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

ARTICLE INFO

Article Type
Review Article

Authors
Maryam Arfaatabar, PhD
Tayebe Shahbazi, MSc
Tahoora Ebrahimi, BSc

How to cite this article

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 gentamicin 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: Enterococcus, Resistance, Vancomycin, Gentamicin.

REFERENCES


Copyright @ 2022, TMU Press. This open-access article is published under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License which permits Share (copy and redistribute the material in any medium or format) and Adapt (remix, transform, and build upon the material) under the Attribution-NonCommercial terms.
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. faecalis* and *E. faecium*, 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...
required data, including first author; year of publication; study period; region of study; positive samples for enterococci; number of \textit{E. faecalis}, \textit{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.

\textbf{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.

\textbf{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 \textit{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).

The present study findings indicated that among \textit{Enterococcus} isolates recovered from clinical samples, \textit{E. faecalis} was more prevalent than \textit{E. faecium} (75.49\% vs. 24.05 \%). Other \textit{Enterococcus} species accounted for 2.43\% of isolates. In addition, the prevalence of vancomycin- and gentamicin-resistant \textit{Enterococcus} isolates was found to be high (41 and 44\% respectively). However, resistance to vancomycin was higher in \textit{E. faecium} isolates than in \textit{E. faecalis} strains in most the reviewed studies. But gentamicin-resistant isolates were differently distributed among \textit{E. faecium} and \textit{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 \textit{Enterococcus} isolates were reported in Ilam and Kermanshah in 2011 (2.20\%) (Fig. 4) [1].

\textbf{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

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>City</th>
<th>Number of Enterococcus spp</th>
<th>E. faecalis</th>
<th>E. faecium</th>
<th>Other Enterococcus spp</th>
<th>Sample Type</th>
<th>City</th>
<th>Vancomycin Resistance</th>
<th>Gentamicin Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghasemi et al. [18]</td>
<td>2009</td>
<td>Kashan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>Urine, wound, blood, pleural fluid, tracheal tube</td>
<td>Kashan</td>
<td>51 HLGR samples</td>
<td>81</td>
</tr>
<tr>
<td>Ghafar pasand et al. [55]</td>
<td>2010</td>
<td>Kashan</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>Stool</td>
<td>Kashan</td>
<td>44%</td>
<td>37%</td>
</tr>
<tr>
<td>Mohammadi et al. [1]</td>
<td>2011</td>
<td>Ilam &amp; Kerman-shah</td>
<td>180</td>
<td>128</td>
<td>52</td>
<td></td>
<td>Urine</td>
<td>Ilam &amp; Kerman-shah</td>
<td>2.20%</td>
<td></td>
</tr>
<tr>
<td>Sharifi et al. [40]</td>
<td>2011</td>
<td>Northwest of Iran</td>
<td>220</td>
<td>152</td>
<td>68</td>
<td></td>
<td>Wound, blood, body fluid, catheter</td>
<td>Northwest of Iran</td>
<td>60.45% HLGR</td>
<td></td>
</tr>
<tr>
<td>Jabbari shiadeh et al. [10]</td>
<td>2012</td>
<td>Kashan</td>
<td>135</td>
<td>79.30%</td>
<td>15.50%</td>
<td>6.80%</td>
<td>Rectal swab</td>
<td>Kashan</td>
<td>46.90%</td>
<td></td>
</tr>
<tr>
<td>Jabbari shiadeh et al. [49]</td>
<td>2013</td>
<td>Kashan</td>
<td>135</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>Rectal swab</td>
<td>Kashan</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Balaei Gajan et al. [17]</td>
<td>2013</td>
<td>Tabriz</td>
<td>105</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>Clinical samples</td>
<td>Tabriz</td>
<td>3.60%</td>
<td>36.20%</td>
</tr>
<tr>
<td>Shokohizadeh et al. [25]</td>
<td>2014</td>
<td>Tehran</td>
<td>85</td>
<td>39</td>
<td>45</td>
<td></td>
<td>Urine</td>
<td>Tehran</td>
<td>42.2% E. faecium 42.2%</td>
<td></td>
</tr>
<tr>
<td>Masoumi Zavariati et al. [47]</td>
<td>2015</td>
<td>Tehran</td>
<td>278</td>
<td>197</td>
<td>43</td>
<td></td>
<td>Urine, wound, blood, other clinical samples</td>
<td>Tehran</td>
<td>5.95%</td>
<td>20.78%</td>
</tr>
<tr>
<td>Mosavi et al. [48]</td>
<td>2015</td>
<td>Khoram-abad</td>
<td>128</td>
<td>81</td>
<td>45</td>
<td></td>
<td>Vaginal swab</td>
<td>Khoram-abad</td>
<td>3.10%</td>
<td>29.30%</td>
</tr>
<tr>
<td>Samadi et al. [49]</td>
<td>2015</td>
<td>Tehran</td>
<td>113</td>
<td>103</td>
<td>103</td>
<td></td>
<td>Urine, stool</td>
<td>Tehran</td>
<td>60.45% HLGR</td>
<td></td>
</tr>
<tr>
<td>Moadab et al. [50]</td>
<td>2015</td>
<td>Tabriz</td>
<td>193</td>
<td>178</td>
<td>15</td>
<td></td>
<td>Urine, stool blood, wound, ascites</td>
<td>Tabriz</td>
<td>HGRC samples 35</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Type</td>
<td>City</td>
<td>Number of E. faecalis</td>
<td>Number of E. faecium</td>
<td>Number of Other Enterococcus spp.</td>
<td>Number of vancomycin-resistant E. faecium</td>
<td>Number of other Enterococcus spp. resistant to vancomycin</td>
<td>Gentamicin resistance</td>
<td>Ciprofloxacin resistance</td>
<td>Sample Time</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Kaveh et al. [51]</td>
<td>Stool</td>
<td>Shiraz</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>108</td>
<td>67</td>
<td>114</td>
<td>Tehran</td>
</tr>
<tr>
<td>Esmaeilzadeh et al. [54]</td>
<td>Rectal swab</td>
<td>Kashan</td>
<td>180</td>
<td>108</td>
<td>72</td>
<td>NR</td>
<td>383</td>
<td>95</td>
<td>119</td>
<td>Ahvaz</td>
</tr>
<tr>
<td>Labibzadeh et al. [15]</td>
<td>Blood, burn wound, skin abscess, urine, stool, rectal swab</td>
<td>Southwest of Iran</td>
<td>179</td>
<td>108</td>
<td>71</td>
<td>NR</td>
<td>383</td>
<td>95</td>
<td>119</td>
<td>Ahvaz</td>
</tr>
<tr>
<td>Mosavian et al. [16]</td>
<td>Rectal swab</td>
<td>Ahvaz</td>
<td>175</td>
<td>34</td>
<td>95</td>
<td>NR</td>
<td>43% (56)</td>
<td>43% (56)</td>
<td>175</td>
<td>Tehran</td>
</tr>
<tr>
<td>Khanmohammadi et al. [12]</td>
<td>Stool</td>
<td>Tbriz</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>95</td>
<td>4</td>
<td>4</td>
<td>Tehran</td>
</tr>
<tr>
<td>Goudarzi et al. [13]</td>
<td>Disc diffusion (36%), MIC (51%)</td>
<td>Lorestan</td>
<td>690</td>
<td>439</td>
<td>228</td>
<td>NR</td>
<td>90</td>
<td>0</td>
<td>0</td>
<td>Tehran</td>
</tr>
<tr>
<td>Sharifzadeh pyvasti et al. [2]</td>
<td>Urine, blood, wound, tracheal tube, pleural fluid</td>
<td>Tehran</td>
<td>195</td>
<td>127</td>
<td>62</td>
<td>NR</td>
<td>99</td>
<td>95</td>
<td>127</td>
<td>Tehran</td>
</tr>
<tr>
<td>Hagi et al. [19]</td>
<td>Urine</td>
<td>Northwest</td>
<td>100</td>
<td>69</td>
<td>10</td>
<td>NR</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Tehran</td>
</tr>
<tr>
<td>Arshadi et al. [52]</td>
<td>Rectal swab</td>
<td>Ahvaz</td>
<td>383</td>
<td>35%</td>
<td>61%</td>
<td>4%</td>
<td>45.6% (4 faecalis and 163 faecium)</td>
<td>NR</td>
<td>NR</td>
<td>Rectal swab, environment</td>
</tr>
<tr>
<td>Taji et al. [41]</td>
<td>Urine, blood, sputum, tracheal tube, abdomen</td>
<td>Shiraz</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>45.30%</td>
<td>50.9%</td>
<td>45.30%</td>
<td>Shiraz</td>
</tr>
<tr>
<td>Sattari et al. [11]</td>
<td>Urine, body fluid, wound</td>
<td>Tehran</td>
<td>189</td>
<td>67</td>
<td>108</td>
<td>NR</td>
<td>9% (E. faecalis), 70% (E. faecium)</td>
<td>49% (E. faecalis), 75% (E. faecium)</td>
<td>189</td>
<td>Tehran</td>
</tr>
<tr>
<td>Mohammadi et al. [53]</td>
<td>Burn wound swab</td>
<td>Tehran</td>
<td>114</td>
<td>73</td>
<td>41</td>
<td>NR</td>
<td>2.7% (E. faecalis), 21.9% (E. faecium)</td>
<td>64 HLGR</td>
<td>64 HLGR</td>
<td>Tehran</td>
</tr>
</tbody>
</table>

*= Not Reported
Antibiotic resistance among Enterococci spp. in the world and created serious problems for antibiotic treatment of infected patients due to limited therapeutic options \cite{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* \cite{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 \cite{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 \cite{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%) \cite{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 \cite{23, 24}. Some studies in Iran have also reported a decrease in the prevalence of *E. faecalis* in nosocomial infections caused by *enterococci* \cite{25}. Based on the present study results, this ratio was almost 2:1 (*faecalis*:

---

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

**Figure 4** Prevalence of gentamicin-resistant enterococcal isolates in Iran
faecium) in Iran during 2007-2019. Similar to this study result, in the studies by Emaneini et al. (2008) [23] and Shokouhizadeh et al. (2014) [24] 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 non-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 hand, 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 intermediate 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...
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) \cite{42} and Vigani et al. (2008) \cite{43}. Moreover, an almost similar prevalence rate of HLGR was reported in a study by Tian et al. (2019) in china \cite{44}. Diab et al. (2019) \cite{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.

**Acknowledgements**
The authors would like to extend their sincere appreciation to Meysam Arabzadeh, Hossein Khoshdel and other colleagues who helped us with this.

**Ethical Permissions:** Not applicable.

**Conflicts of interest:** The authors declare that they have no conflict of interest.

**Authors Contribution:** Conceptualization: MAT; data curation: MAT, TE; formal analysis: MAT, TS; funding acquisition: No fund; Investigation: MAT, TS, TE; methodology: MAT, TS, TE; project administration: MAT; resources: MAT, TS, TE; software: TS, TE; supervision: MAT; writing of the original draft: MAT, TS; writing-review and editing: MAT, TS.

**Funds:** We have no funding to declare.

**Consent to participate:** Not applicable.

**References**


34. Moussa AA, Nordin AFM, Hamat RA, Jasni AS. High

Infection Epidemiology and Microbiology

Winter 2022, Volume 8, Issue 1


