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Prevalence of Vancomycin and Gentamycin Resistance among Enterococci spp. in Iran during 2007-2019: A Systematic Review

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ABSTRACT

Backgrounds: Enterococci are Gram-positive bacteria that colonize the intestine of warm-blooded animals and humans as normal flora. Enterococci cause a variety of community-acquired and nosocomial infections. The emergence of vancomycin and gentamicin resistant enterococci has made a major challenge in the treatment of enterococcal infections worldwide. Therefore, the present study was conducted to evaluate the prevalence of vancomycin and gentamycin resistance among *Enterococcus* spp in Iran during 2007-2019.

Materials & Methods: In this study, 26 studies were reviewed to collect data on the frequency of vancomycin and gentamicin resistant enterococci in Iran. To find studies published during January 2007 to January 2019, a search strategy was performed by searching different Iranian and international databases, including SID, Google Scholar, Scopus, Medline, Pub Med, and Web of Science.

Findings: The prevalence of vancomycin- and gentamicin-resistant enterococci was very high in Iran (41 and 44%, respectively). Accordingly, *Enterococcus faecalis* was more prevalent in clinical samples compared to *E. faecium* (75.49% vs. 24.05%). However, resistance to vancomycin was higher in *E. faecium* strains compared to *E. faecalis.*

Conclusion: Due to the increasing vancomycin and gentamicin resistance among *Enterococcus* species in Iran, it is necessary to design strategies that lead to the rational prescription of antibiotics and limit the spread of resistant enterococci.

Keywords: Enterococci, Resistance, Vancomycin, Gentamicin.

CITATION LINKS

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Introduction

Enterococcus spp are Gram-positive bacteria colonizing the intestine of warm-blooded animals and humans as normal flora [1]. They are also natural inhabitants of the environment and found in soil, water, and plants as well as in dairy and other food products [2]. Their ability to colonize, survive, and persist in a hospital environment allows these pathogens to be easily transmitted through the cross-contamination process [3]. Moreover, the emergence of a diverse array of responses under the effect of selective pressures in a competitive environment and genetic plasticity allow them to easily survive in healthcare settings [4]. Enterococci cause a variety of infections, including urinary tract infections (UTIs), wound infection, and bacteremia. In addition, endocarditis; intra-abdominal, pelvic, and biliary tract infections; as well as rare infections such as otitis, sinusitis, septic arthritis, and endophthalmitis may also occur [2, 5].

Enterococci were previously considered as clinically insignificant bacteria, but since the early 1970s, due to the emergence of resistance to several important antibiotics, including vancomycin, they have been considered as the second most common cause of nosocomial infections [1].

The emergence of vancomycin-resistant *Enterococcus faecium* was first reported in 1986 in England and France. The next year, vancomycin-resistant *E. faecalis* was isolated in the United States. Afterward, the world, including the US and Europe, experienced the rapid spread of VRE in hospitals. Finally, in 2002, when the first vancomycin-resistant *Staphylococcus aureus* (VRSA) acquiring vancomycin resistance genes (VanA) from VRE strains was reported, the threat of VRE colonization and infections increased[6]. The highest levels of vancomycin resistance in the world are in the western Pacific, Europe, and the United States, and the lowest levels are in Southeast Asia and the eastern Mediterranean. Among the reviewed studies, the highest resistance rate was observed in isolated species in Southeast Asia (about 10% resistance). This rate was reported in a study to be over 40% in Iran [7].

Additionally, studies have shown that *Enterococcus* spp., especially *E. feacalis* and *E. feacium*, are intrinsically resistant to low concentrations of gentamicin due to the low penetration of aminoglycosides through cell membranes of these species, so that the minimum inhibitory concentration (MIC) in these bacteria is 4-64 μg/mL. In recent years, high-level gentamicin-resistant (HLGR) strains with MIC values of >2000 μg/mL have been reported, which is due to increased arbitrary use of gentamicin [8, 9]. Since gentamicin and vancomycin are the common treatments of choice for enterococcal infections, the emergence of resistant strains to these antibiotics faces the healthcare system with concerns and challenges in the treatment of such resistant infections [10].

Objectives: The current study aimed to investigate the prevalence of vancomycin and gentamicin-resistant *Enterococcus* spp. in Iran during 2007-2019.

Materials and Methods

This study was designed to systematically review the literature to provide comprehensive data on vancomycin and gentamicin-resistant enterococci in Iran. To find studies published during January 2007 to January 2019, a search strategy was performed by searching different Iranian and international databases, including SID, Google Scholar, Scopus, Medline, Pub Med, and Web of Science. Persian keywords and their English equivalents were used in search engine, including spread, *Enterococcus, E. faecium*, *E. faecalis*, resistance, vancomycin, gentamicin, and Iran. For bias reduction, data extraction was conducted by two authors independently. Predefined criteria were used to extract and collect the

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required data, including first author; year of publication; study period; region of study; positive samples for enterococci; number of *E. faecalis*, *E. faecium*, and other enterococci isolates; the prevalence of vancomycin and gentamicin-resistant enterococci; and types of specimens. The collected data were imported into an Excel spreadsheet.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (Version 2016 for windows). Since the outputs of the studies included in this systematic review were all qualitative data, and they lacked any quantitative data, it was not possible to use meta-analysis for data analysis; thus, data were analyzed descriptively.

Findings

After searching all the mentioned databases and primary evaluations, 42 articles were found. Among which, seven articles were excluded from the study due to no connection with human cases. In addition, eight other articles were also omitted due to duplicate results. Finally, 26 articles were included in this study (Figure 1). The major findings derived from the reviewed articles are summarized in Table 1. In this study, 4306 *Enterococcus* strains isolated from clinical samples were evaluated. The samples were collected from different locations, including urine, wound, blood, abscess, stool, rectal swab, vaginal swab, lung secretion, pleural fluid, synovial fluid, catheter, etc. However, most isolates were obtained from urine, wound, blood, rectal swab, and stool samples, respectively (Figure 2).

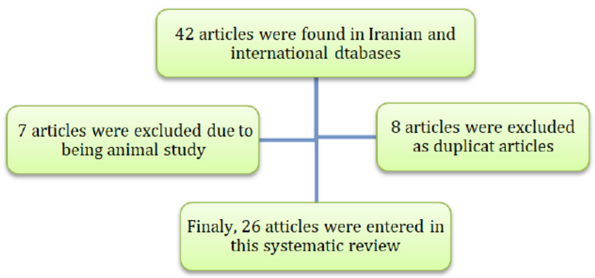

Figure 1) Flow diagram of literature search and article

The present study findings indicated that among *Enterococcus* isolates recovered from clinical samples, *E. faecalis* was more prevalent than *E. faecium* (75.49% vs. 24.05 %). Other *Enterococcus* species accounted for 2.43% of isolates. In addition, the prevalence of vancomycin- and gentamicin-resistant *Enterococcus* isolates was found to be high (41 and 44% respectively). However, resistance to vancomycin was higher in *E. faecium* isolates than in *E. faecalis* strains in most the reviewed studies. But gentamicin-resistant isolates were differently distributed among *E. faecium* and *E. faecalis* isolates.

As shown in Figure 3, among the reviewed articles, the highest rates of vancomycin resistance were reported to be 79, 52, and 51% in studies conducted in Tehran in 2019 [11], Tabriz in 2018 [12], and Lorestan in 2018 [13], respectively. Also, the highest levels of resistance to gentamicin were reported as 82, 74.4, and 63% in studies carried out in Tabriz in 2018 [12],Tehran in 2013 [14], and southwest of Iran in 2018 [15], respectively. In addition, the lowest vancomycin-resistant strains were related to studies conducted in Khoramabad (3.1%) [16], Tabriz (3.6%) [17], and Kashan (4.7%) [18]. However, the lowest gentamicin-resistant *Enterococcus* isolates were reported in Ilam and Kermanshah in 2011 (2.20%) (Fig. 4) [1].

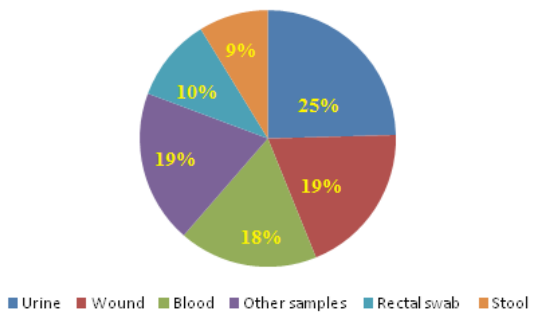

Figure 2) Frequency of Enterococcus spp isolated from different samples

Discussion

Vancomycin-resistant enterococci (VRE) as well as high-level gentamicin-resistant (HLGR) isolates have emerged all over the

Table 1) Articles included in this study

Study	Pubication Time	City	Number of *Enterococcus*	*E. faecalis*	*E. faecium*	Other *Enterococcus* spp.	Vancomycin Resistance	Gentamicin Resistance	Sample Type
Feizabadi et al. [39]	2007	Tehran	114	79	35	NR	NR	51 HLGR samples	Urine
Ghasemi et al. [18]	2009	Kashan	NR*	106	NR	NR	4.70%	39%	Urine, wound, blood, pleural fluid, tracheal tube
Ghafar pasand et al. [55]	2010	Kashan	100	NR	NR	NR	Disc diffusion (34%), MIC (27%)	44%	Stool
Mohammadi et al. [1]	2011	Ilam & Kermanshah	180	128	52	NR	Disc diffusion (83%), MIC (20%)	2.20%	Urine
Sharifi et al. [40]	2011	Northwest of Iran	220	152	68	NR	Disc diffusion (20.5%), MIC (45.2%)	60.45% HLGR	Wound, blood, body fluid, catheter
Jabbari shiadeh et al. [10]	2012	Kashan	135	79.30%	15.50%	6.80%	46.90%	NR	Rectal swab
Jabbari shiadeh et al. [49]	2013	Kashan	135	NR	NR	NR	43%	NR	Rectal swab
Balaei Gajan et al. [17]	2013	Tabriz	105	NR	NR	NR	3.60%	36.20%	Clinical samples
Shokohizadeh et al. [25]	2014	Tehran	85	39	45	1	*E. faecium* 42.2%	*E. faecium* 42.2%	Urine
Masoumi Zavariati et. al [47]	2015	Tehran	278	197	43	38	5.95%	20.78%	Urine, wound, blood, other clinical samples
Mosavi et al. [48]	2015	Khoramabad	128	81	45	2	3.10%	29.30%	Vaginal swab
Samadi et al. [49]	2015	Tehran	113	103	10	NR	Disc diffusion 11 (7 faecalis and 4 faecium)	46% (43 faecalis and 3 faecium)	Urine, stool
Moadab et al. [50]	2015	Tabriz	193	178	15	NR	Disc diffusion 35 (18%)	NR	Urine, stool, rectal swab, wound, blood, ascites

Table 1) Articles included in this study

Study	Pubica-tion Time	City	Number of *Enterococcus*	*E. faecalis*	*E. faecium*	Other *Enterococcus* spp.	Vancomycin Resistance	Gentamicin Resistance	Sample Type
Kaveh et al. [51]	2016	Shiraz	42	NR	NR	NR	33% (10 faecium, 3 casseliflavus,1 gallinarum)	NR	Stool
Esmaeilzadeh et al. [54]	2016	Kashan	180	108	72	NR	NR	23.90%	Rectal swab
Labibzadeh et al. [15]	2018	Sout west of Iran	179	108	71	NR	*E. faecalis* 7%, *E. faecium* 3%	*E. faecalis* 46%, *E. faecium* 16%	Blood, burn wound
Mosavian et. al. [16]	2018	Ahvaz	175	34	95	NR	43.4%(56)	NR	Rectal swab
Khanmohammadi et al. [12]	2018	Tbriz	100	Stool (27 faecalis) Non stool sample (3 faecalis)	Stool (33 faecium), non-stool sample (48 faecium	NR	Stool 30%, non-stool sample 52%	Stool 85%, non-stool sample 80%	Stool, other clinical samples
Goudarzi et al. [13]	2018	Lorestan	690	439	228	23	Disc diffusion (36%), MIC (51%)	Disc diffusion (37%)	Urine, stool, blood, wound, tracheal tube, catheter….
Sharifzadeh pyvasti et al. [2]	2019	Tehran	195	127	62	6	20.56%	42.10%	Urine, blood, wound, tracheal tube, pleural fluid….
Hagi et al. [19]	2019	Nourth west	100	69	10	2100%	21% (10 faecium , 11 other species)	50%	Urine
Arshadi et al. [52]	2019	Ahvaz	383	35%	61%	4%	45.6% (4 faecalis and 163 faecium)	NR	Rectal swab, environment
Taji et al. [41]	2019	Shiraz	NR	NR	NR	NR	45.30%	50.9 HLGR	Urine, blood, sputum, tracheal tube, abdomen, eyes
Sattari et al. [11]	2019	Tehran	189	67	108	14	9% faecalis , 70% faecium	49% faecalis, 75% faecium	Urine, body fluid, wound
Mohammadi et al. [53]	2019	Tehran	114	73	41	NR	2.7% faecalis , 21.9% faecium	64 HLGR	Burn wound swab

*= Not Report

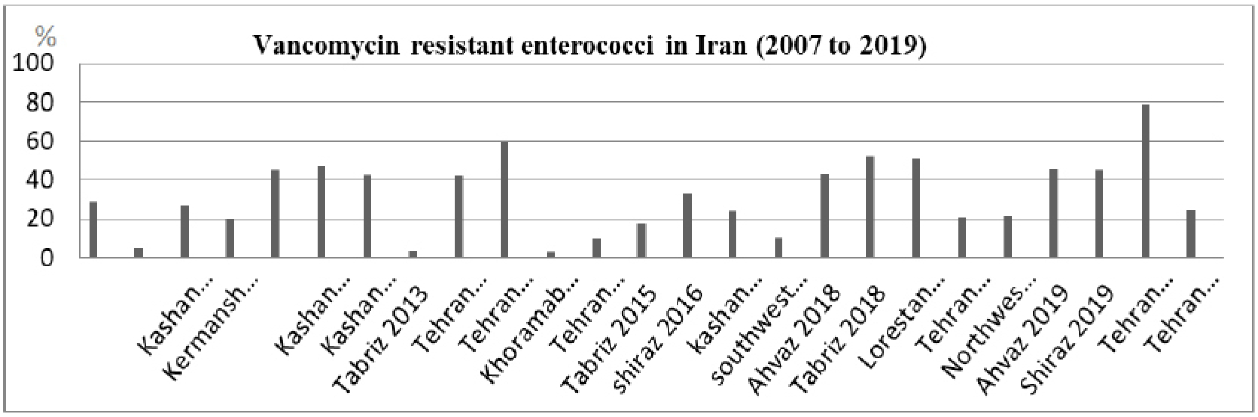

Figure 3) Prevalence of vancomycin-resistant enterococcal isolates in Iran

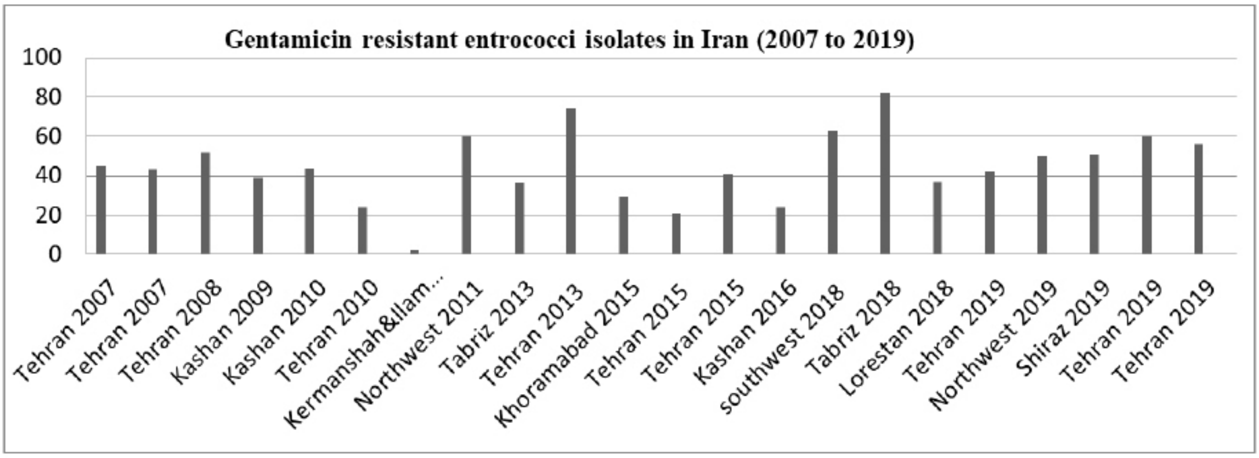

Figure 4) Prevalence of gentamicin-resistant enterococcal isolates in Iran

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world and created serious problems for antibiotic treatment of infected patients due to limited therapeutic options [14, 19]. In this review, the prevalence of vancomycin and gentamicin-resistant *Enterococcus* spp. in Iran was explored.

The most common *Enterococcus* species causing nosocomial infections are *E. faecalis* and *E. faecium* [14]. In this study, the collected data from the evaluated articles showed that *E. faecalis* was the most prevalent species (75.49%), followed by *E. faecium* (24.05%). In a study conducted by Udo et al. (2003) in Kuwait, the predominant *Enterococcus* species were *E. faecalis* and *E. faecium* with a prevalence rate of 85.3 and 7.7%, respectively [20]. In another study, Almeida et al. (2004) reported *E. faecalis* (76%) and *E. faecium* (9%) as the most prevalent species isolated from two hospitals in Brazil [21]. But in contrast, in a study by Jia et al. (2014) in china, the most prevalent species was *E. faecium* with a prevalence rate of 58.7%, followed by *E. faecalis* (33%) [22].

In the past, the ratio of *E. faecalis* infections compared with all other *enterococcal* infections was around 10:1. But in recent years, a progressive decrease in this ratio and a microbiological shift toward the increasing prevalence of *E. faecium* due to the emergence of VRE profile in this species have been reported [23, 24]. Some studies in Iran have also reported a decrease in the prevalence of *E. faecalis* in nosocomial infections caused by enterococci [25]. Based on the present study results, this ratio was almost 2:1 (faecalis:

faecium) in Iran during 2007-2019. Similar to this study result, in the studies by Emaneini et al. (2008) [23] and Shokoohizadeh et al. (2014) [25] in Iran, the ratio of *E. faecalis* infections compared with *E. faecium* has been reported to be 1.8 to 1 and 1.15 to 1, respectively. The present study findings also showed that out of 4306 *Enterococcus* isolates identified, 105 (2.43%) were no*n-faecalis* and non-*faecium* and belonged to other *Enterococcus* spp. Moreover, in line with this study results, several studies have indicated that *E. faecalis* is the most prevalent clinical isolate among enterococci, followed by *E. faecium,* and other *Enterococcus* species are less prevalent [20, 22, 26, 27]. In contrast, Jumah et al. (2018) reported *E. faecium* as the predominant species (56.1%), followed by *E. faecalis* (36.8%); however, in line with other studies, they reported low prevalence rate for other *Enterococcus* spp. (7.0%) [28]. On the other hands, in none of the reviewed studies, non-*faecalis* and non-*faecium* species were reported as the predominant *Enterococcus* spp.

Global increase in vancomycin resistance among *Enterococcus* spp. is a serious healthcare problem, and several studies have reported vancomycin resistance among *Enterococcus* strains isolated from inpatients in Iran and other countries. In the current study, resistance to vancomycin was 41% among the reported strains, and minimal inhibitory concentration of vancomycin was in the range of ≥32 to ≥512 µg/mL. In a study conducted by Moghimbeigi et al. (2018) in Iran from 2000 to 2011, the prevalence rate of vancomycin-resistant enterococci was shown to be 14% (33% *E. faecium* and 3% *E. faecalis*) with MIC values in the range of ≥32 to ≥2000 µg/mL [29]. The present study shows an increasing trend in the prevalence of VRE over time compared to Moghimbeigi's study. Contrary to our results, Salem-Bekhit et al. (2012) in Kuwait obtained a lower prevalence rate for vancomycin resistance (3.9%) with MICs >32 µg/mL [27]. Gupta et al. (2015) in India reported high levels of vancomycin resistance with MIC values in the range of 64 to 128 µg/mL [30]. Sun et al. (2012) in China reported vancomycin MIC values of ≥256 µg/mL in *E. faecium* and *E. faecalis* isolates [31]. Özsoy et al. (2017) in turkey also described vancomycin MIC values of ≥256 µg/mL for enterococcal isolates [32]. In contrast with our study, Biswas et al. (2016) reported low MIC values for some clinical strains of *Enterococcus* (ranging from 8 to ≥16 µg/mL), which were considered as intermediately resistant [33]. Moreover, in a study conducted by Chakraborty et al. (2015) in India, all isolates were sensitive to vancomycin, and minimal inhibitory concentration of vancomycin against all enterococcal isolates was ≤1 µg/mL [26].

High levels of aminoglycoside resistance have become a very serious problem in healthcare settings worldwide [34]. Therapeutic options for invasive enterococcal infections typically include an aminoglycoside (e.g., gentamicin, streptomycin, and tobramycin) in combination with a cell wall active agent (e.g., vancomycin). However, high-level gentamicin resistance (HLGR) profile disables the synergistic activity of cell wall active agents and gentamicin. The production of aminoglycoside-modifying enzymes (AMEs) in *Enterococcus* spp. due to intrinsically possessing resistance genes leads to high levels of aminoglycoside resistance (MIC ≥ 2,000 µg/mL) [35-38].

In this study, antibiotic screening data showed that a total of 44% of *Enterococcus* clinical isolates were gentamicin resistant. In addition, among the reviewed articles, the highest rates of HLGR were reported to be 57, 50.9, 64, and 64% in the studies by Feizabadi et al. (2007) [39], Sharifi et al. (2012) [40], Taji et al. (2019) [41], Mohammadi et al. (2011) [1], and Sattari et al. (2019) [11], respectively. In contrast, low incidence rates of HLGR were reported in the studies by Jannati et al. (2020) in Ardabil in Iran [36] and El-Mahdy et al. (2018) [35] in Egypt. They identified 2.7 and 6.3% of isolates

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as high level gentamicin resistant (HLGR), respectively, which are much lower than the result obtained in this study. In addition, a lower prevalence rate of HLGR was reported in the studies conducted by Mittal et al. (2016) [42] and Vigani et al. (2008) [43]. Moreover, an almost similar prevalence rate of HLGR was reported in a study by Tian et al. (2019) in china [44]. Diab et al. (2019) [45] showed that 78% of isolates were HLGR, which is higher in comparison to this study result.

Limitations

This systematic review has some limitations, such as the heterogeneity of populations and the sample size of the studies included in this systematic review.

Conclusion

The increasing resistance of enterococci to important antibiotics like vancomycin and gentamicin and their ability to transmit resistance genes to other non-resistant bacteria create a major challenge in the management of such resistant pathogens. Therefore, it is necessary to design strategies that lead to the rational prescription of antibiotics and limit the spread of resistant bacteria in hospital environments as much as possible.

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