Risk Factors for Intensive Care Unit Acquired Nasal Colonization of MRSA and Its Impact on MRSA Infection

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Objective: We aimed to determine the risk factors of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, and the impact of colonization on MRSA infection to evaluate the necessity of MRSA survey program in intensive care units (ICUs) in Turkey. **Methods:** The patients hospitalized in medical and neurosurgical ICUs longer than 24 hr were included into the study. To determine anterior nares MRSA colonization, swabs were taken from each patient in the first 48 hr, and followed by once a week till discharge from ICUs. **Results:** During the one-year follow-up period, the number of the hospitalized patients who spent more than 24 hr in ICUs was 195 of 372 and 85 of 619 in medical and neurosurgical ICUs, respectively. Totally, 23 out of 280 patients (14 from medical ICU, 9 from neurosurgical ICU) were colonized with MRSA,

and 11 out of 23 colonized patients were accepted as ICU-acquired infection. The duration of ICU hospitalization in patients with ICU-acquired MRSA colonization was found to be longer than the noncolonized patients (18 days vs. 8 days, P value < 0.001). The presence of gastrostomy and femoral catheter were determined as risk factors for ICU-acquired MRSA colonization. The percentages of MRSA infection in patients with and without MRSA colonization were 8.6% and 1.1%, respectively (P value: 0.009). **Conclusion:** The presence of gastrostomy and femoral catheter, and the duration of ICU hospitalization were found to be related with ICU-acquired MRSA colonization. Also, MRSA nares colonization increased the rates of both MRSA infection and ICU hospitalization. J. Clin. Lab. Anal. 27:412–417, 2013. © 2013 Wiley Periodicals, Inc.

Key words: methicillin-resistant *Staphylococcus aureus*; ICU-acquired colonization; hospital mortality

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA), a prominent cause of nosocomial infection, is an emerging problem worldwide (1). Between 1999 and 2002, the proportion of MRSA in European countries increased steadily (2). The surveys held on patients in intensive care units (ICUs) across European countries in 1992 and 2007 showed that 45–50% of the patients had some infections (in Turkey 49%), and 60–49.5% out of the *S. aureus* originated infections were methicillin resistant (2, 3). More than 13–40% of nosocomial bacteremias are due to *S. aureus*, 54–95% of them are methicillin resistant, the rates were reported to be increased in surgical wound infections to 82% and 62%, respectively (4, 5). The hospital

mortality rates were higher in the patients with MRSA than methicillin-susceptible *S. aureus* (MSSA) (36.4% and 27.0%, P < 0.01) (3). Moreover, MRSA pneumonia associated hospital mortality reached 50% in all patients (6).

With changing information in epidemiology of MRSA during the last decade, the rates of community-associated MRSA (CA-MRSA) are growing all over the world,

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besides the increasing rates of healthcare-associated MRSA (HA-MRSA) infections in ICUs. CA-MRSA infection was first reported from Australia in 1981, and then followed by United States and European countries (4). In Spain, only 3 out of 301 patients in ICU with MRSA were determined as CA-MRSA originated (7), whereas in Asia CA-MRSA proportion has already reached 25.5% in all MRSA infections (8). The incidence of CA-MRSA in European countries is considered to be lower than that in the United States (9). In Turkey, Demir et al. and Gulmez et al. determined that Panton-Valentine leukocidin-carrying CA-MRSA does not seem to be important yet (10, 11).

The risk of MRSA infection reached 30–60% in patients previously colonized with MRSA (12, 13), and moreover 83% of the patients with bacteremia were determined to be colonized with MRSA (14). When acquiring MRSA infection, the rates of mortality and the length of hospital stay increase dramatically (4). And much more, the presence of a patient colonized with MRSA in the same ICU is a serious risk factor for the MRSA infection (15). Hence, for a long time, the authors have focused on ways to prevent contamination and spreading of MRSA.

Main risk factors for MRSA colonization are advanced age, previous hospitalization, hospitalization in ICU, chronic medical illness, prolonged antibiotic usage, presence of any wound, and invasive indwelling devices (15). Intrahospital spreading of MRSA usually happens via the hands of healthcare workers (4, 13), and it is still an important factor in carrying MRSA infections (55% of the cases were HA-MRSA in Spain) (7, 14), hence contact isolation became a key point for MRSA prevention strategies (17).

In many countries, the rates of MRSA infection, the importance of CA-MRSA, and the ongoing survey programs are different (1, 2). In this study, we aimed to determine the risk factors of MRSA colonization, and the impact of colonization on MRSA infection. With the highlights of the results, we can evaluate the necessity of MRSA survey program particularly in ICUs in our country.

MATERIAL AND METHODS

Study Population

The adult patients hospitalized in ICU for more than 24 hr between April 1, 2006 and April 1, 2007 in both neurosurgical and medical ICUs were included into the study. To determine anterior nares MRSA colonization, swabs were taken from each patient in the first 48 hr, and followed by once a week till discharge from ICUs. Each patient was followed up for the next 72 hr after discharging from ICUs.

All the demographic data of the patients were collected from the digital archive of hospital. The possible risk fac-

tors were collected from patients' private folders including age, sex, APACHE II score, underlying diseases, presence of ongoing immunosuppressive drugs, length of hospitalization in ICUs or hospital, history of previous stay in hospital, previous and/or ongoing antibiotic treatments, invasive and/or percutaneous catheters, feeding via par-enteral or enteral nutrition, intubation, mechanical ventilation and their duration, presence of tracheotomy, gastrostomy, history of surgery, and the presence and severity of the wounds, particularly decubitus ulcer.

Laboratory

All nares swabs were inoculated in agar with 5% sheep blood (Blood agar base No. 2, Oxoid, UK) at the bedside. The bedside inoculated agars were assessed in Research Laboratory of Infectious Disease Unit after incubation at 35°C overnight. The Gram staining and catalase test were performed into the suspicious colonies. Tube coagulation test was performed into the isolates positive for both Gram staining and catalase test. The isolates with the presence of positivity with tube coagulation test with rabbit plasma were named as *S. aureus*.

The diagnosis of methicillin-resistant form was performed via disc diffusion test with oxacillin (1 µg, Oxoid). The results were obtained after an incubation period of 24 hr at 35°C.

The diagnosis of nosocomial infection was used, based on the criteria of Centers for Disease Control and Prevention (CDC) (16). When the time at diagnosis of infections was 48 hr after the admission into ICUs, it was accepted as hospital-acquired infection, which is similar with the presence of MRSA at the anterior nares, found in the second swap culture taken 48 hr after the admission into ICUs, and it is called ICU-acquired colonization.

This study was approved by local Ethic committee of Hacettepe University Medical Faculty.

Statistical Analysis

"SPSS 11.5 for Windows" (Statistical Package for the Social Sciences 11.5) was used for statistical analysis. Data were given as means $\pm$ SD or median (range). Continuous variables were compared with student's *t*-test or Mann-Whitney U test, and categorical variables were compared with Chi-square test, and *P* value of <0.005 was accepted as significant. Univariate logistic regression analyses were also performed.

RESULTS

During the one-year follow-up period, the number of the hospitalized patients was 372 and 619 in medical and neurosurgical ICUs, respectively. However, only 195 and

TABLE 1. The Baseline Characteristic Features of the Patients Hospitalized in ICUs

	Medical ICU (N: 195)	Neurosurgical ICU (N: 85)	Total (N: 280)	P value
Mean ages (range), years old	64 (17–106)	58 (18–98)	61 (17–106)	0.619
Male sex, N (%)	108 (55.3)	42 (49.4)	150 (53.5)	0.877
Mean duration of staying in ICUs, days (range)	8 (1–192)	11 (1–164)	9 (1–192)	0.206
Patients transferred from an another hospital, ^a N (%)	20 (10.3)	15 (17.6)	35 (12.5)	0.130
Patients from a ward in the same hospital, ^a N (%)	59 (28.9)	20 (23.6)	79 (28.3)	0.130
Patients from emergency department in the same hospital, ^a N (%)	19 (9.1)	1 (1.2)	20 (7.1)	0.130

^aThe number of the patients who had histories of staying in health care facilities longer than 48 hr before admission to ICUs.

85 of all patients were hospitalized for more than 24 hr in ICUs; respectively. The mean days of hospitalization in ICUs did not differ between the ICUs (8 and 11 days, *P*: 0.206). Totally, 53.6% of the patients were male, and mean age of the patients was 61 years (Table 1). Almost half of the patients did not have any previous hospitalization history before admission to ICUs, and the rest had history of staying longer than 48 hr in health care medicine facilities. The demographical data were similar between the patients in the medical and neurosurgical ICUs (Table 1).

The underlying diseases differ between ICUs as it was expected. Chronic diseases such as diabetes mellitus, coronary heart diseases, and organic dysfunctions were more in medical ICU, and some invasive procedures (hemodial-

ysis, plasmapheresis) were more common in medical ICU. The other procedures (such as lumbar puncture) were more frequent in neurosurgical ICU (see Tables 2A and B).

During the follow-up period, 23 out of 280 patients were colonized with MRSA, 14 of whom in medical ICU. Eleven out of twenty-three patients with nasal MRSA colonization were accepted as ICU-acquired colonization (Table 3), whereas three patients were missed for the nasal swab in the first 48 hr, and the last nine patients were positive in the first swabs. However, the last 12 patients could not be named as community-acquired MRSA colonization because 10 of them came into ICU from other health care facilities; one had a history of hemodialysis and the

TABLE 2A. Underlying Diseases of the Patients in Each ICU

	Medical ICU (N: 195)	Neurosurgical ICU (N: 85)	Total (N: 280)	P value
Hypertension, N (%)	75 (38.4)	75 (38.4)	107 (38.2)	0.897
Diabetes mellitus, N (%)	54 (27.6)	11 (12.9)	65 (23.2)	0.008 ^a
Cardiovascular diseases, N (%)	62 (31.7)	15 (17.6)	77 (27.5)	0.015 ^a
Respiratory insufficiency, N (%)	63 (32.3)	3 (3.5)	66 (23.5)	<0.001 ^a
Liver failure, N (%)	12 (6.1)	0 (0)	12 (4.2)	0.019 ^a
Renal failure, N (%)	30 (15.3)	3 (3.5)	33 (11.7)	0.005 ^a
Solid tumors, N (%)	20 (10.2)	9 (10.5)	29 (10.3)	0.933
Neutropenia, N (%)	10 (5.1)	0 (0)	10 (3.5)	0.025 ^a
Collagen tissue disorders, N (%)	19 (9.7)	0 (0)	19 (6.7)	0.003 ^a

^a*P* value < 0.05 is accepted as significant.

TABLE 2B. The Presence of Invasive and/or Percutaneous Procedures in Patients Hospitalized in Each ICU

	Medical ICU (N: 195)	Neurosurgical ICU (N: 85)	Total (N: 280)	P value
Endotracheal intubation, N (%)	106 (54.3)	55 (64.7)	161 (57)	0.107
Tracheotomy, N (%)	9 (4.6)	14 (16.4)	23 (8.2)	<0.001 ^a
Nasogastric intubation tube, N (%)	45 (23)	44 (51.7)	89 (31.7)	<0.001 ^a
Gastrostomy, N (%)	3 (1.5)	6 (7)	9 (3.2)	0.01 ^a
Femoral catheter, N (%)	17 (8.7)	8 (9.4)	25 (8.9)	0.85
Internal jugular catheter, N (%)	93 (47.6)	34 (40)	127 (45.3)	0.23
Chest tube, N (%)	7 (3.5)	2 (2.3)	9 (3.2)	0.59
Lumbar puncture, N (%)	2 (1)	10 (11.7)	12 (4.2)	<0.001 ^a
Noninvasive mechanical ventilation, N (%)	42 (21.5)	1 (1.1)	43 (15.3)	<0.001 ^a
Dialysis, N (%)	34 (17.4)	2 (2.3)	36 (12.8)	<0.001 ^a
Plasmapheresis, N (%)	10 (0.5)	0 (0)	10 (3.5)	0.03 ^a

^a*P* value < 0.05 is accepted as significant.

TABLE 3. The distribution of 11 ICU-Acquired Colonized Patients According to at Which Day MRSA Positivity Was Found First, and the Date of the First Positive Nasal Swab for MRSA

No. of patients	Days in ICU of first positivity	Date of first positivity	ICU
5	19	18.08.2006	Medical ICU
7	11	08.11.2006	Medical ICU
10	71	20.11.2006	Medical ICU
12	4	24.11.2006	Medical ICU
13	26	24.11.2006	Medical ICU
14	34	24.11.2006	Medical ICU
15	17	24.11.2006	Neurosurgical ICU
17	3	15.12.2006	Neurosurgical ICU
20	25	18.12.2006	Neurosurgical ICU
21	3	23.12.2006	Neurosurgical ICU
23	8	04.01.2007	Neurosurgical ICU

last patient had history of several hospitalizations in the previous months with the diagnosis of acute leukemia.

Another important data were the accumulation of nasal MRSA in the months of November and December (15 out of 23 positive patients).

To determine the risk factors for ICU-acquired MRSA colonization, the underlying diseases and the presence of invasive or percutaneous procedures, ongoing antibiotic therapies were investigated in both groups, in patients with and without ICU-acquired MRSA colonization (Tables 4A and B). With the univariate analysis, the presence of gastrostomy and femoral catheter were determined as risk factors for ICU-acquired MRSA colonization.

The duration of ICU hospitalization in patients with ICU-acquired MRSA colonization was found to be longer than the noncolonized patients (18 days vs. 8 days, P value <0.001). However, the ICU mortality rates between these two groups did not differ from each other (18.1% vs. 37.3%, P value = 0.16).

To evaluate the impact of MRSA colonization on MRSA infection, we included all of the MRSA colonized patients into the statistical analysis, besides patients with the patients in the medical and neurosurgical ICUs-acquired MRSA colonization. The percentages of MRSA infection in patients with and without MRSA colonization were 8.6% (N : 2) and 1.1% (N : 3), respectively (P value: 0.009). It was realized that all of the MRSA infections were respiratory system infections. Three patients in noncolonized group were also diagnosed as MRSA-associated respiratory system infections. The numbers of the negative nasal swabs before and after the diagnosis of MRSA infections were 1, 2, 4, and 4, 4, 11 in these patients, respectively. Two out of five patients with MRSA infection were in medical ICU, and the others were in neurosurgical ICU. Three of five (60%) patients with MRSA infection died in the ICUs.

DISCUSSION

MRSA infections are still a serious problem all over the world (except in a few countries, particularly in northern Europe) (2, 19). In our hospital, the percentage of MRSA isolates increased from 32% to 76%, between 1994 and 2006 (20). Moreover, in 2006, 90% of the *S. aureus*-associated infections in ICUs were related with methicillin-resistant isolates (20). In another words, MRSA is an endemic nosocomial pathogen in our hospital. On the other hand, just 10% of nosocomial infections seen in ICUs were *S. aureus* related. Because all of the MRSA-related infections were seen in medical and neurosurgical ICUs, this study was conducted in these ICUs. During the study period, the infection rates were found to be 20% (42.2/1,000 patient days) in neurosurgical ICU, and 35.5% (45.7/1,000 patient days) in medical ICU (20).

TABLE 4A. The Comparison of the Patients With and Without ICU-Acquired MRSA Colonization According to the Baseline Demographic Features and the Underlying Diseases

	Patients with ICU-acquired MRSA colonization (N : 11)	Patients without ICU-acquired MRSA colonization (N : 257)	Total (N : 268)	P value ^a
Ages, mean (range), years old	62 (32–82)	61 (17–106)	61 (17–106)	0.72
Male sex, N (%)	6 (54.5)	138 (53.6)	150 (53.5)	0.60
Hypertension, N (%)	6 (54.5)	96 (37.3)	105 (39.1)	0.201
Diabetes mellitus, N (%)	3 (27.2)	61 (23.7)	64 (22.2)	0.51
Cardiovascular diseases, N (%)	2 (18.1)	73 (28.4)	75 (27.9)	0.33
Respiratory insufficiency, N (%)	1 (9)	62 (24.1)	63 (23.5)	0.22
Liver failure, N (%)	1 (9)	10 (3.8)	11 (4.1)	0.37
Renal failure, N (%)	2 (18.1)	30 (11.6)	32 (11.9)	0.38
Solid tumor, N (%)	0 (0)	28 (10.8)	28 (10.4)	0.29
Neutropenia, N (%)	0 (0)	9 (3.5)	18 (7.0)	0.68
Collagen tissue disorders, N (%)	0 (0)	18 (7.0)	18 (6.7)	0.45

^a P value < 0.05 is accepted as significant.

TABLE 4B. Comparison of the Patients With and Without ICU-Acquired MRSA Colonization According to the Presence of Invasive or Percutaneous Procedures and Antibiotic Usage

	Patients with ICU-acquired MRSA colonization (N: 11)	Patients without ICU-acquired MRSA colonization (N: 257)	Total (N: 268)	P value
Endotracheal intubation, N (%)	8 (72.7)	147 (57.1)	155 (57.8)	0.24
Tracheotomy, N (%)	2 (18.1)	20 (7.7)	22 (8.2)	0.22
Nasogastric intubation tube, N (%)	6 (54.5)	79 (30.7)	85 (31.7)	0.95
Gastrostomy, N (%)	2 (18.1)	6 (2.3)	8 (2.9)	0.03 ^a
Femoral catheter, N (%)	3 (27.2)	20 (7.7)	23 (8.5)	0.05 ^a
Internal jugular catheter, N (%)	5 (45.4)	115 (44.7)	120 (44.7)	0.59
Chest tube, N (%)	0 (0)	9 (3.5)	9 (3.3)	0.68
Lumbar puncture, N (%)	1 (9)	9 (3.5)	10 (3.7)	0.34
Noninvasive mechanical ventilation, N (%)	0 (0)	42 (16.3)	42 (15.6)	0.14
Dialysis, N (%)	2 (18.1)	34 (13.2)	36 (13.4)	0.44
Plasmapheresis, N (%)	0 (0)	9 (3.5)	9 (1.1)	0.68
Antibiotic usage, N (%)	11 (100)	205 (80)	216 (80.5)	0.09

^aP value < 0.05 is accepted as significant.

The presence of MRSA colonization in nares is routinely investigated and decolonized in some countries, whereas the others do not have any surveillance program to eradicate MRSA colonization (17). Coello and colleagues reported that swab culture just from anterior nares had 78.5% sensitivity, and 95.3% negative predictive value (NPV), and with the adding of perine besides anterior nares, sensitivity reached 93.4% and NPV reached 98.5% (21). With its high sensitivity and NPV, anterior nares swab culture was performed alone.

During the study period, totally 23 patients took the diagnosis of nasal MRSA colonization, in which only 11 of them had ICU-acquired MRSA colonization. Ten out of the rest twelve patients were accepted into ICUs after staying longer than 48 hr in different types of health care facilities, and one of the last two patients were hemodialysis depended; also, they had several times hospitalization history due to the underlying disease, acute leukemia. Till date, there is no case of community-acquired MRSA colonization or infection. Although we did not perform genotype analysis in our patients, we guess that all of our MRSA isolates were nosocomial originated. Similar with the recent articles, MRSA colonization elongated with the duration of ICU stay in our study (from 8 days to 11 days, *P* value <0.001) (22).

It was realized that MRSA infections were seen much more in patients with MRSA colonization, and 30–60% of colonized patients took the diagnosis of MRSA infection (23). These data were supported by our results and the risk of MRSA infection increased eight times with nasal MRSA colonization (*P* value 0.009). That is why the presence of MRSA colonization in nares is routinely investigated.

Longer than five days stay in health care facilities in the last one year, antibiotic usage in the previous three

months, and staying in nursing home were the risk factors for MRSA colonization (24, 25). Even though the data about the patients' demographic features were lacking in the hospital's folders, we could not speculate anything about this topic. As mentioned, almost half of the positive results in the first swab cultures were attributed to the past history of living in health care facilities. In fact, the risk factors of ICU-acquired MRSA colonization were detailed in our article. The underlying diseases and most of the invasive or percutaneous procedures were not found as risk factors of colonization in contrast with some articles published before (15, 26); on the other hand, the presence of femoral catheter, and gastrostomy, seemed to be significant risk factors for ICU-acquired nasal MRSA colonization. Also, advance age, male sex, antibiotic usage, and HIV positivity were not shown as risk factor (15, 27). Perhaps, the conflicting data were according to the low number of the patients with ICU-acquired MRSA colonization in our study.

Interestingly, most of the colonized patients in both ICUs were accumulated in November and December of the year. But we do not know what can be the exact reason of the accumulation of MRSA colonization in winter.

Only two out of five patients with MRSA infections were nasal MRSA carrier, the last three were all negative for nasal swabs taken before and after the diagnosis of MRSA infection. While the sensitivity of nasal swab culture alone is almost 75% (21), the possible explanations are the missing of real carriers, or direct inoculation of MRSA. To overcome the financial problem of long-term surveillance programs, nasal MRSA swab cultures alone is widely acceptable (25).

As for a limitation of the study, during the study period, we did not isolate the patients due to the positivity of nasal swab cultures (contact isolation alone decreased the

contamination rate by 16 times) (28). However, some of the patients were isolated because of other reasons, for example, resistant gram negative bacilli. Overall infection precautions routinely recommended by CDC was taken into account (18).

In conclusion, the high morbidity and mortality rates of MRSA infections are still a serious problem all over the world. Having gastrostomy or femoral catheter, and the duration of ICU hospitalization were found to be related with ICU-acquired MRSA colonization. Nasal MRSA carriage is found to be related with MRSA infection leading to high ICU mortality. Further studies using larger series of patients are needed to confirm these findings.

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