Bacterial Ocular Infections in Iran: A Systematic Review and Meta-analysis

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ARTICLE INFO

Article history:

Received: 12 October 2021 Accepted: 2 March 2022

Online:

DOI 10.5001/omj.2023.22

Keywords:

Eye Infections; Staphylococcus aureus; Staphylococcus epidermidis; Viridans Streptococci; Pseudomonas aeruginosa; Systematic Review; Iran.

ABSTRACT

Objectives: Eye infections can be caused by several microorganisms and the most common causative bacterial agents are staphylococci, streptococci, and *Pseudomonas aeruginosa*. This study aimed to estimate the prevalence of *Staphylococcus aureus, Staphylococcus epidermidis*, viridans group streptococci, and *P. aeruginosa* as the cause of ocular infections in Iran. *Methods*: We conducted a systematic search on the studies published by Iranian authors from January 2000 to December 2020 in Web of Science, PubMed, Scopus, and Embase. Eligible studies were selected according to the defined inclusion/exclusion criteria. Statistical heterogeneity between and within groups was estimated by the Q-statistic and I² index. The funnel plots, Duval and Tweedie trim, and fill methods were obtained to evaluate the evidence of publication bias. *Results:* Twenty-seven studies were included in this review. According to the meta-analysis results, the prevalence of *S. epidermidis* was 19.1% (95% CI: 12.5–28.1). It was estimated 6.9% (95% CI: 4.4–10.6), 6.7% (95% CI: 4.6–9.6), and 3.3% (95% CI: 1.8–5.8) for *P. aeruginosa, S. aureus*, and viridans streptococci, respectively. *Conclusions: S. epidermidis* is the prevalent bacterial agents responsible for eye-associated infections in Iran.

The eye is a unique anatomical organ, protected by the continuous flow of tears having antimicrobial compounds. However, it is often colonized by a range of microorganisms. 1 Eye infections can be caused by several microorganisms, such as bacteria, viruses, parasites, or fungi, and they are able to develop a spectrum of diseases and symptoms. The symptoms of infections are variable, depending on the type of infection and causative agents.2 Ocular infections comprise keratitis, endophthalmitis, conjunctivitis, blepharitis, stye, orbital cellulitis, and dacryocystitis manifestations.3 Infectious keratitis is an infection of the cornea that might be associated with ocular surgery, trauma, contact lens use, suppression of the immune system (such as diabetes), chronic use of topical steroids, or immunomodulatory therapies. Bacterial infection is the most common cause of infectious keratitis.4 Endophthalmitis is a potentially blinding intraocular infection and inflammation, resulting from the entry of bacteria into the interior

part of the eye.⁵ Other inflammatory diseases of the eye usually occur through bacterial infection.⁶⁻⁸ The most common causative bacteria are *Staphylococcus aureus*, coagulase-negative staphylococci, viridans group streptococci, and *Pseudomonas aeruginosa*.^{9,10}

Understanding the epidemiology of eye infections in a region is essential to reinforce effective prevention and control strategies. There is no comprehensive data regarding bacterial ocular infections in Iran. Therefore, the aim of this study was to assess the prevalence of frequent bacteria that cause ocular infections during 21 years in Iran using a systematic review and meta-analysis.

METHODS

In the present systematic review and meta-analysis study, all procedures for identification of papers were carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This study was

approved by the Ethics Committee of Shahrekord University of Medical Sciences (Register code: IR.SKUMS.REC.1400.091).

We conducted a systematic search of studies published by Iranian authors from January 2000 to December 2020 in Web of Science, PubMed, Scopus, and Embase. Records were managed by EndNote X9.0 software to exclude duplicates. We used eye infection-related key terms (conjunctivitis, keratitis, stye, uveitis, endophthalmitis, eye disorder, ocular infection, and eye infection) and key terms to identify Iran. To identify the missing studies, we also searched bibliographies of retrieved articles for additional references.

Cross-sectional or cohort studies that reported the prevalence of S. aureus, S. epidermidis, viridans streptococci, or P. aeruginosa in eye infections were considered. The titles, abstracts, and full texts were screened independently by two reviewers to determine the articles that met the inclusion criteria, and any discrepancies were resolved with a third investigator or by consensus. Articles published in the English or Persian language that were indexed in PubMed or Scopus with the following characteristics and reported the prevalence of S. aureus, S. epidermidis, viridans streptococci, or P. aeruginosa in eye infections were included. Additionally, studies conducted by non-Iranian authors on the Iranian population or samples were also assessed. The studies without reports of bacterial prevalence in eye infections were excluded. The studies with insufficient, unclear, or missing information were also excluded from the meta-analysis. We also excluded studies with a sample size < 10 isolates, non-human studies, published studies in languages other than English or Persian, review articles, meta-analyses or systematic reviews, and congress abstracts.

Data collection was performed in parallel by two investigators who performed the literature searches. Variables such as the first author's name, the time the study was performed, publication date, the study setting, site of infection, sample size (number of bacterial isolates obtained from eye infections), and the prevalence of the mentioned bacteria were extracted.

Analysis of data was performed using Comprehensive. Meta-Analysis software version 2.2 (Bio-stat Company). Meta-analysis was performed using random effects model to estimate the pooled prevalence and corresponding 95% CI. Statistical heterogeneity between and within groups was

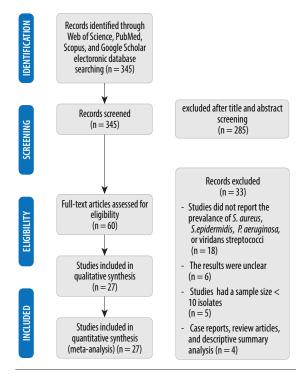


Figure 1: Summary of the literature search and study selection.

estimated by the Q statistic and I^2 index. The funnel plots, Duval and Tweedie trim, and fill methods were carried out to evaluate the evidence of publication bias.

RESULTS

A total of 345 articles were retrieved using the search strategy; 285 were excluded based on the index and review of the titles and abstracts, leaving 60 articles for full-text review. Full-text screening excluded 33 studies, resulting in 27 eligible studies. Figure 1 shows the study selection process and reasons for exclusion. The main characteristics of the included studies and the prevalence of *S. aureus*, *S. epidermidis*, viridans streptococci, and *P. aeruginosa* in eye infections are shown in Table 1.

In 26 studies, the prevalence of *S. aureus* in eye infections was investigated. The pooled prevalence for *S. aureus* isolates was 6.7% (95% CI: 4.6–9.6; range = 0.5–27.1%) [Figure 2]. There was a significant heterogeneity among the 26 studies ($\chi^2 = 136.101$; p < 0.001; $I^2 = 81.6\%$). The symmetric funnel plot showed no evidence of publication bias [Supplement 1a]. Furthermore, using Duval and Tweedie's trim and fill procedures, no evidence of publication bias was found for any of the measures.

 Table 1: Characteristics of studies included in the meta-analysis.

		Stu	Study details reference			Infection	Infectious agents	
Authors	Publication year	Years of study	City or region	Site of infection	S. aureus (%)	S. epidermidis (%)	Viridans streptococci (%)	P. aeruginosa (%)
Tabatabaei et al, ¹¹	2020	2008-2018	Tehran	Iritis and/or vitritis	27.1	1	2.8	4.9
Soleimani et al, ¹²	2020	2008-2017	Tehran	Keratitis	4.3	10.8	1.1	10.8
Abtahi et al, ¹³	2020	2016-2019	Shiraz	Orbital cellulitis	2	2	1	1
Feizi et al, 14	2019	2017	Tehran	Persistent corneal epithelial defects	2	17.5	2	1
Zare et al, ¹⁵	2019	2017-2018	Tehran	Corneal ulcers	9	1	1	3
Nemati et al, 16	2018	2014-2015	Guilan	Nasolacrimal duct obstruction	4.1	16.6	1	11.1
Owji et al, ¹⁷	2018	Unknown	Shiraz	Nasolacrimal duct obstruction	18	62.6	9	1
Eghtedari et al, 18	2018	Unknown	Shiraz	Corneal ulcer	7.9	6.3	1	9.5
Heidari et al, ¹⁹	2018	2016-2017	Shiraz	Corneal infection	7.1	1	1	12.5
Faridi et al, ²⁰	2018	2016	Tehran	External ocular infection	8.6	1	1	1
Eshraghi et al, ²¹	2016	Unknown	Tehran	Unilateral nasolacrimal duct obstruction		40.8	11.2	1
Faghri et al, ²²	2016	2013	Isfahan	Severe pain and comeal ulcers	2.5	49.3	1	6.4
Rahimi et al, ²³	2015	2008-2012	Tehran	Bacterial keratitis	3.8	6.1	9.9	24.7
Abrishami et al, ²⁴	2015	Unknown	Mashhad	Postoperative endophthalmitis	9.3	9.3	1	6.2
Oryan et al, ²⁵	2014	2012-2013	Isfahan	Keratitis infections	2.6	49.3	1	6.5
Sharifi et al, ²⁶	2013	2007-2010	Yasuj	Ocular trauma	2.8	3.8	1	1
Eshraghi etl al, ²⁷	2013	2007-2010	Tehran	Acute dacryocystitis, lacrimal sac empyema underwent incision, and drainage	25	ı	12.5	i
Ghasemi et al, ²⁸	2013	Unknown	Tehran	Serious sulfur mustard-induced ocular injuries	3.5		0.7	1
Falavarjani et al, ²⁹	2012	2006-2011	Tehran	Endophthalmitis	15.3	24.6	1.5	23
Rahimi et al, ³⁰	2012	2005-2009	Shiraz	Acute endophthalmitis	17.1	5.7	1	5.7
Bagheri et al, ³¹	2012	1997–2007	Tehran	Orbital and preseptal cellulitis	7.5	1	1	1
Hosseini et al,³²	2012	2008	Shiraz	Endophthalmitis	11.3	31.8	18.1	2.2
Karimian et al, ³³	2011	Unknown	Tehran	Chronic blepharitis	3	57	1	1
Sedghipour et al,34	2011	2000-2003	Tabriz	Corneal ulcer	ı	23.2	1	1
Razavi et al, ³⁵	2010	2007-2008	Mashhad	Acute and chronic dacryocystitis	13.1	47.5	1.6	3.2
Khosravi et al, 36	2007	2005-2006	Ahwaz	Ocular infection	2.8	7.2	1.5	5.3
Feizi et al, ³⁷	2007	Unknown	Tehran	Ocular infection	21.5	0.5	1	0.5



Meta Analysis

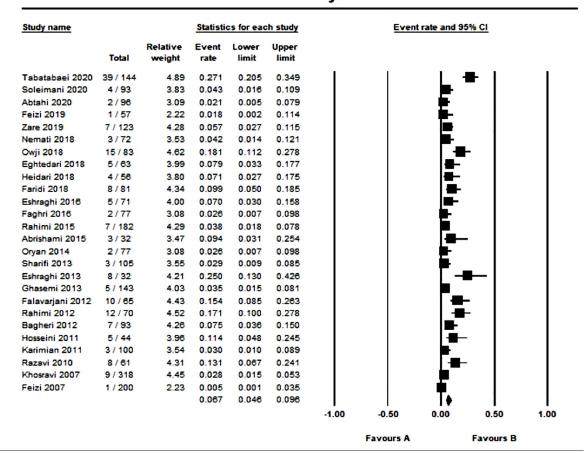


Figure 2: Forest plot of prevalence of ocular infections causative *S. aureus* isolates in Iran.

Meta Analysis

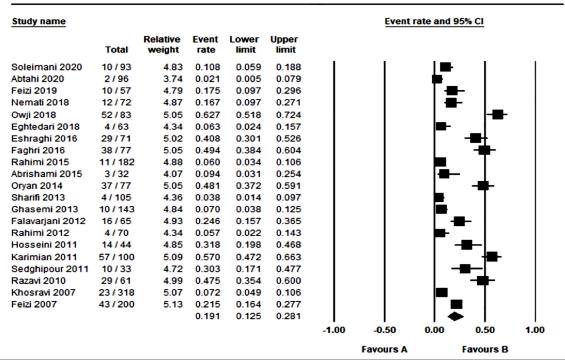
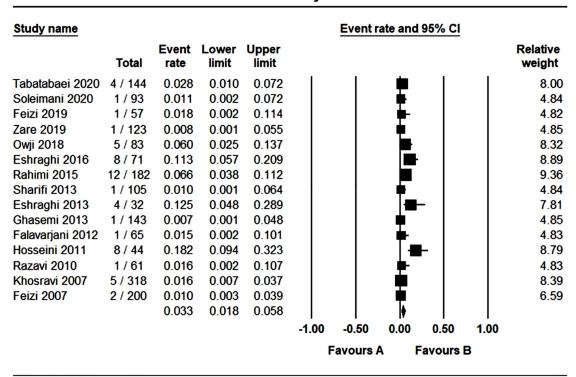


Figure 3: Forest plot of prevalence of ocular infections causative *S. epidermidis* isolates in Iran.

Meta Analysis



Meta Analysis

Figure 4: Forest plot of prevalence of ocular infections causative viridans streptococci in Iran.

Meta Analysis

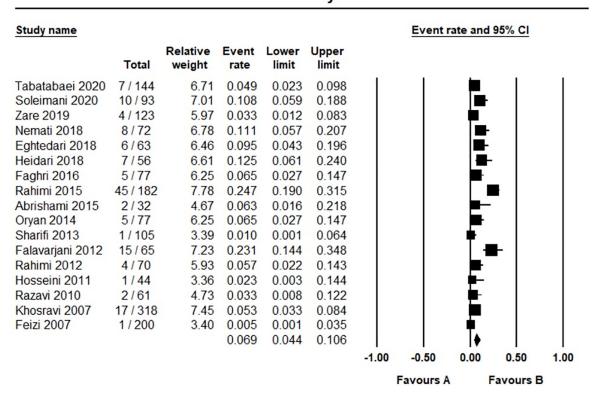


Figure 5: Forest plot of prevalence of ocular infections causative *P. aeruginosa* isolates in Iran.



According to the included studies, the frequency of *S. epidermidis* isolates was investigated in 21 studies. The pooled prevalence of *S. epidermidis* isolates was estimated at 19.1% (95% CI: 12.5–28.1; range = 2.1–62.7%) [Figure 3]. There was a significant heterogeneity among the 21 studies ($\chi^2 = 328.470$; p < 0.001; $I^2 = 93.9\%$). There was no evidence of publication bias [Supplement 1b].

In 15 studies on viridans group streptococci, the pooled prevalence was 3.3% (95% CI: 1.8–5.8; range = 0.7%–18.2%) [Figure 4]. There was a significant heterogeneity among the 15 studies (χ^2 = 54.2; p < 0.001; I² = 74.2%). Publication bias was assessed by funnel plot for the standard error by logit event, with no evidence of bias [Supplement 1c]. Additionally, Duval and Tweedie's trim and fill tests suggested that there was no notable evidence of publication bias.

We found 17 articles that investigated the prevalence of *P. aeruginosa* in bacterial eye infections. The pooled prevalence of *P. aeruginosa* isolates was estimated at 6.9% (95% CI: 4.4–10.6; range = 0.5–24.7%) [Figure 5]. Based on the Q-statistic and I² index, heterogeneity was significant ($\chi^2 = 91.699$; p < 0.001; I² = 82.6%). Also, there was no evidence of publication bias [Supplement 1d].

DISCUSSION

Bacteria are the major contributors to ophthalmic diseases worldwide. The dominant causative bacterial agents of ocular infections are staphylococci, streptococci, and P. aeruginosa. 9,10,38 To the best of our knowledge, this study is the first systematic review on the prevalence of S. aureus, S. epidermidis, P. aeruginosa, and viridans group streptococci isolates that caused eye infections in Iran. According to the meta-analysis results, the pooled prevalence of S. aureus isolates that caused these infections was 6.7%. In a previous systematic review conducted on bacterial profile of ocular infections in several developed and developing countries (including Nigeria, India, Ethiopia, Japan, USA, and Malaysia), the average prevalence of S. aureus was more than 20%.38 Furthermore, our analysis indicated that the pooled prevalence of S. epidermidis isolates was 19.1%, and it was the most common agent responsible for eye infections. Various prevalence rates of S. epidermidis or coagulase-negative staphylococci were reported in previous studies.^{38–46}

These discrepancies may be related to the type of eyeassociated infections. Besides, a variety of factors, such as contact lens wearing, immune system status, anatomical disruption, and traumatic inoculation of the organisms by foreign bodies, could determine the prevalence and distribution of the type of bacterial agents associated with ocular infections. These factors may lead to infection development by normal flora such as members of the staphylococci.³⁸ S. epidermidis is the most commonly found bacteria, colonizing the mucosa and lid margins. Also, underlying diseases (such as diabetes) may affect the S. aureus colonization in the eyes and its subsequent prevalence in such infections. Geographical climate (heat and humidity) has been reported as another factor that affects the composition of ocular surface flora.⁴⁷

Our analysis indicated that the pooled prevalence of viridans streptococci isolates was 3.3%. In a retrospective study in the USA, the viridans streptococci were responsible for the majority of endophthalmitis caused by Streptococcus species (71%).⁴⁸ Another retrospective study from the USA indicated that 11% of ocular infections and 12.1% of endophthalmitis cases were related to viridans group streptococci. 46,49 The prevalence of these bacteria was 2.8% in community-acquired bacterial ocular infections in India. 40 Various rates of viridans group streptococci associated with ocular infections were reported from several regions, such as Spain (5%),50 Mexico (14.3%),⁵¹ Nigeria (1.5%),³⁸ and the UK (0.4%).52 This diversity may be related to different types of ocular infections.

The pooled prevalence of *P. aeruginosa* isolates was estimated at 6.9%. Greater rates were reported from Taiwan (35.2%), 43 Ethiopia (11.7%), 44 India (10.7%,⁵³ 21%,³⁸ and 44%⁵⁴), Nigeria (10.1%), Japan (9.7%), Malaysia (16%),³⁸ and the USA (8-16%).38,46 An analysis in the UK showed that the prevalence of P. aeruginosa was 7.2%.45 However, lower frequencies were reported from India (3%) and Ethiopia (4.9%).³⁸ P. aeruginosa utilizes various virulence factors and mechanisms, such as exotoxins, proteases, elastases, and biofilm formation to develop an infection in the eye tissues. It is a common causative agent in cases of ocular infections, especially corneal ulcer infection and keratitis associated with contact lens use. Moreover, the current evidence suggests that the majority of such infections are related to P. aeruginosa genotypes that encode the exotoxin U. Constant exposure to a sub-inhibitory concentration of lens cleaning solutions and biocides can contribute to resistance to disinfectants. The prevalence of infection caused by *P. aeruginosa* also depends on other predisposing factors, such as ocular surgery, immunodeficiency, diabetes mellitus, and rheumatoid arthritis. These situations may lead to severe infections such as endophthalmitis.^{38,55–58}

CONCLUSION

S. epidermidis was the most common bacterial agent responsible for ocular infections in Iran (19.1%). The prevalence of *P. aeruginosa* isolates was 6.9%, and *S. aureus* and viridans group streptococci accounted for 6.7% and 3.3% of eye-associated infections. Our results will contribute to understanding bacterial agent contributions in ocular infections in Iran.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study. This study was supported by Shahrekord University of Medial Sciences (Project no: 3623).

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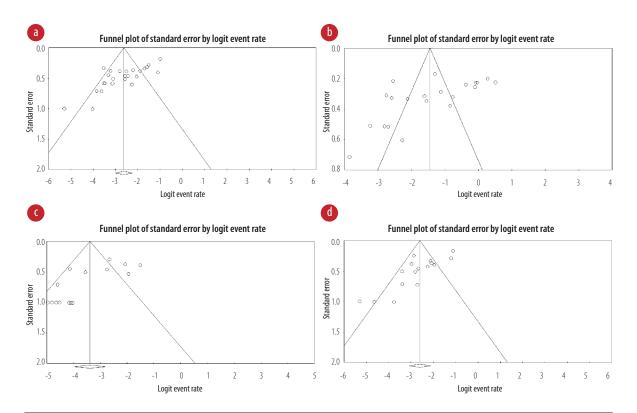
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Supplementary 1: Symmetric funnel plot showing no evedince of publication bias.