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REVIEW

Prevalence of vancomycin-resistant *Enterococcus* in Iran: a systematic review and meta-analysis

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Abstract Vancomycin-resistant *Enterococcus* (VRE) is considered to be a major nosocomial pathogen that results in serious morbidity and mortality worldwide. Limited information is available concerning the prevalence of VRE infections in Iran. We carried out a systematic search by using different electronic databases including: Medline (via PubMed), Embase, Web of Science, and the Iranian Database. Meta-analysis was performed using comprehensive meta-analysis software. The meta-analyses revealed that the prevalence of VRE infections was 9.4 % (95 % confidence interval [95 % CI] 7.3–12) among culture-positive cases for *Enterococcus* species. The prevalence of VRE in Iran is compared with the results of developed countries. The prevalence of VRE in Germany, the United Kingdom (UK), and Italy was 11.2 %, 8.5–12.5 %, and 9 % respectively. Additionally, the frequency of vancomycin resistance among *E. faecalis* isolates was higher than for *E. faecium*. The results of this study indicate that a comprehensive infection control strategy based on hand hygiene, educating the hospital staff members, providing clinical guidance and principles for the appropriate use of antibiotics, sanitizing the hospitals, contact precautions, and active surveillance systems on the basis of international criteria is urgently needed.

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Introduction

Enterococcus is a common commensal bacterium originating from the human gastrointestinal tract and may cause serious infections in humans under certain conditions [1]. Enterococci constitute the second most common cause of nosocomial urinary tract infections [2]. This species has been recognized as the third leading cause of healthcare-associated bloodstream infections in the USA, generating an enormous cost burden for the healthcare system [3]. Enterococci have gained resistance to almost the entire antimicrobial spectrum, including vancomycin, undoubtedly the most potential antimicrobial agent as a treatment for enterococcal infections [4]. In 1986, vancomycin-resistant *Enterococcus* (VRE) was initially was reported from clinical isolates in the UK and France. According to the data, a year later VRE was documented in US hospitals and emerged as one of the crucial hospital-acquired infectious agents [4]. In 2004, VRE strains were initially reported in Iran; and presently pertain to be a highly relevant nosocomial pathogen [5, 6]. It is quite significant to mention that VRE has been identified as a global public health dilemma, as the therapeutic options for the treatment are utterly limited [3]. Infections due to VRE are significantly associated with an increased rate of morbidity, mortality, prolonged hospitalization, and elevated cost burden [7]. Based on the aforementioned data, the prevalence rates of VRE in clinical samples has been reported in several scientific works in Iran [5, 8–12]. However, most of these studies have shown local information, and a comprehensive analysis from different parts

of Iran has not yet been performed. The aim of this surveillance review was to assess the prevalence of VRE in Iran by using a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) statement [13].

Materials and methods

Search strategies

We performed a systematic search by using different electronic databases including: Medline (via PubMed), Embase, Web of Science, and the Iranian Database from January 2000 to January 2016.

"Enterococcus," "vancomycin," vancomycin-resistant enterococci, and related terms were used as scientific keywords in this survey. Two independent reviewers screened the titles and abstracts for its relevance. The original articles were obtained and assessed in detail for inclusion. The scientific studies had to meet all the following criteria for inclusion: a standard method had to be used to detect VRE, reported data on the number of VRE, and enrolled patients who were hospitalized and presented with symptoms of VRE. According to the Clinical and Laboratory Standards Institute (CLSI) guidelines [14], broth microdilution, agar dilution, and E-test are all methods of accurately detecting vancomycin resistance in enterococci.

We excluded studies that did not report the number of VRE. In addition, we disqualified the reports that particularly discuss specific groups of samples. For instance, articles that only focused on stool or urine samples were eliminated. We excluded reports that did not use standardized methods. We

Table 1 Characteristics of studies included in the meta-analysis

Reference	Period of study	Year of publication	Province	Sources of isolate	Sample size	Number of VRE	Detection method
Akhi et al. [26]	2001–2002	2009	Tabriz	Urine, ascetic fluid, wound, catheter	137	6	Microdilution method
Aleyasin et al. [27]	2004–2005	2007	Tehran	Urine, blood, wound	126	12	Agar dilution method
Talebi et al. [12]	2004–2005	2008	Tehran	Urine, wound, blood	450	19	E-test
Talebi et al. [28]	2005–2006	2008	Tehran	Urine, wound, blood, body fluid	830	48	Microdilution method
Pourshafie et al. [29]	2005–2006	2008	Tehran	Urine, wound, blood, body fluid	900	49	E-test
Emaneini et al. [5]	2005–2006	2008	Tehran	Urine, blood, wound	326	38	Microdilution method
Japoni et al. [30]	2005–2008	2009	Shiraz	Blood, urine	297	39	E-test
Yasliani et al. [31]	2006–2007	2009	Tehran	Urine, blood, wound	200	17	Agar dilution method
Ghasemi et al. [32]	2008–2009	2010	Kashan	Urine, blood, wound	106	6	E-test
Sharifi et al. [9]	2008–2010	2012	Tabriz	Urine, blood, body fluid, wound	220	45	Agar dilution method
Hosseinizadeh et al. [33]	2009–2010	2012	Arak	Urine, blood, sputum	150	14	Microdilution method
Shokoohizadeh et al. [10]	2010–2011	2013	Tehran	Urine, wound, blood, abscess	222	45	Agar dilution method
Shokri et al. [11]	2010–2011	2013	Isfahan	Clinical samples	273	29	E-test
Dadfarma et al. [8]	2011–2012	2013	Tehran	Urine, wound, blood	142	11	Microdilution method
Nikouie et al. [34]	2011–2012	2014	Tehran	Urine, CSF, blood	165	40	E-test
Talebi et al. [12]	2011–2012	2014	Tehran	Urine, wound, blood, body fluid	546	33	E-test
Mirzaei et al. [35]	2011–2012	2013	Tehran	Clinical samples	185	27	E-test
Balaei Gajan et al. [36]	2011–2012	2013	Tabriz	Clinical samples	105	4	Microdilution method
Naserpour Farivar et al. [37]	2012–2013	2014	Qazvin	Urine, blood, sputum	226	32	E-test
Abbasi and Zamanzad [38]	2013–2014	2015	Shahr-e Kord	Urine, blood, wound	150	10	Microdilution method

VRE vancomycin-resistant enterococci

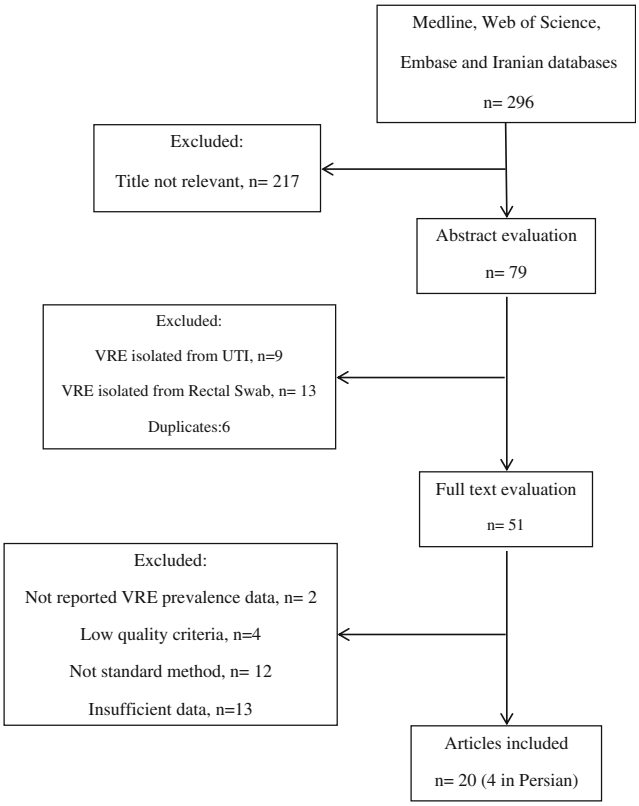

Fig 1 Summary of the literature search and study selection

neglected reports that did not have abstracts in English. Furthermore, to minimize the potential bias caused by an inadequate sample size, articles with less than 100 subjects were omitted.

Data extraction and definitions

The following details were extracted from the manuscripts: the first author's name, the publication year, the date of the study, the study setting, the number of cases involved in the studies, the study method, the source of isolates, the sample size, and the prevalence of VRE infections. Two independent reviewers extracted all data from the articles included and the results were reviewed by the third reviewer. Inconsistencies between the reviewers were resolved by a general consensus.

Quality assessment of studies

Two reviewers independently assessed the study quality by using a checklist, which was provided by the Joanna Briggs Institute [15].

Statistical analysis

Meta-analysis was performed using comprehensive meta-analysis (Biostat V2.2) software. We reported the amount of residual heterogeneity by using the t^2 statistic and the Q statistic to test the heterogeneity between the inquiries. To assess any possible publication bias, Begg's rank correlation and Egger's weighted regression methods were used in combination with a funnel plot ($p < 0.05$ was considered indicative of statistically significant publication bias).

Results

We identified 296 articles, 20 of which fulfilled the criteria mentioned (Table 1). Figure 1 presents the reasons why some records were excluded because of the assessment of title, abstract, and full article texts.

Based on the 20 selected articles, the pooled prevalence of VRE was estimated at 9.4 % (95 % CI 7.3–12.0) among culture-positive cases of VRE in Iran. However, the results were found to be periodically heterogeneous ($I^2 = 85.0$; $p = 0.00$ test for heterogeneity).

The prevalence of *E. faecalis* and *E. faecium* was 77.5 % (95 % CI 60.0–84.0) and 22 % (95 % CI 15.6–30.0) respectively. Details of the meta-analysis for the sub-groups can be found in Table 2. A forest plot for the meta-analysis of VRE isolates is depicted in Fig. 2. As shown in Table 2 and Fig. 3, no evidence of publication bias was observed ($p = 0.1$ for Begg's rank correlation analysis; $p = 0.2$ for Egger's weighted regression analysis).

Table 2 Meta-analysis of the prevalence of VRE in Iran

Subgroups	Number in study	Prevalence of VRE	*n*/*N*	Heterogeneity test, I^2	Heterogeneity test, *p* value	Begg's test	Egger's test
Overall	20	9.4 (7.3–12)	5,756	85	<0.001	0.1	0.2
E. faecalis	12	77.5 (60.0–84.0)	1,907/2,557	90.0	<0.001	0.1	0.4
E. faecium	10	22 (15.6–30.0)	596/2,346	90.5	<0.001	0.7	0.02

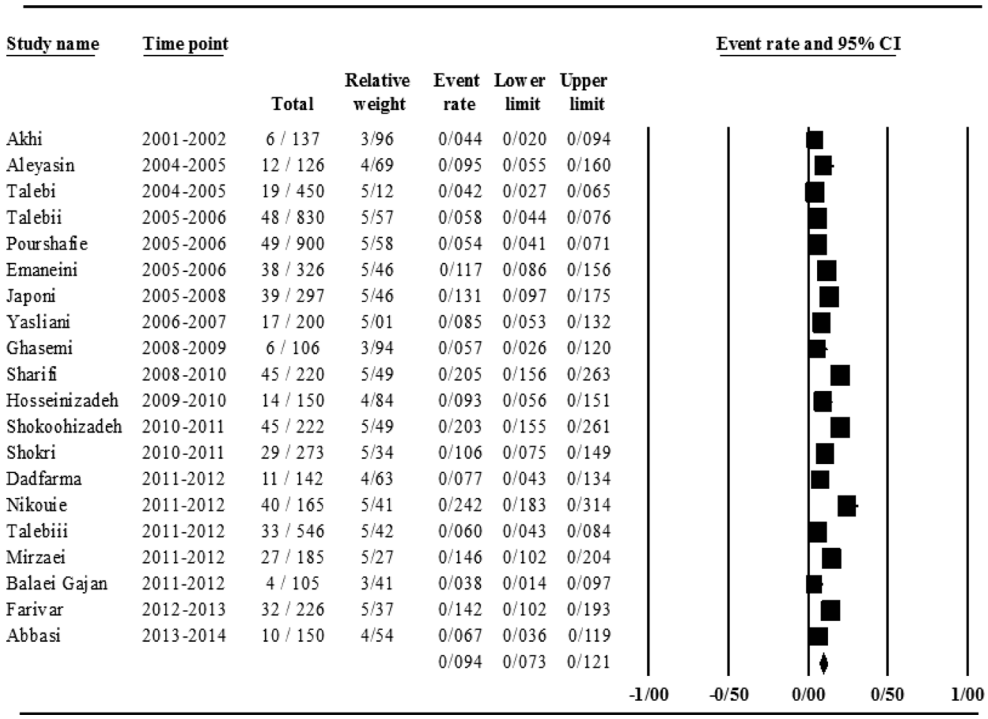

Fig. 2 Forest plot of the meta-analysis of vancomycin-resistant enterococci (*VRE*) isolates

Discussion

To our knowledge, this study is the first comprehensive systematic review on the prevalence of VRE in Iran. Based on the meta-analysis results, the overall estimate of VRE prevalence in Iran was 9.4 %. The prevalence of VRE in Iran is compared with results from developed countries [16–20]. The prevalence of VRE in Germany, the UK, and Italy was 11.2 %, 8.5–12.5 % and 9 % respectively [16–20]. Several factors may explain the prevalence of VRE in Iran. First, infection control programs are not very effective in Iran. For instance, hand hygiene is the most important infection control measure for reducing transmission of VRE in hospitals [21, 22]. In most Iranian university hospitals, compliance with

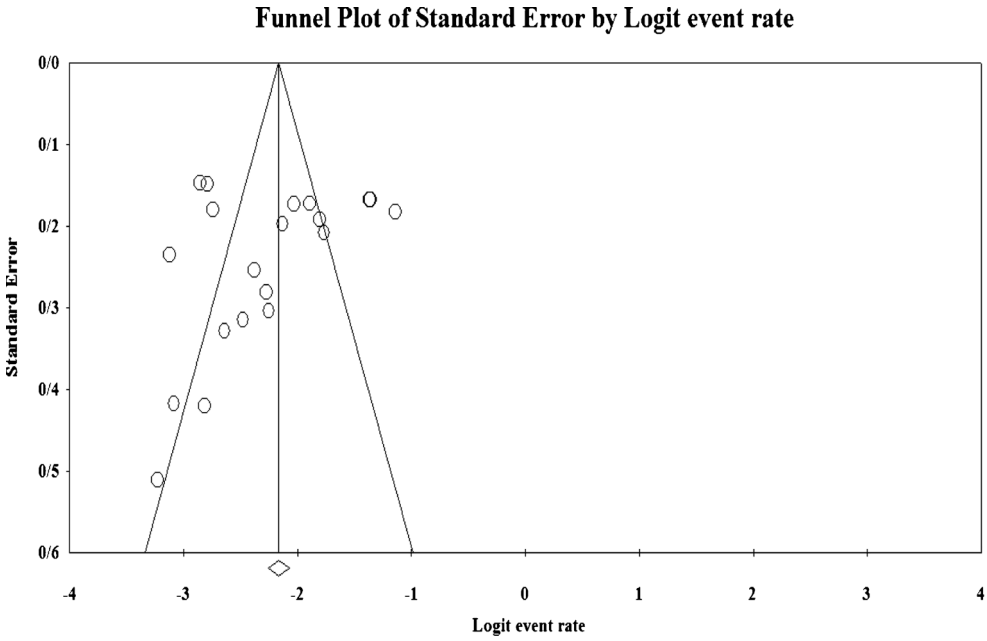

Fig. 3 Funnel plot of the meta-analysis on VRE isolates (funnel asymmetry suggests bias in the meta-analysis)

hand hygiene among healthcare workers is quite poor. Heavy workload, insufficient numbers of healthcare staff, limited infrastructures (lack of sinks, hygiene products that are difficult to access), and behavioral aspects are the major reasons for noncompliance [23–25]. Second, wards with a high bed occupancy rate are the leading cause of poor attention to infection control protocols in Iranian university hospitals. Third, the lack of isolation rooms could be considered another concern in Iranian hospitals, as patients infected with VRE are admitted to the multi-bed rooms together with uninfected patients. Fourth, in developing countries such as Iran, the inappropriate use of antibiotics and empiric therapies by physicians is prevalent. As a consequence, there is an increasing rate of infections with VRE in different parts of Iran [24]. Fifth, sanitizing the hospital environment is generally ineffective [24]. Thus, VRE can directly transfer through contact with contaminated surfaces [3]. Finally, the disk diffusion agar method (Kirby–Bauer method) is currently extensively used by medical microbiology laboratories in Iran. Although not very accurate, it is better to use the minimum inhibitory concentration method of detection.

Stratified analyses were conducted in the present study with regard to the geographic areas. The majority of studies included were performed in Iran's capital (Tehran), where a relatively high prevalence of VRE has been reported. These findings suggest that the many tertiary hospitals in Tehran might play a referral role in almost all regions and most patients from different parts of country are referred to these centers for diagnosis, treatment, and further follow-up. According to our analysis, the rate of vancomycin resistance among *E. faecalis* isolates was higher than for *E. faecium*. This finding could be explained by the fact that *E. faecalis* was the dominant species isolated from infections [5, 9, 10].

In the present review article, we were faced with several constraints. First, the studies could not fully indicate the prevalence of VRE infections in Iran as the magnitude of VRE infections was not identified in different regions of the country. Second, we only considered published articles in the current meta-analysis, exactly like any other meta-analysis; thus the potential for publication bias had to be considered as well. Third, heterogeneity was observed among the studies included.

In conclusion, the present systematic review summarized the prevalence of VRE in Iran. According to the results, the hospital's infection control program in Iran has been dramatically ineffective. Therefore, a comprehensive infection control strategy based on hand hygiene, educating the hospital staff members, sanitizing the hospitals, taking precautions with contact, and an active surveillance system according to international criteria should be enforced in the community.

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Compliance with ethical standards

Funding None.

Conflicts of interest None.

Ethical approval Not applicable.

Informed consent Not applicable.

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