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Methicillin Resistant *Staphylococcus aureus* (MRSA) Strains and the Staphylococcal Cassette Chromosome *mec* Types in Iran

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Background: *Staphylococcus aureus* can cause infections with a wide spectrum of illnesses ranging from benign skin infections to bloodstream infection leading to mortality. Antimicrobial resistance especially methicillin resistance in *S. aureus* (MRSA strains) is currently problematic. The emergence of MRSA infections has developed in both the healthcare and the community settings. The aim of this study was to determine the prevalence of MRSA and SCC*mec* types in Iran according to the previously published studies.
Methods: For this review, the terms of MRSA, Iran, methicillin, *mecA* and SCC*mec* types were searched in searching engines including Google scholar, PubMed, SciVerse, and Scopus. Data from veterinary sources were excluded. Data were analyzed with Graph Pad Prism 6 considering meta-analysis section.
Results: Among several studies and approximately of 1810 results, the prevalence of MRSA was determined as approximately 56.5%. In the year of 2015 and 2016, results exhibited a higher prevalence of MRSA (62.2%) compared to 2013 and 2014, although not exceeded from 46% in healthy individuals. Moreover, among the SCC*mec* types, the SCC*mec* Type III has been reported as the predominant type (60.48%) followed by Type IV (21.2%), Type I (17.72%), Type II (17.12%), and Type V (0.56%).
Conclusion: According to previous data, the prevalence of MRSA is increasing in Iran. However, it may be different for each year depending on several reasons. Moreover, the SCC*mec* Type III is the predominant type in the country. The SCC*mec* Type IV has also emerged in CA-MRSA isolates.

*Key words***:** Iran, *Staphylococcus aureus*, Methicillin resistance, Staphylococcal Cassette Chromosome *mec* types

1. Introduction

Staphylococcal infections are the most common cause of nosocomial ailments and even deaths and constitute 60% of the infections in the intensive care units (ICU). Moreover, surgical wounds, pneumonia and intravenous catheters are the most common nosocomial infections from which *S. aureus* has been mostly collected (1). In the post-antibiotic era, bloodstream infections of *S. aureus* were usually fatal, and more than 95% of the patients with the age of 50 or more, were dead in the early 1940s. Shortly, after the use of beta lactam agents, the strains gained resistance (2). To date, strains with resistance to methicillin (MRSA) have been reported worldwide. The prevalence of MRSA is increasing (3-5). MRSA has emerged as one of the predominant hospital-associated and drug-resistant microorganisms, and up to 53 million people carry MRSA (6). The range of MRSA worldwide varies between 1% in Scandinavian countries to 60% in the United States and Brazil. The three major clones of HA-MRSA since 1960, CA-MRSA since 1990s, and Livestock-associates MRSA (LA-MRSA) since 2000s are now pandemic (7, 8). MRSA is often referred to in the press as a "superbug". The drug-resistant infections due to MRSA have developed in hospital settings (9, 10).

Several studies have determined high prevalence of MRSA in ICUs in addition to other wards of hospitals (9,11,12). Within a year, after the consumption of semisynthetic penicillins such as methicillin, there were reports of resistant isolates in 1961 (13). MRSA was initially associated with hospitals, with reports of outbreaks increasing all over the world, the epidemic was controlled with the search-and-destroy-strategy. Risk factors for community-acquired infections include intravenous drugs, prior antimicrobial usage, and underlying illnesses such as pulmonary disease, diabetes, and chronic skin diseases (14-16). All MRSA isolates express an additional penicillin-binding protein named PBP2a or PBP2 which confers resistance to all the available β-lactam agents in current, including penicillinase-resistant penicillins (such as oxacillin and methicillin) and cephalosporins (such as cefoxitin) (17). PBP2a is encoded by the *mecA* gene that causes resistance to beta lactams because of low affinity of these agents (Figure 2). The defining feature of MRSA strains is the staphylococcal cassette chromosome *mec* (SCC*mec*) element (18). A detailed explanation for the term "SCC*mec*" is available at the website (http://www.*staphylococcus*.net). This is a mobile genetic element that contains the central determinant of resistance to beta lactams, encoded by the *mecA* gene. The acquisition and insertion of the SCC*mec* element into the chromosome of methicillin susceptible strains have culminated in the emergence of methicillin-resistant staphylococcal lineages. The SCC*mec* Types I, II, and III are located in the genome of MRSA from hospital, whereas SCC*mec* Types IV and V have integrated in the genome of community acquired strains (19, 20). Panton-Valentine leucocidin (PVL) suggested being a marker for CA-MRSA together with SCC*mec* Type IV is predominantly associated with severe skin and skin related infections and necrotizing pneumonia. Recent studies have reported that CA-MRSA strains are spreading in hospital settings and are replacing traditional HA-MRSA strains (21-24).

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2. Objectives

Staphylococcus aureus (*S. aureus*) is one of the most important pathogen which causes several infections. Methicillin resistant *S. aureus* (MRSA), which is usually multi-resistant in hospitals, has been a daunting challenge for clinicians for more than half a century.

The aim of this study was to determine the prevalence of MRSA and SCC*mec* types in Iran according to the previously published studies in different regions of Iran.

3. Methods

3. 1.Literature search

For this review, the terms of MRSA, Iran, methicillin, *mecA* and SCC*mec* Types were searched in searching engines including Google scholar, PubMed, SciVerse, and Scopus. Moreover, the Persian published results and the 3 recent congresses (First International and 12th Iranian Congress of Microbiology, The First Iranian International Congress of Medical Bacteriology, The Congress of Infections and Antibiotic Resistance, 13th, 14th and 15th Iranian Congress of Microbiology and The Congress of Rational Usage of Antibiotics) and also a systematic and met analysis of relative prevalence of MRSA in Iran by Askari were included (28).

3.2. Inclusion and exclusion criteria

All the following results were considered as suitable:

1) *Staphylococcus aureus* isolates collected from Iranian hospitals.

2) Clinical specimens from patients and also healthy individuals for instance hospital carriers.

3) The molecular results for the *mecA* detection were preferred to the phenotypic tests. Because the phenotypic tests have several conditions including: media pH, incubation period, the quality of disks and media, different susceptibility test media, and personal skills. Moreover, breakpoints of phenotypic tests may vary over time.

4) In the studies that the method of MRSA detection were not mentioned were excluded.

3.3. Data collection and statistical analysis

All the collected results were designed in an Excel format and Graph Pad Prism and next were analyzed. The authors accompanied in the adoption of correct results and the interpretation of data. We also used the previous review article published by Askari (28).

4. Results

In south of Iran, Ekrami showed that 27.8% of the wound and blood specimens were infected by *Staphylococci*, among which, 60% were identified as methicillin resistant (25). In a study conducted for detection of MRSA, Najar Peerayeh detected 48.2% in 2009 and 47.5% in 2012 (10, 26). Moreover, in Loghman hospital the prevalence of MRSA was lower than 30% in 2014 (4, 5, 27). A systematic review and meta-analysis by Askari determined that relative frequency (RF) of MRSA is high in Iran (48.5%) (28). According to the previous published studies, the average of MRSA in each year is exhibited in the Figure 1. The prevalence of MRSA up to 2012 has been reported by Askari and colleagues (28). According to which in Khuzestan it was higher than 60%. Moreover, in Tehran, Mashhad, Tabriz, Hamadan, Isfahan, and Shahrekord it was 50-60%. Shiraz and Kurdistan cities had the prevalence of 45-50% and lower than 40% respectively. The prevalence of MRSA up to 2012 is shown in Figure 2. Moreover, the results of the MRSA prevalence studies in Iran in the year of 2013 are depicted in Table 1. On the other hand, the SCC*mec* types detected to date in Iran are displayed in Table 2. However, among the SCC*mec* types, the SCC*mec* Type III has been reported as the predominant type (60.48%) followed by Type IV (21.2%), Type I (17.72%), Type II (17.12%), and Type V (0.56%).

Table 1. The results of the MRSA prevalence studies in Iran in the year of 2013.

Author	source	MRSA (%)	City	Reference
Havaei	Milk	7.69	Isfahan	*
Sedigh	Inpatients	44	Shiraz	*
Teyhoo	Inpatients	71.6	Lahijan	*
Ahanjan	Carriers	9.5	Sari	*
Amini	Inpatients	51.6	Golestan	*
Aslanimehr	Inpatients	59	Qazvin	*
Sahebnasagh	Inpatients	75.9	Zanjan	*
Mohajeri	Carriers	36.8	Kermanshah	(29)
Bahmani	Neonates	55	Kurdistan	(30)
Dibah	Inpatients	46.3	Ardabil	(31)

*The study was published in the 13th Iranian and 2nd international congress of Bacteriology.

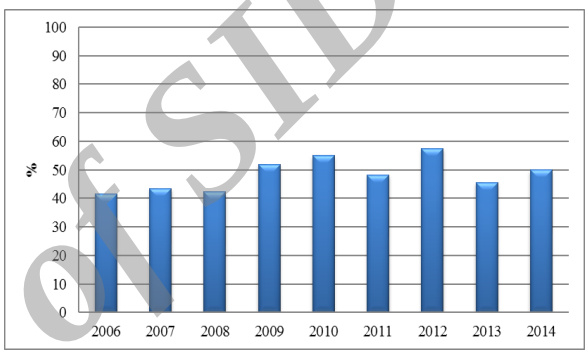

Figure 1. The average of MRSA prevalence alterations in the country between the years of 2006 and 2014.

Figure 2. The prevalence of MRSA in the year of 2012 (28).

4.1. The SCCmec typing results

As most of the previous studies have determined, the SCC*mec* Type III is the predominant SCC*mec* type in Iran (32). For instance, Fatollahzadeh detected the Type III in 98% of the MRSA in Tehran, and also Japoni's survey in southern Iran, resulted in the presence of SCC*mec* Type III in 78% of the MRSA (23). The SCC*mec* Type III is usually detected in the nosocomial MRSA isolates. The different SCC*mec* types prevalence in Iran has been summarized in Table 2.

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Table 2. The SCC*mec* types detected in Iran.

Author	SCC*mec* types (%)					No	Year	reference
	I	II	III	IV	V			
Ghasemian	0	0	94.2	0	5.8	78	2014	(36)
Moghadami	56.9	22	0	0	0	109	2010	(33)
Fatollahzadeh	0	0	98	2	0	199	2008	(23)
Japoni	0	0.6	78	10	2.6	156*	2011	(34)
Havaei	0	0	45	24	0	100*	2012	(35)
Veerarghavan	3.4	13.8	39	13.8	3.4	87*	2011	(36)
Momtaz	0	0	28.52	21	52.83	132	2014	(37)

*These isolates were MRSA

5. Discussion

The MRSA isolates have been detected in both community and healthcare settings. However, the hospital associated isolates have an extended spectrum of antibiotic resistance to antibiotics (38, 39). Numerous previous studies have detected the MRSA with the *mecA* gene amplification. To determine whether MRSA isolates have been originated from healthcare or community settings, the detection of SCC*mec* types have been raised in the country alongside with the other areas of the world (40). As included in the results section, the prevalence of MRSA is approximate to 47% and follows to some extent alterations in every year, although it has determined that the origin/source of isolates plays an important role in the prevalence of MRSA strains. However, two previous worldwide reports did not give an exact percentage of MRSA in Iran. The previous systemic and meta-analysis by Askari in 2012 exhibited that it was 52% (28). In Ohadian Moghaddam's study performed in 2015, the prevalence of MRSA was 61.53% in Tehran (24). The prevalence in different cities is not the same. This is an alarming point because MRSA isolates are multidrug-resistant and may not response to nearly all the antibiotics, except for glycopeptides such as vancomycin and teicoplanin (25). In recent years, vancomycin intermediate resistant isolates (VISA) or even vancomycin-resistant *S.aureus* have emerged and developed in several areas of the world (41). Among the Middle East countries, Iran is the second country for the prevalence of MRSA, after Iraq as the first one. On the other hand, a study among the Asian countries showed that the HA-MRSA prevalence is lower than that of several other countries. Argentina and Mexico are similar to our country in this regard (42), Australia and United States have lower and higher prevalence than Iran, and also the European countries have heterogeneous prevalence (43). The studies have attained different results of the predominant SCC*mec* type and the pattern of types detected in Iran. However, most of the healthcare associated isolates contained SCC*mec* Type III (26-29). From Table 2, it may be revealed that the SCC*mec* Type III predominated among other types but in the year of 2014 the SCC*mec* Type V has increased sharply (28). There is now a suggestion that the community associated MRSA isolates may spread in the hospital as several previous studies have exhibited this phenomenon. In a study in Iraq, 95% of the MRSA isolates harbored the *SCCmec* Type IV (44). The SCC*mec* Types I and II detected in the two studies (Table 2) are also found in healthcare associated isolates. One of the important factors interfering in the prevalence results is the area of the study. Following and surveillance of SCC*mec* types is helpful in the determination of MRSA sources and origins.

6. Conclusion

MRSA as a miscellaneous pathogen is a significant cause of both healthcare and community-associated infections. Its widespread have developed multiple - drug resistant strains, and antibiotic resistant clones are worrying issues. The SCC*mec* Type III is the predominant type detected in hospital settings. However, the community-acquired MRSA containing SCC*mec* Types IV has increasingly developed in healthcare settings. The SCC*mec* typing can contribute to uncovering the possible origin of MRSA.

Conflict of Interests

The authors declare they have no conflict of interest.

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Authors Contribution

All authors contribute in writing different parts of this manuscript.

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