Characteristics and risk factors of hospital acquired — Methicillin-resistant Staphylococcus aureus (HA-MRSA) infection of pediatric patients in a tertiary care hospital in Riyadh, Saudi Arabia

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KEYWORDS
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Abstract  Background and objectives: The prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infections has been steadily increasing. These infections are considered to be either hospital-acquired MRSA (HA-MRSA) or community-acquired MRSA (CA-MRSA). Children are at higher risk of infection than adults. HA-MRSA has been reported to have more serious outcomes than CA-MRSA. However, there are not enough studies in Saudi Arabia to study the characteristics of HA-MRSA in children. We aim to describe the characteristics of HA-MRSA infection, including risk factors, culture site, clinical manifestations, complications, and outcomes among pediatric patients in a tertiary care hospital in Riyadh, Saudi Arabia.

Patients and settings: This is a retrospective chart review study. It was conducted in King Abdulaziz Medical City in Riyadh.

Patients and methods: The study included all patients 14 years of age or younger who were culture-positive from any site in the body during the period from January 1, 2009 to December 31, 2011. The time of culture compared to admission time was used to differentiate between CA-MRSA (within 72 h of admission) and HA-MRSA (more than 72 h after admission). The final sample size was 39 patients.

Results: We found HA-MRSA to be more common in males and those with risk factors such as previous surgery and previous hospitalization. Patients had a high Pediatric intensive care unit (PICU) admission rate and were commonly septic with positive blood cultures. Seventy-four percent of patients fully recovered, 10% recovered with complications and 15% died.
1. Introduction

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection has been steadily increasing. This has coincided with an increase in the number of patients presenting with serious invasive disease due to MRSA [1,2]. The causative organisms are defined as *Staphylococcus aureus* strains with an oxacillin minimum inhibitory concentration (MIC) of at least 4 mcg/mL. MRSA is resistant to all beta-lactam agents, including cephalosporins (with the exception of ceftobiprole) [3]. Its resistance is derived from the mecA gene encoding for the low-affinity binding protein PBP-2a, which allows the organism to grow and divide in the presence of methicillin and other beta-lactam antibiotics [4,5]. Due to its high resistance to previously mentioned antibiotics and the appearance of new strains, MRSA infection has become an increasing medical challenge [6–9]. Infections caused by MRSA have been classified as either nosocomial (hospital acquired) or community acquired [2,8,10]. Infection is considered to be HA-MRSA if positive cultures result from samples drawn after 72 h of admission. Cases considered CA-MRSA include those in which positive cultures have been drawn outside the hospital or drawn within 72 h of admission or in cases in which MRSA was diagnosed in an outpatient setting [8,11,12].

Although MRSA infection rates are not significant in countries such as the Netherlands, Denmark, and Sweden [13,14], the threat has increased significantly in many other countries, such as the USA and Western European countries such as Great Britain, in which MRSA infection has become an epidemic [11,12,14,15]. Furthermore, some Middle Eastern countries such as Iran have recorded high numbers of MRSA infections [16]. Children are at risk of acquiring MRSA infections [17–19]. The risk increases more when they have co-morbidities such as malignancies, recent surgeries, autoimmune diseases, previous antibiotic usage, and long-term hospitalization, with resultant exposure to potentially more dangerous strains of HA-MRSA [17,19–21]. Moreover, the threat of MRSA infection has increased in children and has manifested more frequently in neonates and in countries such as the U.S [22,23]. Risk factors for children are the same as for adults, with the addition of genetic diseases such as cystic fibrosis and congenital immunodeficiencies [17,20,24].

The first report of MRSA in Saudi Arabia was published in 1994 by Zaman in the western region in Jeddah. Over a period of three years covering Zaman’s report, he found that 7.5% of all *Staphylococcus aureus* infections were MRSA positive [25]. Thereafter, a few reports followed from Madani and others in 2002 in the setting of two tertiary care centers in Saudi Arabia. The studies included patients from adult and pediatric wards (both medical and surgical). They found that 33% of all *Staphylococcus aureus* cultured patients were MRSA positive [11,12]. Despite these data, studies describing MRSA infections in the pediatric population in Saudi Arabia remain limited in number. Only one study [18] exclusively described pediatric MRSA infections in Saudi Arabia. Bukhari et al investigated 80 previously healthy pediatric patients with community acquired MRSA infection and found that 6% (five patients) had invasive CA-MRSA with serious complications that included osteomyelitis, deep vein thrombosis, and subdural empyema [18].

The growing risk of MRSA was reported by Bukhari and Abdelhadi from King Fahd University Hospital in Dammam, Saudi Arabia in a study showing that the prevalence of CA-MRSA infections increased from 9.9 per 10,000 admissions in 2001 to 67 per 10,000 admissions in 2008 [8,13].

Rates of MRSA infection are increasing among the Saudi population, including children. The data on pediatric HA-MRSA are limited, but signs indicate that it is also becoming more frequent [2,6–8,11–13,18,26,27]. These data demonstrate that MRSA infection in the pediatric population needs to be studied further. The aim of this study is to describe characteristics of pediatric HA-MRSA infection in a tertiary care hospital in King Abdulaziz Medical City, Riyadh, Saudi Arabia, and determine possible risk factors, in hope that it will add to the body of knowledge on this important infection in this region.

2. Patients and methods

This is a case series retrospective chart review study that was conducted at King Abdulaziz Medical City in Riyadh, a tertiary care center with approximately 1000 beds. It included all patients who were 14 years of age or younger with a documented culture of MRSA from any site of the body between January 2009 and December 2011. Data on patients with MRSA were retrieved from the database of the Infection Prevention and Control Department at our institution, which performs approximately 900 polymerase chain reaction (PCR) screenings per month. The MRSA policy at KAMC-Riyadh is to screen all patients who are:

- Admitted to the Pediatric intensive care unit (PICU).
- Transferred from another hospital or treated in another hospital within the last six months.
- Undergoing cardiac, orthopedic (including spine) surgery, preoperatively.
• Hemodialysis patients on admission for the first dialysis treatment and for placement of any type of vascular access (i.e.: AV-fistula, permanent catheter, graft, or port access device).
• Patients on continuous ambulatory peritoneal dialysis treatment for the first time when scheduled for catheter placement.
• Known to be previously MRSA positive.
• Roommates of MRSA-positive patients not on isolation precautions.

The sites to screen include:

• Anterior nares.
• Non-intact skin areas (e.g., tracheostomy, pressure sores, or surgical wounds).
• The groin and axillae of neonates and pediatric patients awaiting liver or cardiac surgery.

Presentations of MRSA infection that were included in the study were abscess, signs of shock (hypotension, tachycardia, etc.), discharge from any site of the body, fever, respiratory distress, localized swelling, etc. We considered only the first isolate of bacterial culture results. The time of culture was used to differentiate between CA-MRSA (less than 72 h of admission) and HA-MRSA (more than 72 h after admission). Patient data including age, gender, nationality, risk factors, clinical manifestation, culture site, unit of stay, diagnosis, and outcome were retrieved from patient charts into the data collection sheet. Data were then entered and analyzed using a software statistical package (SPSS version 20). Outcomes were divided into favorable (complete recovery) and unfavorable (recovery with complications or death). Patient confidentiality during data collection and entry was ensured using a coding system that prevented disclosure of names or medical record numbers. Statistical methods used to obtain our objectives included the mean, median, standard deviation, minimum, maximum age, and Chi-Square for categorical data. The results were then transferred to Microsoft Office Excel 2007 to create several charts and diagrams (Table 1, Figs. 1–7).

3. Results

Two hundred patients were documented to have MRSA infection. After analyzing the data, we found that nearly one-quarter (22%, 39 patients) of MRSA-infected patients had HA-MRSA. The majority of patients in our study were males (59%, 23 patients), with 40% females (16 patients) (Table 1). The majority of our sample were Saudis (95%, 37 patients) (Table 1). We categorized the pediatric population studied into three age groups (below one year, between one and five years, and more than five years). Nearly half of the patients were below one year old (46%, 18 patients), with 26% (11 patients) between one and five years, and 28% (10 patients) above five years of age (Table 1). The mean age was 3.1 years of age, with a maximum of 12 years and a minimum of nine days. Most of our population had previous surgery (31%, 12 patients), previous hospitalization (26%, 10 patients), or a cardiac anomaly (23%, nine patients) (Fig. 1). Other co-morbidities included conditions such as asthma, burns, renal failure, or metabolic diseases (Fig. 1). 59% (23 patients) presented with fever. 38% (15 patients) presented with skin and soft tissue infection (SSTI) manifestations. And 23% (9 patients) presented with abscess (Fig. 2). Shock manifestations (hypotension, tachycardia, etc.) were found in 21% (8 patients) (Fig. 2). In 19 infected patients (52%), the site of HA-MRSA isolation was blood in 31% (12 patients), skin and soft tissue in 13% (4 patients), and bone or joint in 8% (3 patients) (Fig. 3). Other less frequently reported sites among our study population included CSF and lumbar drain catheter in two patients (5%) and tip of central venous catheter in one patient (3%) (Fig. 3). We found that 12 patients (31%) were admitted to the PICU, 10 patients (26%) were admitted to the pediatric ward, and five patients each (13% each) were admitted to the burn unit, NICU and cardiac CCU (Fig. 4). Twelve patients (31%) were diagnosed with septicemia, seven patients (18%) had pneumonia, and six patients (15%) had cellulitis (Fig. 5). We attempted to correlate the time of year with the rate of infection, but we were unable to establish a relationship. Twenty-nine (74%) of the studied patients fully recovered (Fig. 6). Among the remaining patients (10%, four patients) recovered with complications such as vision impairment, and six patients (15%) died (Fig. 6). We tried to find an association between unfavorable outcomes and co-morbidities associated with HA-MRSA infection and found that unfavorable outcomes were associated with chronic pulmonary diseases such as asthma (P-Value = .03) (Fig. 7). Eighty percent of patients with unfavorable outcomes (eight patients) required PICU care and presented with shock manifestations and/or SSTI manifestations.

4. Discussion

The threat of MRSA infection has been increasing on a national and global basis [2,23]. MRSA infections are considered to be HA-MRSA if positive culture samples are drawn after 72 h of admission. Cases of CA-MRSA infection include patients from whom cultures have been withdrawn outside the hospital or for whom diagnosis occurred in an outpatient setting [8,11,12]. The epidemiological characteristics of HA-MRSA infections vary among geographic regions and from one year to another. A recently published study conducted in Pennsylvania by Casy et al indicated that

| Table 1 Patient demographics (n = 39) |
|--------------------------------------|
| Age category | Number | Percent |
| Up to 1 year | 18 | 46% |
| 1 to 5 years | 11 | 28% |
| 5 to 12 years | 10 | 26% |
| Gender | | |
| Male | 23 | 59% |
| Female | 16 | 41% |
| Nationality | | |
| Saudi | 37 | 95% |
| Non-Saudi | 2 | 5% |
Fig. 1  Comorbidities and associated risk factors.

Fig. 2  Clinical presentation (n = 39).

Fig. 3  Site of isolation (n = 39).

Fig. 4  Unit of stay (n = 39).

Fig. 5  Presenting diagnosis (n = 39).
between 2001 and 2010, the annual incidence of HA-MRSA has increased by 7% [28]. We tried to compare some of our research results to other studies conducted at a similar time in other regions. We found that the risk of acquiring HA-MRSA increased with younger age, with a median age of 3.1 years. The finding was correlated with a study conducted in Minnesota, USA, where the mean age of infection was 2.4 years [29].

We found that patients under one year of age had the highest rate of admission due to HA-MRSA (46%, 18 patients) (Table 1). This concurred with the findings of a study conducted by Gutierrez and others in California, USA, indicating that from 1985 to 2009, those under one year of age had a higher hospitalization rate than did children 1–2 years of age (OR 5.6) [23].

The PICU had the highest rate of admission in our study (31% (12 patients) (Fig. 4). This correlated with results of an MRSA review study conducted at Johns Hopkins Hospital in the United States by David MZ et al. This study found that from 2007 to 2008, 6% (72/1674) of patients in their PICU had MRSA colonization [30].

A 2013 study conducted in Pakistan to investigate nasal colonization among septicemia patients found that nasal screening for MRSA colonization can be helpful in determining the cause of septicemia. The same study detected MRSA infections in 100% of those on dialysis or with surgical site infections [31]. We reported that septicemia (31%, 12 patients) and pneumonia (18%, seven patients) were among the most common consequences of HA-MRSA infection in our study (Fig. 5). Similarly, a 2013 study from China by Wu X et al reported that children who acquired HA-MRSA had an aggressive infection course associated most frequently with pneumonia and septicemia. However, the same study indicated that CNS infections were common, whereas in our study, it was rare (6%, two patients) (Fig. 5) [32]. We did not find a correlation between time of year and infection rates in our study. In contrast, a study conducted in the USA to investigate the epidemiological change of MRSA infections found that the infection frequency was highest between the months of June to October. The same study reported that rates of blood stream and pneumonia-related admissions had not changed compared to data they had collected previously. Additionally, most patients in the study had strains of HA-MRSA [33]. Another study, conducted by Leonard M. Mermel et al, reported that children exhibited a seasonal pattern of HA-MRSA infection, whereas adult infections exhibited no such seasonality [34].

We think that the spread of nosocomial can be reduced or even eliminated by implementing and enhancing general infection control and prevention measures, including hand hygiene. Pereira et al published results of a 2014 study that was conducted in Botucatu, Brazil which concluded that improving hygiene practices in high risk areas such as the PICU and NICU would help to prevent infection [35].

5. Conclusion

HA-MRSA is a serious infection with variable epidemiology that presents the need for further investigation within this geographic region. Young children and children with risk factors, especially those involving pulmonary disease, tend
to have worse prognoses than those who do not. HA-MRSA is responsible for a high number of PICU and NICU admissions. It has been shown in our study to cause serious complications and adverse outcomes, especially for those who require PICU admission. This study emphasizes the need for surveillance of patients who are admitted with HA-MRSA infection. Strict Infection control measures must always be observed when interacting with patients who may be infected with HA-MRSA.

Conflict of interest

None.

References

[1] Gravenkemper CF, Brodie JL, Kirby WM. Resistance of coagulase-positive Staphylococci to methicillin and oxacillin. J Bacteriol 1965 Apr;89:1005–10.
[2] Bukhari HA. Increasing threat of community-acquired methicillin-resistant Staphylococcus aureus. Am J Med Sci 2010 Nov;340(5):378–81.
[3] Swenson JM, Williams PP, Killgore G, O’Hara CM, Tenover FC. Performance of eight methods, including two new rapid methods, for detection of oxacillin resistance in a challenge set of Staphylococcus aureus organisms. J Clin Microbiol 2001 Oct;39(10):3785–8 [Evaluation Studies].
[4] Crisostomo MI, Westh H, Tomasz A, Chung M, Oliveira DC, de Lencastre H. The evolution of methicillin resistance in Staphylococcus aureus: similarity of genetic backgrounds in historically early methicillin-susceptible and -resistant isolates and contemporary epidemic clones. Proc Natl Acad Sci U S A 2001 Aug 14;98(17):9865–70 [Comparative Study Article, Historical Article Research Support, Research Support, Non-U.S. Gov’t Research Support, 2001 Research Support, U.S. Gov’t, P.H.S.].
[5] Enright MC, Robinson DA, Randel G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). Proc Natl Acad Sci U S A 2002 May 28;99(11):7687–92 [Research Support, Non-U.S. Gov’t].
[6] Baddour MM, Abuelheir MM, Fatani AJ. Trends in antibiotic susceptibility patterns and epidemiology of MRSA isolates from several hospitals in Riyadh. Saudi Arabia Ann Clin Microbiol Antimicrob 2006;5:30 [Research Support, Non-U.S. Gov’t].
[7] Baddour MM, Abuelheir MM, Fatani AJ, Bohol MF, Al-Ahdal MN. Molecular epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) isolates from major hospitals in Riyadh. Saudi Arabia Can J Microbiol 2007 Aug;53(8):931–6 [Research Support, Non-U.S. Gov’t].
[8] Bukhari HA. A review of community-acquired methicillin-resistant Staphylococcus aureus for primary care physicians. J Fam Community Med 2010 Sep;17(3):117–20.
[9] Escobar JA, Marquez-Ortiz RA, Alvarez-Olmos MI, Leal AL, Castro BE, Vanegas N. Detection of a new community genotype methicillin-resistant Staphylococcus aureus clone that is unrelated to the USA300 clone and that causes pediatric infections in Colombia. J Clin Microbiol 2013 Feb;51(2):661–4.
[10] Christina R, Hermos RS, Hsiang Michelle, Chambers Henry F, Pan Erica. Epidemiology of community-associated methicillin-resistant Staphylococcus aureus in San Francisco children. J Pediatr Infect Dis 2009;4(3):247–59.
[11] Madani TA, Al-Abdullah NA, Al-Sanousi AA, Ghabrah TM, Afandi SZ, Bajunid HA. Methicillin-resistant Staphylococcus aureus in two tertiary-care centers in Jeddah, Saudi Arabia. Infect Control Hosp Epidemiol 2001 Apr;22(4):211–6.
[12] Madani TA. Epidemiology and clinical features of methicillin-resistant Staphylococcus aureus in the university hospital, Jeddah, Saudi Arabia. Can J Infect Dis 2002 Jul;13(4):245–50.
[13] Bukhari HA, Abdelhadi MS. The epidemiology of methicillin-resistant Staphylococcus aureus at a Saudi university hospital. Microb Drug Resist 2001;7(4):413–6.
[14] Liu C, Graber CJ, Karr M, Diep BA, Basuino L, Schwartz BS, et al. A population-based study of the incidence and molecular epidemiology of methicillin-resistant Staphylococcus aureus disease in San Francisco, 2004–2005. Clin Infect Dis 2008 Jun 1;46(11):1637–46 [Research Support, U.S. Gov’t, P.H.S.].
[15] Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 2005 Apr 7;352(14):1436–44 [Research Support, U.S. Gov’t, P.H.S.].
[16] Askarian M, Zeinalzadeh A, Japoni A, Alborzi A, Memzah ZA. Prevalence of nasal carriage of methicillin-resistant Staphylococcus aureus and its antibiotic susceptibility pattern in healthcare workers at Namazi Hospital, Shiraz, Iran. Int J Infect Dis 2009 Sep;13(5):e241–7 [Research Support, Non-U.S. Gov’t].
[17] Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980–1997. Pediatrics 2000 Jul;106(1 Pt 2):205–9.
[18] Bukhari EE, Al-Otaibi FE. Severe community-acquired infection caused by methicillin-resistant Staphylococcus aureus in Saudi Arabian children. Saudi Med J 2009 Dec;30(12):1595–600.
[19] Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin-resistant Staphylococcus aureus infection in children’s hospitals in the United States. Clin Infect Dis 2009 Jul 1;49(1):65–71 [Research Support, Non-U.S. Gov’t].
[20] Glikman D, Siegel JD, David MZ, Okoro NM, Boyle-Vavra S, Dowell ML, et al. Complex molecular epidemiology of methicillin-resistant Staphylococcus aureus isolates from children with cystic fibrosis in the era of epidemic community-associated methicillin-resistant S. aureus. Chest 2008 Jun;133(6):1381–7 [Multicenter Study Research Support, Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov’t Research Support, 2008 Research Support, U.S. Gov’t, P.H.S.].
[21] Islam SI, Moore C. Prevalence of methicillin-resistant Staphylococcus aureus and associated risk factors on admission to a specialist care eye hospital. Ann Saudi Med 2002 May-Jul;22(3–4):153–7.
[22] Nelson MJ, Gallagher PG. Methicillin-resistant Staphylococcus aureus in the neonatal intensive care unit. Semin Perinatol 2012 Dec;36(6):424–30 [Research Support, N.I.H., Extramural].
[23] Gutierrez K, Halpern MS, Sarnquist C, Soni S, Arroyo AC, Maldonado Y. Staphylococcal infections in children, California, USA, 1985–2009. Emerg Infec Dis 2013 Jan;19(1):10–20. quiz 185.
[24] Lee JK, Seok JY, Lee JH, Choi EH, Phi JH, Kim SK, et al. Incidence and risk factors of ventiliculopertoneal shunt infections in children: a study of 333 consecutive shunts in 6 years. J Korean Med Sci 2012 Dec;27(12):1563–8.
[25] Zaman R, Dibb WL. Methicillin resistant Staphylococcus aureus (MRSA) isolated in Saudi Arabia: epidemiology and antimicrobial resistance patterns. J Hosp Infect 1994 Apr;26(4):297–300 [Comparative Study].
[26] Al-Tawfiq JA. Incidence and epidemiology of methicillin-resistant Staphylococcus aureus infection in a Saudi Arabian
hospital, 1999-2003. Infect Control Hosp Epidemiol 2006 Oct; 27(10):1137–9.

[27] Ahmad S, Alenzi FQ, Al-Juaid NF, Ahmed S. Prevalence and antibiotic susceptibility pattern of methicillin resistant Staphylococcus aureus at Armed Forces Hospital in Saudi Arabia. Bangladesh Med Res Counc Bull Lett 2009 Apr;35(1): 28–30.

[28] Casey JA, Cosgrove SE, Stewart WF, Pollak J, Schwartz BS. A population-based study of the epidemiology and clinical features of methicillin-resistant Staphylococcus aureus infection in Pennsylvania, 2001-2010. Epidemiol Infect 2013 Jun;141(6): 1166–79 [Research Support, N.I.H., Extramural Research Support, 2013 Research Support, Non-U.S. Gov’t].

[29] Jungk J, Como-Sabetti K, Stinchfield P, Ackerman P, Harriman K. Epidemiology of methicillin-resistant Staphylococcus aureus at a pediatric healthcare system, 1991-2003. Pediatr Infect Dis J 2007;26(4):339–44.

[30] David MZ, Daum RS. Update on epidemiology and treatment of MRSA infections in children. Curr Pediatr Rep 2013 Sep 1;1(3): 170–81.

[31] Aslam N, Izhari M, Mehdi N. Frequency of methicillin-resistant Staphylococcus aureus nasal colonization among patients suffering from methicillin resistant Staphylococcus aureus bacteraemia. Pak J Med Sci 2013 Nov;29(6):1430–2.

[32] Wu X, Wang CQ, Yan XF, Wang AM, He LY, Mi ZH, et al. [Clinical features and molecular characteristics of methicillin-resistant Staphylococcus aureus in children]. Zhonghua Er Ke Za Zhi 2013 Jul;51(7):512–7.

[33] Klein EY, Sun L, Smith DL, Laxminarayan R. The changing epidemiology of methicillin-resistant Staphylococcus aureus in the United States: a national observational study. Am J Epidemiol 2013 Apr 1;177(7):666–74 [Research Support, Non-U.S. Gov’t].

[34] Mermel LA, Machan JT, Parenteau S. Seasonality of MRSA infections. PLoS One 2011;6(3):e17925.

[35] Pereira V, Riboli D, da Cunha M. Characterization of the clonal profile of MRSA isolated in neonatal and pediatric intensive care units of a University Hospital. Ann Clin Microbiol Antimicrob 2014 Nov 7;13(1):50.