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

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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 resistancerate, however, was considerably increased for both species during this period. The mean resistance rates for vancomycin, gentamicin, ciprofloxacin, erythromycin, nitrofurantoin, chloramphenicol, trimethoprim-sulfametoxazol, 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.

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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 $p \leq 0.05$ 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.