Epidemiology of meca-Methicillin Resistant *Staphylococcus aureus* in Iran: A Systematic Review and Meta-analysis

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Abstract

**Objective(s)**

*Staphylococcus aureus* is a prevalent pathogen worldwide. 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 systematic review and meta-analysis is to determine the relative frequency (RF) of MRSA in different regions of Iran.

**Materials and Methods**

Search terms “*Staphylococcus aureus*”, “Methicillin”, “meca” and “Iran” were used in PubMed, Scirus and Google Scholar. Two Persian scientific search engines and ten recent national congresses were also explored. Articles/abstracts, which used clinical specimens and had done PCR to detect the meca gene, were included in this review. Comprehensive Meta-Analysis and Meta-Analyst software were used for statistical analysis.

**Results**

Out of 2690 results found in the mentioned databases, 48 articles were included in the final analysis. These studies were done in Ahvaz, Falavarjan, Fasa, Gorgan, Hamedan, Isfahan, Kashan, Mashhad, Sanandaj, Shahrekord, Shiraz, Tabriz, Tehran and Tonekabon. Pooled estimation of 7464 *S. aureus* samples showed that 52.7%±4.7 (95% confidence interval [CI]) of strains were meca positive. MRSA RF in different studies varied from 20.48% to 90% in Isfahan and Tehran, respectively. We found a moderate heterogeneity (I²= 48.5%) of MRSA RF among studies conducted in Tehran (ranging from 28.88% to 90%, mean 52.7% [95% CI: 46.6%±58.8%]).

**Conclusion**

According to the results of this study, MRSA RF in Iran is in the high range. Thus, measures should be taken to keep the emergence and transmission of these strains to a minimum.

**Keywords:** Iran, Methicillin-Resistant *Staphylococcus aureus*, Systematic Review

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Introduction

*Staphylococcus aureus* has been known as a threat to human health for more than a century. This pathogen is responsible for a wide range of maladies from folliculitis and food poisoning to life-threatening conditions such as endocarditis or necrotizing pneumonia (1).

Introduction of penicillin to the market in the 1940s was a cornerstone in treating staphylococcal infections, which was soon followed by the emergence of β-lactamase producing strains. Methicillin, a β-lactamase-resistant antimicrobial agent, was introduced in 1959. The first report of methicillin-resistant *S. aureus* (MRSA) was from London in 1961 (2, 3).

It has been suggested that the *mecA* gene is responsible for resistance to methicillin. *MecA* encodes an altered penicillin-binding protein (i.e. PBP2a) with a low affinity for β-lactam antibiotics (2). The multi-drug resistance phenomenon, seen especially in MRSA strains, is a main cause of treatment failure and increase in treatment costs (4). It is noteworthy that MRSA infections are associated with a higher mortality rate compared to infections with methicillin-susceptible *S. aureus* (5).

MRSA was previously considered as a nosocomial pathogen, but in the past two decades, reports suggest an increasing trend for community-associated MRSA (CA-MRSA). These clones may replace current health care-associated MRSA (HA-MRSA) clones in the future. This hypothesis is supported not only by mathematical models but also by reports that have shown invasion of CA-MRSA clones to hospitals (6). First described in Minnesota, CA-MRSA has now attracted global attention (1). Since 2004, MRSA related to livestock infections has also been reported. However, this type of MRSA seems to be limited to some countries, especially the ones where pig farms are common (7, 8).

Recent studies have revealed an increase in the worldwide prevalence of MRSA. However, some European countries have maintained low rates of MRSA (4, 7). Although there are many reports from different cities of Iran, the average rate of MRSA in Iranian hospitals is still unknown. Our aim in this study is to provide the relative frequency (RF) of MRSA in Iran, as detected by the PCR amplification of the *mecA* gene.

Materials and Methods

**Literature search**

“*Staphylococcus aureus*”, “*S. aureus*”, “Methicillin”, “MRSA”, “MSSA”, “*mecA* gene” and Iran (for non-Iranian databases) were searched with special strategies in PubMed, Google Scholar and Scirus search engines. Two Persian scientific search engines “Scientific Information Database” (www.sid.ir), and "IranMedex" (www.irannmedex.com) were searched as well. The keywords were also searched at all Iranian academic domains (i.e. ending with.ac.ir) by “Google advanced search”. Additionally, abstract books of 10 recent congresses (i.e. “1st-5th Iranian Congress of Clinical Microbiology”, “4th Congress of Laboratory and Clinic”, “First International and 12th Iranian Congress of Microbiology”, “The First Iranian International Congress of Medical Bacteriology”, “The Congress of Infections and Antibiotic Resistance” and “The Congress of Rational Usage of Antibiotics”) were explored. All common dictation mistakes and possible conditions of mentioned words (in English and Persian) were covered as well. Search strategies were followed until 17th May 2012.

**Inclusion criteria**

Among English and Persian articles/abstracts found with above strategies, those with the following features were included in the study:

1. *S. aureus* samples were collected from Iranian hospitals.
2. Clinical specimens were taken from patients. If there were personnel specimens as well, results of the personnel were excluded.
3. PCR method was done to detect *mecA* gene. Phenotypic results were not included because: (A) Phenotypic methods had variable sensitivities and specificities in various studies (9). (B) Phenotypic methods were affected by many factors such as pH of media, concentration of NaCl, incubation period...
of isolates, commercial discs and media used in different studies and also personnel’s/researcher’s skills (10). (C) Generally, avoiding heterogeneity for inclusion of studies is desirable in systematic reviews (11). (D) Breakpoints of phenotypic methods may change over time and make the interpretation of previous results more difficult. For example, Clinical and Laboratory Standards Institute revised the breakpoints for cefoxitin disc diffusion and minimum inhibitory concentration in 2007 and 2008, respectively (12, 13).

Exclusion criteria
During observation, studies with at least one of the aspects mentioned below were excluded:
1. Samples were partially/totally selected from MRSA collections.
2. Method for detecting MRSA strains could not be discovered from the paper.

Data collection
At this stage, articles/abstracts with the following features were excluded as well:
1. Any projects published both in English and Persian. (In these cases, the article published later and/or with more detailed results was chosen for analysis.)
2. Duplicate publications and congress abstracts whose full-text papers were also available.
3. The origin of samples was not clear, meaning that the reviewer(s) could not find out which region or population (i.e. inpatients, personnel, or outpatients) the specimens were gathered from.
4. Nasal, oral or throat swabs were taken from healthy people or patients/healthcare personnel to detect carriers.
5. Unclear report of the results, such as studies that mixed results of “Coagulase-negative Staphylococci and S. aureus” or “healthy people and patients”.

Statistical analysis
Statistical analysis was performed by the Meta-Analyt (version 3.13 Beta) and Comprehensive Meta-Analysis (version 2.0) software. Overall relative frequency of MRSA in Iran was pooled by forest plot using the Meta-Analyt software. Statistical heterogeneity of the results was checked using Cochrane Q-test with significance set at P< 0.1. In order to assess possible publication bias, the Begg and Mazumdar’s test was done using the Comprehensive Meta-Analysis software. The Begg and Mazumdar’s rank correlation test reports the rank correlation between the standardized effect size and the variances (or standard errors) of these effects.

Results
Out of 2690 articles/abstracts found by the aforementioned search strategies, 79 results matched inclusion criteria, out of which 48 (29 full-text articles and 19 abstracts) were selected for analysis (Table 1) (14-61). Sample size and 95% confidence interval (CI) of each study was shown in a Forest plot (Figure 1). According to heterogeneity test, random model methods were used for meta-analysis tests (P< 0.001). I² statistics, the proportion of variation due to heterogeneity, was 0.48, indicating moderate heterogeneity.

Pooled estimation of 7464 S. aureus samples showed 52.7%±4.7 (95% CI) of strains to be meca positive. These samples were taken from 14 different Iranian cities (Figure 2). MRSA RF varied from 20.48% to 90% in Isfahan and Tehran, respectively (22, 55). Amodeate heterogeneity (I²= 48.5%) of MRSA RF in the studies conducted in Tehran, the capital city of Iran (ranging from 28.88% to 90%, mean 52.7% [95% CI: 46.6%-58.8%]) (33-60) was found.

A significant correlation suggested that bias exists but does not directly address the implication of bias (Kendall’s tau= 0.21). The results of a Begg and Mazumdar’s rank correlation test supported its possibility (P= 0.039).
Figure 1. Forest plot of the current relative frequency of *mecA*-MRSA among clinical *Staphylococcus aureus* isolates in different Iranian studies
Discussion
During the past decade, assays for detection of mecA gene for staphylococci became popular among Iranian researchers. Based on these studies, we report the cumulative prevalence of MRSA and provide a map to illustrate the epidemiology of MRSA in Iran. In two previous global reports, the prevalence of MRSA in Iran was unknown (2, 7).

According to our study, the mean prevalence of MRSA in Iran was 52.7%±4.7 and was more than fifty percent in many Iranian cities. This finding indicates that physicians may face difficulties in treatment of more than half of S. aureus infections. Keeping in mind the high prices of newer agents, vancomycin appears to be a suitable agent to fight this pathogen, although recent emergence of vancomycin resistance in Iran is really alarming (36, 62).

In a regional perspective, Iran has a higher prevalence of MRSA compared to reports from neighboring countries in the Middle East with the exception of Iraq (2, 7). The ANSORP study which reported HA-MRSA rates for eight Asian countries showed higher percentage of MRSA in those countries compared to Iran. However, judgment cannot be made because most Iranian studies did not clearly divide their S. aureus population to HA- and CA- infections (63).

From an international stand, our data are in the same range as Argentina and Mexico in Latin America (64). Mean prevalence of MRSA in Iran is moderately higher than Australia and lower than the United States (65, 66). However, recent reports have shown that MRSA rates are declining in United States (67, 68). Prevalence of MRSA in Europe is heterogeneous with average lower than other continents but Portugal seems to have a similar rate of MRSA rates similar to our country (7).
| City         | Type   | Sample size | MRSA | Relative frequency of MRSA (%) | Study team (Reference No.) | Year published/presented |
|-------------|--------|-------------|------|-------------------------------|---------------------------|--------------------------|
| Ahvaz       | Article| 97          | 60   | 61                            | Ekrami et al (14)         | 2010                     |
|             | Abstract| 195         | ≥96  | ≥49.23*                       | Moosaviani et al (15)     | 2011                     |
| Falavarjan  | Article| 95          | 83   | 87.36                         | Khosravi et al (16)       | 2012                     |
| Fasa        | Article| 108         | 92   | 85.18                         | Heidari et al (17)        | 2011                     |
| Gorgan      | Article| 164         | 78   | 47.56                         | Abdollahi et al (18)      | 2012                     |
| Hamedan     | Article| 70          | 35   | 50                            | Zamani et al (20)         | 2007                     |
| Isfahan     | Article| 83          | 17   | 20.48                         | Havaei et al (22)         | 2011                     |
| Kashan      | Article| 150         | 87   | 58                            | Zeinali et al (23)        | 2010                     |
| Mashhad     | Article| 86          | 46   | 53.48                         | NaderiNasab et al (24)    | 2005                     |
| Sanandaj    | Abstract| 96          | 37   | 38.5                          | Vaiseh et al (25)         | 2012                     |
| Shahrekord  | Article| 196         | 96   | 48.98                         | Shariati et al (26)       | 2010                     |
| Shiraz      | Article| 115         | 49   | 42.6                          | Japoni et al (27)         | 2004                     |
|             | Article| 46          | ≥32  | ≥69.5*                        | Nikbakht et al (28)       | 2008                     |
| Tabriz      | Abstract| 56          | ≥7   | ≥12.5*                        | Zarrini et al (29)        | 2008                     |
|             | Abstract| 86          | 34   | 39.5                          | Esfandyari et al (30)     | 2011                     |
|             | Abstract| 90          | 64   | 71                            | Kianinia et al (31-32)*   | 2011                     |
|             | Article| 70          | 28   | 40                            | Mirsalehian et al (33)    | 2003                     |
|             | Article| 338         | 162  | 48                            | Aligholi et al (34)       | 2006                     |
|             | Abstract| 117         | 52   | 44.45                         | Mostafaei et al (35)      | 2007                     |
|             | Article| 356         | ≥149 | ≥41.85*                       | Aligholi et al (36)       | 2008                     |
|             | Article| 277         | ≥100 | ≥36*                          | Fatholahzadeh et al (37)  | 2008                     |
|             | Article| 222         | 122  | 55                            | Habibi et al (38)         | 2008                     |
|             | Abstract| 235         | 110  | 46.8                          | Azimian et al (39)        | 2008                     |
|             | Abstract| 65          | ≥33  | ≥50.8*                        | Bagherzadeh Yazdchi et al (40) | 2008                 |
|             | Abstract| 50          | 22   | 44                            | Dadaei et al (41)         | 2008                     |
|             | Abstract| 80          | 40   | 50                            | Salehipour et al (42)     | 2008                     |
|             | Article| 927         | ≥306 | ≥33*                          | Aligholi et al (43)       | 2009                     |
|             | Article| 322         | 93   | 28.88                         | Emaneini et al (44)       | 2009                     |
|             | Article| 174         | ≥84  | ≥48.2*                        | Najari-peeraieh et al (45) | 2009                 |
| Tehran      | Article| 321         | 282  | 88                            | Rahimi et al (46)         | 2009                     |
|             | Article| 100         | 53   | 53                            | Yadegar et al (47)        | 2009                     |
|             | Abstract| 250         | 109  | ≥43.6*                        | Farhadian et al (48)      | 2009                     |
|             | Article| 150         | 64   | ≥42.67*                       | Javan et al (49)          | 2010                     |
|             | Abstract| 55          | 28   | 50.9                          | Faghri et al (50)         | 2010                     |
|             | Article| 165         | ≥87  | ≥52.72*                       | Aligholi et al (51)       | 2011                     |
|             | Article| 42          | 18   | 42.8                          | Nowroozi et al (52)       | 2011                     |
|             | Article| 186         | 127  | 68.3                          | Saderi et al (53)         | 2011                     |
|             | Article| 106         | 62   | 58.49                         | Shahsavani et al (54)     | 2011                     |
|             | Abstract| 100         | 90   | 90                            | Ghorbani et al (55)       | 2011                     |
|             | Abstract| 150         | 67   | 44.6                          | Mobayen et al (56)        | 2011                     |
|             | Abstract| 104         | 76   | 73.1                          | Sehebnasagh et al (57)    | 2011                     |
|             | Article| 125         | 107  | 85.6                          | Yepehrisershe it et al (58)| 2012                    |
|             | Article| 100         | 56   | 56                            | Razavi Davoodi et al (59) | 2012                    |
|             | Abstract| 48          | 17   | 35.4                          | Azizi Barjini et al (60)  | 2012                    |
| Tonekabon   | Abstract| 55          | 30   | ≥54.54*                       | Forghani et al (61)       | 2011                     |

1 MRSA strains were detected/confirmed by PCR amplification of mecA gene
* PCR of mecA was done only for strains resistant to methicillin by phenotypic methods
† Results were obtained by comparing references (31) and (32)
The heterogeneity of MRSA prevalence at national and international level is not completely understood. Possible explanations are different in infection control practices, antimicrobial administration, human population, predominant strain(s), study design and laboratory testing for determining resistance (2, 69).

This study has some limitations. First, it cannot fully represent Iran because there were no data on meca-MRSA from many parts of the country. However, as described above, this is preferred to mixing the results from different phenotypic methods with genotypic ones. Second, due to limited access to in-press articles and theses, some studies might have been missed, which is also suggested by statistical analysis.

Conclusion
Our study showed that the mean MRSA RF among Iranian studies is in the high range. Thus, measures should be taken to keep the emergence and transmission of these strains to a minimum.

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