METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN TWO TERTIARY-CARE CENTERS IN JEDDAH, SAUDI ARABIA

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ABSTRACT

OBJECTIVE: To review clinical experience with methicillin-resistant *Staphylococcus aureus* (MRSA) in tertiary-care hospitals in Jeddah, Saudi Arabia.

DESIGN: Retrospective review for the year 1998.

SETTING: Two tertiary-care hospitals.

METHODS: Results of MRSA-positive cultures of clinical specimens obtained as part of investigations for suspected infections were retrieved from the microbiology laboratories' records. Charts of patients were reviewed, with standardized data collection.

RESULTS: Of 673 *S aureus* isolates identified, 222 (33%, or 6.8 isolates/1,000 admissions) were MRSA. Overall MRSA prevalence was 2% in 1988. Nosocomial acquisition occurred in 84.2% of cases. All age groups were affected, and 52% of patients had at least one comorbidity. MRSA prevalence was highest in the intensive care units (26.6% of all isolates), the medical wards (24.8%), and the surgical wards (19.8%). Seventy-three percent of isolates caused infection; the rest represented colonization. Surgical wounds (35.2%), the chest (29%), and central venous catheters (13%) were the most common sites of infection. Bacteremia occurred in 15.4% of patients. Local signs (84%) and fever (75.9%) were the most common clinical manifestations. Respiratory distress and septic shock occurred in 30.2% and 13.6% of cases, respectively. Of 162 patients with MRSA infection and 60 patients with MRSA colonization, 95.7% and 70% received antibiotics in the preceding 6 weeks, respectively ($P<.0001$). The total mortality of patients with MRSA infection was 53.7%: 36.4% as a result of MRSA infection and 17.3% as a result of other causes.

CONCLUSIONS: The prevalence of MRSA is high and rapidly increasing in the two hospitals, as it is worldwide. Control measures to prevent the spread of MRSA in hospitals should continue, with reinforcement of hygienic precautions and development of policies to restrict the use of antibiotics (*Infect Control Hosp Epidemiol* 2001;22:211-216).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is primarily a nosocomial pathogen that emerged in the 1980s as a major cause of infection and colonization in hospitalized patients.[1] More recently, this organism has been implicated as a cause of community-acquired infections in individuals with a recognized predisposing risk factor, such as recent contact with a healthcare facility, nursing home residence, or parenteral substance abuse.[2,3] Community-acquired MRSA infections in the absence of identified risk factors also have been reported increasingly.[3-6] The prevalence of MRSA has increased worldwide over the past decade, with marked variations in different regions. It is generally high in the United States,[7] southern European countries,[8] and Japan,[9] but is low in Sweden, Denmark, and The Netherlands.[8,10,11] A high prevalence of MRSA also has been reported from Malaysia,[12] Latin America,[13] Ethiopia,[14] and other developing countries such as Kenya, Sri Lanka, and Tunisia.[15]

The prevalence of MRSA in Saudi Arabia is not well defined. This study describes the prevalence of MRSA and the demographic and clinical characteristics of patients colonized or infected with this organism for the year 1998 at King Abdulaziz University Hospital (KAUH) and King Fahd Hospital (KFH), Jeddah, Saudi Arabia.

METHODS

Institutions and Patient Population

KAUH is a tertiary-care teaching hospital with 265 beds and 18,492 admissions in 1998, the time of this retrospective review. From 1978 to 1996, the hospital was run in temporary buildings. In late 1996, the hospital was moved to permanent buildings. The hemodialysis unit at KAUH was not opened during the study period, and there is as yet no burn unit at this hospital. KFH is a Ministry of Health hospital. In 1998, it had 1,030 beds and 13,953 admissions. KFH has a burn unit and a hemodialysis unit. There is no pediatrics service at KFH, and thus children are not admitted to this hospital except for cases that need special surgical interventions such as cardiac surgery or catheterization or orthopedic surgery. Patients with MRSA-positive cul-

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tures from any body specimen were identified in the two hospitals from January 1, 1998, to December 31, 1998, for this review.

Data Collection

During the study period, specimens for bacterial culture were obtained as part of a septic screen for suspected infections. Surveillance cultures specific for MRSA colonization were not done during this period. All MRSA-positive culture results were obtained from the microbiology laboratories' records. Charts of all patients with these positive cultures were reviewed, with standardized data collection. Information collected included patient demographics, locale of acquisition (nosocomial or community), hospital units where patients stayed, comorbidities, surgery and other invasive procedures, presence of foreign devices, antibiotic use, previous hospitalization, clinical significance of MRSA (colonization vs infection), site and clinical manifestations of infections, complications, and outcome. There was no transfer of any MRSA-positive patients between the two hospitals.

Microbiological Methods

S aureus was identified using routine bacteriological procedures. Susceptibility testing of *S aureus* isolates to oxacillin was performed using the 1-µg oxacillin disk-diffusion method (Oxoid Limited; Basingstoke, Hampshire, England, for KAUH; Mast Diagnostics; Mast Group Ltd, Merseyside, UK, for KFH) according to published guidelines.[16] Oxacillin resistance was demonstrated by a zone of inhibition of 10 mm or less. Strains with a borderline zone of inhibition (11-12 mm) were tested by E-test (AB Biodisk; Dalvagen, Solna, Sweden) to determine the minimum inhibitory concentration (MIC). Strains with MICs of 4 µg/mL or greater were considered resistant; 2 µg/mL or less, sensitive; and between 2 and 4 µg/mL, intermediate.[17] Susceptibility testing to other antibiotics was not performed routinely.

Definitions

MRSA isolates were considered community isolates if they were recovered within 72 hours of admission and nosocomial if they were recovered beyond that period.

The clinical significance of MRSA isolation from different body specimens was classified into either infection or colonization, based on the presence or absence of a potential source of MRSA infection, the patient's clinical status, and other relevant data. In the absence of any potential source or clinical evidence of infection, MRSA was considered to be colonizing the site from which a specimen was obtained.

The source of infection was determined on the basis of clinical evidence and recovery of MRSA from an infected site.

Outcome of patients with MRSA infection was classified into four categories: recovery without complications, recovery following complications such as septic shock or respiratory failure, death due to MRSA infection, or death unrelated to MRSA infection.

Data Analysis

The Statistical Package for Social Science (SPSS) program (release 7.5.1; SPSS Inc, Chicago, IL, 1996) was used for data analysis. The chi-square test was used for comparison of proportions.

RESULTS

The total number of *S aureus* isolates during the study period was 673, of which 222 (33%) were MRSA isolated from 222 patients, representing 6.8 (222/32,445×1,000) MRSA isolates per 1,000 admissions. Thirty-five isolates (15.8%) were community isolates, and 187 isolates (84.2%) were nosocomial. Table 1 shows the epidemiological and clinical characteristics of patients with MRSA colonization or infection in the two hospitals. One hundred forty-six patients (65.8%) were males, and 76 (34.2%) were females; mean age was 39.1±23.9 years. Fifty-eight patients (26.1%) were 60 years of age or older, and at KAUH, 29 patients (26.1%) were 1 year old or younger. One hundred twenty-nine patients (58.1%) were Saudi citizens, and 93 (41.9%) were non-Saudi. A total of 88 patients (39.6%) had one comorbidity, 27 patients (12.2%) had two comorbidities, and the remaining 107 patients (48.2%) had no comorbidity. Comorbidities included diabetes mellitus (63 patients, 28.4%), malignancy (20 patients, 9%), end-stage renal failure (20 patients, 9%), cerebrovascular accidents (19 patients, 8.6%), chronic obstructive pulmonary disease (10 patients, 4.5%), heart failure (9 patients, 4.1%), and human immunodeficiency virus infection (3 patients, 1.4%).

The clinical features and outcome of MRSA infections at the two hospitals are shown in Table 2. MRSA caused infection in 162 (73%) cases, and in the remaining 60 (27%) patients, it represented colonization. The sites of MRSA infection included surgical-wound infections (57 patients, 35.2%), pneumonia (47 patients, 29%), central venous catheter infections (21 patients, 13%), urinary tract infections (13 patients, 8%), and peripheral venous catheter infections (11 patients, 6.8%). Bacteremia occurred in 25 patients (15.4%). Local signs (136 patients, 84%) such as erythema, purulent discharge or tenderness of wounds or intravenous catheters' sites, and fever (123 patients, 75.9%) were the most common clinical manifestations of MRSA infection. Respiratory distress and septic shock occurred in 49 (30.2%) and 22 (13.6%) patients, respectively. Of 162 patients with MRSA infection and 60 patients with MRSA colonization, 155 (95.7%) and 42 (70%) received antibiotics in the preceding 6 weeks, respectively (odds ratio, 9.5; 95% confidence interval, 3.5-27; $P<.001$).

A total of 75 (46.3%) of 162 patients with MRSA infections completely recovered from their infections; 48 (29.6%) had uneventful recovery, whereas the remaining 27 (16.7%) recovered following complications such as septic shock or respiratory failure requiring mechanical ventilation. The total mortality of patients with MRSA infection was 53.7% (87/162); 36.4% (59/162) died as a result of MRSA infection, and 17.3% (28/162) as a result of other diseases (Table 2).

The demographic, epidemiological, and clinical characteristics of patients in the two hospitals were comparable

TABLE 1
EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF PATIENTS WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONIZATION OR INFECTION AT TWO TERTIARY-CARE CENTERS, JEDDAH, SAUDI ARABIA

Variable	KAUH	KFH
Patients	111	111
Number of admissions in 1998	18,492	13,953
Number of *Staphylococcus aureus* isolates	292	381
Number of MRSA isolates (% of *S aureus)*	111 (38.0)	111 (29.1)
Prevalence of MRSA per 1,000 admissions	6.0	8.0
Age		
≤1 y	29	1
>1-15 y	8	10
16-30 y	19	18
31-45 y	20	22
46-59 y	13	24
≥60 y	22	36
Gender, no. (%)		
Male	65 (58.6)	81 (73.0)*
Female	46 (41.4)	30 (27.0)
Nationality, no. (%)		
Saudi	53 (47.7)	76 (68.5)†
Non-Saudi	58 (52.3)	35 (31.5)
Patients with comorbidities, no. (%)		
No comorbidity	58 (52.3)	49 (44.1)
One comorbidity	39 (35.1)	49 (44.1)
Two comorbidities	14 (12.6)	13 (11.7)
Comorbidities, no. (%)		
Diabetes mellitus	24 (21.6)	39 (35.1)*
Malignancy	12 (10.8)	8 (7.2)
End-stage renal failure	10 (9.0)	10 (9.0)
Cerebrovascular accident	8 (7.2)	11 (9.9)
Heart failure	7 (6.3)	2 (1.8)
COPD	5 (4.5)	5 (4.5)
HIV	2 (1.8)	1 (0.9)
Acquisition, no. (%)		
Nosocomial	83 (74.8)	104 (93.7)†
Community	28 (25.2)	7 (6.3)
Clinical significance, no. (%)		
Infection	74 (66.7)	88 (79.3)*
Colonization	37 (33.3)	23 (20.7)
Unit of stay, no. (%)		
ICU	12.8 (10.8)	47 (42.3)‡
Medical ward	30 (27.0)	25 (22.5)
Surgical ward	19 (17.1)	25 (22.5)
Pediatrics	23 (20.7)	NA
NICU	7 (6.3)	NA
Outpatient department	20 (18.0)	10 (9.0)
Hemodialysis unit	NA	2 (1.8)
Burn unit	NA	2 (1.8)
Past history of MRSA, no. (%)	21 (18.9)	11 (9.9)
Previous hospitalization, no. (%)	20 (18.0)	10 (9.0)

Abbreviations: COPD, coronary obstructive pulmonary disorder; HIV, human immunodeficiency virus; ICU, intensive care unit; KAUH, King Abdulaziz University Hospital; KFH, King Fahd Hospital; MRSA, methicillin-resistant *Staphylococcus aureus;* NA, not applicable; NICU, neonatal intensive care unit.
* $P<.05$.
† $P<.01$.
‡ $P<.001$.

TABLE 2
CLINICAL CHARACTERISTICS AND OUTCOME OF PATIENTS WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTIONS AT TWO TERTIARY-CARE CENTERS, JEDDAH, SAUDI ARABIA

Variable	KAUH	KFH
Patients	74	88
Clinical manifestations, no. (%)		
Local signs	51 (68.9)	85 (96.6)*
Fever	45 (60.8)	78 (88.6)*
Respiratory distress	21 (28.4)	28 (31.8)
Shock	5 (6.8)	17 (19.3)†
Site of infection, no. (%)		
Central venous catheter	10 (13.5)	11 (12.5)
Peripheral venous catheter	5 (6.8)	6 (6.8)
Surgical wound	23 (31.1)	34 (38.6)
Chest	20 (27.0)	27 (30.7)
Urinary tract	3 (4.1)	10 (11.4)
Other	13 (17.6)	0
Bacteremia, no. (%)	20 (27.0)	5 (5.7)*
Outcome, no. (%)		
Recovery without complications	21 (28.4)	27 (30.7)
Recovery following complications	8 (10.8)	19 (21.6)
Death due to MRSA infection	28 (37.8)	31 (35.2)
Death due to other causes	17 (23.0)	11 (12.5)

Abbreviations: KAUH, King Abdulaziz University Hospital; KFH, King Fahd Hospital; MRSA, methicillin-resistant *Staphylococcus aureus*.
* $P<.001$.
† $P<.05$.

(Tables 1 and 2), with the following exceptions: male and Saudi patients were significantly more commonly affected at KFH than at KAUH (73% and 68.5% vs 58.6% and 47.7%, respectively; $P<.05$ and $<.01$); diabetes mellitus as a comorbidity was more common at KFH than at KAUH (35.1% vs 21.6%, respectively; $P<.05$); significantly more patients were in the intensive care unit (ICU) at KFH than at KAUH (42.3% vs 10.8%, respectively; $P<.001$); nosocomial acquisition of MRSA was significantly more common at KFH than at KAUH (93.7% vs 74.8%, respectively; $P<.001$); the prevalence of MRSA infection as opposed to colonization was more common at KFH than at KAUH (79.3% vs 66.7%, respectively; $P<.05$); local signs (96.6% vs 68.9%; $P<.001$); fever (88.6% vs 60.8%; $P<.001$), and shock (19.3% vs 6.8%; $P<.05$) were more commonly encountered at KFH than at KAUH, respectively; and bacteremia occurred more frequently at KAUH than at KFH (27% vs 5.7%, respectively; $P<.001$).

DISCUSSION

In the United States, the prevalence of MRSA increased from 2% of *S aureus* isolates in 1974 to approximately 50% in 1997.[18,19] In England and Wales, resistance to methicillin among *S aureus* isolated from blood or cerebrospinal fluid was stable at approximately 1.5% of isolates during 1989 and 1991, but increased thereafter to 13.2% in 1995.[20] Currently, in UK hospitals, prevalence of MRSA has reached epidemic levels, and incidents involving MRSA have risen 12-fold since 1991. In 1999, MRSA represented 37% of all *S aureus* infections, compared with only 3% in 1991.[21] A prevalence of more than 30% also was observed in southern European countries such as Spain, France, and Italy.[8]

This study at KAUH and KFH demonstrated a high prevalence of MRSA (33% of all *S aureus* isolates). At KAUH the prevalence gradually has increased from less than 2% in 1988 (unpublished data) to the current rate of 38%. Similarly, at KFH the prevalence increased from 15% in 1994 (unpublished data) to the current rate of 29.1%. The organism affected all age groups, with more than one fourth of patients being 60 years of age or above. At KAUH almost one half of the patients were in the "extremes of age" group ($\leq$1 or $\geq$60 years of age). There was no predilection for any gender or nationality at KAUH, whereas at KFH, male and Saudi patients were more than two times as commonly affected as female and non-Saudi patients. This male Saudi preponderance at KFH is explained by the fact that approximately three quarters of 13,953 patients admitted to KFH during the study period were Saudi men.

More than three quarters of cases were nosocomial, and the rest were community isolates. The prevalence in the ICU was 10.8% at KAUH, compared to 42.3% at KFH. The high prevalence of MRSA infection and colonization in the ICU at KFH is likely to be due to a break in the standard infection control measures.

Once confined mainly to hospitals, MRSA has been increasingly implicated in community-acquired infections

and colonization in patients with predisposing risk factors, such as recent contact with a healthcare facility, nursing home residence, or parenteral substance abuse,[2,3] as well as in patients without any recognized predisposing risk factor.[3-6] In two hospitals in the United States in the early 1990s, 28% to 67% of patients with MRSA colonization had probable community acquisition.[22,23] In five Canadian tertiary acute-care teaching hospitals in three provinces, patients with MRSA detected at admission accounted for 62% of MRSA isolations from 1990 through 1992.[5] In a US university hospital, 36 (41%) of 87 patients with MRSA had community acquisition; of these, 8 (22%) had no identified risk factors.[24] In a US pediatric hospital, 8 and 35 cases of community-acquired MRSA infections were identified in the time periods 1988 through 1990 and 1993 through 1995, respectively. One (12.5%) and 25 (71.4%) cases had no identified risk factors, respectively, and the prevalence of community-acquired MRSA without identified risk increased from 0.1 per 1,000 admissions from 1988 through 1990 to 2.6 per 1,000 admissions from 1993 through 1995.[6] The prevalence of community isolates of MRSA in our study (15.8% of all MRSA isolates, or 1.1/1,000 admissions) is moderately high when compared to published data. These studies, collectively, indicate that MRSA now may be more widespread in the general population than has been appreciated previously.

Risk factors that have been associated with MRSA acquisition include older age, prolonged hospitalization, prior antibiotic therapy, more severe underlying disease and degree of disability, surgical procedures, presence in an ICU or burn unit, having a surgical-wound infection, intravascular devices, mechanical ventilation, tracheostomy, pressure ulcers, or exposure to other infected or colonized individuals.[1,25,26] Not only does antibiotic therapy predispose to colonization with MRSA, but it also increases the risk of invasive disease and infection, as demonstrated by this study where significantly more patients with MRSA infection than those with MRSA colonization received antibiotics prior to positive MRSA culture (95.7% vs 70%; $P<.001$). Other host factors associated with progression from colonization to infection include recent prior hospitalization, preceding surgery or wound debridement, and the number of invasive procedures.[27]

Approximately three quarters of cases represented infection, and the remainder represented colonization. This high infection-to-colonization ratio has been observed by other researchers. For instance, in an American MRSA outbreak, 260 (90.9%) of 286 affected patients were infected and not simply colonized.[28] Healthcare facilities that routinely perform MRSA surveillance cultures, which were not undertaken in either center during this study period, obviously have substantially lower infection-to-colonization ratios due to detection of more colonized patients. Therefore, this information is essential for appropriate comparison of MRSA prevalence and infection-to-colonization ratios of different centers.

Bacteremia and septic shock occurred in 15.4% and 13.6% of cases with MRSA infections, respectively. The total mortality of patients with MRSA infections was high (53.7%), as was the mortality attributable to MRSA infection (36.4%). It was generally believed that MRSA strains are not more virulent than methicillin-susceptible (MSSA) strains.[19,29,30] Recent reports, however, have suggested that MRSA bacteremia was associated with a significantly higher mortality rate than MSSA bacteremia.[31,32] For instance, Romero-Vivas et al compared 100 cases of MSSA bacteremia and 84 cases of MRSA bacteremia; the mortality rates were 32% and 58.3%, respectively ($P<.01$), and methicillin resistance was found to be associated independently with mortality.[31]

Vancomycin has been the drug of choice for MRSA infections for the past 2 decades. Recent reports, however, described strains of MRSA that were intermediately resistant to glycopeptides (glycopeptide-intermediate *S aureus* [GISA]) and that were associated with therapeutic failure of vancomycin. Such strains have been reported from Japan,[33,34] the United States,[35] Europe (France, the United Kingdom, and Spain), and the Far East (Hong Kong and Korea).[36] The isolates from the United States, France, and strain Mu50 from Japan appear to have developed from preexisting MRSA infections.[36] The isolation of such strains from several parts of the world suggests that GISA will continue to emerge worldwide, portending the emergence of MRSA strains for which there will be no effective therapy, a situation similar to that in the pre-antibiotic era.

In conclusion, the prevalence of MRSA is high and rapidly increasing in the two tertiary-care centers in Jeddah, Saudi Arabia, as it is worldwide. One can foresee a time in the near future when the majority of *S aureus* isolates would be resistant to methicillin, as happened with penicillin, to which most isolates of *S aureus* now are currently resistant. Spread of vancomycin resistance among MRSA is also fearfully expected. Attempts to control the spread of MRSA in hospitals therefore should continue, with reinforcement of hygienic precautions and infection control measures.[37] Hospitals also should develop policies to restrict the use of antibiotics and establish monitoring systems for rapid identification of epidemics and determination of factors responsible for spread and colonization, to allow for a more targeted approach.

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New Agents Cause Nosocomial Fungemia

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The primary cause of nosocomial fungemia has been *Candida* species, but increasingly molds and other yeasts are being implicated in disease. *Exophiala jeanselmei* and members of the genus *Rhinocladiella* are dematiaceous molds, which have been associated infrequently with systemic infection and have not been described as causes of fungemia. Nucci and coinvestigators from Hospital Universitario Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil, recently reported the occurrence of 23 cases of fungemia due to these organisms over a 10-month period. They also describe the clinical characteristics of patients and outcomes.

The majority of patients were immunosuppressed; 21 (91%) of 23 had received blood products, and 78% had a central venous catheter. All patients had at least one manifestation of fever, but only 1 patient had signs or symptoms suggesting deep-seated infection. Antifungal therapy was given to 19 of the 23 patients; of those who did not receive therapy, 3 died prior to the culture result, and 1 had been discharged without therapy.

Antifungal susceptibility of the organisms showed activity of amphotericin B, itraconazole, and the new triazole antifungals voriconazole and posaconazole. *E jeanselmei* and *Rhinocladiella* species are potential causes of nosocomial fungemia and may be associated with systemic infection.

FROM: Nucci M, Akiti T, Barreiros G, Silveira F, Revankar SG, Sutton DA, et al. Nosocomial fungemia due to *Exophiala jeanselmei* var. *jeanselmei* and a *Rhinocladiella* species: newly described causes of bloodstream infection. *J Clin Microbiol* 2001;39:514-518.