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Prospective Analysis Methicillin-resistant *Staphylococcus aureus* and its Risk Factors

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ABSTRACT

Background: Since the early nineties, a new methicillin-resistant *Staphylococcus aureus* (MRSA) has existed in a form correlating with community health personnel. Community-acquired MRSA (CA-MRSA) could be differentiated from healthcare-associated MRSA (HA-MRSA) microbiologically, epidemiologically, and molecularly. **Aims:** To determine the prevalence, risk factors of MRSA infections in community and hospital. **Settings:** The incidence and risk factors for CA-MRSA and HA-MRSA among patients of medical, surgical, and pediatrics wards and ICU at a Kuwaiti teaching hospital between 1 March 2011 and 30 November 2011 were studied. **Materials and Methods:** Cultures for MRSA were taken from nasal (nostril), groin, axilla, wound, sputum, or throat, and the inguinal area in all enrolled patients upon admission. All preserved isolates were examined for their susceptibility to different types of antibiotics. **Results and Conclusion:** A total of 71 MRSA patients admitted to different hospital wards were examined. Among these patients, 52 (73.2%) were carriers of MRSA before they were admitted to the hospital. Nineteen patients (26.8%) were found to have acquired MRSA during their stay in the hospital. Twenty-nine patients (40.8%) were given mupirocin local skin antibiotic. Binomial and the *t*-test (paired) were used to compare the prevalence of CA-MRSA and HA-MRSA; significant correlation ($P < 0.05$) between the type of MRSA and different wards, sites, and lengths of hospital stay was found. The level of serum albumin that is routinely measured at hospital admission is a predictor to MRSA infection. This study suggests that *S. aureus* and MRSA should become a national priority for disease control to avoid outbreaks.

Key words: Community acquired, Methicillin-resistant *Staphylococcus aureus*, Nosocomial, Risk factors

INTRODUCTION

Staphylococcus aureus is an important pathogen in both community and hospital settings.[1,2] It is a commensal and adaptable pathogen in humans, causing surface lesions, such as wound infections and skin abscesses, and systemic infections, such as endocarditis, pneumonia, osteomylitis, bacteremia, and toxemic syndromes.[3,4] Microbial pathogenicity in this strain is a complex phenomenon involving a number of virulence factors: (a) exotoxins that damage host cells and interfere with immune response, (b) cell wall associated proteins, and (c) protection against host defenses.[5]

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains have appeared in the late nineties as significant pathogens in community-associated settings as well as healthcare-associated ones.[6-9] Many studies revealed that the strains of CA-MRSA were significantly responsible for healthcare-associated infections (nosocomial) in the healthcare settings, and that these infections were previously and mainly caused by strains of healthcare-associated MRSA (HA-MRSA).[10] Despite the name CA-MRSA referring to colonization or infection in the community rather than actual possession,[11] CA-MRSA strains often originate from isolates picked up in healthcare facilities on previous visits or through contact with other entities who have previously been exposed to HA-MRSA strains. Reports of infections caused by MRSA have begun to emerge in recent years among patients not previously exposed to nosocomial MRSA risk factors.[12]

CA-MRSA has now become known in many countries,[13,14] especially in the USA.[15,16] CA-MRSA infections are acquired by persons who have not been hospitalized nor have had certain medical procedures such as dialysis,

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surgery, or catheterization before admission to hospital. Extensive information on CA-MRSA infections includes almost 13,000 cases; the common theme in all these reported cases is that no obvious risk factors appeared among the patients.[17,18] Many cases are misdiagnosed as spider bites, but the spread was related with negligible skin trauma, sharing of sports or individual care apparatus, and sharing of close lodgings.

The aim of this study is to determine the prevalence, risk factors, and microbiological characterization of CA-MRSA and HA-MRSA infections among patients at a Kuwaiti teaching hospital. This was carried out in order to address issues relevant to the identification, incidence, prevention, and management of CA-MRSA infections in comparison to the HA-MRSA at a teaching hospital in Kuwait.

MATERIALS AND METHODS

This prospective study was conducted at the internal medicine department of a Kuwaiti teaching hospital between 1 March 2011 and 30 November 2011. A group of microbiologists, a physician, and an infection control specialist participated in this study. The hospital's records were used to assemble patient characteristics including age, gender, and socioeconomic status, in addition to clinical and microbiological data such as date of admission and discharge, period of stay in each ward, recent operations, invasive therapeutic procedures, and prior usage of antimicrobials.

During the study period, all patients were suffering and experiencing different medical problems and were mainly diagnosed by the physician with or without some co-morbid conditions such as upper gastrointestinal bleeding, gastrostomy tube replacement, aspiration pneumonia, cerebral stroke, pulmonary embolism, urinary tract infections, chest infection, septicemia, acute and chronic renal failure, sepsis, septic shock, arthritis, diabetes mellitus, asthmatic heart disease, pulmonary edema, myocardial infarction, and nephritic syndrome. This study is concerned with both CA-MRSA and HA-MRSA patients. Samples were collected from patients not only for microbiological examinations, but also for clinical investigations including white blood cell count, hemoglobin, platelets, glucose, urea/creatinine, sodium/potassium, and protein/albumin. Patients positive for MRSA were then transferred to contact isolation.

Patients with MRSA infections that met all of the following criteria were likely to have CA-MRSA infections, while if not, they were considered to be HA-MRSA infections. The criteria were included: (a) diagnosis of MRSA that was made in outpatient setting or by a culture positive for MRSA less than 48 h after admission to the hospital, (b) no medical history of MRSA infection or colonization, (c) no medical history in the past year of hospitalization, dialysis, or surgery, and (d) no permanent indwelling catheters or medical devices that pass through the skin into the body.

Patients in the medical, surgical, and pediatric wards and the medical-surgical ICU were the target of this study. Specimens were collected from all suspected MRSA patients in the previously mentioned locations on the first day of admission. All isolates were collected from patient groups aged from less than 14 years to above 50 years and classified into four age categories – <14, 15-24, 25-49, and >50 – with documented blood, respiratory tract, urine, skin, wound, or body fluid infections, or infections from other defined sources. The culture sites of every collected culture included nostril and tracheal secretions if the patient was on tracheotomy tube, throat, axillae, wound, and inguinal area. All swabs were sent to the hospital main laboratory within 6 h for bacterial culture and microbiological studies. The period of stay at the hospital for each patient was also recorded.

For MRSA culturing and identification, each swab was plated onto a blood agar plate and incubated at 37°C for 48 h. Each isolate was identified using the VITEK 2 system and GeneXpert system (bioMérieux, Marcy l'Étoile, France). Isolates of *S. aureus* were first subjected to catalase test and Gram stain, and then coagulase test for identification. All preserved isolates were examined for their susceptibility to different types of antibiotics, including clindamycin, erythromycin, gentamicin, minocycline, ciprofloxacin, rifampicin, vancomycin, trimethoprim–sulfamethoxazole, tygacil, piperacillin, linezolid, and meropenem using the disk diffusion method on Muller-Hinton as described by the Clinical and Laboratory Standards Institute.[19]

According to hospital policy, important procedures have been applied for MRSA treatment as a protocol using an appendix sheet. The antibiotic ointment mupirocin (Bactroban) was applied for the people with nasal isolates three times daily for 5 days. Regarding cutaneous MRSA, the following method was applied. Four percent chlorhexidine (or Octenisan for neonate) body wash was applied undiluted as liquid soap with a disposable cloth, and then rinsed off. The hair was washed with (Hibiscrub) as undiluted shampoo at day 2, and again at day 5. During this period, five repeat sets of cultures were investigated. If positive for MRSA, the patient was kept in contact isolation and the protocol was repeated for

three sets. After these three sets, if the cultures were still MRSA positive, then the patient was labeled as a carrier.

Statistical analysis

Analyses of data were carried out using SPSS for Windows (Version 14) and Microsoft Office Excel 2003. To characterize the number of successes over a series of observations, binomial distribution test and *t*-test (paired) were used to compare the relative prevalence of CA-MRSA and HA-MRSA, and the correlation of the different wards, sites, and duration of hospital stay with the two MRSA types. A probability of $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, a total of 71 MRSA patients admitted to different hospital wards were examined. The number of patients with CA-MRSA and HA-MRSA in 9 months of the year 2011 is shown in Table 1. Among these patients, 52 (73.2%) were carriers of MRSA before they were admitted to the hospital. Nineteen patients (26.8%) were found to have acquired MRSA during their stay in the hospital, as shown in Figure 1. Figure 2 shows that 64 patients (90.1%) were from the medical ward, 48 patients (75%) had CA-MRSA, and 16 patients (25%) had HA-MRSA. Three patients (4.2%) were from the surgical ward, two patients (2.8%) from pediatrics, two patients (2.8%) were from the ICU areas.

Ninety-nine isolates of *S. aureus* were obtained from the clinical samples of the previously mentioned MRSA patients. Statistically, a significant relationship occurred between the number of CA-MRSA patients and the different wards ($P < 0.05$), while for the number of HA-MRSA patients, binomial distribution showed a significant correlation ($P < 0.05$) in the different wards. Figure 3 represents the number of patients and the sites of infections for both community- and hospital-acquired MRSA. Thirty-seven isolates (37.3%) were from nasal carriage, 27 isolates (72.9%) from patients with CA-MRSA, and 10 isolates (27.1%) were isolated from HA-MRSA patients. Twenty-one isolates (21.2%) were taken from the groin, out of which 18 isolates (85.7%) were of the CA-MRSA type and 3 isolates (14.3%) were from patients with HA-MRSA. Seven isolates (7%) were from axilla, nine isolates (9%) from wounds, and 25 isolates (25.2%) were from different sites including 9% from blood, 6% from gastrostomy, 4% from endotracheal, and 4.4% from

Table 1: Number of patients with community-acquired-MRSA and healthcare-associated-MRSA per month/2011

Month	March	April	May	June	July	August	September	October	November
CA-MRSA patients	12	5	1	9	8	6	3	7	1
HA-MRSA patients	4	3	1	2	3	2	0	3	1

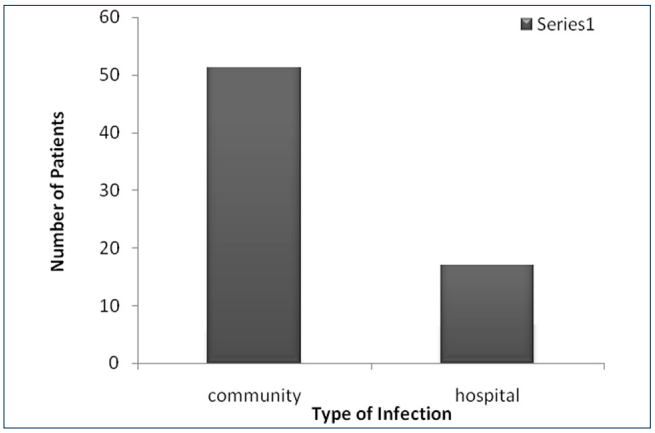

Figure 1: Number of patients by type of infection

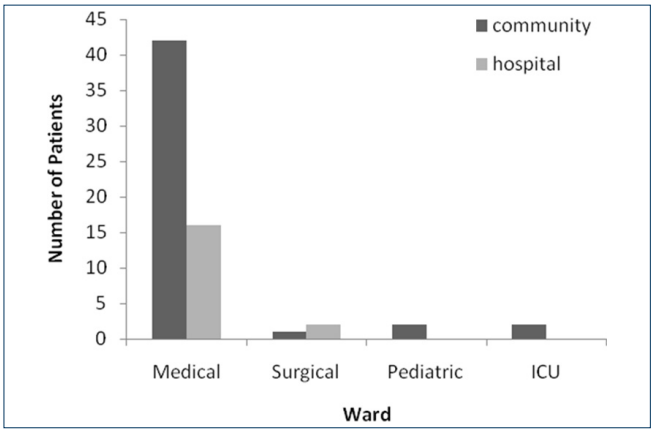

Figure 2: Number of patients with CA-MRSA and HA-MRSA in different wards

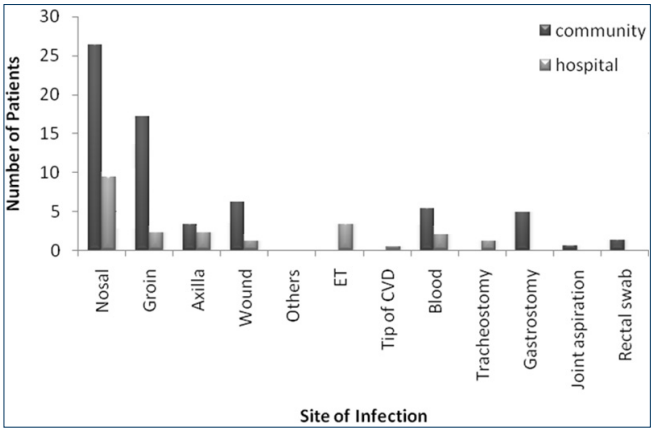

Figure 3: Number of patients with CA-MRSA and HA-MRSA by site of infection

the remaining sites, bed sore, joint, tracheostomy, and rectal swab. In some patients, more than one isolate was collected from different sites, such as nasal and groin, and sometimes with axilla or gastrostomy or wound. Some isolates were collected from nasal and wound, or from groin and gastrostomy. Some other isolates were collected from groin and axilla.

Statistically, a highly significant relationship occurred between the number of CA-MRSA patients and the different sites of infections ($P < 0.005$). However, no significant relationship occurred between the number of patients with HA-MRSA and the sites of infections.

According to age group, it was found that 58 cases (81.6%) were in the >50 years age group (the elderly), 45 (77.5%) of whom were infected with CA-MRSA and 13 (22.4%) were infected with HA-MRSA. Seven patients (9.8%) were in the 25-49 years age group, five (71.4%) of whom were infected with CA-MRSA and two (28.5%) were infected with HA-MRSA. No patients were in the 15-24 years age group. Six patients (8.4%) were in the <14 years age group, of whom three patients were CA-MRSA and the other three patients were HA-MRSA. Statistical binomial distribution showed a highly significant relationship ($P < 0.005$) between the number of patients of both CA-MRSA and HA-MRSA and the >50 years age group (the elderly), <14 years age group (infants and young children), and the 25-49 years age group. However, no significant relationship was observed between the number of patients (CA-MRSA and HA-MRSA) and the 15-24 years age group.

Regarding the period of stay at hospital, five periods were grouped in this study: 60 patients (84.5%) were in the <3 months group, 47 (78.3%) of whom were CA-MRSA and 13 (21.6%) were HA-MRSA. Four patients (5.6%) were in the 3-6 months period, and one (1.4%) belonged to the group 6-9 months; no patients belonged to the 9-12 months group and one patient (1.4%) belonged to the >12 months group [Figure 4]. Finally, poor statistical significance was found between the number of patients with CA-MRSA and HA-MRSA and the period of hospitalization.

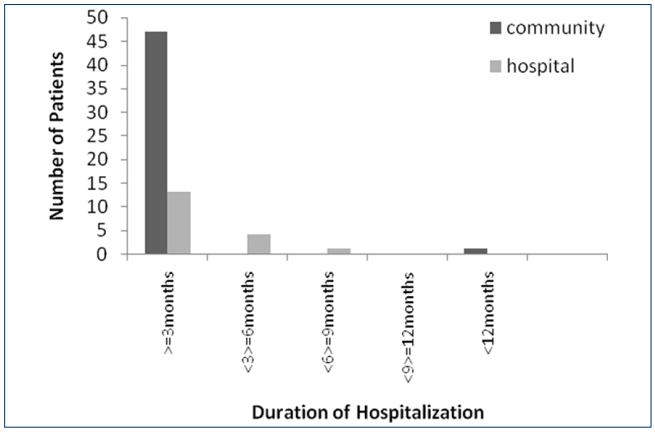

Figure 4: Number of patients with CA-MRSA and HA-MRSA by duration of hospitalization

Antibiotic susceptibility results indicate that a group of antibiotics was used: 29 patients (40.8%) were given mupirocin local skin antibiotics, 11 patients (15.4%) were given meronem (meropenem) antibiotics, and 7 patients (9.8%) were given vancomycin. Five patients (7%) received teicolplanin intravenously. Other antibiotics were subsequently used for treatment, such as clindamycin, piperacillin, linezolid, ceftzidine, fluconazole, fucidine, amikacin, and rociphin. Five patients (7%) received the antibiotic tazocin, which is a combination of tazobactum and piperacillin. HA-MRSA patients were found to have more multidrug resistant characteristics than CA-MRSA patients.

DISCUSSION

The percentage of CA-MRSA in hospital units was greater than before. This is significant because professional healthcare personnel habitually move between patient care settings and hospitals, which might lead to the spread of the pathogens. Many studies reported that CA-MRSA strains are not replacing the HA-MRSA strains, but rather are adding to the problem of MRSA.[20] The coexistence of both strains and protection of CA-MRSA can occur in the hospital because of the arrival of numerous colonized and infected patients.

In the present study, it was found that the majority of patients with CA-MRSA were above 45 years old, forming about 80% of the study group. This result differs from those reported in other studies; the group of patients who had acquired CA-MRSA was commonly younger due to many causes, including the use of the same equipment in sport places. However, in Kuwait, the awareness and hygiene among these young people is very high. Some observations could be added: Risk factors could include patients with chronic diseases, high liver function, or anemia.

The present study demonstrated that 81% of MRSA isolates originated from the medical wards and 4.2% were acquired during the stay in the surgical wards. These results confirm those from the previous studies which indicate that CA-MRSA strains are now endemic in hospital environments and cause healthcare-associated infections or prevalence.[6,7,10,21,22]

Our study identified 71 cases of MRSA over a 9-month period from March to November, and confirmed 52 cases (37.2%) due to CA-MRSA and 12 cases (16.9%) due to HA-MRSA. The rate of MRSA among medical-surgical patients in the present study was 61 cases (85.9%).

CA-MRSA has different characteristics from those of HA-MRSA, including the population affected, site of infections, risk factors, transmission, and different microbiological characteristics such as some antimicrobials susceptibilities.[23] On the other hand, CA-MRSA isolates are typically susceptible to more antimicrobials than HA-MRSA isolates are, including clindamycin, trimethoprim–sulfamethoxazole, and the aminoglycosides. CA-MRSA also possesses different gene profiles, including Panton–Valentine leukocidin, which can result in increased toxicity.[24]

According to the hospital policy, the molecular tests, such as Pulse Field Gel Electrophoresis (PFGE) and sequencing, are not routinely applied until the number of concurrent MRSA infections within the ward exceeds four, which is considered an outbreak. It is essential to mention that isolates of CA-MRSA possess a novel cassette chromosome, SCCmecA type IV, which is smaller than that found in nosocomial isolates and can be transferred horizontally between isolates.[25] It is dominated by the ccrAB2 allotype, which is prevalent among emerging CA-MRSA strains compared with the less common ccrAB4 allotype.[26] The ability of CA-MRSA to transfer its SCCmecA IV gene horizontally might eventually result in the appearance of SCCmecA IV among HA-MRSA isolates, making these strains even more difficult to distinguish in the future.

Although CA-MRSA is always related to younger patients than the HA-MRSA,[27] CA-MRSA may occur in healthy persons with unusual MRSA-associated risk factors.[11] In our study, CA-MRSA showed no age limits, though it was documented mainly in the elderly and sometimes in infants. All patients had no permanent indwelling urinary catheters.

There were different criteria used to distinguish CA-MRSA from HA-MRSA. For CA-MRSA, these criteria include the diagnosis of MRSA for the outpatients by a culture positive less than 48 h after admission to the hospital, no medical history of MRSA infection or colonization, and no other medical history, such as hospitalization, admission to a nursing home, dialysis, or surgery.

In the present study, it is also observed that the majority of the patients had good socioeconomic status – almost all were socially dependent (bed ridden, partially dependent, restricted mobility). The majority of the patients were hemodynamically stable, which means they did not experience the instability indicators such as (a) low blood pressure, (b) very high heart rate, (c) feverish high temperature, or (d) hypothermic very low temperature. Patients did not have instability factors unless they have had invasive MRSA (that reached the blood stream). Some patients had concomitant sepsis, which means infection rather than MRSA, and also means that MRSA was not responsible for this instability. WBC is a sign of sepsis, but most patients had normal WBC unless with invasive MRSA. Most of the patients were anemic. Most of the patients were hypoalbuminemic (decreased albumin indicates serious disease). Malnutrition affects the immune system and leads to susceptibility to MRSA. Albumin in the presence of renal impairment might be a risk factor to increase the MRSA infections. This is in accordance with some community studies, which reported a correlation between a low serum albumin level and an increased risk of death.[28,29] In studies of other hospital settings, it has been reported that there was a relationship between serum albumin level with MRSA infections[30] and length of stay.[31] Most of the patients were diabetic (diabetes affect the function of the neutrophils and prevents them to move to engulf the MRSA, and so they stay in the same place, thereby making these patients more susceptible to MRSA infections).

Despite the partial similarities that occurred between strains of CA-MRSA and HA-MRSA, strains of CA-MRSA were more sensitive to different types of antimicrobials rather than the β-lactams, as compared to HA-MRSA strains that were more resistant in the present study. However, CA-MRSA strains were not only resistant to the commonly used antibiotics for *S. aureus* treatment, but also were observed to be more virulent, and therefore patients may suffer severe infection manifestation. The best antimicrobials used for the confirmed virulent CA-MRSA strains are mupirocin, meronem, vancomycin, and clindamycin. Some similarities have been observed with other studies that successfully used trimethoprim–sulfamethoxazole, tetracycline, or clindamycin for the treatment of CA-MRSA.[32,33]

Diabetics, young children, the elderly, intravenous drugs users, and weak immune systems were observed to be the highest risk factors in this study, which is supported by previous studies.[34] Dermatological conditions were the most common manifestations of CA-MRSA among pediatric patients, while for adults the dermatological, smoking, and diabetes conditions were the most common medical conditions.[27]

Moreover, it was observed that the majority of patients were dependent, with poor education or awareness and poor nutritional system, which could be considered as risk factors. In addition, contaminated tools or water in the physiotherapy area, as well as governmental hospital, may contribute as risk factors.

Zetola *et al.*[35] reported that CA-MRSA affects persons in jails, military staff, sporty inhabitants, male homosexuals, and ethnic populations. They also stated that CA-MRSA is related to skin and soft tissue infections, including abscesses, cellulitis, and furunculosis. In addition, severe cases were associated with septic shock, bacteremia, and necrotizing pneumonia.

CA-MRSA is easier to treat than HA-MRSA. CA-MRSA did not develop mutation in the community strain, but represents a cross mix between MRSA strains that spread from the hospital environment and strains that were easily treatable in the community. Most of the cross mix strains also acquired a factor that increases their virulence, which leads to the development of deep-tissue infections from negligible scratches and cuts, as well as many cases of fatal pneumonia.[36]

CONCLUSIONS

Information on the type of MRSA community- or healthcare-associated organism and on the place of origin of these organisms is useful for the clinical expression and for determining appropriate treatment. HA-MRSA and CA-MRSA differ clinically and biologically. MRSA strains' incidence and epidemiology are varying and have become a worldwide problem. It is important to determine the difference of these two strains to effectively prevent, treat, and handle patients. Although the center for disease control (CDC) does not recommend pre-admission screening, routine screening for MRSA upon hospital admission is still debatable. Follow-up of discharged patients to measure MRSA cultures and sensitivities is more important than ever. Screening can help reduce the incidence of MRSA in hospital admissions.

MRSA is not a new clinical disease, but the incidence continues to grow at an alarming rate. This study suggests that *S. aureus* and MRSA should become a national priority for disease control due to strains' increased resistance to many antibiotics to avoid outbreaks and also worldwide pandemics. Only avoidance and completion of the most current treatment protocols will provide an increased margin of safety. The level of serum albumin, iron deficiency anemia, and diabetes that are routinely measured at hospital admission, in addition to the period of hospital stay are predictors and risk factors to CA-MRSA infection.

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