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Risk Factors for Nosocomial Bacteremia due to Methicillin-Resistant *Staphylococcus aureus*

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In a prospective surveillance study (February 1990–December 1991) performed at a 1000-bed teaching hospital to identify risk factors for nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, 309 patients were found to be colonized (n = 103; 33 %) or infected (n = 206; 67 %) by MRSA. Sixty-three of them developed bacteremia. Compared with 114 patients who had nosocomial bacteremia caused by methicillin-sensitive *Staphylococcus aureus* during the same period of time, MRSA bacteremic patients had more severe underlying diseases ($p < 0.01$), were more often in intensive care units ($p < 0.01$) and had received prior antibiotic therapy more frequently ($p < 0.01$). To further identify risk factors for MRSA bacteremia, univariate and multivariate analyses of this series of 309 patients were performed using the occurrence of MRSA bacteremia as the dependent variable. Among 14 variables analyzed, intravascular catheterization, defined as one or more intravascular catheters in place for more than 48 h, was the only variable selected by a logistic regression model as an independent risk factor (OR = 2.7, CI = 1.1–6.6). The results of this study reinforce the concept that recent antibiotic therapy may predispose patients to MRSA infection and suggest that among patients colonized or infected by MRSA, those with intravascular catheters are at high risk of developing MRSA bacteremia.

Since 1989 (1, 2) methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected in the majority of Spanish tertiary hospitals as a microorganism responsible for an increasing number of nosocomial staphylococcal infections. The introduction of an epidemic strain in our hospital at the end of 1989 resulted in a large outbreak of infections. Between February 1990 and December 1991, we prospectively identified all patients with MRSA colonization or infection, using a specific protocol. One of the most striking clinical observations was that 30 % of infected patients had MRSA bacteremia. As we were concerned about the relevance of bloodstream infections in this population, we performed the present study to determine the risk factors for development of nosocomial MRSA bacteremia among hospitalized patients with MRSA colonization or infection.

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Patients and Methods

Setting. Hospital de Bellvitge is a 1,000-bed teaching hospital for adult patients in the Barcelona area which provides acute medical and surgical care, excluding pediatrics, obstetrics and burns. Our hospital has five intensive care units (ICUs) with 60 beds and an active organ transplant program. Yearly admittance is about 22,000 patients.

Infection Control Policy. A bloodstream infection surveillance program has been carried out in our hospital since 1984. All patients with bacteremia identified daily at our microbiology laboratory are visited by an infectious diseases physician who fills out a computer-assisted protocol and provides medical advice when indicated. An active MRSA infection control program was introduced in 1990 after the detection of initial isolates. The program involves identification and isolation of all patients with MRSA colonization or infection, use of nasal mupirocin for health care workers and patients, and reinforcement of careful handwashing and educational programs throughout the hospital. Cases are identified by daily laboratory surveillance of positive cultures, screening of the roommate in sporadic cases, screening of the ward when a cluster of cases occurs, and detection of rehospitalized patients with previous MRSA. All MRSA infected or colonized patients are visited by one of the authors and included in a computer-assisted surveillance protocol.

Study Design. With the data collected in the above-mentioned surveillance program during 1990 and 1991, we performed two types of analyses. First, we compared consecutive patients with nosocomial bacteremia due to methicillin-sensitive *Staphylococcus aureus* (MSSA) and patients with nosocomial bacteremia due to MRSA. Variables compared in this analysis were age and sex; underlying diseases; clinical status; length of hospitalization prior to bacteremia; prior surgery; prior antibiotic therapy; prior intensive care setting; devices in place such as endotracheal intubation, intravascular catheterization and urinary catheter; sources of infection; and outcome. Secondly, we carried out univariate and multivariate analyses of all cases of MRSA colonization or infection, using the occurrence of bacteremia as the dependent variable. Variables analyzed before the development of bacteremia were demographic characteristics, underlying diseases, clinical status, length of hospital stay prior to the first MRSA culture, prior surgery, prior antibiotic therapy, prior intensive care setting, intravascular catheterization, administration of total parenteral nutrition, urinary catheterization, tracheostomy, decubitus ulcers and source of infection.

Colonization and Infection. Patients with MRSA-positive cultures at any body site but without related signs or symptoms of infection were considered to be colonized. Centers for Disease Control (CDC) standard definitions for nosocomial infections (3) were used for suspected MRSA infections. Patients were considered to have staphylococcal bacteremia when one or more blood cultures were positive for *Staphylococcus aureus* in a clinical course of infection. Bacteremia was considered nosocomially acquired if it appeared 72 h after admission and no evidence of staphylococcal infection had been present at admission.

Source of Infection. Primary bacteremia was defined according to CDC criteria (3) as those episodes of bacteremia of unknown source and those due to intravascular catheter infection. An intravascular catheter was considered to be the source of infection when no other focus of infection was found and when one or more of the following conditions were confirmed: semiquantitative tip culture using the technique of Maki et al. (4) indicating ≥ 15 cfu of *Staphylococcus aureus*, inflammation at the site of insertion, or clear resolution of febrile syndrome after catheter removal. Other localized foci of bacteremia such as respiratory tract infection or surgical wound infection, for example, were considered to be secondary foci of bacteremia.

Exposure to Risk Factors. Underlying diseases were classified into three groups according to the classification of McCabe and Jackson (5): Group 1, chronic or curable disease; Group 2: malignancy or any other disease with a life expectancy of less than five years; and Group 3, diseases with a life expectancy of less than one year. Previous antibiotic therapy was defined as that administered for more than 48 h during the ten days prior to the patient's first positive culture for MRSA. Intravascular catheterization was defined as the presence of one or more intravascular catheters for more than 48 h in the week prior to the first positive MRSA culture. Other devices such as urinary catheter and endotracheal tube were considered risk factors if they were in place for more than 48 h during the ten days prior to the isolation of MRSA. Clinical status was measured by Apache II score.

Outcome. Death was considered attributable to staphylococcal bacteremia when one or more of the following conditions were present: blood culture positive for *Staphylococcus aureus* at the time of death, persistent signs or symptoms of staphylococcal infection at death, or death within the first week of staphylococcal bacteremia without other clear explanation.

Microbiological Methods. Screening swabs collected from the anterior nares of infected or colonized patients and all other clinical specimens submitted to the laboratory for MRSA screening were inoculated onto mannitol-salt agar plates. All cultures were incubated at 35 °C for two days and examined daily for evidence of growth.

Blood cultures were performed by inoculating 5–10 ml of blood into a commercial two-bottle system (Bactec system; Becton Dickinson Diagnostic Instrument Systems, USA). Gram-positive, catalase-positive cocci were identified as *Staphylococcus aureus* in accordance with their growth characteristics on mannitol-salt agar, DNA hydrolysis, latex agglutination (Slidex StaphKit; bio-Mérieux, France) and the coagulase reaction. One isolate of *Staphylococcus aureus* per patient was stored frozen at -20 °C in skim milk.

Susceptibility to oxacillin was tested by disk diffusion and microbroth dilution methods. For the disk diffusion test, a 1 μg oxacillin disk and standard zone size criteria were used (6). Other antibiotics tested by disk diffusion methods were gentamicin, erythromycin, tetracycline, clindamycin, rifampin, ciprofloxacin, chloramphenicol, trimethoprim/sulfamethoxazole, vancomycin, fosfomycin, mupirocin and fusidic acid. The minimum inhibitory concentration (MIC) was determined by commercial plates (Pos Combo Panel 4I; MicroScan, USA), with two oxacillin dilution wells of 1 μg/ml and 2 μg/ml, supplemented with 2 % NaCl. The microdilution trays were inoculated with an inoculum of 10^5 cfu/ml and incubated at 35 °C for 24 h. Using NCCLS criteria, the organism was considered resistant to oxacillin if the MIC was greater than 2 μg/ml.

Bacteriophage typing was performed by the Reference Laboratory (Centro Nacional de Microbiología de Majadahonda Madrid) using standard methods (7) with the international test of phages and standard routine test dilution. Plasmid pattern profiles in the first 40 isolates were determined by agarose gel electrophoresis (8).

Statistical Analysis. Rates of monthly staphylococcal bacteremia were compared using the Chi-square test for trends. Risk factors among patients with nosocomial MRSA bacteremia and among those with nosocomial MSSA bacteremia were compared using the Chi-square, Fisher's exact, or Student's t-test when appropriate. Univariate analyses were also done to determine the significance of risk factors for development of nosocomial bacteremia among patients with MRSA colonization or infection. Unconditional logistic regression analysis was used to assess the independence of variables found statistically significant in the univariate analysis. Statistical analyses were executed by using the SPSS/PC microcomputer statistical package.

Results

Description of the Outbreak. Before October 1989 less than 2 % of nosocomial *Staphylococcus aureus* isolates were methicillin resistant in our hospital, and none was either aminoglycoside or quinolone resistant. In November 1989 an MRSA-colonized patient, transferred directly from the ICU of another medical center, apparently was the index case preceding an outbreak of MRSA infections. Special control measures were established promptly, but the microorganisms spread extensively through the ICUs and some surgical wards during 1990. During the study period 98 health care workers had MRSA nasal colonization, and seven swab cultures of several environmental surfaces in ICUs were positive for MRSA. An outbreak of five cases of postsurgical MRSA mediastinitis was controlled after the identification and treatment of a nasal carrier belonging to a cardiac surgical team. Colonized patients, nasal carriage among health care workers, and environmental contamination in some ICUs were the most important factors in the maintenance of the outbreak.

The incidence of new cases subsided during 1992, and at present the outbreak has been partially controlled. Nevertheless, MRSA has become endemic in two of our ICUs, with a current incidence of around ten cases per month, most of them being mucocutaneous colonization.

The antibiotic susceptibility patterns of the MRSA strains indicated resistance to methicillin, aminoglycosides, erythromycin, rifampin, ciprofloxacin and imipenem, and susceptibility to chloramphenicol, trimethoprim/sulfamethoxazole, vancomycin, teicoplanin, fosfomycin, mupirocin and fusidic acid. Phage typing was performed in 135 isolates. According to the International Phages Set, 25 isolates of MRSA belonged to phage Group III, two isolates to phage Group I, and eight isolates were lysed with phages of phage Groups I and III. One hundred isolates were nontypeable. Plasmid pattern profiles studied in 40 isolates showed a single plasmid (2), suggesting a unique epidemic strain as the

Table 1: Clinical and epidemiological characteristics of 309 patients with MRSA.

Mean age in years (± SD)	53 (± 18.9)
Male/female ratio	225 (72 %)/84 (28 %)
Mean days of hospitalization prior to MRSA acquisition (± SD)	29.3 (± 28.6)
No. (%) with MRSA colonization/infection	103 (30)/206 (60)
No. (%) with underlying disease, McCabe Group 1/2–3	248 (80.2)/61 (19.8)
No. (%) with previous surgery	209 (67.6)
Acquisition area	
No. (%) in ICUs	144 (46.6)
No. (%) in surgical wards	143 (46.3)
No. (%) in medical wards	22 (7.1)
No. (%) with prior antibiotic therapy	212 (68.6)
Beta-lactams	121 (39.1)
Aminoglycosides	45 (14.5)
Quinolones	67 (21.6)
Vancomycin	19 (6.1)
No. (%) of sites of colonization (103 patients)	
Nasal	68 (66)
Mucous membranes	36 (35)
Cutaneous sites	26 (25)
No. (%) of sites of infection (206 patients)	
Surgical wound	76 (36.8)
Respiratory tract	60 (29.1)
Skin and soft tissues	31 (15)
Intravascular catheter	28 (13.6)
Bacteremia	63 (30.5)
No. (%) of deaths attributable to MRSA	
Among infected patients	22/206 (10.6)
Overall mortality	91/309 (29.5)

agent responsible for the outbreak, similar to those strains found in other university hospitals in the Barcelona area.

Characteristics of MRSA Colonized and Infected Patients. From January 1990 to December 1991, 309 patients were identified as being colonized (n = 103; 33 %) or infected (n = 206; 67 %) by MRSA. Table 1 describes the most outstanding clinical and epidemiological features of these patients, including common sites of MRSA colonization and infection. Nasal mucosa was the most frequent site of colonization (66 %), followed by mucous membranes and other cutaneous sites.

Among 206 patients infected by MRSA, 67 episodes of MRSA bacteremia were detected in 63 patients (30.5 %). Primary bacteremia, detected in 48 cases, was the most important source among the 67 cases of nosocomial MRSA bacteremia.

Bacteremia and other serious infections were treated with vancomycin, 500 mg i.v. every 6 h. Less severe infections such as superficial incisional wound infection or tracheobronchitis were treated with oral cotrimoxazole. Colonized patients, except those with nasotracheal tubes, tracheostomies and large decubitus ulcers, were treated with nasal soft paraffin mupirocin. Mortality attributable to MRSA among infected patients was 10.6 %. Overall mortality among the entire MRSA patient group was 29.5 %.

Comparison between MRSA and MSSA Bacteremia. During the two-year study period, 181 episodes of nosocomial staphylococcal bacteremia were studied prospectively. Two or more positive blood cultures were obtained in 116 episodes (64 %). Sixty-seven episodes (37 %) were caused by MRSA and 114 (63 %) by MSSA. Since the introduction of MRSA, a clear upward trend in monthly rates of nosocomial staphylococcal bacteremia has been observed (Chi-square for trends, $p < 0.01$) (Figure 1).

A comparison of the two types of bacteremia (Table 2) revealed that MRSA bacteremic patients differed significantly from the MSSA group in sex, underlying disease, severity of clinical status, length of hospital stay, prior exposure

Table 2: Comparison of epidemiological and clinical features of MRSA versus MSSA episodes of bacteremia.

Characteristic	Type of bacteremia		p value
	MRSA (n = 67)	MSSA (n = 114)	
Mean age in years (± SD)	49 (± 20.6)	52.1 (± 19.8)	NS
Sex (male/female)	53/14	72/42	0.02
No. (%) with underlying disease			
McCabe (Group 1)	51 (75)	59 (51.8)	< 0.01
Apache II (score > 15)	49 (73)	43 (37.7)	< 0.01
Mean days of prior hospital stay (± SD)	27.3 (± 25.1)	13.7 (± 18.3)	< 0.01
No. (%) with previous surgery	41 (61.1)	31 (27.1)	< 0.01
No. (%) with previous antibiotics	46 (68.6)	25 (21.9)	< 0.01
Beta-lactams	20	18	0.03
Aminoglycosides	11	6	0.02
Ciprofloxacin	15	2	< 0.01
No. (%) with previous ICU setting	36 (53.7)	31 (27.2)	< 0.01
No. (%) with devices in place			
Intravascular catheter	60 (89.6)	103 (90.3)	NS
Parenteral nutrition	30 (44.7)	17 (14.9)	< 0.01
Endotracheal tube	27 (40.3)	27 (23.6)	0.01
No. (%) with tracheostomy	24 (35.8)	7 (6.1)	< 0.01
No. (%) with following source of infection:			
Pneumonia	3	10	NS
Mediastinitis	5	0	0.01
Endocarditis	2	4	NS
Miscellaneous	9	15	NS
No. (%) with primary bacteremia	48 (71.6)	85 (74.6)	NS
Catheter-related	42	71	
Unknown source	6	14	
No. (%) of deaths	17 (38.2)	25 (30.7)	NS

Table 3: Univariate analysis of risk factors for MRSA bacteremia in 309 colonized or infected patients.

Significant variable	No. (%)	Odds ratio	p value
Prior ICU setting	38 (61)	1.6	0.06
Tracheostomy	18 (29)	1.8	0.06
Parenteral nutrition	26 (42)	1.9	0.01
Intravascular catheter	53 (85)	3	< 0.01

to surgery, prior antibiotic therapy, prior ICU setting, administration of total parenteral nutrition, mechanical ventilation and tracheostomy. A more detailed analysis of previous antibiotic therapy showed notable differences between the administration of beta-lactams, aminoglycosides and quinolones, and other antibiotics. However, there were no significant differences in age, sources of infection (except mediastinitis), intravascular devices in place, and outcome between the two groups.

Risk Factors for MRSA Bacteremia. The univariate analysis of risk factors for development of bacteremia (Table 3) among 309 patients with MRSA infection or colonization selected prior ICU setting, presence of tracheostomy, prior or current administration of total parenteral nutrition, and intravascular catheterization as statistically significant factors. Non-significant variables were age, sex, underlying disease, prior antibiotic therapy, intubation, urinary catheter, decubitus ulcers and source of infection. Unconditional logistic regression analysis using MRSA bacteremia as the dependent variable selected only intravascular catheterization (OR 2.78; CI 95 %, 1.1 to 6.6) as an independent risk factor for development of MRSA bacteremia. Variables included in the analysis were prior ICU setting, administration of total parenteral nutrition, presence of tracheostomy and intravascular catheterization.

Discussion

The major epidemiological features of our outbreak did not differ significantly from those of other outbreaks (9–11). The outbreak was focused in the ICUs, with sporadic clusters occurring in the surgical wards. In only a few cases did MRSA acquisition occur in the operating room, linked with the detection of nasal carriers among the surgical team. Besides colonized patients and health care workers, the inanimate hospital environment appeared to be, in our experience, an important hospital reservoir of MRSA, as described previously (9, 12, 13). It is noteworthy that in one of our ICUs, cultures of gloves worn for purposes of universal precautions after environmental contact and before any contact with patients were positive for MRSA. However, regarding the experience of other authors, the current relevance of environmental contamination may be considered controversial.

A long interval from hospital admission to MRSA acquisition was characteristic, with a mean of 29.4 days. Prior administration of antibiotic therapy was also very frequent. The role of

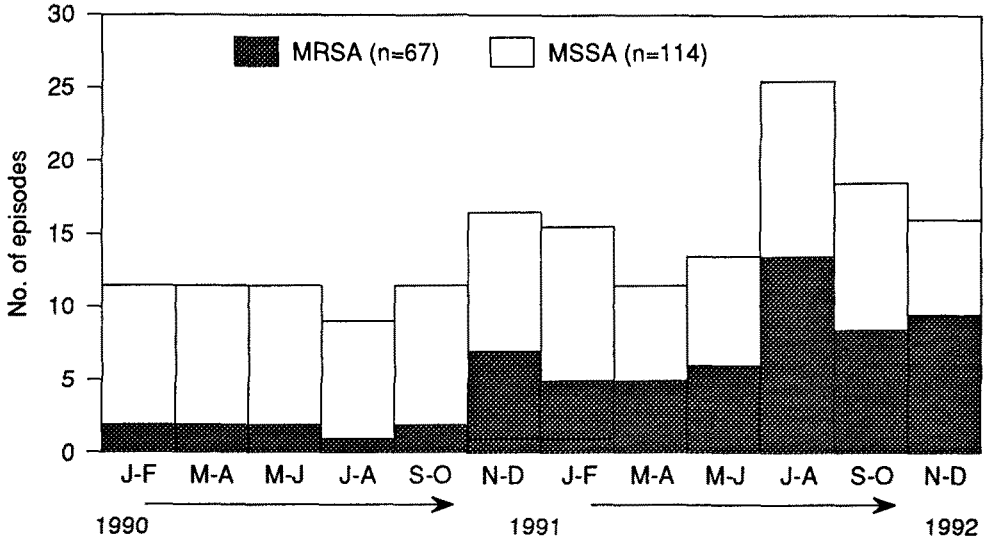

Figure 1: Monthly rates of nosocomial staphylococcal bacteremia.

antibiotics in the selection of resistant strains and in cross-colonization appears to be relevant, but mechanisms have not yet been well established.

Anterior nares and the respiratory tract in intubated patients were the most frequent sites of colonization. It should be noted that nasogastric tubes did not permit the use of mupirocin in these cases (14). The clinical spectrum and sites of our patients' infections were in accordance with their underlying diseases and clinical characteristics. An observation of major concern was the high incidence of patients with MRSA bacteremia. In our opinion the 30 % incidence of bacteremia observed among the entire MRSA infected population, similar to that reported by Peacock et al. (15), is higher than that among hospitalized patients harboring MSSA or gram-negative bacilli. Nevertheless, this hypothesis is difficult to assess due to the lack of knowledge of the entire population at risk infected with MSSA or gram-negative bacilli.

In contrast to some previous reports (9, 16), the data from our surveillance program of all bloodstream infections clearly showed that MRSA isolates did not simply replace MSSA, but rather emerged as a distinct microorganism, increasing the total number of cases of staphylococcal bacteremia. This observation, of marked epidemiological interest, has been made by Boyce et al. and Wenzel et al. in both bacteremic and non-bacteremic patients (17, 18).

The comparison between patients with nosocomial bacteremia due to MRSA and patients with nosocomial bacteremia due to MSSA revealed that both groups had important epidemiological differences, but they did not differ in clinical features and outcome (19–21). Epidemiological factors differentiating MRSA and MSSA bacteremic patients were similar to those described as risk factors for acquiring MRSA colonization or infection among the hospital population (22, 23).

A large number of episodes of staphylococcal bacteremia were defined as primary bacteremia in both groups (MRSA 71.6 % and MSSA 74.6 %), and the majority of them were catheter-related, as has previously been reported by others (19, 20, 22, 24). It remains uncertain whether MRSA differs from MSSA in its intrinsic ability to cause catheter-related infections. Nevertheless, taking into account that the number of patients colonized by MSSA should be greater than those colonized by MRSA, it may be possible that MRSA strains possess a greater capacity to progress to infection from a colonized state. Again, this impression is difficult to assess, because we do not know the number of MSSA colonized patients in the entire hospital.

A major difference between susceptible and resistant strains was the previous administration of antibiotics. Besides the beta-lactams and aminoglycosides, whose role has been previously emphasized in the literature (25), it is important to point out the potential role of quinolones as a risk factor for selecting MRSA strains, since these antibiotics are being widely used in critical care units.

Risk factors for the development of MRSA bacteremia among colonized or infected patients have not been established in previous reports. Although the univariate analysis identified several variables associated with the development of MRSA bacteremia in our series of patients, the only variable selected by the logistic regression model as an independent risk factor was intravascular catheterization. This data suggests that colonized patients with one or more intravascular catheters in place are at high risk of developing bacteremia. This risk is perhaps higher than that of those colonized by MSSA or by other nosocomial pathogens. It is possible that MRSA strains possess a unique ability to adhere to intravascular devices and other prosthetic materials, but this hypothesis should be proven in prospective studies.

Recent data show that MRSA strains are at least equally as pathogenic as susceptible strains (26) and might be even more virulent (27), although more studies are needed to confirm this finding.

Nevertheless, the relationship between virulence, spread and adherence is difficult to elucidate, and the factors that influence colonization and adherence, as well as the role of extracellular toxins and enzymes, should be further clarified (28). In conclusion, the main risk factors for nosocomial MRSA bacteremia identified in our study are similar to those described for MRSA colonization elsewhere. Recent antibiotic therapy, including treatment with the new quinolones, seems to play a major role. Among patients colonized or infected by MRSA, those with intravascular devices are at very high risk of developing MRSA bacteremia.

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