ORIGINAL ARTICLE

Eleven-Year surveillance of methicillin-resistant *Staphylococcus aureus* infections at an Academic Health Centre

SAFIYA AL MUSAWI[1], QASSIM ALKHALEEFA[2], SAMIA ALNASSRI[3], AISHA M ALAMRI[4], AMANI ALNIMR[2]
[1] Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain; [2] Department of Microbiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia; [3] Department of Infection Control, King Fahad Hospital of the University, Dammam, Kingdom of Saudi Arabia; [4] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia

Key words

Staphylococcus aureus • Infection • Methicillin-Resistant

Summary

Introduction. *Methicillin-resistant Staphylococcus aureus (MRSA) is an important human pathogen associated with nosocomial and community infections. There is a continual focus on the epidemiology of this public health threat owing to the increase in its spread and rapid development of resistance.*
Aim. *We aimed to demonstrate the time trend of antibiotic resistance by describing the epidemiology of MRSA infections at an academic health centre.*
Methodology. *We retrospectively reviewed cases during an 11-year period (from January 2009 to December 2019) with positive cultures for MRSA from various clinical sites in King Fahad Hospital of the University, to understand their clinical and microbiological profiles. Screening and colonisation samples were excluded.*
Results. *A total of 1338 MRSA isolates were identified, with an increasing trend from 5.2% to 14.5% during 2009-2019. Skin and soft tissue samples were the most common source (52.4%) of MRSA infections. Vancomycin activity remained stable against MRSA, and only one isolate showed resistance to linezolid (< 1%). A significant reduction in susceptibility to clindamycin ($p = 0.003$), trimethoprim-sulfamethoxazole ($p = 0.001$), and rifampin ($p < 0.0001$) was detected over the study period.*
Conclusions. *MRSA infections still represent a significant burden on healthcare systems. Our data support the need for constant local and regional surveillance to devise relevant protocols to manage MRSA infections. Empirical therapy needs to consider the changing antimicrobial susceptibility trends among MRSA isolates.*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of community-acquired and hospital-acquired infections worldwide [1, 2]. MRSA was first identified more than five decades ago and has since undergone epidemiologic expansion and rapid evolutionary changes, causing a wide range of infections potentially leading to sepsis and death [1, 3]. The first MRSA outbreak was described in the 1960s [4]. The Centers for Disease Control and Prevention (CDC) categorised MRSA as a 'serious threat' [1]. MRSA infections represent a major challenge to hospitals because of increased morbidity, mortality, hospital stays, and costs, as well as the emergence and spread of clones that show decreased susceptibility to a wide range of antimicrobial agents [1, 3, 5]. The increasing resistance to multiple antimicrobial agents, including glycopeptides and oxazolidinones, among MRSA strains is a healthcare concern worldwide, causing considerable difficulty in the management of staphylococcal infections [3, 6, 7].
In Saudi Arabia, the prevalence of MRSA varies among different regions [8-10]. A pooled estimation study from 2002 to 2012 showed that the prevalence of MRSA in Saudi Arabia was 35.6% [11]. A retrospective review in the western region of Saudi Arabia from 2009 to 2010 showed that the most common infections caused by MRSA were skin and soft tissue infections (87.3 %) [10]. Moreover, in another study, a greater proportion of community-acquired MRSA infections was recovered from skin and soft tissue specimens (76%) than healthcare-associated infections (58.7%) [12]. The rates of resistance to rifampin, trimethoprim-sulfamethoxazole, erythromycin, and clindamycin were variable in several studies [10, 12, 13]. However, most MRSA isolates were shown to be susceptible to vancomycin and linezolid [10, 13]. Surveillance of MRSA infections in both healthcare systems and the community is important because of the continuously changing epidemiologic and susceptibility profiles.
We aimed in this study to describe the epidemiology of MRSA infections, the antimicrobial susceptibility patterns, and to demonstrate the time trend of resistance to three agents (sulfamethoxazole-trimethoprim, clindamycin, and rifampin) in pathogenic MRSA isolates.

Methods

Study settings

This was a retrospective, cross-sectional study at King Fahad Hospital of the University (KFHU) Al-Khobar, a

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550-bed secondary care and academic training facility. Culture-positive MRSA samples representing infections, obtained from various sites between January 2009 and December 2019 in patients of all age groups, were included. Cases with clinically significant isolates were identified by reviewing electronic charts individually, eliminating screening samples for colonisation sites. Patients' data (sex, age, and location of patients when specimens were collected) and microbiological results from the laboratory information system were analyzed for the included cases. Routine testing of MRSA isolates in the laboratory was performed using the VITEK 2 automated system (bioMérieux Inc., Durham, NC, USA) between 2009 and 2016 and the VITEK MS (bioMérieux Inc.) between 2017 and 2019. Cefoxitin 30 µg discs on Muller-Hinton agar (SPML, Dammam, Saudi Arabia) were used to screen for MRSA, followed by susceptibility testing using the VITEK 2 automated system throughout the study period. The results were interpreted based on the Clinical & Laboratory Standards Institute (CLSI) breakpoints [14]. Any discrepancy between the cefoxitin inducer test and VITEK 2 system was resolved by molecular testing (GeneXpert MRSA). Patients with repeated MRSA positive culture result within 6-month period were excluded in the analysis.

Statistical analysis

Statistical analysis was performed using version 23.0 of the Statistical Package for Social Sciences (IBM Corp., Armonk, NY, USA). The Pearson chi-square test was applied to measure the proportion difference, and a p-value < 0.05 was considered statistically significant.

Results

Demographic profile

A total of 1338 MRSA isolates were included during the study period, of which 138 (10.3%) were from the intensive care unit (ICU). Demographic data of the patients are summarised in Table I. Over the 11-year study period, there was an increase in the absolute number of MRSA cases from 5.2% in 2009 to 14.5% in 2019. In 2010, there was a reduction in MRSA cases (4.8%) compared to the other years. A large proportion of the patients (n = 324, 24.2%) were aged < 1-9 years, with an overall female to male ratio of 1:1.17. Figure 1 illustrates the number of MRSA cases per sex over the study period, and Figure 2 highlights the age trend of MRSA over the years.

Distribution of MRSA in different clinical samples

Skin and soft tissue specimens were found to be the major source of MRSA cases (52.4%; n = 702) in the cohort, followed by lower respiratory specimens (15.1%; n = 203). Lower respiratory specimens were the dominant source of MRSA infections in the ICU (71.7%; n = 99). Table II shows the distribution of MRSA among the different types of clinical specimens.

Tab. I. Demographic characteristics of MRSA cases, 2009-2019.

		Number	%
Year	2009	69	5.2
	2010	64	4.8
	2011	74	5.5
	2012	104	7.8
	2013	117	8.7
	2014	115	8.6
	2015	120	9.0
	2016	124	9.3
	2017	179	13.4
	2018	178	13.3
	2019	194	14.5
Gender	Male	722	54.0
	Female	616	46.0
Nationality	Saudi	1270	94.9
	Non-Saudi	65	4.9
	Data not available	3	0.2
Age	< 1-9	324	24.2
	10-19	130	9.7
	20-29	198	14.8
	30-39	186	13.9
	40-49	144	10.7
	50-59	150	11.2
	60-69	80	5.9
	70-79	84	6.3
	≥ 80	42	3.1

Fig. 1. Gender distribution of MRSA cases, 2009-2019.

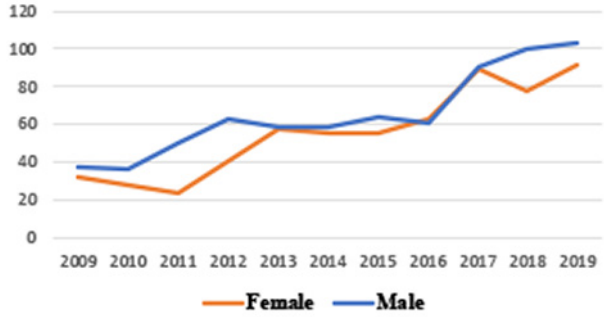
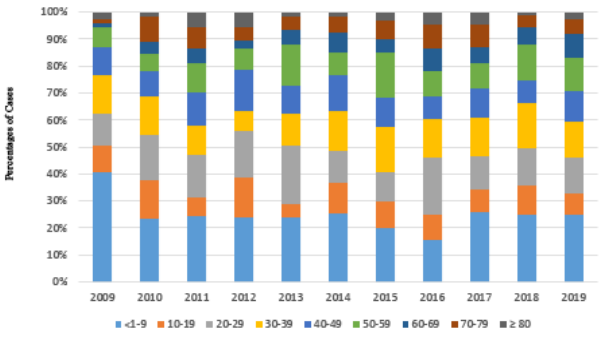


Fig. 2. Age trend of MRSA cases over 2009-2019.The columns show yearly proportions (%) of age groups.



Tab. II. Distribution of MRSA cases among the type of clinical specimen.

Type of specimen	Number	%
Skin and soft tissue	702	52.4
Lower respiratory tract	203	15.1
Ear samples	158	11.8
Blood	92	6.9
Ophthalmic	59	4.4
Tissue biopsies	50	3.7
Urine	23	1.7
Peritoneal Fluid	9	0.7
Tracheostomy	9	0.7
Umbilical cord	4	0.3
Bile	3	0.2
Pleural Fluid	3	0.2
CSF	2	0.1
Synovial Fluid	2	0.1
Others	19	1.4

Tab. III. Antimicrobial susceptibility among MRSA isolates during 2009-2019

Antibiotic	Number	%
Vancomycin	1338	100
Linezolid	1337	99.9
Rifampin	1256	93.9
Trimethoprim-sulfamethoxazole	1006	75.2
Clindamycin*	888	73.6
Erythromycin*	295	68.3

* Reported based on the site of infection

Antibiotic susceptibility pattern

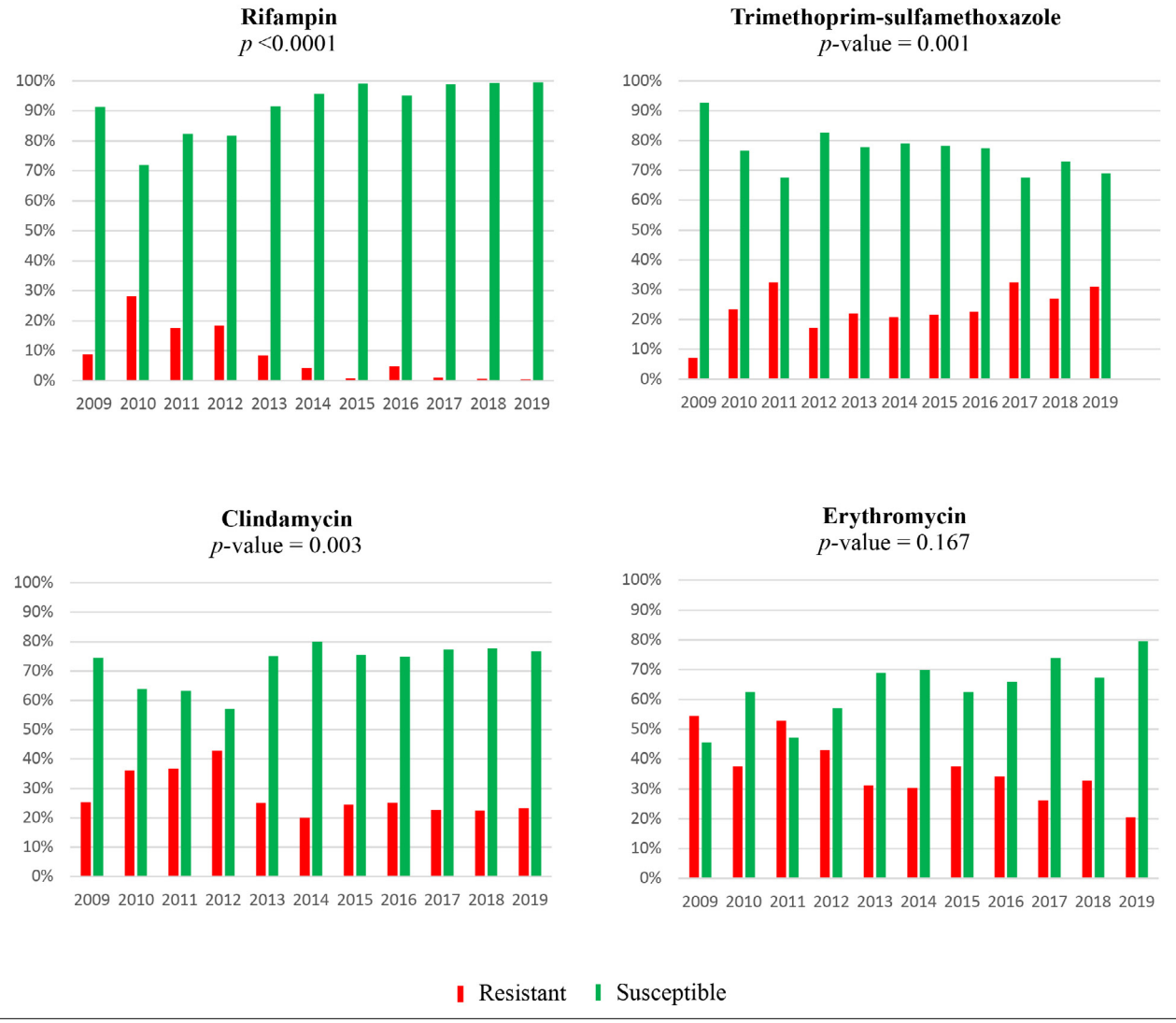
Overall, the MRSA isolates were highly susceptible to glycopeptides, oxazolidinone, and rifampin (Tab. III). In contrast, moderate susceptibility was noted for lincosamides and sulfonamides, and low sensitivity rates were noted for macrolides. The linezolid-resistant strain was isolated from an 80-year-old Filipino male patient who presented with a left forearm abscess. Confirmatory linezolid E-test was performed for this strain, which showed a minimal inhibitory concentration (MIC) > 256 µg/mL. This isolate was also resistant to clindamycin and chloramphenicol but retained susceptibility to sulphonamides. Moreover, the resistance rate to erythromycin (31.7%) was high, followed by that to clindamycin (26.4%). Of the 137 erythromycin-resistant MRSA isolates, 81%, 32.8%, and 8% were also resistant to clindamycin, trimethoprim-sulfamethoxazole, and rifampin, respectively. There was a significant reduction in clindamycin ($p = 0.003$), trimethoprim-sulfamethoxazole ($p = 0.001$), and rifampin ($p < 0.0001$) susceptibility over the years. However, no significant difference was noted in the susceptibility to erythromycin over time ($p = 0.167$) (Fig. 3).

Discussion

The global epidemiology of MRSA infection in community and healthcare settings has evolved rapidly in recent years [1-3]. In Saudi Arabia, the prevalence of MRSA varies widely, ranging from 2 to 38% [11, 15, 16] In our study, MRSA isolate numbers showed an increasing trend from 5.2% in 2009 to 14.5% in 2019. Approximately 24% of MRSA isolates in this study were from patients aged < 1-9 years. In the United States and Canada, the clinical epidemiology and molecular characteristics of MRSA infections in the paediatric age group changed dramatically between 2000 and 2010. This was owing to an epidemic of community-associated MRSA skin and soft tissue infections (SSTIs) and the introduction of the USA300 pulsed-field gel electrophoresis typing of MRSA in the health care and community settings [17]. MRSA was previously shown to be distributed differently in different age groups. In two local studies, MRSA isolates were found in the extreme age groups of patients who were ≥ 60 and ≤ 5 and ≤ 1 years old [13, 18]. Another study showed that patients aged 56 years and older had the highest prevalence of MRSA [10]. In the United States, one study found a trend of declining age over a 10-year period of observation, while another study at the same time showed that greatest increase in MRSA rate was in people aged ≤ 17 years [13, 19]. These observations clearly indicate the variations based on geographical location. Regarding gender distribution, 54% of the isolates were recovered from male patients, while 46% were from females. Other studies have also shown that MRSA isolates were recovered relatively more from males than females in Saudi Arabia [18, 20, 21].

Skin and soft tissue infections were the most common infections caused by MRSA in the present study, in concordance with the established evidence from a number of studies [10, 22-24]. In a US study conducted between 1996 and 2006, Frei et al. discovered 58,942 MRSA infection cases (9.6%) from clinical infections in the skin and soft tissue of paediatric patients [22]. As stated by the CDC, 33% of humans have *S. aureus* in their nose and approximately 2 in every 100 have MRSA. One of the main limitations of this study was that the screening and colonization samples were excluded. Despite the fact that many people are MRSA nasal carriers, the majority do not develop serious MRSA infections [25]. However, nasal and skin carriage of *S. aureus* have been reported as a potential source of infected skin and soft tissue [26, 27]. In our study, lower respiratory samples were the most common site of MRSA in the ICU, in contrast to that in other studies where blood stream infections were the most common site of ICU-related MRSA infections [28, 29]. MRSA infections of the skin and soft tissues, as well as pneumonia, may cause bloodstream infections and are linked to higher mortality rates, higher hospital costs, and longer hospital stays than infections caused by methicillin-susceptible *S. aureus* isolates [21, 30, 31]. In the current study, 6.9 % of MRSA isolates originated from the blood. MRSA bacteraemia is a serious, life-threatening infection with an estimated mortality rate of

Fig. 3. Trend of susceptibility among MRSA isolates during 2009-2019.



20-40% [32, 33]. According to the 2014 World Health Organization Antimicrobial Resistance Report, MRSA represents a widely variable proportion (20-80%) of cases of staphylococcal bacteraemia [34].

Several antimicrobial therapies are available for the treatment of MRSA infections. However, numerous publications, including the 2019 antibiotic resistance threats report by the CDC, demonstrate that MRSA has become resistant to many first-line antibiotics [2, 3, 25]. In the current study, all MRSA isolates were susceptible to vancomycin. Similar results have been reported in several other local studies [10, 23, 24]. Several countries have reported clinical strains of *S. aureus* with reduced susceptibility to vancomycin after the appearance of the first case in Japan [35-37]. In 2010, the first detected MRSA strain (D958) with reduced susceptibility to vancomycin was reported in Saudi Arabia [38]. While MRSA with reduced vancomycin susceptibility has not been identified at our institution, the unique ability of *S. aureus* to acquire resistance necessitates the use of surveillance programs to combat this problem. In the present study, in line with previous studies, one MRSA strain (0.1%) was reported to be resistant to linezolid [13, 39, 40]. The phenotype exhibited by the strain is suggestive of the rare *cfr* methyltransferase mechanism that confers resistance to erythromycin, clindamycin, chloramphenicol, and linezolid; however, this is uncertain since the isolate was not available for molecular characterisation at the time of the study. Staphylococcal resistance to linezolid is uncommon and is usually mediated by the G2576T point mutation related to the 23S rRNA binding site DOMAIN V [41]. Regarding the other antimicrobial agents, a significant reduction in the susceptibility to clindamycin, trimethoprim-sulfamethoxazole, and rifampin was noted over the years. A recently published large global surveillance study showed that these antimicrobial agents exhibited increased resistance over time, which is consistent with our findings [42]. Variations observed in the susceptibility of MRSA isolates over the years and the geographical variation and diversity in susceptibility

patterns necessitate continuous local and regional surveillance in order to devise comprehensive protocols. Although MRSA is traditionally classified as healthcare-associated (HA-MRSA) and community-associated (CA-MRSA), this classification also overlaps at the molecular and epidemiological levels [43]. Thus, the Disease Control and Prevention Active Bacterial Core (CDC-ABC) Surveillance System recommends subdividing HA-MRSA based on the setting of onset: hospital or community [44]. A limitation of our study is that we were unable to retrospectively differentiate between community-and hospital-acquired MRSA infections. A published study from Saudi Arabia showed an increasing proportion of community-acquired MRSA infections from 41.7% in 1999 to 66.6% in 2002, and reduced nosocomial MRSA infection from 33% in 1999 to 19% in 2003 [12]. According to a cross-sectional study published by KFHU from January 2010 to September 2011, SCCmec type IV was the most frequently found genotype in a total of 106 MRSA isolates from infection and carrier colonisation sites. This shows that most strains were of community origin [45].

Conclusions

With the help of the present study, we inferred that skin and soft tissue are the primary sources of MRSA at King Fahad Hospital of the University (KFHU) in Al-Khobar, Saudi Arabia. Throughout the 11-year study period, the trend of MRSA infections has increased with the emergence of new strains that showed resistance to one or more antibiotic classes. These findings highlight the need for continuous surveillance to understand microbial infections, their antibiotic resistance patterns, and to identify the emergence of new strains for successful management and control.

Ethical approval

Ethical approval for this study was obtained from the Institutional Review Board of Imam Abdulrahman Bin Faisal University (IRB-PGS-2020-01-368).

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Consent for publication

Not applicable.

Availability of data and material

Data available on request from the authors.

Conflict of interest statement

No conflict of interest to disclose that is relevant to this study.

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Authors' contributions

A.A. and S.A.L. conceived of the presented idea conceptualization. A.A. and A.M.A designed the investigational methodology. S.A.M., Q.A. and S.A.L performed the collection and formal analysis of the data. S.A.M. wrote the manuscript. A.A. and A.M.A supervised the project administration. All authors reviewed and approved the final manuscript.

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Correspondence: Amani Mansour Mohmad Alnimr, Department of Microbiology, Collage of Medicine, Imam Abdul Rahman Bin Faisal University (IAU), P.O. Box 1982, Dammam 31441, Saudi Arabia - Tel.: +966 56 318 1019 - E-mail: amalnimr@iau.edu.sa

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