sup>b</sup>
<b>General wards</b>			
No. of MRSA-infected patients	6	13	62
MRSA crude mortality	50.0 %	46.2 %	17.7 %
MRSA attributable mortality	33.3 %	30.8 %	14.5 %
Vancomycin consumption	536 g	928 g	3,682 g
No. of patient-days	70,752	57,123	238,703
MRSA infection rate (no./1000 patient-days)	0.08	0.23 (p = 0.0180) <sup>a</sup>	0.26 (p = 0.3300) <sup>b</sup>
MRSA crude mortality rate (no./1000 patient-days)	0.04	0.11 (p = 0.1840) <sup>a</sup>	0.05 (p = 0.0870) <sup>b</sup>
MRSA attributable mortality rate (no./1000 patient-days)	0.03	0.07 (p = 0.2880) <sup>a</sup>	0.04 (p = 0.2753) <sup>b</sup>
Vancomycin consumption rate (grams/1000 patient-days)	7.57	16.2 (p < 0.0001) <sup>a</sup>	15.42 (p = 0.0790) <sup>b</sup>

<sup>a</sup> p value of the outbreak period compared with the pre-epidemic period.

<sup>b</sup> p value of the program period compared with the outbreak period.

1989) and 28 during the outbreak period (December 1989 to June 1990). In both periods the MRSA incidence rate was 40-fold greater in the intensive care unit than in the general wards (p < 0.0001). The sources of infections were intravascular catheter-related (n = 13), respiratory tract (n = 10), surgical wound (n = 6), urinary tract (n = 5) and miscellaneous (n = 9). There were six cases of primary bacteremia and 19 cases of secondary bacteremia. Twenty-seven patients with MRSA infection died, resulting in a crude mortality of 63 %. In 19 patients death was thought to be related to the infection, resulting in an estimated attributable mortality of 44 %. In the intensive care unit MRSA crude and attributable mortality within the outbreak period reached 87 % and 67 %, respectively.

Compared with the pre-epidemic period, in the outbreak period there was a 2.7-fold increase in the MRSA incidence rate in both the intensive care unit and the general wards (Table 2). Differ-

ences in MRSA incidence rates between the pre-epidemic and the outbreak period were 5 per 1,000 patient-days (CI95 0.36–9.64, p < 0.0001) in the intensive care unit and 0.14 per 1,000 patient-days (CI95 0.07–0.21, p = 0.0180) in the general wards. In the intensive care unit MRSA crude and estimated attributable mortality rates increased 4-fold and 5.1-fold, respectively. Crude and estimated attributable mortality rate differences between the outbreak period and the pre-epidemic period were 5.3 per 1,000 patient-days (CI95 1.6–9.0, p = 0.0050) and 4.4 per 1,000 patient-days (CI95 0.5–8.3, p = 0.0067), respectively. Vancomycin consumption increased 1.4-fold (p = 0.0016). In the general wards MRSA crude and estimated attributable mortality rates increased 2.7-fold (p = 0.0180) and 2.3-fold (p = 0.2880), respectively. Vancomycin consumption increased 2.1-fold (p < 0.0001) (Table 2).

*MRSA Control Program Period.* According to the measures described in Table 1, MRSA-in-



The estimated proportion of MRSA cases prevented in the intensive care unit was 76 % (CI95 28–91,  $p < 0.0001$ ), and the estimated proportion of deaths prevented was 85 % (CI95 62–94,  $p < 0.0001$ ). The program had no significant effect on vancomycin consumption or on MRSA rates in the general wards, although the proportion of expected deaths prevented was estimated to be 45%.

## Discussion

From December 1989 to June 1990 a single strain of MRSA caused severe infections in 28 patients in our hospital. Among patients with bacteremia, over 50 % died. Subsequently, an infection control program was implemented to control this outbreak. Thereafter, MRSA infection rates decreased sharply in the intensive care unit, from 8.2 to 0.7 cases per 1,000 patient-days. The program was estimated to have prevented 76 % of new MRSA cases and 85 % of expected deaths due to MRSA in the intensive care unit. On the general wards of the hospital, MRSA cases continued to occur at a low level of endemicity, with a rate of 0.26 cases per 1,000 patient-days. However, a decrease of expected MRSA mortality of 45 % was estimated. Stringent control measures successfully controlled the outbreak in the intensive care unit and secondarily decreased MRSA mortality. In addition, in areas in which MRSA was endemic there was a reduction in the expected MRSA mortality that might be attributable to earlier detection and therapy of MRSA-infected patients.

Control measures necessary to stop MRSA outbreaks include a system of isolation and identification of MRSA reservoirs. Colonized patients and hospital personnel should be actively identified and undergo nasal decolonization (18–20). Nasal carriage by patients is well known to be associated with increased nosocomial infection rates (21). Furthermore, Murder et al. (22) found that MRSA-colonized patients were four times more likely to acquire staphylococcal infections than those not colonized. On the other hand, the importance of colonization among hospital personnel has been controversial (23). Nevertheless, in some studies nasal decolonization of health care workers contributed toward ending the outbreaks (24, 25).

In our institution MRSA nasal colonization was detected in 58 % of MRSA-infected patients.

Therefore, nasal decolonization, in addition to treatment of infection, was required in this group of patients. Asymptomatic MRSA carriage was also found in 20 % of MRSA roommates and in up to 8 % of hospital personnel. Moreover, five of 27 (18.5 %) patients with negative baseline screening cultures became MRSA carriers during their hospitalization period. This finding underscores the importance of maintaining microbiological surveillance until patients are discharged.

Nasal mupirocin is considered the best choice for eradication of MRSA carriage (26), but for the period studied, mupirocin was not approved in our country. Classical schemes with topical plus oral antimicrobial agents can also eradicate the carrier status efficiently (27). Oral trimethoprim-sulfamethoxazole plus fusidic acid ointment eradicated MRSA in 81 % of carriers found in our hospital. Although no resistance to fusidic acid or trimethoprim-sulfamethoxazole was observed, seven of 31 patients relapsed after a median follow-up of 52 days. Similar and even greater relapse rates have been observed with other therapeutical schemes, including the use of mupirocin (28).

An ancillary measure recommended to control MRSA spread is the identification, on admission, of patients with previous infection or colonization due to MRSA by means of a registration system. This measure was not available in our hospital. Despite the lack of a registration system, the measures implemented in our institution successfully ameliorated the effect of MRSA infections.

An additional aim of this study was to examine the evolution of vancomycin consumption as an indicator of the impact of MRSA infections. Vancomycin usage increased 1.4-fold in the intensive care unit and 2.1-fold in the general wards during the outbreak. After controlling the outbreak, vancomycin consumption remained unchanged. In addition to the expenses incurred during an outbreak, which are related to the extended length of stay and other associated conditions or increased staffing demands (19), excess vancomycin use remained as a consequence. This may have been a result of fear of MRSA infections by concerned physicians. Continuous feedback is needed to keep physicians updated about the distribution and frequency of MRSA infections. Furthermore, automatic stop orders limiting courses of empirical vancomycin to 24–48 hours might be effective.

In summary, although MRSA outbreaks are difficult to eradicate, stringent control programs can

ameliorate the morbidity and mortality of MRSA infections. Even after the MRSA outbreak is controlled, vancomycin consumption may remain elevated. Therefore, in institutions with a history of MRSA outbreaks, vancomycin should be included in the category of antibiotics requiring close monitoring.

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