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Review

High-level Gentamicin Resistance among Clinical Isolates of Enterococci in Iran: a Systematic Review and Meta-analysis

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Abstract

Enterococci have been considered as one of the most common causes of nosocomial infections. The spread of antibiotic resistance has posed a serious challenge to treating the enterococcal infections. High-level aminoglycosides resistance leads to failure in the synergistic combination therapy.

This study aimed to estimate the prevalence of high-level gentamicin resistance (HLGR) among clinical isolates of enterococci in Iran.

Systematic literature search was conducted in the Web of Science, PubMed, Scopus and Google Scholar electronic databases from articles which were published from April 2000 to September 2018. Literature search yielded 918 studies. Eligible studies were selected according to the defined inclusion and exclusion criteria. Statistical heterogeneity was estimated by Q statistic and the I^2 index. The Begg's rank correlation test and Egger's weighted regression tests were used to evaluate possible publication bias.

Nineteen studies were included in this review. According to the meta-analysis results, the prevalence of HLGR among *Enterococcus* spp. was 49.4% (95% CI: 42.2%-56.6%). It was estimated 44.3% (95% CI: 38.1%-50.8%) and 66.3% (95% CI: 51.4%-78.6%) for *E. faecalis* and *E. faecium*, respectively.

Since notable rate of HLGR in enterococci was seen in this analysis, improving the implementation of all aspects of the infection control programmes is required. Accurate and regular monitoring of infection control procedures are necessary for reducing the dissemination of such infections.

Keywords

Enterococcus, Iran, high-level gentamicin resistance (HLGR), meta-analysis, systematic review

INTRODUCTION

Enterococci are common inhabitants of the human gastrointestinal tract and they are known to be potent pathogens responsible for several infections in humans.[1] Enterococci have been considered as one of the most common causes of nosocomial infections worldwide.[2] The spread of antibiotic resistance has posed a serious challenge to the treatment of the enterococcal infections.[3] Simultaneous prescription of aminoglycosides and cell wall active agents (such as β-lactams or vancomycin) will be synergistically effective against severe infections.[4] In 1979, high-level aminoglycosides resistance in enterococci was initially described in the US.[5] High-level resistance (HLR) to the aminoglycosides leads to failure in the synergistic combination therapy.[4,6] Moreover, horizontal HLR associated genes transfer is common between various strains and it can increase the risk of the development and dissemination of such resistance in enterococci.[7]

According to available data, the prevalence rates of high-level gentamicin resistance (HLGR) in enterococci have been reported from several parts of Iran.[1,8-11] However, there is no comprehensive analysis regarding HLGR amongst *Enterococcus* isolates, obtained from several infections in the country. Therefore, the aim of the present study was to assess the prevalence of HLGR among clinical isolates of enterococci in Iran using a systematic review and meta-analysis conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

MATERIALS AND METHODS

Search strategies

A systematic literature search was conducted in the Web of Science, PubMed, Scopus, and Google Scholar electronic databases from papers that were published from April 2000 to September 2018 following the PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The following keywords, "*Enterococcus*" or *"E. faecalis"* or *E. faecium* and "high level aminoglycoside resistant" or "high level gentamicin resistant" or "HLGR" in combination with "Iran" were searched as scientific terms in the present survey. We also searched bibliographies of retrieved articles for additional references.

Eligibility criteria and study selection

Cross-sectional or cohort studies that reported the prevalence of HLGR in Iran were considered. To determine the articles which had inclusion criteria, the titles, abstracts and full texts were screened independently by two reviewers and any discrepancies were resolved by consensus. The articles published in English or Persian language which were indexed in PubMed or Scopus with the following characteristics were included: standard used methods for HLGR detection in *Enterococcus* strains and reported data on number of HLGR among *Enterococcus* strains. According to the Clinical and Laboratory Standards Institute (CLSI) guidelines[12], standard methods for detecting HLGR among *Enterococcus* strains are broth dilution, agar dilution, and disk diffusion methods by high-content gentamicin (120 μg). Additionally, research that has been conducted by non-Iranian authors on the Iranian population or samples were also assessed. Studies with nonstandard methods and without report of HLGR prevalence were excluded. We also excluded studies which their sample size was less than 10 isolates, nonhuman studies, review articles, meta-analyses or systematic reviews, congress abstracts and duplicate publication of the same studies.

Data extraction and definitions

Data collection was performed in parallel by two authors and discrepancies were resolved by a third author. Data collected included: first author's name, the study performing time, publication date, the study setting, sample size (number of *Enterococcus, E. faecalis* and *E. faecium* isolates) and prevalence of HLGR.

Statistical analysis

Analysis of data was performed by Comprehensive Meta-Analysis Software v. 2.2 (Bio stat Company). Meta-analysis was performed using random effects model to estimate pooled prevalence and corresponding 95% confidence interval (CI). Statistical heterogeneity between and within groups was estimated by the Q statistic and the I^2 index. The Begg's rank correlation test and Egger's weighted regression tests were used to evaluate possible publication bias ($p<0.05$ was considered indicative of a statistically significant publication bias).

RESULTS

The literature search yielded 918 studies, 856 were excluded based on their index and review of title and abstract, leaving 62 articles for full text review. Of 62 reviewed studies, HLGR was not detected in 22 studies according to the standard methods, 12 studies did not report the prevalence of *Enterococcus* or *Enterococcus* spp., 4 studies had sample size less than 10 isolates, and the results of 5 studies were unclear. Eventually, 19 eligible studies were chosen for final analysis. There were no overlapping study populations in the final review. **Fig. 1** shows the study selection process and reasons for exclusion. None of the included studies received direct funding from pharmaceutical companies. The full results of included articles, the prevalence of *E. faecalis* and *E. faecium* and the frequency of HLGR amongst them are presented in **Table 1**.

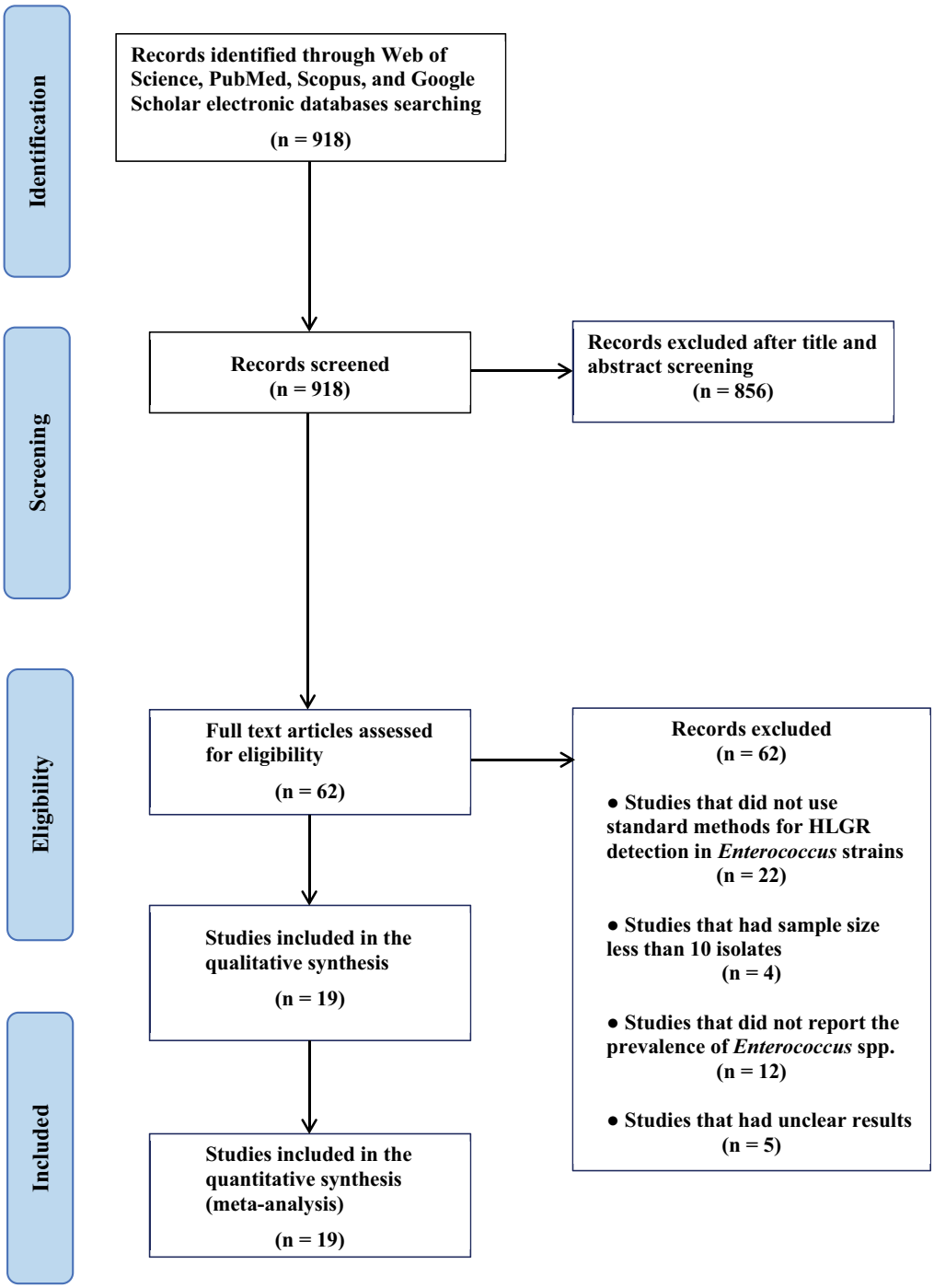

Figure 1. Summary of the literature search and study selection. HLGR: high-level gentamicin resistance.

Nineteen studies investigated the frequency of HLGR among *Enterococcus* spp. The pooled prevalence for HLGR among *Enterococcus* isolates was 49.4% (95% CI: 42.2%-56.6%) ranging from 15% to 96% **(Fig. 2)**. There was a significant heterogeneity among the 19 studies (χ^2=301.393; p<0.001; I^2=94%). Additionally, Begg's and Egger's tests were performed to quantitatively evaluate the publication biases. The results of Begg's test (z=0.42, p=0.67) and Egger's test (t=0.54, p=0.6) showed no evidence of publication bias.

According to the included publications, in 15 studies the frequency of HLGR in *E. faecalis* strains was investigated. The pooled prevalence of HLGR among *E. faecalis* isolates was 44.3% (95% CI: 38.1%-50.8%) ranging from 24% to 65% **(Fig. 3)**. There was a significant heterogeneity among the 15 studies (χ^2=111.703; p<0.001; I^2=87.47%). There was no evidence of publication bias according to Begg's rank correlation analysis (z=0.1, p=0.92). Egger's regression analysis also confirmed there is no evidence of publication bias (t=1.08, p=0.3).

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Table 1. Characteristics of studies included in the meta-analysis

Study Details					Size (n)			HLGR		
Author	**Publication year**	**Years of study**	**City or Region**	**Diagnostic method**	**Sample size**	***E. faecalis***	***E. faecium***	**Total**	***E. faecalis***	***E. faecium***
Feizabadi et al.[13]	2003	2000-2001	Tehran	Broth microdilution method	59	59	-	18	18	-
Feizabadi et al.[14]	2004	2000-2002	Tehran	Macro-broth dilution method	182	182	-	76	76	-
Feizabadi et al.[15]	2006	2002-2004	Tehran	Broth microdilution method	114	79	35	59	42	17
Saifi et al.[16]	2008	2005-2006	Tehran	Broth microdilution method	638	496	142	295	158	137
Emaneini et al.[17]	2008	UN	Tehran	Agar dilution method	326	210	116	171	106	65
Soltan Dallal et al.[18]	2008	2005-2006	Tehran	DDM by high-content gentamicin (120 μg)	147	104	43	98	64	34
Feizabadi et al.[19]	2008	2006-2007	Tehran	DDM by high-content gentamicin (120 μg)	102	102	-	66	66	-
Aligholi et al.[20]	2009	UN	Tehran	Broth microdilution method	495	320	157	233	134	93
Saifi et al.[21]	2009	2005-2006	Tehran	Broth microdilution method	320	-	75	48	-	-
Jabalameli et al.[22]	2009	2002-2004	Tehran	Agar dilution method	413	277	123	215	-	-
Hasani et al.[23]	2012	2008-2010	Northwest Iran	Agar dilution method	220	152	68	136	79	54
Dadfarma et al.[8]	2013	2009	Tehran	Broth microdilution method	142	90	47	62	38	21
Behnood et al.[10]	2013	2009-2011	Northwest Iran	Agar dilution method	111	89	22	36	23	13
Emaneini et al.[24]	2016	2012	Tehran	DDM by high-content gentamicin (120 μg)	27	19	8	26	-	-
Khani et al.[25]	2016	2011-2012	Kermanshah	Broth microdilution method	138	63	33	123	-	-
Esmailzadeh et al.[26]	2016	2013-2014	Kashan	Broth microdilution method	180	108	72	43	26	17
Heidari et al.[1]	2016	2013-2014	Tehran	Broth microdilution method	57	46	2	31	30	1
Heidari et al.[9]	2017	2015-2016	Shiraz	DDM by high-content gentamicin (120 μg)	51	51	-	27	27	-
Amini et al.[11]	2018	2016	Kermanshah	DDM by high-content gentamicin (120 μg)	108	94	14	46	33	13

DDM: *disk diffusion method*

We found 10 articles which investigated the frequency of HLGR in *E. faecium* isolates (one study was excluded because the sample size for *E. faecium* was less than ten). The pooled prevalence of HLGR in *E. faecium* isolates was 66.3% (95% CI: 51.4%-78.6%) ranging from 24% to 96% **(Fig. 4)**. Based on Q statistic and the I^2 index, heterogeneity was significant (χ^2=100.387; p<0.001; I^2=91%). Also, the Begg's rank correlation analysis (z=1.25, p=0.21) and Egger's regression analysis (t=1.2, p=0.26) confirmed no evidence of publication bias.

DISCUSSION

To the best of our knowledge, this study is the first systematic review regarding the prevalence of HLGR amongst

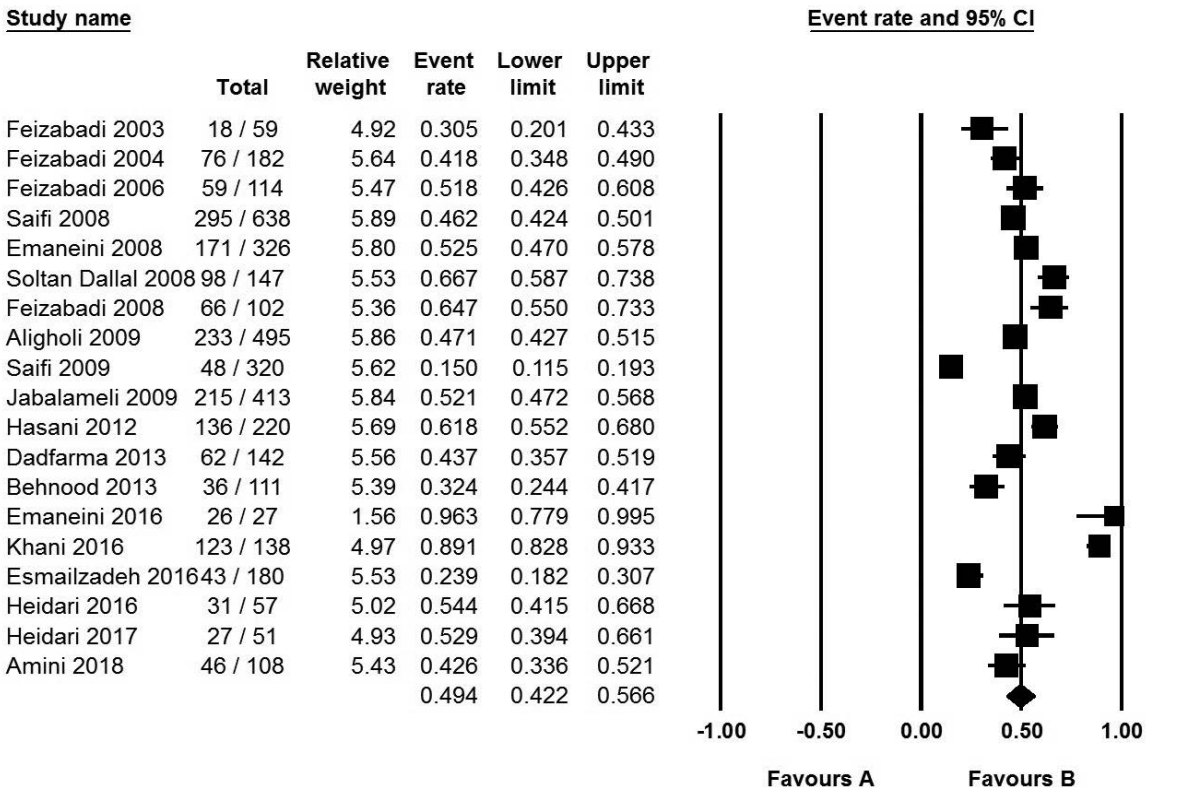

Figure 2. Forest plot of prevalence of HLGR among *Enterococcus* spp. in Iran.

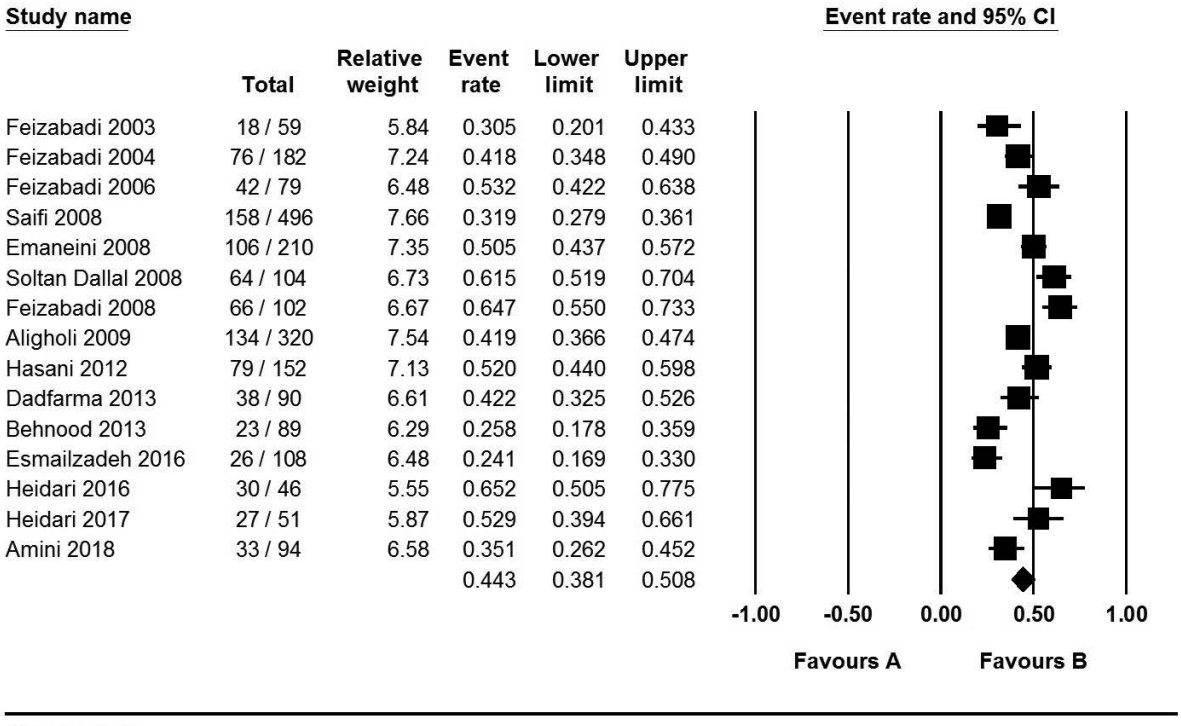

Figure 3. Forest plot of prevalence of HLGR among *E. faecalis* isolates in Iran.

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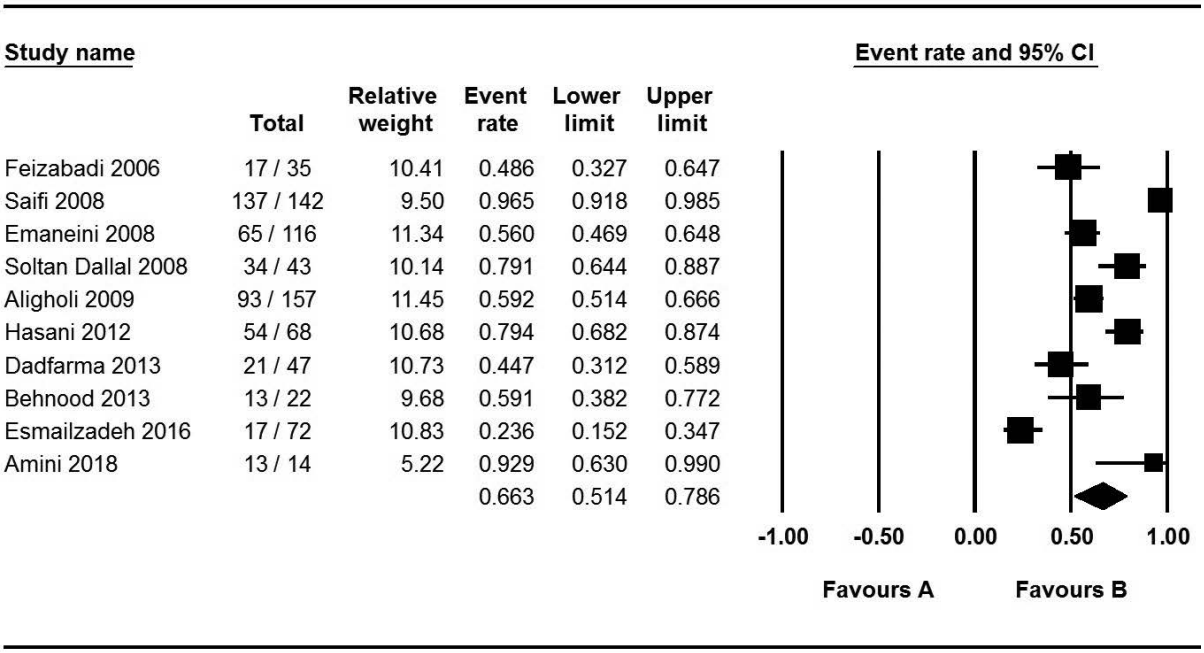

Figure 4. Forest plot of prevalence of HLGR among *E. faecium* isolates in Iran.

enterococci that caused several infections in Iran. According to the meta-analysis results, the pooled prevalence of high-level gentamicin resistant *Enterococcus* isolates was 49.4% (95% CI: 42.2%-56.6%). The prevalence of HLGR in *Enterococcus* in Iran is more than the one reported in a previous investigation in a neighbor country, Kuwait (14%).[27] However, high rates of HLGR in enterococcal bacteremia have been described in industrialized countries such as Korea (63%) and Spain (60.4%).[28,29]

Our results indicated that the pooled prevalence of high-level gentamicin resistant *E. faecalis* isolates was 44.3% (95% CI: 38.1%-50.8%). More rates have been reported from Saudi Arabia (75.3%) and Taiwan (60%).[30,31] The prevalence of HLGR in *E. faecalis* in Iran was more than that in other countries such as Japan (34.2%), Turkey (30%), Kuwait (14.7%), and USA (15%).[27,32-34] Nevertheless, notable HLGR prevalence of bacteremia causative *E. faecalis* strains has been reported from Spain (62.9%), China (40.9%), Denmark (38.2%), New Zealand (38%), and Japan (32%).[29,35-38]

Based on the meta-analysis results, the pooled prevalence of HLGR in *E. faecium* isolates was 66.3% (95% CI: 51.4%-78.6%) in Iran. It is more than the prevalence in two other Asian countries such as Kuwait (15.6%) and Japan (9.2%).[27,32] Also, higher rates of HLGR in *E. faecium* (Up to 88%) has been described in Turkey.[33] However, high prevalence of high-level gentamicin resistant *E. faecium* isolated from blood stream was reported from developed countries such as Canada (71.6%), Denmark (64.4%), and Spain (53.8%).[29,35,39] It was lower for China (43.2%), New Zealand (25%), and Japan (24%).[36-38] The mentioned data, suggested that high-level gentamicin resistant strains possess significant ability to cause invasive infections such as blood stream infection.

Prevalence of resistant enterococcal strains amongst patients may be due to several factors; recently, various studies described the effects of diet on gut microbiota composition. Special diet such as fiber (as a non-digestible carbohydrate) consumption change *Enterococcus* species population in gastrointestinal tract.[40,41] Also, drug-resistant *Enterococcus* isolates of animal origin can easily contaminate the food chain and infect humans and affect the intestinal colonization.[42,43] Hospitalization of colonized patients by such strains may lead to dissemination of drug-resistant strains in hospital environment and among patients. Therefore, diverse ranges of high-level gentamicin resistant enterococci isolated from hospitalized patients in various countries may be related to their diverse dietary habits.

Enterococci are able to survive under environmental stresses such as dryness and selective antimicrobial pressure. Therefore, hospital setting has an important role in the spread of resistant strains among patients and high-quality disinfection and cleaning of all surfaces and medical equipment are necessary.[44-46] Inadequate efficacy of utilized disinfectant due to reduced biocide sensitivity in enterococci may be one of the major issues in the infection control implementation in hospitals.

In addition, unfavourable condition may induce viable-but-nonculturable (VBNC) strains.[44] This phenomenon can lead to transmission of resistant strains among patients, despite the effective appearance of the infection control policies.

Emergence of drug-resistant bacteria has accelerated by overuse and misuse of antibiotics.[47,48] Ineffective ami-

noglycosides prescription may contribute to selection of high-level gentamicin resistant strains. Colonization and dissemination of selected strains in hospital enhance the prevalence of HLGR among hospitalized patients.

HLGR in enterococci often occurs through acquisition of *aph(2")-Ia-aac(6')-Ie* gene.[7] This bifunctional gene is most commonly located on a transposon. Therefore, horizontal gene exchange and acquired HLR traits will occur quickly among colonized *Enterococcus* spp. Other HLGR encoding genes are most frequently in *E. faecium*.[7] It can explain the greater prevalence of HLGR among *E. faecium* strains.

Considering the mentioned features of enterococci, it seems that the most effective strategy among the many possible strategies for reducing the transmission of healthcare-associated infections, is hand hygiene compliance amongst healthcare workers. As mentioned in a previous systematic review in Iran, training of healthcare workers seems to be necessary for prevention and control of nosocomial infections.[49]

There are some limitations to the present review. First, only the published articles which were indexed in PubMed or Scopus were included in this meta-analysis. Secondly, few studies had been performed in different region of the country and most of the evaluated articles were related to Tehran (the capital of Iran).

CONCLUSIONS

The present systematic review indicates notable prevalence of high-level resistance to gentamicin amongst *Enterococcus* species in Iranian patients. According to the papers published from April 2000 to September 2018, diverse ranges were reported from Iran. This comprehensive analysis showed that, the prevalence of high-level gentamicin resistant *Enterococcus* spp. was 49.4%. Also, the prevalence of HLGR in *E. faecium* strains was greater than that in *E. faecalis*. Therefore, improving the implementation of all aspects of the infection control programs according to the international standards is necessary.

Conflict of Interest

All authors declare no conflicts of interest.

Funding

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Устойчивость к гентамицину высокого уровня среди клинических изолятов энтерококков в Иране: систематический обзор и метаанализ

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Резюме

Enterococci считаются одной из наиболее частых причин внутрибольничных инфекций. Высокая устойчивость к аминогликозидам приводит к недостаточности синергетической комбинированной терапии.

Целью этого исследования было оценить частоту высокой устойчивости к гентамицину (HLGR) среди клинических изолятов энтерококков в Иране.

Был проведён систематический обзор литературы в электронных базах данных Web of Science, PubMed, Scopus и Google Scholar на предмет поиска статей, опубликованных с апреля 2000 г. по сентябрь 2018 г. Поиск в доступной литературе выявил 918 исследований. Подходящие исследования были отобраны в соответствии с заранее определенными критериями включения и исключения. Статистическая неоднородность измерялась Q-статистикой и индексом I^2. Для оценки возможной субъективности публикаций использовались тест ранговой корреляции Бегга и регрессионный тест Эгера.

В этот обзор было включено девятнадцать исследований. По результатам метаанализа частота HLGR к *Enterococcus* spp. составила 49.4% (95% CI: 42.2% -56.6%). Результаты показали 44.3% (95% CI: 38.1% –50.8%) и 66.3% (95% CI: 51.4% –78.6%) для *E. faecalis* и *E. faecium*, соответственно.

Поскольку в ходе этого анализа была обнаружена высокая частота HLGR в отношении enterococci, мы пришли к выводу, что необходимо улучшить все аспекты процедур инфекционного контроля, чтобы уменьшить распространение таких инфекций.

Ключевые слова

Enterococcus, Иран, высокая устойчивость к гентамицину (HLGR), метаанализ, систематический обзор