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Abdullah Al-Saleh,[1] Mohammad Shahid,[1] Eman Farid1 and Khalid Bindayna[1]

[1]Department of Microbiology, Immunology and Infectious Diseases, College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain (Correspondence to: A. Al-Saleh: abdullahaas@agu.edu.bh)

Abstract

Background: Methicillin-resistant Staphylococcus aureus (MRSA) is a ubiquitous pathogen that is increasing in Gulf Cooperation Council (GCC) countries. It is implicated in a wide range of infections, from superficial skin infections to life-threatening syndromes. MRSA has moved beyond healthcare facilities, affecting individuals in the community without substantial risk factors.

Aims: To review the prevalence and molecular characterization of MRSA in GCC countries during 2011–2021.

Methods: We comprehensively searched PubMed using the following keywords: MRSA, Staphylococcus aureus, GCC, Kuwait, Saudi Arabia, Bahrain, Oman, Qatar, UAE, prevalence, and molecular characterization for articles published after 2011.

Results: Thirty-nine of 111 articles examined, fulfilled the purpose of this review. Most studies were in Kuwait (44%), Saudi Arabia (28%) and United Arab Emirates (10%). Studies from other GCC countries were sporadic. Several studies demonstrated a clear emergence in antibiotic resistance especially against fusidic acid, ciprofloxacin and clindamycin. Regional prevalence of MRSA is reported as 25–35%, with clear dominance of community-acquired (CA)-MRSA. Panton–Valentine leucocidin (PVL)-producing strains accounted for 35–45%, with clear association with CA-MRSA emergence, but there were some sporadic reports of incorporation of PVL in healthcare-associated (HA)-MRSA. The reported dominant strains included EUST80, USA1100 and WA-MRSA-51. Novel strains are more likely to produce PVL and show fusidic acid resistance.

Conclusion: There is a need for national and regional MRSA surveillance programmes, especially with the emergence of strains that require no underlying risk factors to cause illness, as well as the propagation of chimeric resistance elements in both HA-MRSA and CA-MRSA.

Keywords: MRSA, Gulf Cooperation Council, antibiotic resistance, molecular characterization, Staphylococcus aureus

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Introduction

Staphylococcus aureus is a versatile, Gram-positive bacterium that acts as a human pathogen in clinical settings. However, it is conceivable for S. aureus to be a part of the human skin microbiota in areas such as the axillae and groin, with persistent nasal colonization in ~20% of the population. This allows the bacteria to cause infection when host defences are compromised (1). S. aureus infections range from superficial skin infections to life-threating syndromes, including subcutaneous abscess, impetigo, osteomyelitis, infective endocarditis, pneumonia, sepsis and septic shock syndrome (1). This wide spectrum of diseases is often linked to the large number of virulence factors produced by S. aureus; from degradative enzymes and cytotoxins such as haemolysins, leucocidins, nucleases, proteases and lipases; to the ability to construct and shelter in biofilms, and acquisition of antibiotic resistance genes (2,3).

In the early efforts to combat S. aureus, penicillin improved the clinical outcome of staphylococcal infections; however, the rapid emergence of penicillin-resistant Staphylococcus aureus in the early 1950s prompted the need for an alternative antibiotic, which was methicillin

(4). The now-obsolete methicillin was a successful alternative to penicillin for a time, but, within a decade, new strains emerged that were crossresistant to almost all β-lactams. This began the dominance of methicillin-resistant S. aureus (MRSA) in healthcare facilities, which through unclear mechanisms, acquired further resistance to multiple classes of antibiotics including aminoglycosides, macrolides and glycopeptides, reaching the threshold of last-resort drugs, mainly vancomycin and linezolid (4,5).

MRSA is not restricted to healthcare facilities, and in the 1990s, many cases of MRSA infections were reported in individuals around the world without substantial risk factors. These infections were caused by strains that differed from healthcare-associated (HA)-MRSA, and were later called community-associated (CA)-MRSA (4). It has been postulated that CA-MRSA strains are more likely to be susceptible to non-β-lactam antibiotics, and are associated with necrotizing infections and acute cytotoxin production. However, promiscuous transfer of genetic elements has been suggested in S. aureus lineages, which blurs the line of phenotypic differentiation between HA-MRSA and CA-MRSA (6,7). Nevertheless, the reliance on SCCmec types in MRSA isolates is still widely accepted as a mode of differentiation between HA and CA strains, as HA-MRSA harbour types I–III, and CA-MRSA harbour the much smaller types IV–VI (6). Additionally, supporting the differentiation with multilocus sequence typing or staphylococcal protein A (Spa) typing is recommended to accurately characterize any divergent or nontypical MRSA strains (6).

Neglecting the adverse impact of MRSA would be a dangerous precedent for healthcare systems and general well-being of the community. Hence, publishing surveillance reports and regional prevalence studies would shed some light on the burden of MRSA, prompting any necessary intervention in a timely manner. In that sense, the present study aimed to review the prevalence and molecular characterization of MRSA in the Gulf Corporation Council (GCC) countries during 2011–2021.

Literature search

A comprehensive search was conducted on PubMed using the following keywords: MRSA, Staphylococcus aureus, GCC, Kuwait, Saudi Arabia, Bahrain, Oman, Qatar, UAE, prevalence, molecular characterization, with a time-frame filter set at 2011. Thirty-nine of 111 articles examined fulfilled the purpose of the review (Figure 1).

We found 39 articles discussing the molecular characterization and antibiotic resistance of MRSA in GCC countries. Most studies were in Kuwait (44%), Saudi Arabia (28%) and United Arab Emirates (UAE) (10%). Studies from other GCC countries were sporadic (e.g. Oman, 8%; Qatar, 3%) and may not provide a comprehensive assessment of the epidemiological situation

in their countries. We could not find a published article meeting our criteria in Bahrain as most articles were published prior to 2011.

Trends in antimicrobial resistance

The most common sources of MRSA isolates in GCC countries were skin and soft tissue infections, wounds and nasal swabs (8–16). Some antibiotics are administered, depending on the area affected, to prevent persistence and festering of infections. Antibiotics of interest for the aforementioned sources of MRSA include: fusidic acid, mupirocin, vancomycin, clindamycin, ciprofloxacin and linezolid, as per the updated guidelines for MRSA treatment (17). A clear emergence of fusidic acid resistance can be seen throughout the GCC (Table 1), with the highest rate being 100% in the eastern province of Saudi Arabia compared with 53% in Riyadh. Fusidic acid resistance has increased by 3-fold over 5 years in the UAE (18–20). Similar findings have been noted in Kuwait, with a steady increase in fusidic acid resistance in MRSA since 2012 in 14 public hospitals (21). This trend is postulated to be due to several factors such as: extensive use of over-the-counter fusidic acid cream; importation of foreign MRSA genotypes; and carriage of chimeric genetic cassettes comprising methicillin resistance elements (SCCmec or mecA) and fusidic acid resistance elements (SCCfusC or fusC) (10,20,22). A large number of MRSA isolates carrying these chimeric elements have been identified throughout Kuwait, Saudi Arabia and UAE in many healthcare facilities (Table 2). These isolates belong to various strains and variants, which suggests successful propagation across different MRSA lineages in the region (10,11,16,20,22). It is worth noting that these chimeric SCCmec–SCCfus elements present a new aspect of MRSA pathological evolution as they have the potential to transfer multiple resistance genes within the borders of normal SCC. Also, these dual-resistance cassettes exhibit a selective advantage when considering the high consumption of fusidic acid in the community, as fusidic acid resistance would promote MRSA in the community, and in turn, MRSA would promote fusidic acid resistance in healthcare facilities, further propagating these strains (11,23).

Like fusidic acid resistance, mupirocin-resistant MRSA strains have been isolated in various settings in the GCC, but to a lesser extent. Dash et al. (24) detected 6% mupirocin resistance prevalence in CA-MRSA in a referral hospital in UAE, whereas, Eed et al. (15) reported 18% prevalence among HA-MRSA and 12% prevalence in all MRSA isolates in the western province in Saudi Arabia. Unexpectedly, a favourable development has been reported in Kuwaiti public hospitals as a steady decline of mupirocin resistance in MRSA has been detected, from 9.3% in 2012 to 3.6% in 2015. However, this decline could be due to the extensive use of fusidic acid and preservation of mupirocin (21).

Resistance to ciprofloxacin in MRSA has been reported across GCC countries within similar ranges (Table 1), with some reservations regarding settings and sample size, and similar

trends have been found for clindamycin resistance. However, in Kuwait's maternity hospital, a noteworthy increase in clindamycin resistance has been reported from 9% in 2013 to 15.5% in 2017, with most of the strains isolated being CA-MRSA (25,26). Some fluctuations in resistance rates have been reported from Oman, with 18% and 24% for ciprofloxacin and clindamycin, respectively, in the capital, compared with higher rates of 69% and 78% in the north of the country (13,14). In contrast, Sonnevend et. al. (19) showed a significant decline in ciprofloxacin and clindamycin resistance in MRSA over 5 years at a tertiary care hospital in the eastern borders of UAE. Similar rates were reported in the western borders of UAE at 28% and 6% for ciprofloxacin and clindamycin, respectively (24). This divergent trend remains to be explained, although local prescription practices have been suggested to influence the resistance profiles of MRSA. A better understanding of the situation will be achieved with larger study populations and consistent investigation methods.

Vancomycin serves as the cornerstone of MRSA management and is considered the drug of choice in invasive MRSA infections, hence, any reported resistance should not be ignored (17). Fortunately, most reports in the GCC stated no vancomycin resistance in MRSA, although a few did report otherwise. For instance, in Al Qassim Province in Saudi Arabia, a study of nasal carriage of MRSA by outpatients found that 4% of isolates were vancomycin resistant (27); in Muscat, Oman, 9% of HA-MRSA were reported to be vancomycin resistant (28); and in Kuwait, 2% of MRSA isolated in the surgical intensive care unit (ICU) of a tertiary care hospital were vancomycin resistant (9).

GCC countries are not immune to the global emergence of antibiotic resistance, and the lack of national surveillance programmes hinders the efforts to have a clear profile on each country. The issue is worsened by misuse of antibiotics, as some reports claim that ~68% of pharmacies in Saudi Arabia and UAE have sold antibiotics without prescription, and liberal prescription of antibiotics without microbiologically proven infection is suggested to contribute to this emergence (29). Consequently, this emergence prompts microbial evolutionary selection for enhancements in gene transfer and persistence factors, leading to increased ICU mortality, failure in infection control practices, and exhaustion of reserved antibiotic options. Nonetheless, by discussing, analysing and preventing the drivers of antibiotics resistance, the effective clinical use of current antibiotics could be extended.

Emerging virulence elements

MRSA is a well-known common pathogen in healthcare facilities and the community, and about 44% of healthcare-associated infections in Europe are caused by MRSA (30). Isolated reports throughout the GCC have found a similar prevalence of MRSA among S. aureus isolates (Table 2), averaging about 25–35% (8,12,13,27,31). However, these rates were gathered from a single or a collection of healthcare facilities, and not from nationwide surveys; hence, subsequent

fluctuations in rates may occur. This problem can be illustrated by looking at Eed et al. (15) and Ashgar (32). Both studies were conducted in the western province of Saudi Arabia (

CA-MRSA has shown a substantial emergence in healthcare facilities throughout the GCC (Table 2). A good example of this emergence can be seen by examining 3 reports from a tertiary care hospital in Kuwait about isolates collected in 2005, 2010 and 2019 where they stated a prevalence of CA-MRSA of 24%, 45% and 60%, respectively (10,31,33). Also in Kuwait, when analysing MRSA isolates from 13 healthcare facilities in 1992–2010, Boswihi et al. (34) found a CA-MRSA prevalence of 40%, whereas, in a more recent study where they analysed isolates from 14 public hospitals in 2011–2015, the prevalence had increased to 60% (21). Similarly in the UAE, within 10 years, CA-MRSA emergence increased from 30% to a regional highest at 98% (11, 24). In contrast, 2 reports from the western province in Saudi Arabia demonstrated HA-MRSA dominance in the area and recorded a 40% and 31% CA-MRSA prevalence in 2014 and 2015, respectively (15,32). However, in the eastern province, the rates of CA-MRSA were consistent with other GCC reports at 63% (18,35).

The emergence of CA-MRSA is also reflected at the molecular level (Table 2), with the clear dominance of SCCmec type IV across GCC reports, with a few exceptions that stated type III as the dominant type. It is worth noting that this emergence of CA-MRSA is a global phenomenon, with no clear explanation. Some reasons have been suggested for this proliferation in the region: this area is a travel hub for many people carrying various strains; the expatriatic workforce from all over the world transfer different strains with different mutations and mobile genetic elements; and admission of colonized patients without prior tests permits potential spread into healthcare facilities (10,11,18).

One important emerging virulence factor is Panton–Valentine leucocidin (PVL) as more severe clinical sequelae have been reported for infections caused by PVL-producing isolates (4). A significant rate of PVL-producing MRSA isolates has been recorded, averaging 35–45% in the GCC, with clear association with the emergence of CA-MRSA in healthcare facilities

(Table 2) (4). Some studies have reported incorporation of PVL in HA-MRSA; for instance, in Qatar, a 7% prevalence of PVL-producing HA-MRSA has been reported (8). There are a few reports in Kuwait, with the highest being in the maternity hospital at a rate of 28%, but the GCC's highest recorded rate was in the eastern province of Saudi Arabia at 63% (18,26,31,36). Subsequently, this development sustains an evolutionary fitness for HA-MRSA strains when considering the dual ability to maintain and acquire antimicrobial resistance genes while causing aggressive necrotizing infections.

Other virulence elements have been reported to lesser extent (Table 2); one of which is toxic shock syndrome toxin (TSST)-1, which is implicated in TSS and Kawasaki syndrome (2). TSST used to be carried only by HA-MRSA, but recently CA-MRSA has also produced this toxin. In a study examining HA-MRSA in Kuwait, the prevalence rate was around 62; however, the sample size was small (36). Another virulence element reported in the region is arginine catabolic mobile element (ACME), which is a putative pathogenicity island associated with enhanced fitness of carrier strains in bacterial colonization, propagation and endurance (37). More insights are needed with regard to this pathogenic genetic element, including prevalence in the region because few studies have investigated ACME (Table 2).

Dominant and novel strains

Throughout the 10 years, the clonal dominance of MRSA isolates in healthcare facilities has shifted in favour of CA strains; a trend that reflects the global epidemiological picture of MRSA. However, some HA-MRSA strains remain in epidemiological prominence in the region (Table 3). One mainly reported CA-MRSA strain throughout the GCC is CC80-ST80-IV/t044(PVL+), otherwise known as the European CA-MRSA clone (EUST80). This PVL-producing clone represents the most common CA-MRSA strain circulating in the GCC (mainly Kuwait and Saudi Arabia) as well as in North Africa, and more prominently than in Europe, with the occasional reports of PVL variants (8,10,11,14,16,18,19,38). Another dominant CA-MRSA strain is CC30-ST30-IV/t019(PVL+), which is named: the Southwest Pacific clone, West Samoan phage pattern clone, and USA1100. This PVL-producing strain is propagated in the region to a lesser extent than EUST80, except in Qatar and UAE where it was the dominant strain and represented 28% and 11% of total MRSA isolates respectively (8,11,38). Another global CA strain that is dominant in the region is CC6-ST6-IV/t304, the Western Australia (WA) MRSA-51 clone. It is the most common strain in Oman, accounting for about 39% of total MRSA isolates, it codominates in the UAE with USA1100 at a prevalence of 10% of total MRSA isolates, and has shown an upward trend in prevalence in Kuwait of 36% in 1 year (11,14,38). Hence, this clone is showing high emergence in the region, which is suggested to be due to interspecies transfer from camels infected with CC6-methicillin-sensitive S. aureus (16). The sporadic isolation of the epidemic CA-MRSA strains USA300 (CC8-ST8-IV[PVL+, ACME+]) and USA400 (CC1-ST1-IV[PVL+]) in the region has prompted concern of further spread of these highly successful pathogens; therefore, it is important to actively monitor their propagation among healthcare workers and patients (8,18,38).

Some HA-MRSA clones have persisted and remained dominant, such as those belonging to the clonal complex 5 (CC5), specifically the paediatric clone (CC5-ST5-V,IV/t002) otherwise called USA800 and the new paediatric clone (CC5-VI/t688+SCCfus) harbouring fusidic acid resistance (Table 3) (39). In Kuwait, a study reported a 45% increase in CC5-MRSA, which includes the

aforementioned clones, and a study from Qatar stated that USA800 clone accounted for about 21% of the isolated MRSA; however, in UAE, Oman and Saudi Arabia, the rates were lower (8,11,14,18,38). Some epidemic HA-MRSA strains were transmitted to the region and have shown distinct evolution through acquiring virulence factors as seen in epidemic MRSA 15 (EMRSA-15, CC22-ST22-IV/t223[tst+]). True EMRSA 15 was only isolated in Kuwait, yet variations of this clone (Middle Eastern variants) were more prevalent throughout the region (36,38). An emerging variant that expresses PVL and carries Spa type 852 is becoming prevalent in the region, as reported in Kuwait, Oman, Qatar and UAE. This poses new challenges in MRSA management because these clones can be multiresistant strain and produce both TSST-1 and PVL (8,10,11,14,22). The pandemic strain CC8-ST239-III/t860, Vienna/Hungarian/Brazilian clone, which used to be highly prevalent in the GCC, has declined significantly since the emergence of CA-MRSA but remains prevalent in sporadic reports. For example, a prevalence of 21% has been reported from the capital of Saudi Arabia, yet within the same sample collection period, the prevalence in the eastern province was

A consequence of modernization in the GCC and becoming an international commercial hub that attracts expatriates from all over the world is the high potential of novel strains arising. By looking at the reported novel strains in Table 3, it is clear that PVL is becoming more common, and fusidic acid resistance through fusC is being propagated in horizontal fashion among various strains. A particularly interesting clone has been identified in Saudi Arabia and Kuwait; CC15-ST1535-V+SCCfus, which harbours the SCCfus composite element and is associated with retail camel meat products in Saudi Arabia (40, 41). Additionally, this clone has been isolated from 8 different healthcare facilities in Kuwait, accumulating 42 isolates belonging to various Spa types, which suggests different sources of emergence and evolution. This is one of the few reported examples of livestock-associated MRSA in clinical settings in the GCC (40, 41). Another interesting novel clone is the PVL-producing CC1153-I+SCCfus [PVL+], which carries a novel composite element consisting of SCCmec type I and SCCfus isolated in Kuwait, whereas in Saudi Arabia these clones carried another novel composite element, SCCmec type V with SCCfus. Both variations were isolated in UAE, which may support the premise of the independence of SCCmec types acquisition among MRSA isolates (11,20,22,42).

Conclusion

This review aimed to illustrate the urgent need for national and regional MRSA surveillance programmes, especially, with the emergence of strains that require no underlying risk factors to cause illness, as well as the propagation of chimeric resistance elements in both HA-MRSA and CA-MRSA. The current epidemiological situation necessitates the implementation of preventative guidelines (e.g. antimicrobial stewardship) to avoid repeating what caused the rampant emergence of fusidic acid resistance. Special attention should be paid to regional novel clones and newly adapted variants (e.g. livestock-associated MRSA) since they have the potential to introduce and propagate virulence factors into healthcare facilities. Other practices may help in solidifying the effectiveness of these nationwide programmes, such as targeted epidemiological studies focusing on specific populations (e.g. paediatrics, sickle cell disease patients and geriatrics). Symposia that review accumulated epidemiological data, as well as nationwide rotation of healthcare providers should provide more experience and understanding

of the epidemiological status of the region. Some hospital-level practices could also be supportive, such as complementary programmes that emphasize the importance of simple preventive measures like hand hygiene and wearing masks and gloves, as well as periodical bulletins to remind and explain to healthcare providers the aims of these nationwide programmes.

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Tendances du Staphylococcus aureus résistant à la méthycilline (SARM) dans les pays du Conseil de Coopération du Golfe (CCG) : résistance aux antibiotiques, facteurs de virulence et souches émergentes

Résumé

Contexte : Le Staphylococcus aureus résistant à la méthycilline (SARM) est un agent pathogène omniprésent qui est en augmentation dans les pays du Conseil de Coopération du Golfe (CCG). Il est impliqué dans un large éventail d'infections, allant des infections cutanées superficielles à des syndromes potentiellement mortels. Le SARM a dépassé le cadre des établissements de soins de santé et touche désormais des individus dans la communauté sans facteurs de risque importants.

Objectifs : Examiner la prévalence et la caractérisation moléculaire du SARM dans les pays du CCG entre 2011 et 2021.

Méthodes : Nous avons effectué une recherche exhaustive sur PubMed en utilisant les mots-clés suivants : SARM, Staphylococcus aureus, CCG, Koweït, Arabie saoudite, Bahreïn, Oman, Qatar, Émirats arabes unis, prévalence et caractérisation moléculaire dans le cadre des articles publiés après 2011.

Résultats : Trente-neuf des 111 articles examinés ont répondu à l'objectif de cette analyse. La plupart des études ont été réalisées au Koweït (44 %), en Arabie saoudite (28 %) et aux Émirats arabes unis (10 %). Les études provenant d'autres pays du Conseil de Coopération du Golfe étaient sporadiques. Plusieurs études ont mis en évidence une émergence claire de la

résistance aux antibiotiques, notamment l'acide fusidique, la ciprofloxacine et la clindamycine. La prévalence régionale du SARM est signalée comme étant comprise entre 25 et 35 %, avec une prédominance marquée des infections communautaires à SARM. Les souches productrices de leucocidine de Panton-Valentine (PVL) représentaient 35 à 45 % des cas, avec une association claire avec l'émergence des infections communautaires à SARM, mais quelques rapports sporadiques ont fait état de l'incorporation de PVL dans des infections à SARM nosocomiales. Les souches dominantes signalées comprenaient les souches EUST80, USA1100 et WA-MRSA-51. Les nouvelles souches sont plus susceptibles de produire des PVL et de présenter une résistance à l'acide fusidique.

Conclusion : Il est nécessaire de mettre en place des programmes nationaux et régionaux de surveillance du SARM, en particulier avec l'émergence de souches qui ne nécessitent aucun facteur de risque sous-jacent pour provoquer la maladie, ainsi que la propagation d'éléments de résistance des chimères à la fois dans les infections communautaires à SARM et les infections à SARM nosocomiales.

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