

High Frequency of Colonization and Absence of Identifiable Risk Factors for Methicillin-resistant *Staphylococcus aureus* (MRSA) in Intensive Care Units in Brazil

Gustavo P. Korn, Marinês D. V. Martino,
Igor M. Mimica, Lycia J. Mimica,
Paulo A. Chiavone and Luiz R. de S. Musolino

Medical School of Santa Casa de São Paulo,
Department of Microbiology and Immunology
of Medical School of Santa Casa de São Paulo,
Service of Intensive Therapy of Santa Casa
de São Paulo, Brazil

Colonization of hospitalized patients with methicillin-resistant *Staphylococcus aureus* (MRSA) is of increasing concern. To evaluate this problem in Intensive Care Units (ICUs) in Brazil, we studied 100 patients admitted to two ICUs from April to June, 1997. Of the 100 patients, 70 were male, 53 were age 60 years or older, 55 were previously hospitalized, 78 were transferred to the ICU from other hospital units, 49 had received antibiotic therapy, and 66 had undergone recent surgery. Nasal and axillary swab cultures were obtained on admission and every 48 hours thereafter until discharge. MRSA were identified by plating any cultured *S. aureus* on Mueller-Hinton agar containing 6µg/ml of oxacillin. At the time of admission, 46 (46%) of the patients were colonized with MRSA. No associated risk factors for acquiring MRSA (age, previous hospitalization, prior surgery) could be identified. Of the 54 patients negative for MRSA on admission, 28 (52%) became colonized while in the ICU. Sixteen (22%) of the 74 colonized patients (colonized either on admission or during ICU stay) had associated respiratory or urinary tract infections due to MRSA, and 9 (56%) died. No correlation with special risk factors (invasive procedures, antibiotic use, age, chronic disease) was identified. MRSA occurred frequently, but there was minimal evidence of associated risk factors. Thus, control of MRSA cannot be accomplished by targeting special factors alone, but requires attention to preventing microbial spread in all areas. Of special concern is the high frequency of acquiring the organism in the ICU (52%). Education concerning the importance of hand washing, environmental surface cleaning, and barrier protection from infected patients is needed.

Key Words: *Staphylococcus aureus*, methicillin resistance, hospital infections.

The emergence of multiresistant microorganisms is an increasing problem that requires continuous and, often expensive, precautions to control the associated nosocomial infections. A multiresistant strain has been defined as one resistant to three groups of drugs [1].

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Address for correspondence: Dr. Gustavo P. Korn. R. Dr. Chibata Miyakoshi, 300 Ap. 111-B, Paraíso do Morumbi. Zip Code: 05750-170. São Paulo – SP, Brazil. Phone: (55 11) 9189-3485. Fax : (11) 3758-2869. E-mail: guga.korn@uol.com.br

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Following the introduction of penicillin, there were reports as early as 1945 [2], strains of *S. aureus* were unaffected by penicillin by their production of penicillinase or betalactamase. Initially, they were recorded rarely but they soon became reported worldwide. In spite of the development of semi-synthetic penicillins, resistant to the betalactamase activity, other strains appeared that were resistant to methicillin. Synthesis of other penicillins, such as oxacillin, cloxacillin and dicloxacillin, did not delay the emerging multi-resistant organisms [3].

Methicillin-resistant *S. aureus* (MRSA) emerged as a nosocomial pathogen in the early 1960s [4] when outbreaks of infection were reported in British hospitals

[5] and in other European countries including Switzerland, Denmark and France [6, 7]. Up to 1976, only two outbreaks [8] were reported in the United States. After 1976, according to National Nosocomial Infections Surveillance System (NNISS) data, strains of *S. aureus* to oxacillin increased from 2.4% in 1976, to 29% in 1991 [9]. Strains of MRSA resistant to methicillin, as well as strains resistant to newer penicillins, remained sensitive to glycopeptide antibiotics such as vancomycin and teicoplanin.

Two basic mechanisms are responsible for the resistance of *S. aureus* to the betalactamic antimicrobials: betalactamase production that destroys these agents; and the alteration of proteins located in the cellular wall of the bacteria, called penicillin binding proteins (PBPs) [10]. All MRSA strains produce altered PBP (PBP2 α or 2') [11, 12]. This protein is coded by a chromosomal gene denominated *mec A* [13]. Methicillin resistant *S. aureus* (intrinsic resistance) strains carry the *mec A* gene and PBP 2' [14, 15].

Introduction of MRSA into a health care setting may occur as a result of an infected or colonized patient being admitted, or by the presence of health care professionals colonized with the organism [5]. The main mechanism of MRSA transmission within the hospital is via the hands of health professionals who become colonized by direct contact with patients or contaminated patient materials [11]. Transmission is possible this way because MRSA can survive on the hands for hours [16].

Environmental surfaces also can be a source for MRSA transmission, although this hypothesis is controversial [17]. Before the infection is established, patients go through phases that include strain acquisition, followed by varying periods of time to achieve colonization of contaminated mucosa or skin [18].

Risk factors for colonization or infection have been identified. They include advanced age, masculine sex, previous hospitalization, length of hospital stay, admission to a burn unit or intensive care unit (ICU), chronic disease, previous antibiotic therapy, exposure to a colonized or infected patient, exposure to burn wounds or surgical wounds, and undergoing invasive procedures [4, 19].

Surveillance cultures can be collected from several anatomical sites including wounds, nostrils, perineum, anal area, feces, and tracheostomy secretions. The process of selecting patients for inclusion in this kind of study is controversial. Some authors recommend starting the study at the time of patient admission and then culturing sequentially during the hospital stay. In spite of logistical difficulties and high cost [20], some authors recommend tracking the spread of the infection from the sentinel case where the infection was detected. This approach is not necessary when the epidemic occurs in a closed unit, such as an ICU [21].

The largest reservoirs of organisms are found in the nostrils of colonized patients. Systematically administered antibiotics remain in low levels in this tissue, allowing for persistence of the microbe.

In Brazil, methicillin is not used. Organisms referred to as MRSA are actually oxacillin resistant *Staphylococcus aureus* (ORSA). However, as methicillin and oxacillin are similar antibiotics, MRSA is the usually accepted designation. As infections caused by these strains have become more frequent, especially in ICUs [22], establishing the epidemiology of these microorganisms in our hospital environments is of great interest.

The objectives of this study were to evaluate the frequency of patient colonization and /or infection by MRSA at the time of admission to an ICU to identify patients that acquired MRSA during their hospital stay, to describe diseases related to colonization by MRSA, and to determine risk factors (previous admission and/or transfer from another hospital site, advanced age, masculine sex, chronic disease, previous antibiotic therapy, surgery, invasive procedures) for colonization and/or infection by MRSA.

Materials and Methods

During the 3 month period of April through June, 1997, 100 patients admitted to the adult ICU of general hospitals were evaluated. Axillary and nasal swabs were collected from each patient on admission day, and

Table 1. Distribution of patients by risk factors and according to whether or not they acquired MRSA while in the ICU

Risk Factor	Acquired MRSA (n=28)			Did not acquire MRSA (n=26)			No. and percentage of risk factors for MRSA +MRSA/at risk (%)
	Yes (%)*	No	data missing	Yes (%)**	No	data missing	
Prior surgery (n = 36)	17 (61%)	7	4	19 (73%)	3	4	17/36 (47%)
Prior hospitalization	16 (57%)	12	-	14 (54%)	12	-	16/30 (53%)
Transfer from another unit in the hospital	24 (86%)	4	-	19 (73%)	7	-	24/43 (56%)
Age 60 or older	20 (71%)	8	-	10 (39%)	16	-	20/30 (67%)
Male	22 (78%)	6	-	17 (65%)	9	-	22/39 (56%)
Chronic disease	5 (18%)	19	4	3 (12%)	19	4	5/ 8 (63%)
Previous antibiotics	13 (46%)	9	6	10 (39%)	12	4	13/23 (57%)
Invasive procedure	14 (50%)	10	4	10 (39%)	12	4	14/24 (58%)

* percentage of the total who acquired MRSA.

** percentage of total who did not acquire MRSA.

Table 2. Distribution of colonized patients with or without infection according to risk factors

Colonized (n=74)	With infection (n=16)			Without infection (n=58)		
	Yes	No	data missing	Yes	No	data missing
Prior surgery	10 (63)	6	-	35 (60)	20	3
Prior hospitalization	7 (44)	9	-	31 (54)	25	2
Transfer from other unit	14 (88)	2	-	45 (78)	11	2
Age 60 years or older	7 (44)	9	-	36 (62)	22	-
Masculine sex	12 (75)	4	-	41 (71)	17	-
Chronic disease	7 (44)	9	-	10 (17)	45	3
Prior antibiotics	10 (63)	5	1	29 (50)	23	6
Invasive procedure	9 (56)	7	-	30 (52)	23	5

Table 3. Distribution of all patients colonized and not colonized according to the risk factors

Risk factor	Colonized with MRSA (n=74)			Not colonized (n=26)		
	Yes	No	data missing	Yes	No	data missing
Prior surgery	45 (61)	26	3	21 (81)	4	1
Prior hospitalization	38 (51)	34	2	14 (54)	12	-
Transfer from other unit	59 (80)	13	2	19 (73)	7	-
Age 60 years or older	43 (78)	31	-	10 (39)	16	-
Masculine sex	53 (73)	21	-	17 (65)	9	-
Chronic disease	17 (23)	54	3	03 (12)	22	1
Prior antibiotics	39 (53)	28	7	10 (39)	15	1
Invasive procedure	39 (53)	30	5	10 (39)	15	1

successively at every 48 hours during the hospital stay, plus an additional sample at the time of transfer to another unit.

Swabs were done each day between 7:00 and 9:00, 12:00 and 14:00, 16:00 and 18:00 hours to ensure that the first collection was performed as close to each patient's time of admission to the unit as possible. All the swabs were plated immediately on Chapman medium and incubated for 16 h to 18 h at 35°C to 37°C. At the end of that period, and when the presence of *Staphylococcus aureus* was confirmed, a sample was placed in a broth culture and maintained until a bacterial concentration of 10⁸ colony forming units per ml (CFU/ml) was achieved. Screening for MRSA was done as follows: a sample from a *S. aureus* culture was inoculated, with the aid of a swab, onto a plate of Mueller-Hinton agar supplemented with oxacillin at a concentration of 6 µg/ml, and containing 4% of NaCl (Probac of Brazil). An organism was considered resistant if the strain grew after incubating the plate for 24 h at 35°C to 37°C.

To evaluate the contribution of risk factors in colonization by MRSA, the following demographic data were collected on each patient; previous surgery, previous hospitalization, admission to another hospital ward and then transfer to the ICU, advanced age (60 years of age or older), gender, the presence of chronic disease, and previous antibiotic therapy.

The data were processed in Epi-Info using the chi-Square for analysis of statistical significance, considering $\alpha = 0.05\%$.

Results

Demographic data

The 100 adults admitted to the ICU included 70 males and 30 females. They had a mean age of 57 years distributed as follows: 6 under age 21, 12 age 21-40, 29 age 41-60 and 53 over 60 years of age (3 of those over 60 were in the age range of 81 to 90 years). A total of 880 swab cultures were obtained, one from the axillary and one from the nasal region, at 440 different time points. The number of swab cultures collected from each patient was 1 to 5 from 82, 6 to 10 from 11, 11 to 15 from 3, and more than 15 cultures from 4 patients. A chronic disease was recorded in 20 patients. These included hypertension, chronic airway disease and diabetes mellitus. Forty nine had received antibiotic therapy within the past 6 months. Fifty-five patients had had a previous hospitalization, and 78 were transferred to the ICU from another unit of the hospital. Sixty-six patients had undergone previous surgery. These demographic features were used to evaluate risk factors for acquiring MRSA.

Patients with MRSA identified or not at the time of admission to the ICU

Of the 100 patients, 46 had MRSA isolated at the time of admission; none of these had evidence of ongoing infection due to the organism. Of those colonized, 36/78 (46%) arrived at the ICU from another area of the hospital; 26/66 (39%) had previous surgery; 22/55 (40%) had a previous hospital admission; 25/49 (51%) had received antibiotics previously; 23/53 (43%) were older than 60 years; 31/70 (44%) were male; and 12/20 (60%) had a chronic disease. None of these potential risks for acquiring MRSA indicated a statistically significant factor for having the organism. Of particular note is that 9 patients, from whom MRSA was isolated at the time of admission to the ICU (20%), had no history of previous hospitalization, nor were they transferred from another unit in the hospital.

Patients who acquired MRSA were in the ICU

Twenty eight of the 54 patients not colonized with MRSA at the time of admission to the ICU acquired the organism while being cared for in the unit (52%). By examining risk factors for acquiring the organism while in the ICU, the following were found: over age 60 years, 20/30 (66%) became colonized; chronic disease, 5/8 (63%); invasive procedures 14/24 (58%); previous antibiotics 14/24 (58%); undergoing prior surgery 17/36 (47%); male gender (56%); transferred from another unit 24/43 (56%); and previous hospitalization 16/30 (53%). Thus, for those over 60 and with chronic disease, there is a slightly greater risk of acquiring MRSA while in the ICU, although this did not reach statistical significance. Table 1 presents this data in tabular form.

Risk factors for infection in those colonized by MRSA

Table 2 shows the distribution according to risk factors of the 16 patients who developed infections after isolation of MRSA. The most frequent risk factor was the presence of an underlying chronic disease 7/

17 (41%). Other risk factors ranged between 16% and 24%. The types of infections manifest among those infected included respiratory or urinary tract infections.

Nine of the 16 patients infected with MRSA (56%) died from their infections, thus confirming the high mortality associated with this infection.

Overall summary of risk factors for MRSA

Table 3 includes the data on all of the 74/100 patients (74%) who had MRSA at the time of admission to the ICU, or acquired it in the unit. Of those with previous surgery, 45/66 (68%) were colonized; 59/78 (76%) of those transferred from other units, 38/52 (73%) with previous hospitalization, 43/53 (81%) were over the age of 60 years; 39/49 (80%) underwent invasive procedures; 39/49 (80%) had received prior antibiotics; and 53/70 (76%) males acquired the MRSA organism. These data indicate that no special group was protected or more susceptible to acquiring the organism. On the other hand, the data indicated that acquisition of MRSA is a very common problem and is associated with the occurrence of infections resulting in a high mortality rate.

Discussion

S. aureus has been an important pathogen for many decades. Due to the increasing number of infections caused by strains of methicillin-resistant *S. aureus* (MRSA), the therapies for these microorganisms have become progressively more difficult [23].

The data in this work led to a series of reflections regarding MRSA. Due to the high colonization level present at the time of admission to the ICU (46%), or during treatment in the ICU (52% of those that did not have MRSA on admission), and knowing that the presence of the bacteria in those patients can be a source of contamination in this type of unit, great emphasis must be placed on instituting control measures to prevent its spread.

In accordance with the current norms of the CDC [24], patient carriers of multi-resistant bacteria are targeted to receive "Contact Precautions". These include the need for an isolated room or, when this is not possible, the patients can share a room with other carriers of the same bacteria (cohorts).

Many studies have shown advantages in using antiseptics in the hand washes [27, 28], since this is the most important route for MRSA transmission. The use of gloves for all the people that enter the room is recommended, since these patients are generally colonized at multiple anatomic sites and the patient's environment remains massively contaminated [25]. In contrast, the use of a mask and gown has not been shown to have documented value [26].

General measures of control include: 1) identification of patients who are colonized or infected with MRSA at the time of admission and during the period of hospitalization; 2) careful attention to the precautions described above to avoid the dissemination of the organism to the health care staff and visitors.

The 22% of colonized patients that developed infection is slightly lower than the 30% to 60% described in the literature [29, 30]. The antibiotics needed to treat them are expensive, and include drugs such as vancomycin and teicoplanin. There is further concern regarding observations of increasing resistance of enterococcus to vancomycin in some countries, and for the possibility that this type of resistance could be transmitted to *S. aureus*. Recent reports indicate isolation of strains of *S. aureus* with intermediary sensitivity to vancomycin (VISA) [31, 32].

In this study, no significant factors associated with colonization and/or infection were identified. One interesting finding was that 20% of the patients colonized at admission did not have a previous admission or transfer from another unit, even though these strains are typically from the hospital environment. In another study in the USA, 8 cases of MRSA were considered to be from the community [33].

The increasing frequency of MRSA strains remains a problem which must be solved quickly.

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