Rise of antibiotic resistance in clinical enterococcal isolates during 2001–2016 in Iran: a review

P. Asadollahi1, Sh. Razavi1,2, Kh. Asadollahi3,4, M. R. Pourshafie5 and M. Talebi1
1) Department of Microbiology, School of Medicine, Iran University of Medical Sciences, 2) Microbial Biotechnology Research Centre, Iran University of Medical Sciences, Tehran, Iran, 3) Department of Social Medicine, School of Medicine, Ilam University of Medical Sciences, 4) Biotechnology and Medicinal Plants Researches Center, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran and 5) Department of Microbiology, Pasteur Institute of Iran, Tehran, Iran

Abstract

Introduction: The clinical significance of enterococci is mostly related to its antibiotic resistance which contributes to colonization and infection, in particular amongst the hospitalized patients. The present review has examined the literature to provide a comprehensive data on enterococci antibiotic resistance during the last 20 years in Iran.

Methods: Search engines such as Google Scholar and PubMed were used to identify all Persian and English-language articles investigating enterococci in Iran from 1996 to 2017. The search terms were “enterococci”, “enterococcal”, “enterococcus”, “Iran”, “bacterial resistance”, “antibiotic resistance” and “resistance”.

Results: Decrease in the resistance trend against ampicillin, gentamycin and ciprofloxacin was observed over a period of 15 years (2001 to 2016) in Iran. During a 10 years period from 2001 to 2015, the rate of resistance among Enterococcus faecalis species was less than Enterococcus faecium. The resisrance rate, however, was considerably increased for both species during this period. The mean resistance rates for vancomycin, gentamicin, ciprofloxacin, erythromycin, nitrofurantoin, chloramphenicol, trimethoprim-sulfamethoxazol, imipenem and teicoplanin were higher among complicated cases (patients with underlying debilitating disorders) compared to general cases (hospitalized or outpatients with no specific underlying disorder).

Conclusions: E. faecalis and E. faecium showed a rise in the mean resistance against all the antibiotics during a 10-year period from 2010 to 2015. With the exception of penicillin and ampicillin, resistance to all antibiotics was higher amongst complicated cases compared to general patients.

Corresponding author: T. Malihe, Department of Microbiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran. E-mail: talebi.m@iums.ac.ir

Introduction

Enterococci are natural parts of the intestinal flora in humans and animals which are ubiquitously present in nature, soil, plants, vegetables and treated or untreated water. They can cause severe opportunistic infections, including endocarditis as well as urinary tract (UTIs), intra-abdominal and wound infections [1]. Enterococci gain entry into foodstuffs through water supplies, food processes or unsanitary conditions related to food handling [2]. Drug resistance is the main reason for the dramatic emergence of these organisms as a cause of healthcare-associated infections throughout the world, including Iran [3].

The treatment of enterococcal infection has been complicated by the emergence of strains possessing a high level resistance to almost all of the antibiotics used in clinical settings, especially aminoglycosides, β-lactams and glycopeptides. Alternative therapeutic options are consequently being evaluated to manage multidrug-resistant strains [4]. In Iran, enterococci have gained resistance to almost the entire antimicrobial spectrum used against this organism. This includes resistance to
vancomycin, the most important antimicrobial agent for the treatment of enterococcal infections; resistance has been reported to be as high as 9.4% in Iran [5]. The high rate of antibiotic resistance among enterococci isolates has greatly limited the therapeutic options to treat infections caused by this organism in Iran.

Enterococcal clinical and epidemiologic data in each country are needed in order to make informed decisions on ways to control enterococcal infections. Such information could help scientists, healthcare workers and policy makers to understand the emergence of multidrug-resistant strains of enterococci and their association with underlying diseases at both regional and global levels.

We performed a review to evaluate the published literature over the last 20 years regarding the evolution of enterococcal infections and antibiotic resistance in Iran.

Methods

Search strategy and selection criteria
A detailed search was conducted of the Google Scholar, Scopus, PubMed, ISI, Iranmedex, Magiran, SID and ISC databases with articles published from 1996 to 2017 to identify all of the Persian- and English-language articles which have investigated enterococci in Iran. The search terms were ‘enterococci,’ ‘enterococcus,’ ‘enterococcal,’ ‘Iran,’ ‘bacterial resistance’ and ‘antibiotic resistance.’

All of the articles were carefully examined for the reports of antibiotic susceptibility patterns among general and complicated cases. General cases were defined as hospitalized patients or outpatients, with no specific underlying disorder, who had transient general illnesses such as diarrhoea, UTIs and blood infections. Complicated cases included patients with underlying debilitating disorders such as cardiovascular diseases, diabetic foot, gallbladder stones, lymphoblastic leukaemia, and renal or hepatic failure, as well as patients undergoing haematopoietic stem-cell transplantation, patients receiving chronic haemodialysis and patients hospitalized in the intensive care unit.

Articles which had no examination of the antibiotic susceptibility pattern and those investigating nonclinical isolates of enterococci, as well as duplicate articles and studies presented only in abstract form, were excluded from analysis.

Data extraction
The following data were extracted from each article: corresponding author’s name, year of data collection, country, number of isolates, resistance rate (as a percentage) for all the antibiotics investigated in the article and the specific disorder of the patients, if present.

Statistical analysis
Spearman correlation was used to analyse the significance of resistance trends over time. The independent t test method was used to compare the changes in antibiotic resistance over a period of 10 years (2005–2015) either in Enterococcus faecium or Enterococcus faecalis spp. and to evaluate the significance of any possible difference in antibiotic resistance between general and complicated cases. The means ± standard deviation of different variables are indicated in the tables and figures, and p ≤ 0.05 was considered statistically significant.

Results

During the initial database search, a total of 150 articles were found. After exclusion of the articles according to our criteria, a total of 44 articles were included in the analysis [3,6–48]. Among these 44 articles, 24 were associated with general patients (3071 isolates), 12 studies assessed their enterococcal populations on the basis of species (3906 isolates) and eight investigated colonization of enterococci among complicated patients with specific underlying conditions (589 isolates). The most common methods used to assess the antimicrobial susceptibility pattern in these studies included disc diffusion and broth microdilution.

In total, 38 antibiotics were assessed within the 44 articles (Table 1). The most commonly examined antibiotics in these studies were vancomycin (n = 32 studies), gentamycin (n = 21), ciprofloxacin (n = 20), ampicillin (n = 18), penicillin (n = 19) and erythromycin (n = 17), whereas amoxicillin, tobramycin, kanamycin, fusidic acid, nafcillin, tazobactam/piperacillin and ofloxacin were only investigated by one study each (Table 1). Enterococci isolated from general patients showed the highest resistance to meropenem (97%), cefazolin (94%), fusidic acid (90%), cephalothin (87%), kanamycin (80%), cefotetan (76%), nafcillin (75%), penicillin (74%), clindamycin (68%), nalidixic acid (65%) and erythromycin (58%). However, the isolates were highly sensitive to the following antibiotics: co-amoxiclav (0 resistance), linezolid (1%), ofloxacin (5%) and tobramycin (11%) (Table 1).

E. faecalis had a high resistance rate against erythromycin (67% resistance), gentamicin (65%), trimethoprim/sulfamethoxazole (54%), ciprofloxacin (51%) and oxacillin (49%), whereas nitrofurantoin (4% resistance) and teicoplanin (9%) were the most active agents against this species.

E. faecium isolates were mostly resistant against erythromycin (78%), norfloxacin (84% resistance), imipenem (82%) and trimethoprim/sulfamethoxazole (81%), whereas linezolid with no resistance and nitrofurantoin (16%) were the most effective antibiotics.
Enterococci isolated from complicated cases were fully resistant (100% resistance) against trimethoprim/sulfamethoxazole and clindamycin. Linezolid with 0.5% resistance was the most effective antibiotic against these isolates (Table 1).

**Trend of antibiotic resistance during 2001–2016**

The antibiotic resistance profiles of ampicillin, gentamicin, ciprofloxacin, vancomycin and erythromycin were found to be reported by more than 90% of the studies during 2001–2016 (Figs. 1 and 2). A lack of data on the remaining 32 antibiotics did not permit us to estimate the resistance trend over time for these antibiotics.

An insignificant decrease in the resistance trend for ampicillin (p 0.149) and erythromycin (p 0.356), and an insignificant increase trend was observed for vancomycin (p 0.292) during the 15 years of study. The decrease was significant for

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**TABLE 1. Number of total studies and mean resistance rates associated with different antibiotics among enterococci in Iran during 2001–2016**

| Antibiotic Total studies (n) | Total isolates (n) | Mean resistance (%) | General cases | Complicated cases | Enterococcus faecalis | Enterococcus faecium |
|-----------------------------|-------------------|---------------------|---------------|------------------|----------------------|----------------------|
| Vancomycin                  | 32                | 6703                | 15.6          | 21.8             | 12.5                 | 47.0                 |
| Gentamicin                  | 21                | 4155                | 51            | 76.0             | 65.1                 | 74.9                 |
| Ciprofloxacin               | 20                | 3885                | 35.4          | 61.0             | 51.0                 | 77.4                 |
| Penicillin                  | 19                | 3107                | 74            | 57.5             | 45.1                 | 70.7                 |
| Ampicillin                  | 18                | 5141                | 43.5          | 34.3             | 17.1                 | 69.0                 |
| Erythromycin                | 17                | 4656                | 58.3          | 42.7             | 67.0                 | 76.3                 |
| Nitrofurantoin              | 15                | 1962                | 19            | 35.3             | 3.5                  | 16.2                 |
| Chloramphenicol             | 14                | 2503                | 17.2          | 26.4             | 34.4                 | 28.8                 |
| Trimethoprim/sulfamethoxazole | 14          | 2346                | 48.6          | 100.0            | 53.8                 | 80.5                 |
| Tetracycline                | 12                | 2592                | 56            | —                | —                    | 65.3                 |
| Imipenem                    | 10                | 1978                | 21.5          | 41.2             | 26.2                 | 81.7                 |
| Linezolid                   | 10                | 1588                | 1.4           | 0.5              | —                    | 0.0                  |
| Teicoplanin                 | 10                | 1599                | 23.2          | 39.4             | 9.2                  | 62.8                 |
| Amikacin                    | 8                 | 708                 | 43.0          | —                | —                    | —                    |
| Clindamycin                 | 8                 | 1436                | 68.0          | 100.0            | —                    | —                    |
| Oxacillin                   | 7                 | 1202                | 56.6          | —                | 49.0                 | —                    |
| Sulfadiazine                | 5                 | 986                 | —             | 23.5             | —                    | 24.3                 |
| Rifampicin                  | 5                 | 1413                | 55.4          | 70.1             | —                    | 86.5                 |
| Streptomycin                | 5                 | 393                 | 33.0          | 85.3             | —                    | 90.0                 |
| Cephalothin                 | 4                 | 924                 | 86.7          | —                | —                    | —                    |
| Nalidixic acid              | 3                 | 247                 | 65.3          | —                | —                    | —                    |
| Cephalexin                  | 3                 | 199                 | 33.3          | —                | —                    | —                    |
| Cefazoxime                  | 3                 | 140                 | 57.4          | —                | —                    | —                    |
| Cefotaxime                  | 3                 | 1189                | 51.7          | —                | —                    | —                    |
| Ceftriaxone                 | 3                 | 1009                | 41.5          | —                | —                    | —                    |
| Norfloxacin                 | 3                 | 276                 | —             | 85.3             | —                    | 84.0                 |
| Meropenem                   | 3                 | 121                 | 96.7          | —                | —                    | —                    |
| Levofloxacin                | 2                 | 149                 | 25.6          | —                | —                    | —                    |
| Co-amoxicillin              | 2                 | 137                 | 12            | —                | —                    | —                    |
| Cefazolin                   | 2                 | 102                 | 94.0          | —                | —                    | —                    |
| Cefotaxime                  | 2                 | 772                 | 76.0          | 85.3             | —                    | —                    |
| Nafcillin                   | 1                 | 736                 | 74.6          | —                | —                    | —                    |
| Amoxicillin                 | 1                 | 606                 | 16.7          | 33.3             | —                    | —                    |
| Tobramycin                  | 1                 | 138                 | 11.4          | —                | —                    | —                    |
| Kanamycin                   | 1                 | 138                 | 80.2          | —                | —                    | —                    |
| Fusidic acid                | 1                 | 220                 | 89.5          | —                | —                    | —                    |
| Tazobactam/piperacillin     | 1                 | 180                 | 42            | —                | —                    | —                    |
| Ofloxacin                   | 1                 | 89                  | 5.0           | —                | —                    | —                    |

*Amoxicillin/clavulanic acid.

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ciprofloxacin (p 0.053) and somewhat consistent for gentamicin (p 0.760) during this time period.

The highest and lowest rates of enterococci resistance, with reduced resistance over time, occurred during 2003 (95%) and 2014 (8%) for ampicillin, 2008 (83%) and 2010 (8%) for ciprofloxacin, 2001 (11%) and 2008 (98%) for erythromycin and 2009 (6%) and 2011 (97%) for gentamycin (Figs. 1 and 2). However, the highest and lowest rates of enterococci resistance, with increased resistance over time, occurred in 2003 (0.1%) and 2010 (57%) for vancomycin (Fig. 2). Increases and decreases in the resistance rates are, however, observed for all antibiotics during 2001–2016 (Figs. 1 and 2).

Antibiotic resistance among *E. faecalis* and *E. faecium* spp.

The total number of studies associated with enterococci resistance against the four most frequently investigated antibiotics—erythromycin, gentamicin, vancomycin and ampicillin—during 2004–2006 were 20 for *E. faecalis* and 18 for *E. faecium* spp. The studies were 11 for *E. faecalis* and eight for *E. faecium* spp. for the same antibiotics during 2014–2016 (Table 2). The mean resistance rates against the above-mentioned antibiotics for both species are indicated in Table 2.

The mean resistance rates of *E. faecalis* and *E. faecium* spp. against four commonly investigated antibiotics in 10-year period time (2005 and 2015) were compared (Fig. 3). Using the independent t test, the following p values were attained by comparing resistance between the two species during 2005: erythromycin (p 0.14), gentamicin (p 0.041), vancomycin (p 0.032) and ampicillin (p 0.007). The same comparison during 2015 was made, and the results showed the following p values: erythromycin (p 0.216), gentamicin (p 0.08), vancomycin (p 0.048) and ampicillin (p 0.029).

The mean rate of resistance was generally higher among *E. faecalis* species compared to *E. faecium* for all antibiotics either in 2005 or 2015; except for gentamicin during 2015, the resistance to which was higher among *E. faecium* species.

The mean antibiotic resistance rate was considerably increased for both *E. faecium* and *E. faecalis* during this 10-year time period (2005–2015) (Fig. 3). Statistical analysis revealed that the mean resistance rates during this time period were as follows for *E. faecalis* and *E. faecium*, respectively: erythromycin (p 0.018, p 0.038), gentamicin (p 0.071, p 0.08), vancomycin (p 0.159, p 0.163) and ampicillin (p 0.014, p 0.162).

**Antibiotic resistance among general and complicated cases**

Table 3 shows a resistance assessment among enterococci in more than ten investigations conducted during 2001–2016 of 12 antibiotics. The lowest and highest antibiotic resistance rates belonged to vancomycin (14%) and penicillin (75%) for general
cases and to vancomycin (26%) and trimethoprim/sulfamethoxazole (100%) for complicated cases, respectively. Overall, the analysis of the data suggested that the mean resistance rates for all of the examined antibiotics were higher among complicated cases compared to general cases, except for penicillin and ampicillin (Table 3).

**Discussion**

As normal residents of the gastrointestinal tract, vagina and male urethra, enterococci can occasionally cause infections in humans. Resistance is the main reason for the dramatic emergence of these organisms as a cause of healthcare-associated infections throughout the world. The current review is to our knowledge the first to inclusively report the prevalence and trend of antibiotic resistance of enterococci over 20 years in Iran. Data analysis showed noticeable increases and decreases in the trends of resistance to ampicillin, gentamicin, ciprofloxacin, vancomycin and erythromycin during 2001–2016. A decreased resistance trend for ampicillin and erythromycin and an insignificant increased trend was observed for vancomycin. However, the trend was significantly decreased for ciprofloxacin. The level of gentamicin resistance was consistent during this time period.

The reasons for the observed increases and decreases in the level of the antibiotic resistance of enterococci could be sample size, geographic location and methodology. For example, in a study carried out in the east of Iran (Azerbaijan) in 2003, only eight enterococcal isolates were isolated from 676 samples from cases of UTI [14]. All eight isolates were resistant to ampicillin. Another study which was carried out in the same year in Tehran reported 90% ampicillin resistance among enterococcal isolates recovered from cases of UTI. The small sample size of these two articles, and hence during 2003, might have caused a bias (overestimation) in the rate of resistance to ampicillin during this year. However, no variations were observed in different provinces where the same methodology was used.

During 2014, the mean rate of ampicillin resistance from two distinct studies, one in the south of Iran (Bandar Abbas, n = 54) and another in its south-central region (Shiraz, n = 24), was

| Antibiotic                  | Total studies (n) | Total isolates (n) | General cases | Complicated cases | Significance of difference between general and complicated cases (p) |
|-----------------------------|-------------------|-------------------|---------------|-------------------|---------------------------------------------------------------|
| Vancomycin                  | 32                | 6703              | 15.6          | 26                | 0.597                                                         |
| Gentamicin                  | 21                | 4155              | 51            | 76                | 0.440                                                         |
| Ciprofloxacin               | 20                | 3885              | 35            | 61                | 0.155                                                         |
| Penicillin                  | 19                | 3885              | 74            | 58                | 0.560                                                         |
| Ampicillin                  | 18                | 5141              | 43.5          | 39                | 0.676                                                         |
| Erythromycin                | 17                | 4656              | 58.3          | 85                | 0.425                                                         |
| Nitrofurantoin              | 15                | 1962              | 19            | 35                | 0.235                                                         |
| Chlorophenicol              | 14                | 2503              | 17            | 27                | 0.604                                                         |
| Trimethoprim/sulfamethoxazole| 14               | 2346              | 49            | 100               | 0.141                                                         |
| Tetracycline                | 12                | 2592              | 56            | —                 | —                                                             |
| Imipenem                    | 10                | 1978              | 22            | 41                | 0.065                                                         |
| Teicoplanin                 | 10                | 1599              | 23.2          | 39                | 0.289                                                         |

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determined as 14% [49,50]. Moreover, no significant difference was seen where different methodologies were used. For example, a low mean rate of resistance was deduced for gentamicin during 2008 (7%), 2009 (6%) and 2014 (7%) [3,35,41,45].

Ciprofloxacin, as an occasional empirical prescription for UTIs, showed a significant decreased resistance trend among enterococcal infections in Iran. A possible reason for this decrease over time might be the scarcity of studies in regions where ciprofloxacin is frequently used. However, ciprofloxacin is typically an antibiotic of choice for outpatients, whereas the majority of studies reported and examined were of hospitalized patients.

Since 2001, resistance to erythromycin has been high among enterococcal isolates. High emergence of resistance has precluded its empirical use in clinical settings. Macrolides are not generally used to treat enterococcal infections; however, incidental exposure of enterococci to these antibiotics might happen during the course of therapy for other bacterial infections. The most frequent type of macrolide resistance is the production of a methylase enzyme, which specifically methylates an adenine residue in the 23S rRNA of the 50S ribosomal subunit. This reduces the binding affinity of macrolides for the ribosome and hence renders macrolides ineffective [51].

The trend of resistance to vancomycin was insignificantly increased during 2001–2016. The year 2002 seems to be the start of a sudden rise in vancomycin resistance in Iran. A study carried out in Tehran during 2002 revealed that 102 (8%) of 1231 urine bacterial isolates were identified as enterococci, among which 46% were found to be vancomycin resistant.

The apparent upsurge and downsurge in vancomycin resistance seems to have occurred every 2 to 3 years during the last 15 years in Iran. During 2007, 8.5% vancomycin-resistant enterococci (VRE) was reported among clinical enterococci recovered from two hospitals in Tehran [44]. In 2016, 4% VRE were isolated from patients in southeast Iran (Zabol province), which included the first reported case of vancomycin-resistant Enterococcus mundtii in Iran [18]. In the same year, another study in the south of Iran (Shiraz) reported 45% VRE [52]. The difference in the percentages reported within the same year from different provinces could be due to the lack of proper medical reporting in some provinces, different methodology and in particular different vancomycin discs used, or geographic variations.

Fig. 3 shows a clear indication that both E. faecalis and E. faecium have had an increase in the mean resistance against all the antibiotics during a 10-year period. This increase in resistance was only significant in the case of erythromycin and ampicillin for E. faecalis and erythromycin in the case of E. faecium species. Erythromycin, as an empirical therapy, might have increased during this time period, resulting in constant exposure with enterococcal species and eventual evolving of resistance mechanisms by the microorganism.

The mean resistance rates against gentamicin, vancomycin and ampicillin were significantly higher among E. faecium species compared to E. faecalis during 2005. In 2015, however, gentamicin resistance among E. faecium species fell below that of E. faecalis. This decrease, however, was statistically insignificant.

Higher rates of antibiotic resistance among E. faecium compared to E. faecalis has been well documented. The presence of resistance genes and mechanisms such as the aminoglycoside modifying enzymes Aph(2’)-Ib and Ant(3’)-Ia, responsible for high-level gentamicin and streptomycin resistance or altered cell wall structures due to L,D-transpeptidase causing resistance to β-lactams, have been extensively reported in E. faecium [53]. Such alterations have resulted in MICs for β-lactams to be typically about 2 to 8 mg/mL for E. faecalis and 8 to 16 mg/mL for E. faecium. Additionally, because of the species genomic structure, vancomycin resistance by vanA is relatively uncommon in clinical isolates of E. faecalis compared to E. faecium.

Our analysis showed that with the exception of penicillin and ampicillin, resistance to all antibiotics was higher (although not statistically significant) among complicated cases compared to general patients. Complicated patients are more exposed to antibiotics through hospitalization. The balance in the microbiota becomes altered by the overuse of antibiotics such as cephalosporins and metronidazole, which are often used empirically in critically ill patients. These antibiotics are able to exterminate many Gram-negative and anaerobic bacteria, leaving more resistant enterococci intact. Moreover, some cephalosporins (such as ceftriaxone) are concentrated in the gut through gut secretions, thus emphasizing its effect against gut microbiota and facilitating the expansion of resistant enterococci from the gut to other sites within the body [53].

Conclusion

A notable increase and decrease in the trends of enterococcal resistance to ampicillin, gentamicin, ciprofloxacin, vancomycin and erythromycin were found during 2001–2016. The mean resistance against all the antibiotics has continued to rise in E. faecalis and E. faecium during a 10-year period from 2010 to 2015. With the exception of penicillin and ampicillin, resistance to all antibiotics was higher among complicated patients compared to general patients. Although more data are needed to confirm our results, it seems that the use of newer antibiotics such as linezolid, and in case of E. faecium infections Synercid, appears to be a potentially reasonable therapeutic choice in Iran.
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Conflict of interest

None declared.

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