Inducible Clindamycin Resistant *Staphylococcus aureus* in Iran: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 30 Mar 2015
Revised: 10 Apr 2015
Accepted: 17Apr 2015

Keywords:
Staphylococcus aureus, Inducible resistance, Cindamycin, Iran, Systematic review

ABSTRACT

Introduction: *Staphylococcus aureus* is a prominent human pathogen. One of the drugs used in the treatment of staphylococcal infections (particularly infections of skin and soft tissue), is clindamycin. Resistance to clindamycin includes two types: inducible and constitutive. Routine laboratory methods of antibiotic susceptibility testing cannot detect the inducible type and D-test is required for its detection. The purpose of this systematic review was to determine the relative prevalence of this type of resistance in Iran.

Methods: Search terms "inducible clindamycin resistant", "D-test", "*Staphylococcus aureus*" and "Iran" were used to find relevant articles in PubMed, Google Scholar and two Persian search engines. Also, the abstracts of the recent national microbiology congresses were checked. All studies used D-test to find $iMLS_B$ (inducible macrolide, lincosamide and streptograminB resistance) phenotype among clinical isolates (not nasal swabs) of *S. aureus*, were included. In order to perform meta-analysis, we used "comprehensive meta-analysis" software (ver. 2).

Results: In total, 9 articles and 8 abstracts related to the topic of the study were found. Random effects meta-analyses showed a pooled estimate for percentage of $iMLS_B$ phenotype among 2683 samples of *S. aureus* was about 10% (95% confidence interval: 0.07-0.12). Using the fixed effect model, the odds of positive $iMLS_B$ in methicillin-resistant *S. aureus* was about 5 times more likely to occur in comparison with methicillin-susceptible *S. aureus* (95% CI: 3.49 to 7.76).

Conclusion: Fortunately, the relative frequency of inducible resistance to clindamycin in our country is relatively low. However, we believe that D-test should be performed for all erythromicin-resistant isolates in order to identify inducible resistance to clindamycin. Moreover, reevaluation of inducible resistance to clindamycin in forthcoming years is highly recommended.

- ***Please cite this paper as:*** Zarifian AR, Setayesh Y, Askari E, Amini AR, Rahbar M, Naderinasab M. Inducible Clindamycin Resistant *Staphylococcus aureus* in Iran: A Systematic Review and Meta-Analysis. *J Med Bacteriol.* 2015; 4 (1, 2): pp.43-52.

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Introduction

According to the estimates of center for disease control and prevention (CDC), approximately 1.7 million Americans are infected annually by hospital-acquired infections and 99,000 of them die (1). One of the most frequent causes of hospital-acquired infections in many parts of the world is *Staphylococcus aureus* (2). Out of every hundred people in America who are admitted to the hospitals, one person is suffering from infections caused by *S. aureus*. In other words, this bacteria is responsible for about 390,000 infections per year (3). *S. aureus* is a well adapted human/zoonotic colonizer which can also cause a wide range of diseases and its treatment is becoming more difficult because of an increasing rate of drug resistance. Therefore, due to the fact that primary empirical therapy should be done according to an antibiotic susceptibility pattern of the geographical region, knowing the drug resistance of strains is vital for microbiologists and infectious diseases specialists (4, 5). In the past, penicillin was used for the treatment of Staphylococcal infections. As time passed, bacteria became resistant to penicillin by producing β-lactamase. Therefore, physicians proceeded to prescribe new drugs, nafcillins (a group of β-lactamase resistant β-lactams) for instance (6). Increasing resistance to these agents obliged physicians to use other antibiotics such as vancomycin and clindamycin. However, widespread use of these antimicrobial agents has led to an increase in the number of *S. aureus* strains resistant against them (7). Macrolide, lincosamide and streptogramin (MLS) antibiotics have differences in their chemical structure, but have a similar mode of action and are classified in the same group. These antibiotics, including clindamycin, which is among the lincosamide antibiotics, inhibit bacterial protein synthesis by binding to 23S rRNA in 50s ribosomal subunits (8, 9). Therefore, one feature for clindamycin is its capability to stop the synthesis of staphylococcal enterotoxins which are the known causes of food poisoning and toxic shock syndrome (10). Four main mechanisms have been reported for acquiring resistance to antibiotics in the MLS group: (A) target modification, (B) efflux of antibiotics, (C) ribosomal methylation (by a group of genes called *erm* (erythromycin ribosome methylase) and (D) mutation (8, 9). Among various types of resistance to MLS group, the MLS_B phenotype is one of the most important types because it is resistant to nearly all of the antibiotics in the MLS group. MLS_B phenotype can be either constitutive ($cMLS_B$; i.e. rRNA methylase is always produced) or inducible ($iMLS_B$; i.e. methylase is produced only in the presence of an inducing agent) (8, 11). It is possible that $iMLS_B$ isolates (inducible resistant isolates) mutate into $cMLS_B$ in the course of treatment; Therefore, accurate detection of antibiotic resistance is very important (10). To detect the inducible clindamycin resistance, clinical and laboratory standards institute (CLSI) has included double disk diffusion methods (D-test) since 2004 (12). Limited data is available for the prevalence of $iMLS_B$ phenotype in Iran. The purpose of this systematic review was to determine the relative prevalence of this type of resistance in Iran.

Materials and Methods

Time period and keywords

Systematic search of the literature was performed in December 2011 and repeated in December 2012. All articles, including the words "*Staphylococcus aureus*" or "*aureus*", "inducible clindamycin"or "inducible resistance" or "inducible macrolide" or "D-test" and "Iran" (in English journals) were retrieved from PubMed and Google Scholar.

Searching for farsi articles

For Persian articles we searched in two Persian scientific search engines (in both English and Farsi): Scientific information database (www.sid.ir) and Iran Medex (www.iranmedex.com). The English and Farsi keywords were also searched at all Iranian academic domains (i.e. ending with .ac.ir) using "Google advanced search".

Searching in the abstract books of congresses

Abstract books of nine national microbiology congresses (i.e. 1st-5th Iranian congresses of clinical microbiology, 12th Iranian and 1stinternational congress of microbiology, the 1st Iranian international congress of medical bacteriology, 13th Iranian and 2st international congress of microbiology and 4thcongress of clinic and laboratory) were also searched.

Inclusion and exclusion criteria

Finally, all studies used D-test to find $iMLS_B$ phenotype among clinical isolates (not nasal swabs) of *S. areus*, were included. Studies, which investigated genetic resistance markers (such as *ermA*, *ermB*, *ermC* and *msrA*) were also summarized.

Statistical analysis

We performed meta-analyses with the Der-Simonian and Laird random effects model to obtain the pooled overall prevalence of methicillin-resistant *S. aureus* (MRSA). Using the fixed effect model, we obtained the pooled odds ratio (OR) for positive iMLSB in MRSA. We used the Cochran's Q-test (with significance level at $P< 0.1$) to assess between-study differences and the I^2 statistic to quantify the proportion of observed inconsistency across study results not explained by chance.

All analyses were performed with comprehensive meta-analysis software (ver. 2).

Publication bias

There are concerns that studies with statistically significant results are more likely to be published compared to studies with non-significant (negative) results. Several lines of evidence show that studies that report relatively high effect sizes are more likely to be published than studies that report lower effect sizes. Since published studies are more likely to find their way into a meta-analysis, any bias in the literature is likely to be reflected in the meta-analysis as well. This issue is generally known as publication bias (13). However, by contrast to analytical studies, this bias does not arise within a meta-analysis of descriptive studies as we did in this article. Thus, in a small descriptive study a true value of an effect (or a parameter) may be estimated higher or lower than it was, however it does not result in easily considering that a small descriptive study is less likely to be published. Given that, a meta-analysis of descriptive studies will generally not reflect the publication bias (14).

Results

Among 334 possibly related articles, 17 studies investigated $iMLS_B$ among clinical isolates (9 papers, 8 abstracts) (Figure 1). All these studies were presented/published between 2007 and 2012. The largest sample size was 721 and the smallest one was 32 (Table 1).(7, 10, 15-29) Out of 17 studies, 13 studies had mentioned the rate of MRSA (7, 10, 16, 17, 19-22, 24, 25, and 27-29). Pooled estimate for the rate of MRSA among *S. aureus* isolates was 0.45 (95% CI: 0.39-0.52).

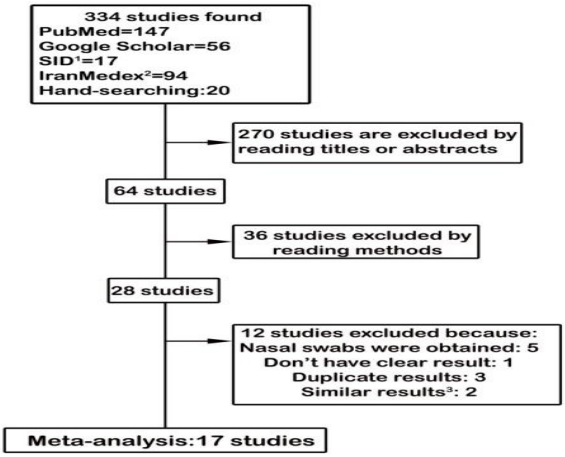

Figure 1. The flow chart of study selection.
[1]Scientific Information Database (available at: www.sid.ir)
[2]Available at: www.iranmedex.com
[3]We selected one study for the prevalence of inducible clindamycin resistant isolates and anotherone which reported relative prevalence of iMLS$_B$ in MSSA and MRSA

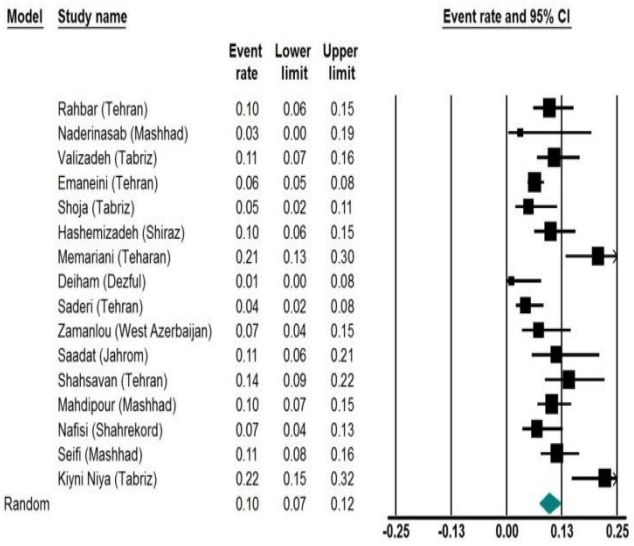

Figure 2. pooled estimates for rate of D-phenotype among *Staphylococcus aureus* isolates in different studies. ES: estimate, CI: confidence interval

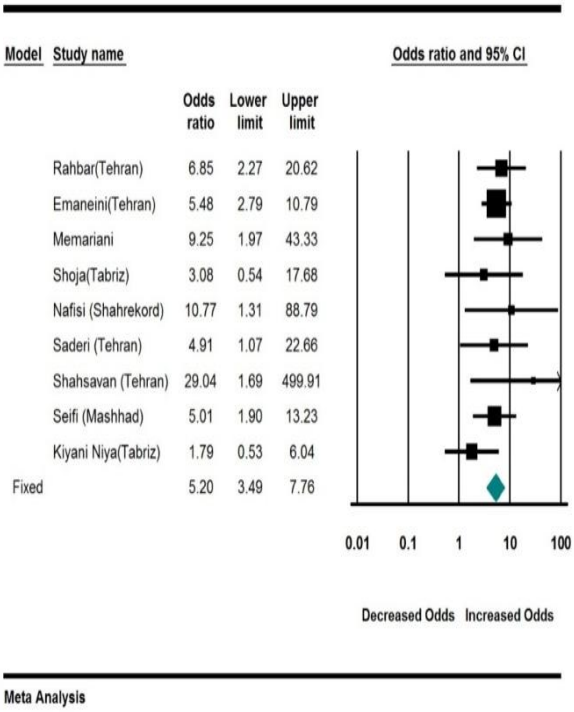

Figure 3. Pooled estimates for the odds of D-phenotype among methicillin resistant *S. aureus* compared to methicillin susceptible *S. aureus*. OR: odds ratio

For pooling the rates, first the heterogeneity chi-squared test was considered which showed significance, suggesting the presence of heterogeneity (Q = 101.72, d.f. = 12, P-value <0.001). Thus, the random effect model was used. Heterogeneity chi-squared test for pooling the prevalence of Imlsb phenotype was significant, suggesting the presence of heterogeneity (Q= 54.8, d.f. = 15, P-value <0.001). Since the heterogeneity test was significant, the random effect model was used for our study. Using random effects model, the pooled estimate for percentage of iMLS$_B$ phenotype was 10% (95% confidence interval (CI): 0.07-0.12) whereas the raw values varied from 1 to 22 percent reported in different studies (Figure 2).

Table 1: Papers and abstracts found by search strategy (sorted by year of publication/presentation)

First Author	Year/ Reference	*S.aureus*	iMLS$_B$ (%)	MRSA	MSSA	iMLS$_B$ in MRSA	iMLS$_B$ in MSSA
Babbar (Tehran)	2007/(20)	175	17 (9.7%)	53	122	12	5
Naderinasab (Mashhad)	2007/(18)	32	1 (3.1%)	NA	NA	NA	NA
Valizadeh (Tabriz)	2008/(23)	167	18(10.7%)	-	NA	NA	-
Emaneini (Tehran)	2009/(16)	721	46 (6.4%)	264	457	34	12
Memariani (Tehran)	2009/(10)	87	18 (20.7%)	48	39	16	2
Saderi (Tehran)	2009/(7)	244	Not included	133	111	11	2
Shoja (Tabriz)	2009/(22)	100	5 (5.0%)	41	59	4	2
Hashemizadeh (Shiraz)	2009/(17)	170	17 (10.0%)	85	85	Not included	Not included
Deilam (Dezful)	2010/(15)	86	1 (1.2%)	NA	NA	NA	NA
Nafisi (Shahrekord)	2011/(19)	131	9 (6.9%)	60	71	8	1
Saderi (Tehran)	2011/(21)	186	8 (4.3%)	86 (Not included)	NA	5 (Not included)	3 (Not included)
Zamanlou (West Azerbyjan)	2011/(24)	96	7 (7.3%)	16	80	NA	NA
Saadat (Jahrom, Fars)	2011/(25)	71	8 (22%)	36		NA	NA
Mahdipour (Mashhad)	2011/(26)	254	26 (10.2%)	??			
Shahsavan (Tehran)	2011/(27)	106	15 (14.15%)	62	44	15 (24.19%)	0 (0 %)
Seifi (Mashhad)	2012/(28)	211	24 (11.37%)	88	123	18 (20.5%)	6 (4.88%)
KiyaniNiya (Tabriz)	2012/(29)	90	20 (22.2%)	61	26	15 (24.6%)	4 (15.4%)

iMLS$_B$: inducible macrolide, lincosamide and streptograminB resistance; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; NA: Not Available

The heterogeneity index I^2, which shows the proportion of variation due to heterogeneity, was 72.63% indicating an almost high heterogeneity. After removal of 2 outlets (i.e. references no. 10 and 31), the pooled prevalence was 8.6% (95% CI: 0.069-0.104), and the heterogeneity became moderate (I^2= 49.3%) (Data not shown). Heterogeneity chi-squared test - for pooling the ORs for positive $iMLS_B$ in MRSA compared to methicillin-resistant *S. aureus* (MSSA) - was not significant so it informs us about the absence of heterogeneity (Q= 5.96, d.f.= 8, P-value = 0.65). Hence, the fixed effect model was used. The pooled OR was 5.2 (95% CI: 3.49-7.76) which means that the odds of positive $iMLS_B$ in MRSA was about 5 times more likely to occur in comparison with MSSA. As it turned out, the odds ratio shows that D-phenotype is significantly more frequent among MRSA isolates as compared to MSSA isolates.

Also, I^2 statistic was 0.0 %, indicating the absence of heterogeneity. Moreover the forest plot shows that there is a high overlapping among the confidence intervals of studies (Figure 3).

Genetic assays in iMLSB studies

In the study of Hassani and colleagues, $iMLS_B$ strains were found to have *ermA*, *ermB* or *ermC* genes, among which, *ermA* was the most frequent. The distribution of MLS resistance genes among *S. aureus* strains isolated in two different studies by Emaneini *et al*. and Saderi *et al*., which had MLS_B resistance is summarized in the Table 2 (16, 21).

Table 2: Distribution of macrolide resistance genes among *S. aureus* strains isolated in studies of Saderi *et al*. and Emaneini *et al*. (7, 16)

Resistant Phenotype	Number of genes						
	ermA	*ermB*	*ermC*	*msrA*	*ermA+ermC*	*ermA+msrA*	*ermA/ermC* Negative
$cMLS_B$	111	-	157	31	109	7	39
$iMLS_B$	21	1	18	-	11	-	1
Total	132	1	175	31	120	7	40

Conclusion

Nowadays, the increasing frequencies of *S. aureus* resistance have led to the renewed interest in the use of MLS_B antibiotics, especially clindamycin, in many countries (30). Although clindamycin is an appropriate antimicrobial agent for the treatment of mild to moderate MRSA infections, many of erythromycin-resistant MRSA strains have inducible clindamycin resistance that may lead to treatment failure (5). Some previous studies performed in the United States have indicated that approximately 45% of erythromycin-resistant *S. aureus* isolates have inducible clindamycin resistance (31). However, the prevalence of D-phenotype was much lower in our country. According to our study, the average prevalence of $iMLS_B$ in Iran was 10 %. Although this is not in a high-risk range, physicians should prescribe more carefully and precisely because these inducible strains have the potential to change into constitutive type and ultimately cause treatment failure. In a regional outlook, the prevalence of $iMLS_B$ in Iran is quite lower than Turkey (ranging from 11 to 39%), its adjacent country in the Middle East (32-34). From a global perspective, our data are partly similar to those in the United States found by Huang *et al*.(10.2%), (35) but seem to be higher than Nepal (3%) (36). There are heterogeneous data available from different cities of India, most of which are significantly higher than our results (ranging from 16% to 37%) (37, 38). On the other hand, there are some data, which are approximately equal to the ones in our study (9.15%) (39). There is also a report from south India indicating that all their MRSA isolates were inducible clindamycin resistant, which clearly represents the emergence of extended antibiotic resistance in *S. aureus* strains (40). A Canadian study published in 2010, detected 82% of their clindamycin resistant isolates to show $iMLS_B$ phenotype, using D-test (41). Pardo *et al*. in their 2013 study, which was performed on Uruguayan children, found 101 community acquired MRSA (CA-MRSA), of which about 40% showed $iMLS_B$ phenotype (42). This is relatively similar to the results of Amorim *et al*. who reported inducible MLS_B phenotype in 36.8% of their clindamycin resistant isolates (43). In conclusion, the relative frequency of inducible resistance to clindamycin in our country is comparatively low. Nevertheless, we believe that D-test should be performed for all erythromycin-resistant isolates in order to identify inducible resistance to clindamycin. Besides, reevaluation of inducible resistance to clindamycin in forthcoming years is highly recommended.
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Conflict of interest

None declared conflicts of interest.

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