

New epidemiology of *Staphylococcus aureus* infections in the Middle East

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Abstract

Staphylococcus aureus is a bacterial pathogen that is distributed worldwide and represents an increasing problem, both in hospitals and in the community. Global transmission of methicillin-resistant *S. aureus* (MRSA) has been the subject of many studies. Determining the incidence of colonization with community-acquired MRSA in hospitalized patients and outpatients has been the aim of several studies conducted in the Middle East (western Asia). The local epidemiology within countries in this region is changing, owing to the introduction of new strains with the intercontinental exchange of several clones. Sequence type 80-MRSA-IV is one common clone detected in different countries within the region showing country-based differences, and hence more likely to form clonal lineages. MRSA is endemic in this region, and the burden and the difficulty in detecting imported strains are increasing. This is also increasing the risk of domestic and global transmission. To counter the threat associated with the high incidence of MRSA carriage and infections, systematic surveillance of both hospital and community isolates is required, along with appropriate measures designed to limit their spread. Additionally, antibiotic stewardship is needed to contain the further development of the observed resistance and to help in preserving antibiotics as precious therapeutic resources. It is critical for countries in this region to establish both national and international initiatives to develop better measurements designed to limit and control the spread of infections. Finally, more sequence-based studies are needed to better understand the pathogenicity and epidemiology of these important pathogens.

Keywords: Epidemiology, methicillin-resistant *S. aureus*, Middle East, resistance, ST80-MRSA-IV

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Introduction

Staphylococcus aureus is a major human pathogen that causes a broad range of serious community-acquired and nosocomial diseases in humans, from minor skin infections to severe infections such as septicaemia [1]. The increasing prevalence of methicillin-resistant *S. aureus* (MRSA) and its ability to spread in hospitals and the community have posed a major challenge for infection control [2].

Since the introduction of methicillin for the treatment of penicillin-resistant *Staphylococcus* strains in 1959, MRSA has emerged as an important hospital-associated pathogen, because of increased morbidity and mortality rates, healthcare costs, and length of hospital stays [3,4]. Hospital-associated MRSA (HA-MRSA) infections arise in individuals with

predisposing risk factors, such as surgery or the presence of an indwelling medical device. In contrast, many community-acquired MRSA (CA-MRSA) infections arise in otherwise healthy individuals who do not have such risk factors, and are known to be epidemic in some countries [5,6]. These features suggest that CA-MRSA are more virulent and transmissible than are traditional HA-MRSA [5,6].

The epidemiology of MRSA varies considerably on a global basis, and the spread of several CA-MRSA clones and their dissemination into hospitals have made understanding the epidemiology more difficult [1]. CA-MRSA lineages are genotypically and phenotypically unrelated to multidrug-resistant HA-MRSA, and have recently started to replace the once pandemic HA-MRSA clones (clonal complex (CC)5, CC8, CC22, CC36, and CC45) in healthcare facilities [7,8]. CA-MRSA infections have been dominated by five lineages:

sequence type (ST)I-IV (USA400), ST8-IV (USA300), ST30-IV (Pacific/Oceania; South West Pacific clone), ST59-IV/IV (USA1000, Taiwan), and ST80-IV (European CA-MRSA), each being geographically restricted [6]. However, these originally continent-specific clones have spread to other parts of the world; ST1 clone USA400, for example, has been detected in Europe and Asia. Some Pantón–Valentine leukocidin (PVL)-positive clones, such as ST1 and ST30, are pandemic, having been detected in America, Europe, and Asia [5]. ST80, known as the European clone, has also been reported in Libya, Jordan, and Lebanon [9,10].

Global transmission of MRSA linked to international travel has been the subject of many studies [9–11]. However, in countries with a high prevalence of MRSA, imported cases of MRSA are not easily distinguished from the domestic background prevalence. Information about the epidemiology of MRSA in non-European countries of the south-eastern Mediterranean has been sparse. Borg *et al.* [11] collected the largest dataset on the epidemiology of MRSA in this region, and showed the significant presence of MRSA in this part of the world, with many hospitals showing evidence of endemicity. It is worth noting that healthcare in such countries is more concentrated in urban areas. The reported catchment populations can therefore be underestimated, as it is difficult to estimate the proportion of the population coming from the rural areas to a particular hospital in the city [11].

The purpose of this review is to summarize what has recently been reported about the epidemiology of CA-MRSA in the Middle East, specifically covering western Asia, and touch upon the clinical spectrum of infectious syndromes associated along with resistance patterns.

Epidemiology of MRSA in the Middle East

The incidence of patient colonization with CA-MRSA has been the aim of several studies conducted in the region. Epidemiological data on CA-MRSA carriage and infection in the Middle East are limited; there is no information on the MRSA population structure, and little attention has been paid to the molecular epidemiology of this pathogen. CA-MRSA infections have changed markedly, and are expanding to also become causative agents of nosocomial infections. Recently, several studies have reported on MRSA carriage and/or infection coming from different countries in the south-eastern Mediterranean region.

Palestine

A study conducted throughout the Gaza strip by Biber *et al.* [12] revealed widespread CA-MRSA carriage, whereby 30% of healthy children and their parents carried *S. aureus*. Nine-

ty-four MRSA were identified, and further molecular characterization revealed the predominance of CC22, which included 70 strains. The SCCmec type of the Gaza strain was IVa, whereas nine pulsed-field gel electrophoresis-related isolates carried SCCmec V, and seven of these belonged to ST22. Interestingly, eight of the 94 MRSA were PVL-positive and belonged to ST80-MRSA-IV. The authors hypothesized that the origin of the Gaza clone was either an HA-MRSA that spread in the community, or a local ST22-methicillin-sensitive *S. aureus* (MSSA) that evolved into a novel CA-MRSA clone. In a study conducted to determine the carriage rate and characteristics of CA-MRSA in patients admitted to Ramallah Governmental Hospital, a total of 843 swabs were obtained from patients who had no contact with healthcare workers at the time of hospital admission. For comparison purposes, the study also included samples collected from 72 volunteer healthcare workers working in close contact with patients in the internal medicine wards. The study revealed that the rate of *S. aureus* colonization at the time of admission was 26%, and that the rate of MRSA carriage was 2% [13]. Among the healthcare workers, *S. aureus* was detected in 21% and MRSA in 14%. Sabri *et al.* [14] also attempted to study the molecular epidemiology of MRSA circulating in Palestine, Jordan, and Iraq. Investigation of the genetic association between 12 representative MRSA from the predominant antibiotic resistance pattern revealed that 11 of these isolates shared a common *spa* type (t932) and were SCCmec type III. Few of the isolates were PVL-positive, being mainly hospital-acquired. This regional clustering was attributed to cross-border patient mobility. Finally, the prevalence of nasal carriage of *S. aureus* and MRSA was investigated among 360 healthy university students at An-Najah National University, Palestine [15]. The study also included 46 clinical MRSA obtained from three different health centres in northern Palestine within the same period of the study. Nasal carriage of *S. aureus* was detected in 24% of the students with MRSA, accounting for 9% of the isolates. Almost half of the MRSA belonged to SCCmec types IVa and V, and the other half belonged to SCCmec types II and III. SCCmec type IVa was found to be circulating among nasal carriers both in students and in healthcare workers.

Jordan

The incidence of colonization with CA-MRSA has also been the subject of several studies conducted in Jordan. Daghistani *et al.* [16] showed that 22.7% of nasal specimens collected from 132 healthy students were positive for *S. aureus*. The study included 80 *S. aureus* recovered randomly from wound specimens, and showed that toxic shock syndrome toxin-1 production was higher among the nasal isolates. More recently,

among 860 nasal and stool specimens collected from 430 infants admitted to the neonatal intensive-care unit or referred to the outpatient clinics of Jordan University Hospital, 12.4% of the samples were positive for *S. aureus* [17]. The incidence of MRSA was 53%; 28% of the isolates were PVL-positive, and they were mainly recovered from outpatients. All PVL-positive isolates carried SCCmec IV, except for one with SCCmec type III. On another note, a study of the prevalence of natural carriage and molecular epidemiology of MRSA in a Jordanian community revealed that the MRSA carriage rate in 227 healthy volunteers was 7.5%, with the majority of isolates (81%) harbouring SCCmec IVe and being of the novel *spa* type t9519 (76%) [18]. Other detected *spa* types were t233 (14.7%) and t044 (5.9%). Moreover, Khalil *et al.* [9] performed molecular characterization of 103 *S. aureus* (41 MRSA and 62 MSSA) recovered from stool and nose specimens collected from children admitted to the Jordan university hospital. Genotyping revealed 48 different *spa* types and identified distinct allelic profiles, with the majority belonging to ST80. Eight different pulsotypes were detected; SCCmec IV was seen in 53% of the isolates, and clustering revealed that ST80-MRSA-IV was the dominant type.

Lebanon

The situation in Lebanon is similar to that in Jordan and Palestine, with limited data being available on *S. aureus* colonization and its prevalence in patients. Sfeir *et al.* [19] conducted a study to evaluate the rate of *S. aureus* nasopharyngeal colonization in a population of individuals in an outpatient department in Beirut, and to correlate this with the impact of several possible risk factors. Of 1526 outpatients tested, 133 (8.7%) carried *S. aureus* in the nose and/or throat, with only two cases being MRSA. Risk factors for *S. aureus* colonization included the following: a relative working in healthcare, the presence of an intravascular device, a recent dental procedure, and health club use. Nonetheless, molecular characterization of 130 *S. aureus* (93 MRSA and 37 MSSA) recovered from patients at the Clinical Microbiology Section of the American University of Beirut in Lebanon revealed the presence of 48 *spa* types that clustered into 30 different *spa* CCs. Multilocus sequence typing revealed ten STs among the isolates, and the majority of the PVL-positive isolates (53%) were ST80-MRSA-IVc [20]. However, a similar, more recent, study was conducted on 132 *S. aureus* non-duplicate clinical isolates recovered in a period of 6 months at the Clinical Microbiology Section of the American University of Beirut [10]. The proportion of MRSA collected in this study was 30%, which was significantly lower than the percentage reported previously (72%) by Tokajian *et al.* [20]. This was attributed to the fact that the study by Tokajian *et al.* [20] was based on a

number of randomly collected isolates. SCCmec typing again showed the prevalence of the mobile genetic element SCCmec type IV (85%), with all of the isolates being positive for the PVL gene. Higher diversity was detected than that reported previously [20]; 71 different *spa* types as compared with 48. The most common were: t021 (6%), t044 (5%), and t267 (5%). Clustering of SCCmec types with multilocus sequence types identified seven MRSA and 20 MSSA clones, and confirmed that the PVL-positive ST80-MRSA-IV was the dominant clone in Lebanon, followed by PVL-positive ST30-MSSA (5%) [10].

Egypt and Algeria

A randomized study in Egypt on healthcare workers in different hospital departments was conducted to test for the effect of linezolid on nasal and throat colonization [21]. A total of 134 healthcare workers were screened, and 43 (32%) were found to be MRSA carriers (41 nasal carriers and two nasal plus throat carriers). The study concluded that linezolid was effective in eradicating both nasal and nasal plus throat colonization. However, a study of the prevalence of PVL in CA-MRSA isolated in Egypt showed that the prevalence of PVL-positive MRSA was 19% [22]. These belonged to different genetic clones, with the multilocus sequence types being ST30, ST80, and a novel type, ST1010. Interestingly, however, the Egyptian ST80 was different from the CA-MRSA ST80 isolated from other countries. The Egyptian ST80 contained the *etd* and *pvl* genes and carried SCCmec IV, but had a different *spa* type (983/t042) and a unique antimicrobial resistance pattern, i.e. no resistance to tetracycline and fusidic acid, but resistance to sulphamethoxazole [22].

In Algiers, 24 of 25 MRSA implicated in infections of neonates and children admitted to a hospital during an 18-month period carried SCCmec type IVc and belonged to ST80, with 22 carrying the *pvl* gene. The study concluded that PVL-positive ST80-MRSA-IVc was the dominant MRSA clone causing disease in neonates and children [23].

Resistance Patterns

Different antibiotic regimens between countries in this region possibly contributed to the development of heterogeneous strains. An investigation of the prevalence of nasal carriage of MRSA at An-Najah National University in Palestine, and a comparison with clinical isolates, revealed that 35% were multidrug-resistant, being resistant to β -lactams and two or more of ciprofloxacin, erythromycin, and clindamycin [15]. MRSA (eight nasal and 46 clinical) had a broad range of antibiotic resistance. Rates of resistance to non- β -lactam antibiotics were also high: erythromycin, 96%; clindamycin,

52%; and ciprofloxacin, 48% [15]. Sabri *et al.* [14] reported similar high rates of resistance in clinical MRSA to erythromycin, clindamycin, ciprofloxacin, gentamicin and sulphamethoxazole–trimethoprim in the West Bank of Palestine, Jordan, and Iraq. However, Kaibni *et al.* [13] determined the carriage rate of CA-MRSA in Palestine in samples collected from Ramallah Governmental Hospital (patients and healthcare workers). The study, which was based on 27 MRSA (17 from patients and ten from healthcare workers), showed that the rates of resistance to non- β -lactam antibiotics were 29.6% for ciprofloxacin, 18.5% for erythromycin, 11.1% for clindamycin, and 7.4% for tetracycline. This was in contrast to results obtained in Jordan by Al-Bakri *et al.* [18], who also studied carriage rates in apparently healthy volunteers, and reported that all MRSA were resistant to all β -lactam antibiotics but susceptible to other tested agents. In line with these results, Shehabi *et al.* [17], who also investigated the colonization of hospitalized and outpatient infants with *S. aureus*, found that almost 94% of PVL-positive MRSA were susceptible to gentamicin, clindamycin, chloramphenicol, and vancomycin.

In Lebanon, a study on *S. aureus* nasopharyngeal colonization in outpatients revealed the continued effectiveness of cephalosporins as first-line therapy for community-acquired skin and soft tissue infections. Nonetheless, a study on susceptibility patterns in clinical isolates collected from the same country revealed that 56% were susceptible to all tested antibiotics, with the rest being resistant to one or more of the used antibiotics [9]. Finally, Kanj *et al.* [24] recently, and under the Tigecycline Evaluation and Surveillance Trial, reported that all *S. aureus*, including MRSA, were susceptible to tigecycline, linezolid, and vancomycin.

Conclusion

In conclusion, MRSA has emerged as an important pathogen of community infections in many countries in the Middle East. With the global transmission of MRSA, the local epidemiology within countries in the Middle East is changing, owing to the introduction of new strains, with the intercontinental exchange of several clones. ST80-MRSA-IV is one common clone detected in different countries within the region, and is more of a clonal lineage, with country-based differences being detected. In Lebanon, most of the isolates belonging to this clonal lineage were found to be related to the European ST80-MRSA-IV clone [9,10,20,25], this was not the case however, for the isolates from Jordan, which were distinguished particularly by being positive for the toxic shock syndrome toxin-I gene [9,10,17,18].

MRSA is endemic to the Mediterranean region [11], which increases the burden and the difficulty in detecting imported strains. This increases the risk of domestic transmission, in light of patient and personnel movements, and global transmission through travellers and immigrants. To counter the threat associated with the high incidence of MRSA carriage and infections in this region, systematic countrywide surveillance of both hospital and community isolates is required, along with appropriate measures designed to limit their spread. Screening and decolonization of carriers has been successful in containing some outbreaks of CA-MRSA, and may lead to appropriate measures that would additionally help to reduce the rate of MRSA infections. Additionally, antibiotic stewardship has an important role in containing the further development of the observed resistance in this region, and in preserving antibiotics as precious therapeutic resources.

One of the major additional difficulties encountered in these countries is the lack of sourcing of relevant clinical and demographic information, which explains the lack of accurate incidence rates. A high degree of variation of MRSA has been reported, which might be attributable both to the surge of MRSA infections and, more importantly, to the fact that most of the published interpretations were based on a few hospitals in one city rather than being countrywide.

Hence, endemicity of MRSA is clearly a problem in the region, and has major consequences for the countries themselves, as well as for neighbouring nations. The ineffectiveness of MRSA infection control and prevention is driving regional dissemination. It is therefore critical for countries in this region to improve systematic surveillance, and to establish both national and international initiatives to develop better measurements designed to limit and control the spread of infections. Finally, more sequence-based studies are needed to better understand the pathogenicity and epidemiology of these important pathogens.

Transparency Declaration

Nothing to declare.

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