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Prospective Study of Infection, Colonization and Carriage of Methicillin-Resistant *Staphylococcus aureus* in an Outbreak Affecting 990 Patients

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In the three years between November 1989 and October 1992, an outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) affected 990 patients at a university hospital. The distribution of patients with carriage, colonization or infection was investigated prospectively. Nosocomial acquisition was confirmed in at least 928 patients, 525 of whom were identified from clinical specimens as being infected (n = 418) or colonized (n = 107) by MRSA. An additional 403 patients were identified from screening specimens, of whom 58 subsequently became infected and 18 colonized. Screening of the nose, throat and perineum detected 98 % of all carriers. Of the 580 infections in 476 patients, surgical wound, urinary tract and skin infections accounted for 58 % of the infections. Of the 476 infected patients, death was attributable to MRSA infection in 13 %. Colonization with MRSA was found in 127 patients and 42 % of 165 colonized sites were the skin. Auto-infection from nasal carriage or cross-infection, probably via staff hands, seemed to be the most common mode of acquisition of MRSA infections.

The increasing incidence, worldwide, of nosocomial infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the late 1970s and in the 1980s (1–8) often resulted from extensive hospital outbreaks (9–16). The first outbreak of MRSA was not described in Spain until 1981 (17). The prevalence of MRSA remained low (18) until recently, when MRSA became an epidemic problem in several hospitals (19–21) and a new phage type was identified amongst MRSA isolates from several Spanish hospitals (22). At the Hospital Universitario San Carlos in Madrid, MRSA was not a problem until November 1989, when a large outbreak that ultimately affected more than 900 patients began.

Despite many other published studies of MRSA outbreaks, there are still uncertainties about the number of carriers and colonized patients compared with the number of clinically infected patients; furthermore, there seems to be no conclusive data about the sensitivities and negative predictive values of the various combinations of screening specimens. We therefore investigated prospectively the distribution of patients with carriage, colonization or infection in a large hospital outbreak.

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Materials and Methods

Hospital. The Hospital Universitario San Carlos is a 1500-bed teaching hospital with all major specialities and serves a population of 600,000. It has a 32-bed intensive care unit and three surgical recovery units with 28 beds. Wards of 18 beds contain mostly six-bed rooms, although several double-bed rooms are interspersed. The average nurse-to-patient ratio on the general wards is 1:18.

Surveillance Programme. Patients with MRSA were identified from clinical specimens, with results reported daily from the diagnostic microbiology laboratory. All patients were entered into a prospective surveillance programme and followed up until discharge from the hospital.

Microbiological testing of clinical specimens usually identifies only those patients infected with MRSA and those with MRSA in clinical lesions. In this study we identified, in addition, those patients with MRSA at the recognized staphylococcal carriage sites by an active screening programme that was started in November 1990. We therefore defined a patient with MRSA as one from whom MRSA had been isolated on one or more occasions from any body site. Infections with MRSA were defined according to the Centers for Disease Control (CDC) standard definitions (23). Carriers were patients from whom MRSA was isolated from one or more normal carrier sites, i.e.

from the anterior nares, throat, perineum, groin or axilla. Colonized patients were defined as those without clinical symptoms who harboured MRSA at non-carriage sites. Hospital-acquired MRSA was defined as the isolation of MRSA 48 h or more after hospital admission from patients without previous hospitalization. Relapse was defined as a new episode of MRSA infection or a new episode of colonization or carriage in a patient who had had at least three specimens that were previously negative for MRSA.

Information on each patient was collected prospectively and included the patient's registration data, the day of MRSA acquisition, the dates and sites of all positive cultures, the location of the patient in the hospital at the time of MRSA isolation, and his or her exposure to topical and systemic anti-staphylococcal treatment.

Microbiological Methods. MRSA was isolated and identified by standard microbiological methods that included testing for methicillin resistance by a controlled disk diffusion method on Mueller-Hinton agar plates that were incubated for 24 h at 35 °C. Phage typing of 188 screening isolates was performed by standard methods (24) at the Instituto Carlos III, Madrid, Spain. Phage typing of selected isolates with experimental phages was carried out by the Staphylococcus Reference Laboratory of the Central Public Health Laboratory, London, England (22).

Control Measures. From November 1990, the programme for the control of MRSA was a local modification of the UK Guidelines for the control of MRSA (25) and will be described in full elsewhere. These guidelines include the prompt identification of patient and staff carriers by screening, the elimination of nasal carriage with intranasal mupirocin applied three times a day for five to seven days and the use of topical antiseptics such as chlorexidine to other positive skin sites.

Results

Outbreak. The first patient with MRSA infection was detected in July 1989. By October 1992 MRSA had been isolated from 1,074 patients. Eighty-four (7.8 %) were re-infected, re-colonized or were re-admissions known to have had MRSA previously. Of the 990 patients with newly acquired MRSA, 928 (93.7 %) acquired the organism after admission. Eleven patients had MRSA at the time of their hospital admission; for 51 patients who had previous hospitalization it was not possible to define the time of acquisition.

The index case probably initiated the outbreak in November 1989. She was a neurosurgical patient who had been infected and colonized with MRSA and transferred through several hospital departments, including the intensive care unit. From

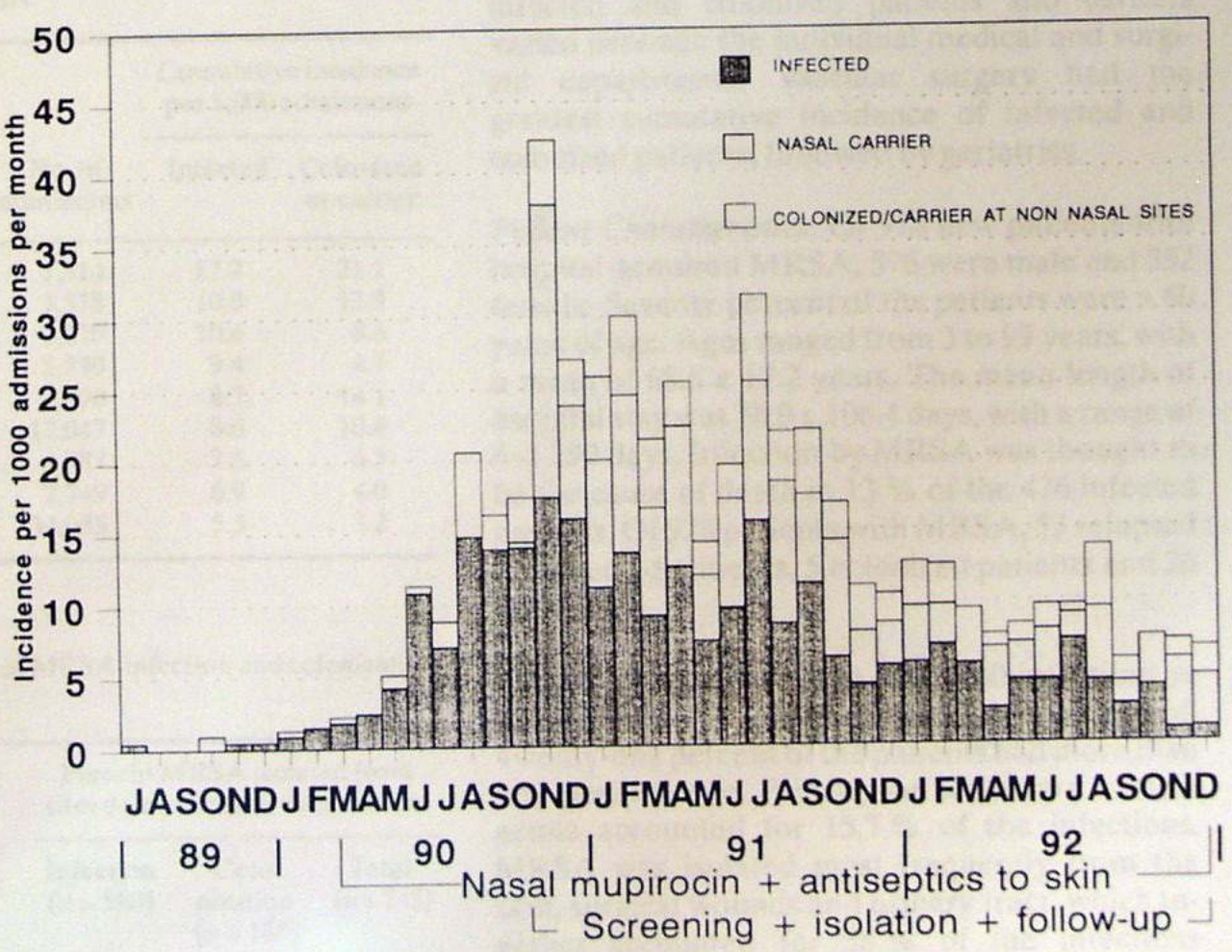

Figure 1: Epidemic curve showing the incidence of MRSA infection, nasal carriage, and carriage and colonization at other sites before and after an active screening programme.

November 1989, MRSA spread rapidly throughout the hospital and affected 12 of 13 medical and 8 of 10 surgical departments.

Methicillin-resistant *Staphylococcus aureus* was identified from clinical specimens in 525 patients (418 infected and 107 colonized), and an additional 403 patients (43.4 % of the outbreak) were identified from screening specimens, of whom 58 subsequently became infected and 18 colonized.

The antibiograms for the MRSA isolates usually indicated sensitivity only to vancomycin, trimethoprim, chloramphenicol, fosfomycin, fusidic acid and mupirocin. Of 188 strains isolated from screening specimens, 6 % belonged to phage group III and 94 % were non-typable with standard phages. Using experimental phages, a new phage type 29/77/84/932 was identified amongst 86 % of 29 strains from staff carriers and from patients who were infected, colonized or carriers.

Table 1: Distribution by service of 928 new patients with hospital-acquired MRSA.

Service	No. of admissions	Cumulative incidence per 1,000 admissions	
		Infected	Colonized or carrier
Vascular surgery	1,514	17.2	21.1
Geriatrics	1,578	10.8	13.9
General surgery	9,270	10.6	8.8
Intensive care unit	5,739	9.4	4.7
Urology	2,190	8.7	14.1
Internal medicine	17,047	8.6	10.6
Orthopaedics	4,787	7.5	6.5
Gastroenterology	2,749	6.9	4.0
Other	34,085	5.5	3.2

Table 2: Distribution of MRSA infection and colonization by site.

Site	Percent MRSA isolated from sites of infection or colonization		
	Infection (n = 580)	Colonization (n = 165)	Total (n = 745)
Surgical wound	22.1	20.0	21.6
Urinary tract	19.1	20.6	19.5
Skin	17.2	42.4	22.8
Blood	15.7	–	12.2
Lower respiratory tract	14.0	12.1	13.6
Faeces	4.1	–	3.2
Intravenous catheter	3.8	3.0	3.6
Others	4.0	1.9	3.5

The epidemic curve is shown in Figure 1. The peak of the outbreak was in November 1990, with a cumulative incidence of 17.4 new infected patients per 1,000 admissions per month. At this time we started the active screening programme and identified many more carriers. The cumulative incidence was found to be 20.4 nasal carriers per 1,000 admissions and 4.7 colonized patients or carriers at non-nasal sites per 1,000 admissions. By October 1992 the cumulative incidence of infected patients and nasal carriers was reduced to 3.9 and 3.5 per 1,000 admissions, respectively. By March 1993 the cumulative incidence was less than 3 infected patients per 1,000 admissions per month.

During the outbreak MRSA spread widely throughout the hospital. The intensive care unit and the entire surgical department had higher cumulative incidences of infection (9.4 and 7.1 per 1,000 admissions, respectively) than the medical departments (6.5 infected patients per 1,000 admissions). Table 1 shows that the distribution of infected and colonized patients and carriers varied between the individual medical and surgical departments. Vascular surgery had the greatest cumulative incidence of infected and colonized patients, followed by geriatrics.

Patient Characteristics. Of 928 new patients with hospital-acquired MRSA, 576 were male and 352 female. Seventy percent of the patients were > 60 years of age. Ages ranged from 3 to 99 years, with a mean of 68.6 ± 17.2 years. The mean length of hospital stay was 78.9 ± 106.4 days, with a range of 4–1,190 days. Infection by MRSA was thought to be the cause of death in 13 % of the 476 infected patients. Of 928 patients with MRSA, 53 relapsed (22 infected patients, 5 colonized patients and 26 carriers).

Clinical Infections. There were 580 infections in 476 patients, and 124 patients were colonized. Twenty-one percent of the patients had more than one positive site. Primary or secondary bacteraemia accounted for 15.7 % of the infections. MRSA was isolated most frequently from the skin, surgical wounds and urinary tract, which together accounted for 58 % of the infections (Table 2). MRSA colonized the skin in 42.4 % of the colonized sites, with bedsores accounting for 78 % of the skin colonization.

Screening Results. Table 3 shows the distribution of MRSA amongst the carriage sites of patients who were carriers, colonized or infected. The nose was the most common carriage site of

Table 3: Distribution of MRSA carriage by site.

Patient group	Site					
	Nose	Throat	Perineum	Groin	Axilla	Total
Carriers						
No. screened	403	289	378	262	188	403
Percent positive in first sample	83.9	30.8	38.1	15.6	10.1	100.0
Percent positive in subsequent samples	4.5	10.4	5.6	6.5	1.1	–
Colonized						
No. screened	63	56	57	57	55	63
Percent positive in first sample	32.2	14.3	28.1	21.1	9.1	44.4
Percent positive in subsequent samples	6.3	5.4	12.3	8.8	1.8	9.5
Infected						
No. screened	323	291	288	301	276	323
Percent positive in first sample	37.5	27.1	22.6	15.0	10.5	55.4
Percent positive in subsequent samples	9.0	12.4	12.5	9.6	2.5	11.8

Table 4: Patterns of 181 MRSA carriers detected with five screening swabs.

Screening pattern					No. (%) of patients
Nose	Throat	Perineum	Groin	Axilla	
+	–	–	–	–	62 (34.2)
+	+	–	–	–	23 (12.7)
+	–	+	–	–	23 (12.7)
+	+	+	–	–	9 (5.0)
+	+	+	+	–	3 (1.7)
+	+	–	+	–	3 (1.7)
+	+	–	–	+	2 (1.1)
+	+	+	+	+	2 (1.1)
+	and other patterns				15 (8.3)
–	–	+	–	–	18 (9.9)
–	+	–	–	–	9 (5.0)
–	+	+	–	–	3 (1.7)
Other patterns					9 (5.0)

Table 5: Sensitivities and negative predictive values of MRSA screening samples.

Samples	Sensitivity (%)	Negative predictive value (%)
Nose alone	78.5	95.3
Nose and throat	85.6	96.8
Nose and perineum	93.4	98.5
Nose, throat and perineum	98.3	99.6

MRSA in infected and colonized patients and in carriers, but the frequency of nasal carriage varied from 84 % in the carriers to 37 % and 32 % in the infected and colonized groups, respectively. After the nose, the throat or perineum was the most frequent site for MRSA carriage but were more often positive in non-infected asymptomatic carriers. Fifty-five percent of infected patients and 44 % of colonized patients were found to have MRSA at one or more of the carriage sites on the first screening. Subsequent screening samples yielded further positive carriage sites in both infected and colonized patients. Thirty-three percent of infected patients and 46 % of colonized patients were always negative for MRSA carriage.

Table 4 shows the patterns of MRSA carriage in 181 non-infected asymptomatic carriers, all of whom were sampled at all five carriage sites, i.e. nose, throat, perineum, groin and axilla. The most frequent positive specimens were nose alone (34.2 %) or nose in combination with the throat or perineum (12.7 %). The perineum alone was positive in 9.9 % of the carriers and throat alone in 5%. The sensitivities and the negative predictive values of the screening samples for MRSA carriage in 975 patients are shown in Table 5. Nasal swabs alone would have identified 78.5 % of the carriers. The inclusion of throat and perineum samples would have increased the sensitivity to 85.6 % and 93.4 %, respectively. Nose, throat and perineum swabs would have identified 98.3 % of the carriers, with a negative predictive value of 99.6 % (Table 5).

Of 2,303 screening swabs from hospital staff, MRSA was isolated from the nose in 72 staff members on 84 occasions, giving a prevalence of 3.6 %. The greatest prevalence was found during the final quarter of 1990, coinciding with the peak of the outbreak.

Discussion

Since 1989, the rate of isolation of MRSA in Spain has increased (18–21) and a new phage type 29/77/84/932 has been identified amongst MRSA isolates from several Spanish hospitals (22). This particular strain of MRSA, the "Spanish strain", has similarities, including epidemicity, to EMRSA-1, described in the UK (6, 22, 26). Spanish MRSA was identified in our hospital and spread readily to most of the medical and surgical departments and caused a large hospital outbreak that affected more than 900 patients over a three-year period. This supports the view that certain MRSA strains have enhanced transmissibility (3, 4, 27, 28, 29).

The widespread distribution of MRSA within the hospital could be related to the transfer of patients and staff between several hospital departments. Infection, colonization or carriage occurred on almost all clinical services and varied between different departments in the hospital. In our experience, as other authors have found (12, 13, 20, 21, 30–33), surgical services and intensive care units had the greatest cumulative incidence of infection. The high incidence of infection in the geriatrics department may be explained by the high susceptibility of these patients to hospital-acquired infection, the severity of their underlying disease, the presence of decubitus ulcers, the use of medical devices and the multiple hospital admissions.

The hospital reservoir of MRSA includes infected and colonized patients, patient carriers, staff carriers and, possibly, the inanimate hospital environment (3, 13, 33, 34). In this outbreak an active screening programme identified an additional 403 new asymptomatic carriers (43 % of the total outbreak) who would not have been detected by clinical specimens. Identification and treatment of these carriers coincided exactly with the reduction in the number of newly infected patients and the control of the outbreak. This confirms the importance of asymptomatic MRSA carriers as a source of MRSA that sustains the outbreak by continuing cross-infection (35).

Several studies have shown that MRSA strains are at least as pathogenic as methicillin-sensitive strains (8, 12, 13, 30). From the experience of the 1980s it seems clear that MRSA can cause significant morbidity and mortality (36, 37). We found that more than two-thirds of the patients with MRSA who were identified by clinical specimens had clinical infection. Post-operative wound infections and skin infections accounted for nearly 40 % of total MRSA infection, as found by other authors (10, 30, 38). Although bacteriuria caused by *Staphylococcus aureus* is infrequent, we found the urinary tract to be the second most common site of MRSA infection and colonization. We believe that the high frequency of MRSA bacteriuria in our study could be explained by the high proportion of patients with urinary tract catheters (more than 60 %), underlying urology disorders or urologic manipulation. These risk factors have been suggested by other workers (39). The high frequency of bacteraemia (15.7 % of 476 MRSA infections) and the number of deaths associated with MRSA infections (13 %) leave no doubt that our strain of MRSA was truly pathogenic.

The skin was the most common site of colonization. Skin colonization occurred mostly in older patients with decubitus ulcers who had persistent colonization and were unable to leave the hospital because of their poor functional status. This population provides a persistent reservoir of MRSA (40, 41).

Early studies in the 1960s showed that nasal carriage of *Staphylococcus aureus* by patients or staff provides a source of organisms for the acquisition of *Staphylococcus aureus* by other patients (42–46). It has also been known for many years that surgical patients who are nasal carriers of *Staphylococcus aureus* are more likely to acquire post-operative staphylococcal wound infection (47).

We found that more than 50 % of the MRSA-infected patients also yielded MRSA from one or more carriage sites that could have been the source of MRSA for auto-infection. Thirty-seven of the infected patients, for example, carried MRSA in their anterior nares, where staphylococci are known to provide the source of organisms for auto-infection (35, 48). In contrast, one-third of the infected patients and nearly half of the colonized patients were consistently negative for MRSA carriage, independent of the number of samples and sites screened, a finding that is in agreement with other authors (49). This suggests that nasal acquisition does not always precede the isolation of the organism from clinical

specimens. In these patients it seems that their cross-infection via staff hands may have occurred through portals of entry such as damaged skin, urinary tract or intravascular devices (50). The number of nasal carriers amongst hospital staff seemed to be related to the prevalence of patients with MRSA, with a peak in the final quarter of 1990 that coincided with the peak of the outbreak (51).

Although the nose is the most frequent carriage site for *Staphylococcus aureus*, several other skin carriage sites have been described (34, 44). We screened five different carriage sites in 181 non-infected asymptomatic carriers. The most common positive carriage site was the nose alone (34 %) or the nose in combination with other screening sites (78.5 %). Perineal carriage alone was found in 9.9 % of the patients. Although infrequent, perineal carriage could be important, as there is some evidence that perineal carriers are more likely to be dispersers (35). Throat carriage alone was found in only 5 % of the patients but could be a source of MRSA for the re-colonization of the anterior nares, as suggested by Solberg (52).

It is not clear from the literature which screening samples are required to identify MRSA carriers. In this study we evaluated the sensitivities and negative predictive values of the different screening samples for MRSA carriage and found that examination of nose, throat and perineum samples from each patient identified almost all carriers. As it is usually necessary to limit the number of screening specimens, we have decided from our results to screen nose and perineum samples, which would identify 93.4 % of carriers, and to take nose, perineum and throat swabs for following up patients after anti-staphylococcal topical treatment.

We conclude that our MRSA strain spread easily and was pathogenic. An active screening programme identified more than 40 % of the patients in an MRSA outbreak and was significantly associated with subsequent control of the outbreak.

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