Chapter

Infectious Keratitis: The Great Enemy

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Abstract

Infectious keratitis tops the list of diseases leading to visual impairment and corneal blindness. Corneal opacities, predominantly caused by infectious keratitis, are the fourth leading cause of blindness globally. In the developed countries, infectious keratitis is usually associated with contact lens wear, but in developing countries, it is commonly caused by trauma during agricultural work. The common causative organisms are bacteria, fungus, Acanthamoeba, and virus. Severe cases can progress rapidly and cause visual impairment or blindness that requires corneal transplantation, evisceration, or enucleation. The precise clinical diagnosis, accurate diagnostic tools, and timely appropriate management are important to reduce the morbidity associated with infectious keratitis. Despite the advancement of diagnostic tools and antimicrobial drugs, outcomes remain poor secondary to corneal melting, scarring, or perforation. Eye care strategies should focus on corneal ulcer prevention. This review addresses the epidemiology, diagnostic approach, clinical manifestations, risk factors, investigations, treatments, and the update of major clinical trials about common pathogens of infectious keratitis.

Keywords: infectious keratitis, corneal ulcer, corneal scar, blindness, visual impairment

1. Introduction

Infectious keratitis tops the list of diseases leading to visual impairment and corneal blindness. Globally, it is approximated that 1.3 billion people live with visual impairment [1]. The major causes of corneal blindness included infectious keratitis, ocular trauma, trachoma, bullous keratopathy, corneal degenerations, and vitamin A deficiency [2]. Corneal opacities, predominantly caused by infectious keratitis, are the fourth leading cause of blindness globally [3]. Recent paper reported that 3.5% of global blindness could be attributed to corneal opacity [4]. According to the goal of the "Vision 2020: The Right to Sight," which was proposed by WHO, the prevention of avoidable corneal blindness should receive more awareness [5, 6].

Interestingly, the majority of visual impairment is avoidable [1]. Infectious keratitis accounts for 10% of avoidable visual impairment in the world's least-developed countries [3]. The number of people with avoidable visual loss has increased considerably because of population growth and aging. This trend will continue beyond

2020 [7] and will inevitably impact the eye care need in the near future. In the developed countries, infectious keratitis is usually associated with contact lens wear, but in developing countries, it is commonly caused by trauma during agricultural work [8–17]. Infectious keratitis is characterized by a corneal epithelial defect with underlying stromal inflammation caused by replicating microorganisms [14]. Acute eye pain and redness are the common presentation [14]. The common causative organisms are bacteria, fungus, Acanthamoeba, and virus [10, 17]. However, corneal infection involving more than one microorganisms such as bacteria and fungus is relatively uncommon [17] Microbial keratitis requires acute ophthalmic care and aggressive treatment to stop the disease progression and limit the extent of corneal scarring, which can cause loss of vision [14]. The precise clinical diagnosis, accurate diagnostic tools, and timely appropriate management are important to reduce the morbidity associated with infectious keratitis. This review addresses the epidemiology, diagnostic approach, clinical manifestations, risk factors, investigations, treatments, and the update of major clinical trials about common pathogens of infectious keratitis. The purpose of this review is to provide a concise and essential knowledge about common etiologic pathogens of infectious keratitis to improve understanding and reduce morbidity and visual loss due to this condition.

2. Global epidemiology, global etiologies, and burden of diseases

2.1 Global epidemiology

The precise prevalence of infectious keratitis is unknown [18]. The actual prevalence may be higher due to the underreporting or reporting under the term of corneal blindness, which also includes traumatic, infectious, inflammatory, and inherited causes [8]. Overall cases may exceed 2 millions cases per year worldwide [8]. The global incidence of infectious keratitis shows wide disparity among regions. The incidence of infectious keratitis was high in south, south-east, and east Asia, but lower in developed world [8]. The estimated general incidence of infectious keratitis per 100,000 population per year varies from 11 to 27.6 in the United States [19, 20], 40.3–52.1 in the United Kingdom [8, 21], 6.3 in Hong Kong [22], 113 in India [23], 339 in Bhutan [24], 710 in Burma [24], and 799 in Nepal [25]. In contact lens wearers, the incidence is about 6 times higher [8, 18, 20]. It has been reported that nearly 90% of the global cases of ocular trauma and infectious keratitis leading to corneal blindness occur in developing countries [2].

2.2 Global etiologies

The principal organisms of infectious keratitis have regional variation [18]. In developed countries such as Europe [21, 26, 27], North America [28, 29], and Australia [14], the highest proportions of infectious keratitis are attributable to bacteria. This incidence correlated with the prevalence of contact lens wear and high gross national income [30]. On the contrary, in developing countries, the proportions of infectious keratitis attributable to bacteria were less [31–33] than or similar to those from fungus [34]. The Asia Cornea Society Infectious Keratitis Study (ACSIKS) group that included data from 13 study centers and 30 subcenters from 6626 eyes of 6563 subjects demonstrated the similar percentage of bacterial and fungal infections. Overall, bacterial keratitis was diagnosed in 2521 eyes (38.0%) and fungal keratitis in 2166 eyes (32.7%) [34]. But in India and China, fungal keratitis was the majority of nonviral microbial keratitis [34]. Similarly, data from the large trial in India by Lalitha et al. that included 17,948 patients demonstrated

that 6218 of 10,207 (60.9%) culture-positive patients had a fungal etiology [31]. The recent studies from China by Lin et al. [35] and Xie et al. [33] reported proportions of fungal keratitis to be 44.6% and 77.9%, respectively. Vision 2020: "The Right to Sight" also suggests that we acquire a clearer and more precise understanding of infectious keratitis in each country [6, 33].

The frequency of causative organisms of keratitis among different geography may vary by countries [30]. In North America, Australia, the Netherlands, and Singapore, the highest proportion of infectious keratitis was bacterial in origin. The highest proportion of pseudomonas keratitis was reported in a study from Bangkok, whereas the highest proportion of staphylococcal ulcers was reported in a study from Paraguay. On the other hand, the highest proportions of fungal keratitis were reported in studies from India and Nepal [30]. Interestingly, recent data from the Asia Cornea Society Infectious Keratitis Study (ACSIKS) group demonstrated that the commonest etiology of infectious keratitis was viral keratitis, which accounted for 47.7% [34]. A recent population-based study in China estimated that the prevalence of herpes simplex keratitis was 0.11%, similar to that in the United States and France [5].

For the worldwide frequency of Acanthamoeba keratitis, around 1% of infectious keratitis was reported [30]. Although the number of infections caused by these organisms is low, Acanthamoeba keratitis is an emerging disease mostly due to the increased use of contact lens worldwide [36]. Cariello et al. reported the higher rate of 7.4% of infectious keratitis caused by Acanthamoeba in Brazil [37].

2.3 Burden of diseases

Despite the fact that infectious keratitis is a significant cause of corneal blindness [2, 38, 39], there has been relatively little evidences available about the definite global burden of infectious keratitis. Moreover, the actual burden may be higher due to the underreport [8] and a fact that most of the patients reside in countries with less-developed economics [38].

Collier et al. reported the burden of this disease in the United States. Infectious keratitis causes an estimated 930,000 doctor's office and outpatient clinic visits and 58,000 emergency department visits per year. Nearly 80% of keratitis visits lead to antimicrobial prescriptions. The direct health care costs for keratitis and contact lens disorders were approximately 175 US dollars. Moreover, it consumed over 250,000 hours of clinician time annually [8, 40].

Data from the national surveys in China and India reported that infectious keratitis is responsible for the major burden of corneal blindness [5, 23, 41]. However, in other endemic areas of infectious keratitis such as China and India, the actual costs were not available. It may be underreported or underestimated in poor rural and agricultural farm-based populations [8]. The cost of infectious keratitis is magnified as it usually affects the poorest populations during their most productive years [8, 42]. Moreover, the cost may be derived from poor access to health care, corticosteroid abuse, inadequate empiric antibiotics, and difficulty to obtain diagnostic cultures that leads to delay presentation of or fulminant infection [8, 42].

3. Diagnostic approach

It is helpful for ophthalmologists to be familiar with the typical signs and symptoms of different organisms that are responsible for infectious keratitis. The provisional diagnosis may help to ensure the prompt management prior to the revelation of the definite diagnosis from investigations.

3.1 History

The common symptoms of infectious keratitis include pain, foreign body sensation, redness of conjunctiva and eyelids, tearing, discharge, photophobia, blurry vision, eyelids swelling, and notice of a white mark on the cornea [24, 43, 44]. In Acanthamoeba keratitis, the patients usually have severe pain out of proportion to the corneal lesion because of perineuritis. Bacterial keratitis usually has an acute onset, and gradual onset of symptoms usually suggests nonbacterial causes such as atypical keratitis or fungal keratitis [43]. Careful history taking about risk factors of infectious keratitis will help confirm the diagnosis. The important risk factors such as history of eye trauma, contact lens wear and hygiene, history of ocular surface disease, previous bacterial or HSV keratitis, history of corticosteroid abuse, hot tub exposure, prior ocular surgery, systemic diseases such as diabetes, immunodeficiency, and vitamin A deficiency will aid in the clinical diagnosis [43–45].

3.2 Physical examination

If the ophthalmologist is familiar with the characteristics of different etiologic agents of infectious keratitis, this helps confirm the diagnosis and determine the possible etiologic organisms. A thorough physical examination from general appearance and eye examination will aid in the provisional clinical diagnosis [43–45]. Visual acuity will be invariably affected depending on the location of the lesion and degree of intraocular inflammation [43]. Intraocular pressure should be examined unless corneal perforation is suspected such as deep lesion on slit lamp examination, and visible protrusion of intraocular content unless corneal perforation is suspected [43]. Ocular hypotony will be present in perforation cases. On the other hand, a high intraocular pressure can be suggestive of HSV, which is associated with trabeculitis [43]. External examination for the general appearance, lid closure, blinking, and corneal sensation are vital to determine the predisposing factors. For example, the patient that has a lagophthalmos is usually prone to an infectious keratitis at inferior cornea. A slit lamp examination is also crucial to determine the etiology of a suspected lesion. Eyelids may appear swollen, and conjunctiva may reveal injection and tearing and/or mucopurulent discharge. Ciliary flush is common. Cornea examination should document the characteristics of the lesion such as the size, shape, border, density, location, depth, and color. For instances, Pseudomonas ulcer usually shows the classic clinical feature of "ground glass appearance," which is a diffuse ulceration with stromal infiltrate or edema involving adjacent or whole cornea [24]. The classical clinical picture of the filamentous fungal keratitis is dry, raised infiltrate with feathery edges. A brown or dark pigmentation may be presented in dematiaceous fungal keratitis and can be an important diagnostic clue [24, 46]. The size and border of the lesion should be documented because it can suggest a positive response to a treatment if the size is decreased and/or the border is consolidated [44]. The depth of the lesion should be evaluated. In fungal keratitis, if the lesion is superficial, it may have a better response to the antifungal eye drop treatment than the deeper lesion because of poor ocular penetration and unpredictable bioavailability of antifungal agents [47]. If there is a significant corneal thinning and/or descemetocele, urgent management is required. The patient may have decreased visual acuity if the infiltration is located over the pupil or have a significant intraocular inflammation [24]. Fluorescein staining and cobalt blue light aid in the document of epithelial defect and detect the corneal perforation by Seidel test [24, 44]. The anterior chamber should be documented for a cell, flare, and/or hypopyon. Essential history and physical examination are listed in **Table 1**.

Essential history	Essential physical examination

• Duration of symptoms
• Eye trauma
• Contact lens wear (types and hygiene)
• Swimming, using a hot tub, or showering while wearing contact lenses
• Past ocular diseases
  ○ Previous infection, e.g., bacteria, fungus, herpes simplex virus (HSV)
• Past ocular surgery
• Previous and current eye drops usage
  ○ Current treatment
  ○ Contaminated ocular medication
  ○ Topical nonsteroidal anti-inflammatory drugs (NSAIDs)
  ○ Topical anesthetics
  ○ Topical corticosteroids
  ○ Preservatives
  ○ Glaucoma medications
• Past medical history
  ○ Medical conditions
  ○ Immunosuppression
• Medication allergies
	• Visual acuity
	• Intraocular pressure (contraindicated in corneal perforation)
	• External examination
	  ○ General appearance, lid closure, blinking, corneal sensation
	• Slit lamp examination
	  ○ Eyelid margins
	  ○ Eye lashes abnormality
	  ○ Discharge
	  ○ Conjunctival injection, ciliary flush
	  ○ Characteristics of lesion, size, shape, border, density, location, depth, color
	  ○ Endothelial plaque
	  ○ Seidel test
	  ○ Pupillary examination
	  ○ Anterior chamber reaction
	  ○ Sclera
	  ○ Foreign body
	• Complete eye examinations
	• Contralateral eye for clues to etiology
	• Signs of previous corneal or refractive surgery

References based on references [43, 44].	

Table 1.
Essential history and examination in infectious keratitis patient.

3.3 Microbiological investigations

Most of the bacterial keratitis cases resolve with the empiric topical antibiotics before the results of culture are available [26, 44].

The smears and cultures are indicated as follows [44, 48]:

1. A corneal infiltrate is central, large, and/or is associated with significant stromal involvement or melting.

2. The keratitis is chronic or unresponsive to broad-spectrum antibiotic therapy.

3. History of corneal surgeries is found.

4. Atypical clinical features that are suggestive of fungal, amoebic, or mycobacterial keratitis are identified.

5. There are multiple locations of cornea infiltrates.

Corneal culture helps to identify the causative organisms and determine antibiotics sensitivity [44]. Moreover, culture can help in modifying therapy in

unresponsive cases and eliminating unnecessary medications to decrease ocular surface toxicity [44]. Corneal scraping should be obtained from the advancing borders of infected cornea. The hypopyon in bacterial keratitis cases is usually sterile, and aqueous and vitreous tapping should not be done unless suspected of microbial endophthalmitis. Cultures should be performed before starting antimicrobial therapy, and if cultures are negative, the ophthalmologist may consider stopping antibiotic treatment for 12 to 24 hours and then re-culturing the infectious keratitis [44]. The stain provides provisional diagnosis of pathogenic organisms of infectious keratitis. However, cultures were the gold standard to identify the definitive pathogens and provided antibiotics susceptibility testing [26, 49]. Data from the large trial that enrolled 3300 eyes with infective keratitis in India demonstrated that the sensitivity of KOH was higher in the detection of fungi than that of Gram-stained smears (99.3%; 95% CI 98.6 to 99.6) and (89.2% (95% CI 87.3 to 90.8), respectively [50]. The Gram stain has diagnostic accuracy of 60–75% for bacteria keratitis detection and 35–90% for fungal keratitis [51]. The KOH alone has 62–99% sensitivity and 73–99% specificity for fungal keratitis detection [51]. Giemsa stain has 40–85% sensitivity and 70–96% specificity in detecting fungal keratitis [51].

All media are examined for growth daily and are incubated for 1–2 weeks before considering negative culture. Bacteria such as atypical mycobacteria, Nocardia spp., and Acanthamoeba grow slowly and require prolonged incubation [52]. Nonnutrient agar plate should be observed for at least 10 days [49]. Fungus grows within 24 hours to maximum of 2 weeks, so prolonged incubation at least for two to 3 weeks before the culture is considered negative [49]. The vital stains and cultures that are used for infectious keratitis are concluded in **Table 2**.

Even among the cornea specialists, they can correctly differentiate bacterial keratitis from fungal keratitis in less than 70% of cases [55]. Classic clinical figures may be obscured in large keratitis due to tissue destruction [53]. Acanthamoeba keratitis may be responsible for many cases of clinically presumed herpes simplex keratitis [54]. Cultures and smears are the gold standard to diagnose bacterial and fungal keratitis, but fungal cultures consume several days to weeks to obtain growth and can be falsely negative for deep infiltrates [56]. In these cases, other investigations such as in vivo confocal microscopy (IVCM) and PCR may have a role.

3.3.1 In vivo confocal microscopy (IVCM)

Bacteria and virus cannot be identified by IVCM but Acanthamoeba and fungal filaments are large enough and can be visualized [56]. Early detection of Acanthamoeba keratitis is associated with favorable outcome. Two most commonly used types of corneal IVCM include slit-scanning (ConfoScan; Nidek Technologies) and laser-scanning (Heidelberg Retina Tomograph with Rostock Corneal Module) [56]. In vivo confocal microscopy provides a rapid, noninvasive diagnostic tool and monitors treatment response, which has 85.7 to 88.3% sensitivity and 81.4 to 91.1% specificity for fungal keratitis detection and 88.2 to 88.3% sensitivity and 91.1 to 98.2% specificity for Acanthamoeba keratitis diagnosis [53–55, 57]. However, the branching angle of Fusarium and Aspergillus spp. was not easily differentiated by IVCM, and culture remains essential to address fungal species [58]. Amoebas are visible as double-walled cysts or as brightly reflective ovoid structures [54, 59]. However, diagnostic performance of IVCM is highly dependent on the operator's experience [60].

Type		Organism visualized
Stains	Gram stain	Most of the pathogenic bacteria, fungi, Acanthamoeba
	Giemsa stain	Chlamydia trachomatis Herpes simplex virus Varicella zoster virus Acanthamoeba
	Potassium hydroxide (KOH)	Fungi, Acanthamoeba
	Calcofluor white	Fungi, Acanthamoeba
	Special stains • Ziehl-Neelsen and/ or Kinyoun stain • Immunoflorescence stain • Periodic acid Schiff (PAS) stain • Gomori methenamine silver (GMS) stain	• Mycobacterium and Nocardia • Chlamydiae and viruses • Fungi • Fungi, Acanthamoeba
Cultures	Blood agar	Aerobic and facultatively anaerobic bacteria, fungi such as *P. aeruginosa*, *S. aureus*, *S. epidermidis*, and *S. pneumoniae*
	Chocolate agar	Aerobic and facultatively anaerobic bacteria including *H. influenzae*, *N. gonorrhea*
	MacConkey agar	Lactose fermenting (e.g., *Escherichia coli*, Enterobacter, Klebsiella) VS Lactose nonfermenting bacteria (Salmonella, Shigella, Proteus spp., Pseudomonas)
	Thioglycolate broth	Aerobic and facultatively anaerobic bacteria
	Sabouraud dextrose agar	Fungi
	Optional culture media • Lowenstein Jensen medium • Nonnutrient agar	• *Mycobacterium* and Nocardia spp. • Acanthamoeba

References based on [18, 24, 43, 48–54].

Table 2.
Common stains and cultures used to identify common pathogens of infectious keratitis.

3.3.2 PCR

Although not yet widely available, the advantages of PCR are rapid specific identification and requiring small clinical sample [51, 61, 62]. PCR is generally a required test for viral diagnosis and detection of organisms that are difficult to culture such as Microsporidia, *Mycobacterium tuberculosis*, fungi, and Acanthamoeba [52, 61, 63, 64]. PCR can be used as adjunct to smear and culture especially in cases where routine diagnostic procedures failure [65]. When compared to standard culture technique, real-time PCR had 100% sensitivity and 96% specificity in the diagnosis of Acanthamoeba keratitis [63].

4. Etiological agents of infectious keratitis

The common causative organisms of infectious keratitis are bacteria, fungus, Acanthamoeba, and virus [5, 14, 18, 34]. This review addresses the epidemiology, clinical manifestations, risk factors, and treatment of each pathogen. The classic clinical features of common causative organisms of infectious keratitis are show in **Figure 1**.

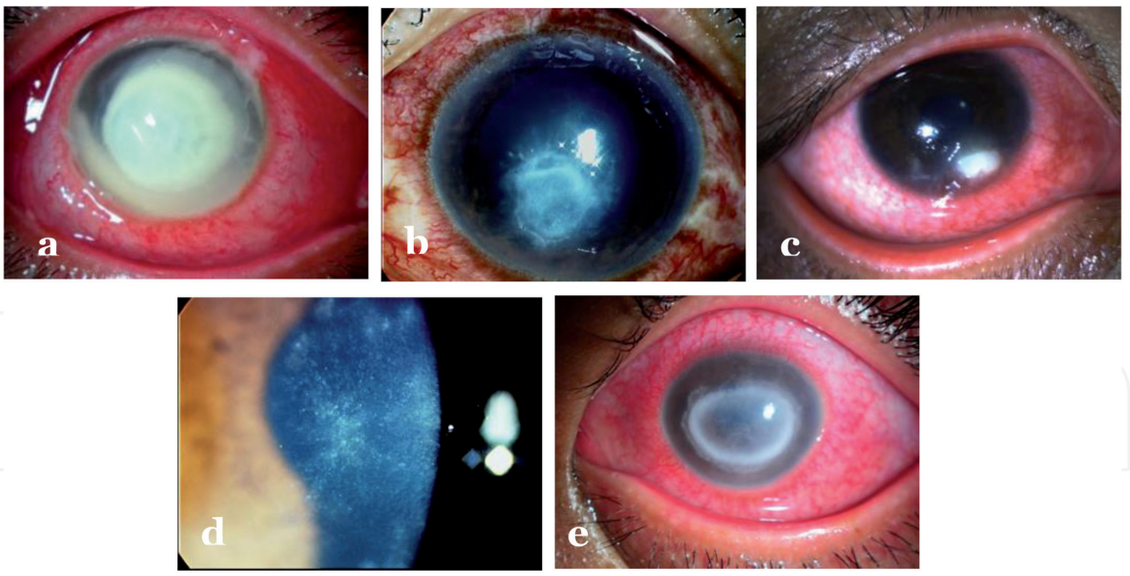

Figure 1.
The classic clinical features of common causative organisms of infectious keratitis: (a) Bacterial keratitis. (b) Fungal keratitis. (c) Herpes necrotizing stromal keratitis. (d) Early Acanthamoeba keratitis. (e) Late Acanthamoeba keratitis.

4.1 Bacterial keratitis

4.1.1 Epidemiology

Bacterial pathogens are responsible for a majority of infectious keratitis cases especially in developed countries and in contact lens wearers [21, 26, 27, 30, 43]. The keratitis can occur after a break in the corneal epithelium that allows bacteria to enter [43, 45]. The important pathogens of bacterial keratitis can be classified as follows: [18].

1. Gram-positive bacteria

   - Gram-positive cocci, e.g., *Staphylococcus aureus*, *Coagulase-negative staphylococcus, Streptococcus pneumoniae*

   - Gram-positive bacilli, e.g., *Nontuberculous mycobacteria (Mycobacterium fortuitum, Mycobacterium chelonae), Nocardia* spp.

2. Gram-negative bacteria

   - Gram-negative bacilli*; e.g., Pseudomonas aeruginosa, Enterobacteriaceae, Moraxella, Haemophilus*

   - Gram-negative cocci; e.g., *Neisseria gonorrhea*

The major bacterial causes are *Staphylococcus aureus*, *Coagulase-negative staphylococcus, Streptococcus pneumoniae Pseudomonas aeruginosa, and Streptococcus* spp. [18, 24, 66, 67].

4.1.2 Manifestations

The patient with bacterial keratitis usually presents with rapid onset of pain, photophobia, blurry vision, and eye redness. Slit lamp examination usually reveals

clearly defined infiltrations with stromal edema and inflammation (**Figure 1**) [43, 45]. The classic clinical figures for Gram-positive cocci are "localized round or oval ulceration, grayish-white stromal infiltrates, distinct borders with minimal surrounding stromal haze, or no edema" [18, 24]. *Nontuberculous mycobacteria* usually have a "cracked wind-shield"-type of appearance. *Nocardia* spp. usually has a multiple small white infiltrate that resembles "wreath pattern." Gram negative bacterial infection usually presented as a dense stromal suppuration, hazy surrounding cornea, "immune ring" [18]. Pseudomonas keratitis may develop as ring abscess without epithelial defect [24]. Gram-negative bacterial keratitis can perforate within few days if not properly managed [24]. Keratitis caused by Gram-negative cocci usually present with lid edema and copious purulent discharge, perforate rapidly, and may have bilateral involvement [24]. However, the slit-lamp manifestation alone may not specify the definite pathogens. For instance, satellite lesions, immune ring, and endothelial plaques may be present in both bacterial and fungal keratitis and cannot help to differentiate between bacterial and fungal keratitis [24]. Appropriate microbiological investigation is needed to confirm the specific pathogens. Even among the cornea specialists, they can correctly differentiate culture-proven bacterial keratitis and smear-positive fungal keratitis in photographs in less than 70% of cases [55]. In the case that the keratitis is unresponsive to the initial treatment or has an atypical course, the mixed-organism infection such as bacterial combined with fungal keratitis should be suspected [17].

4.1.3 Risk factors

The keratitis usually occurs after a break in the corneal epithelium [45, 68]. The major risk factors are contact lens wear, corneal abrasions, and ocular trauma [43, 45]. Other important risk factors include prior ocular surgery, chronic ocular disease, use of corticosteroids, contaminated ocular medications, and diabetes [66]. Contact lens wear and lagophthalmos were identified as the major risk factors for the development of Gram-negative infection [18, 66]. Preexisting ocular disease and previous HSV keratitis were associated with Gram-positive infectious keratitis [18, 68].

4.1.4 Treatment

Topical antibiotic eye drops can achieve high tissue concentration and are the preferred method of treatment in most cases [69]. Topical fluoroquinolones usually prescribed as first-line empiric initial treatment of suspected bacterial keratitis are at least as effective as combined fortified antibiotics [69]. Even though the susceptibility of Gram-negative bacteria to fluoroquinolone monotherapy was high, the susceptibility of Gram-positive bacteria was less and more variable [11, 68]. Because of shift in antibiotics resistance patterns, in some regions, fluoroquinolone monotherapy is not recommended for severe infectious keratitis, but combined fortified antibiotics should be prescribed instead [11]. Fortified topical antibiotics should be considered for large and/or visually significant keratitis, unresponsive to initial treatment, especially if a hypopyon is present [11, 44]. In contact lens wearers, the disease pattern and etiologic organisms may be altered to increase incidence of *Pseudomonas aeruginosa* [70]. Fluoroquinolones and aminoglycosides are good empirical antibiotics for infectious keratitis treatment [70]. In noncontact lens wearers, it tends to be caused by other organisms such as *coagulase-negative Staphylococci, Staphylococcus aureus*, *and Streptococcus pneumoniae*, which are largely sensitive

to fluoroquinolones [70]. In terms of patients' tolerance to medications, fluoroquinolones are more favorable than combined fortified antibiotics [69]. The initial empirical therapy should be prescribed until definite microbial identity and sensitivity are disclosed [11]. For central or severe keratitis, a loading dose every 5–15 minutes followed by frequent applications such as every hour is recommended [24, 44]. Subconjunctival antibiotics may be useful in impending scleral spreading and questionable adherence to topical treatment. In cases of scleral or intraocular extension of infection, perforation, or systemic infection, systemic therapy may be helpful [24, 44]. Oral tetracycline class antibiotics (including doxycycline) could be used to inhibit corneal stromal thinning by matrix metalloproteinases [71].

Reevaluation depends on the extent and severity of disease. The initial treatment should be modified when the eye shows a lack of improvement or stabilization within 48 hours [44]. Coexisting conditions and/or complications, such as glaucoma, corneal perforation, endophthalmitis, and eye lid abnormalities, should be treated promptly. The progressive corneal stromal thinning should be managed by application of tissue adhesive, penetrating keratoplasty, or lamellar keratoplasty [44]. Therapeutic keratoplasty may be indicated in cases of large corneal perforation or uncontrolled infection [24, 44]. Corneal transplantation in active infection has high failure rate [34]. However, the result is usually better than fungal keratitis, and 40–50% of these patients recover useful vision [24].

4.2 Fungal keratitis

4.2.1 Epidemiology

Fungal keratitis, potentially blinding condition, is an important cause of infectious keratitis [72]. Fungal keratitis is very common, accounts for 30–62% of infectious keratitis, in tropical region, but is uncommon in temperate climates [72]. The important pathogens of fungal keratitis can be classified as follows [18, 24, 45, 61, 72]:

Filamentous fungi such as *Aspergillus* spp., *Fusarium* spp., *Curvularia* spp., and *Scedosporium* spp. are frequent causes.

Yeasts such as *Candida albicans*, *Candida* spp., and *Cryptococcus* spp., are less common [18]. The fungi invade the ocular surface only when it is compromised or has a defect in the epithelial barrier and access into the corneal stroma [72]. However, the keratitis may present as chronic infiltration or even with an intact epithelium [56].

4.2.2 Manifestations

Symptoms of fungal keratitis typically are not as acute as other microbial keratitis [72]. The pain, redness, and lid edema are similar with bacterial keratitis. Early fungal keratitis may appear like a dendritic ulcer of herpes simplex virus. The feathery edge is a pathognomonic clinical feature [24]. Satellite lesions, immune ring, and unlevelled hypopyon may support the diagnosis but not specific clinical figures [24]. The surface is raised with grayish-white creamy infiltrates, which may or may not appear dry [24]. The keratitis due to pigmented fungi such as Curvularia spp., Bipolaris, and Exserohilum spp. will appear as brown or dark, raised, dry, rough, leathery plaque on the corneal surface [24, 46]. A recent report from the Mycotic Ulcer Treatment Trial II (MUTT II) stated that the presence of hypopyon at baseline indicated 2.28 times the odds of the patient developing corneal perforation and/or needing therapeutic keratoplasty [73].

4.2.3 Risk factors

Fungal keratitis must be suspected if the patient is in agricultural work [24]. For filamentous fungi, trauma with subsequent exposure to plant or vegetable material is usually the only predisposing factor, although previous use of corticosteroids, native medicine, and contact lens wear are increasing in importance as risk factors [24, 45, 61]. For yeast, there is usually some systemic or ocular surface compromise [61].

4.2.4 Treatment

The currently available antifungal drugs have multiple drawbacks such as poor ocular penetration, unpredictable bioavailability, and adverse effects associated with systemic medications [47]. Filamentous fungal keratitis is difficult to treat despite the use of topical and systemic antifungal agents and adjuvant surgery, such as corneal transplantation [61]. About one-third of fungal keratitis patients have pharmacological failure that required surgical interventions to get rid of infection [72]. Thus, early diagnosis of fungal keratitis is the most important determinant of their prognosis [56]. Topical corticosteroids are contraindicated in the treatment of fungal keratitis and also in the early postoperative therapeutic keratoplasty [72]. For filamentous fungi, the first-line drug is 5% natamycin, and the second-line drugs are 1% itraconazole and 2% Econazole [18]. There is evidence that natamycin is more effective than voriconazole in the treatment of filamentous fungal keratitis especially in Fusarium keratitis [74, 75]. *Candida keratitis* is usually initially treated with 0.15% amphotericin B followed by fluconazole eye drop if the first-line drug is not responsive [18]. The systemic antifungal agents, including oral ketoconazole, itraconazole, voriconazole, and posaconazole, are needed for severe keratitis or cases with extension beyond the anterior chamber [18, 43]. Seventy percent of Fusarium keratitis with deep lesion does not respond to sole medical treatment, and surgical intervention may be required [61]. More than 80% of Aspergillus keratitis responds to medical therapy alone; however, in deep keratitis, surgical intervention is needed [61]. For Candida keratitis, medical therapy generally has a favorable response, and the presence of deep lesions is not a major issue [61]. Severe fungal keratitis patients that are still smear-positive despite being pretreated with appropriate antifungal agents may benefit from aggressive multimodality therapy [76]. Various drugs and route of antifungal agents for fungal keratitis are available as listed below [9, 18, 47, 60, 61, 75, 77–79].

1. Topical: natamycin (5%), amphotericin B (0.15–0.3%), Econazole (1%), Flucytosine (1%), clotrimazole (1%), miconazole (1%), ketoconazole (1–2%), itraconazole (1%), fluconazole (1%), voriconazole (1–2%), and caspofungin (0.5%)

2. Subconjunctiva: fluconazole (0.5–1.0 mL of a 2% solution), miconazole (10 mg in 0.5 mL), and voriconazole (10 mg)

3. Intravenous: amphotericin B and miconazole (600–1200 mg/day), and voriconazole (6 mg/kg)

4. Oral: ketoconazole (200–600 mg/day), itraconazole (100–200 mg/day), fluconazole (50–200 mg/day), and voriconazole (400 mg/day)

5. Intrastromal injection: voriconazole (50 μg per 0.1 mL) and amphotericin B (5–10 μg per 0.1 mL)

6. Intracameral: voriconazole (50 μg /0.1 mL) and amphotericin B (5–10 μg/0.1 mL)

Surgical debridement of the epithelium and base of the fungal keratitis is crucial in the management because it debulks the organisms and enhances drug penetration into cornea [79]. Surgery for fungal keratitis, ranging from lamellar or penetrating keratoplasty to evisceration or enucleation, plays a role as an adjunct to medical therapy for initial management and when medical therapy fails or impending corneal perforation [51, 61, 79]. The prognosis of fungal keratitis is worse than bacterial keratitis [80]. The course is favorable with medical treatment in 50—70% of cases. A surgery is required in 30 to 54% of cases [80]. These infections may lead to loss of the globe in 10 to 25% of cases [80]. High risk of developing corneal perforation and the need to undergo therapeutic penetrating keratoplasty (TPK) are due to infiltrate size of more than 6.6 mm, an infiltrate involving the posterior one-third of the stroma, and the presence of a hypopyon [73]. Unfortunately, recurrence keratitis can occur approximately 6–7% after therapeutic keratoplasty [81]. Hypopyon, corneal perforation, and corneal infection expanding to limbus and lens infection are predominant risk factors for the recurrence of fungal keratitis after corneal transplantation [81]. After therapeutic keratoplasty, systemic and topical antifungal treatments should be used for 2 weeks routinely and possibly for 6 to 8 weeks in high-risk cases [81]. Generally, if no typical signs of recurrence were present 2 weeks after surgery, low-concentration topical steroids may be administered with caution [81].

4.3 Viral keratitis

4.3.1 Epidemiology

Herpes simplex virus (HSV) is a common cause of viral keratitis and the most common cause of unilateral infectious corneal blindness in the world [5, 9]. Varicella-zoster and cytomegalovirus can also cause viral keratitis but are much less common [9]. The prevalence of viral keratitis was 0.11% in a recent population-based study [5]. The majority of corneal HSV-1 infection is not the outcome of primary ocular infection, but in response to reactivation of latent virus from the trigeminal ganglion [82]. However, recurrent corneal epithelial infection with HSV-1 can have stromal involvement known as herpes stromal keratitis (HSK), which can be necrotizing, nonnecrotizing, or a mix of both [82, 83]. One study with HSV stromal keratitis reported that disease was of the necrotizing type in 7%, nonnecrotizing in 88%, and a mix of the two in 5% [84]. In this review, we address only the herpes necrotizing stromal keratitis that may mimic infectious keratitis from other organisms.

4.3.2 Manifestations

Viral keratitis differs from bacterial and fungal keratitis in that it can become recurrent and chronic [9]. In necrotizing HSV stromal keratitis, necrosis, ulceration, and dense leukocytic infiltration of the stroma are present and often associated with an overlying epithelial defect and neovascularization [18, 83, 85]. The viral keratitis diagnosis is usually based on clinical findings [43] and diagnosis by exclusion. However, in atypical cases, the investigations such as tissue culture, ELISA, and PCR may aid in the diagnostic confirmation [43].

4.3.3 Risk factors

The risk of HSV reactivation can occur after excimer laser refractive surgery such as LASIK or PRK. The exposure to ultraviolet light during corneal collagen cross-linking

(CXL) can reactivate latent HSV infection [86]. Previous stromal keratitis increased the risk of stromal keratitis, and the risk was strongly related to the number of previous episodes [86, 87].

4.3.4 Treatment

Both immune and active viral replications are responsible for the disease pathogenesis [83]. In contrast to nonnecrotizing stromal keratitis where topical corticosteroid is the mainstay treatment, oral acyclovir is used to control the viral invasion and replication in cornea, while low-dose topical corticosteroids are given to control inflammation in necrotizing stromal keratitis [18]. Topical CsA administration can resolve stromal inflammation and neovascularization in 50 and 64% of cases, respectively [83]. Without timely and effective treatment, necrotizing HSV stromal keratitis can rapidly lead to corneal perforation [83]. Amniotic membrane transplantation onto the ocular surface promotes corneal epithelial healing and reduces stromal inflammation, angiogenesis, and scarring [83]. Various oral antiviral agents to treat active viral replication and prevent recurrences are available as mentioned below [86]:

1. Acyclovir: 800 mg, 3–5 times/day, 7–10 days

2. Valacyclovir: 1 g, 3 times per day, 7–10 days

3. Famciclovir: 500 mg, 2 times/day, 7–10 days

Data from the Herpetic Eye Disease (HEDS) study concluded that the HSV stromal keratitis patients who received 400 mg oral acyclovir twice per day for 12 months had reduced rate of recurrent HSV stromal keratitis by about 50%. The research about HSV vaccination is underway, and no vaccine is currently available [83, 86, 88].

4.4 Acanthamoeba keratitis

4.4.1 Epidemiology

Acanthamoeba is a free-living protozoan found in soil and in freshwater that can cause keratitis primarily in contact lens (CLs) wearers [45]. The epidemiological features of Acanthamoeba keratitis may vary among different geographic regions, climate, and living environments [36].

Acanthamoeba is responsible for less than 5% of infectious keratitis [24].

4.4.2 Manifestations

The classic presentation of patients with Acanthamoeba keratitis is pain out of proportion to ophthalmological finding, photophobia, and slow progressive course [36, 43, 45]. The keratitis usually presents in one eye, but in CL users, it can present with bilateral involvement [36]. The examination may reveal various findings depending on the stage of ocular involvement. Within the first month, the disease can manifest as diffuse punctate epithelial lesions, dendritic-like lesions (mimic herpes simplex epithelial keratitis), epithelial or subepithelial infiltrates, or perineural infiltrates, and ring-shaped stromal infiltrates may be presented [45, 89]. After a month, the disease is characterized by ring-shaped stromal infiltrates, anterior uveitis, endothelial plaque, and disciform keratitis

[36]. Limbitis is a common feature in both early and advance disease [36]. If not managed properly, the disease can progress and late stage findings can develop such as scleritis, iris atrophy, anterior synechiae, secondary glaucoma, mature cataract, chorioretinitis, and retinal vasculitis [89].

4.4.3 Risk factors

The majority of cases are found in contact lens wearers [43]. Infections related to contact lens are often associated with improper wear such as poor cleaning, overuse, and sleeping or swimming with them [36]. Other risk factors for Acanthamoeba keratitis are cornea trauma or exposure to contaminated fresh water, soil, or vegetation and after corneal laser refractive surgery [36, 43, 90].

4.4.4 Treatment

There are two principal issues that lead to severe visual outcomes that are misdiagnosis or late diagnosis, and lack of a fully effective therapy for highly resistant cyst stage of Acanthamoeba [36]. The current diagnostic techniques are insensitive and poor turn around time. Moreover, the better yields and rapid test such as PCR or IVCM are not widely available [62]. This keratitis should be treated as soon as possible to prevent loss of visual acuity or even blindness [36]. Thus, ophthalmologists should be familiar with varied clinical pictures of Acanthamoeba keratitis. Currently, there are n0 FDA-approved medications for Acanthamoeba keratitis [62]. Treatment for Acanthamoeba keratitis includes the following medications [62]:

1. Diamidines (propamidine and hexamidine)

2. Biguanides (polyhexamethylene biguanide and chlorhexidine)

3. Aminoglycosides (neomycin and paromomycin)

4. Imidazole/triazoles (voriconazole, miconazole, clotrimazole, ketoconazole, and itraconazole)

Unfortunately, only the biguanides have been proven to be effective against both the cysts and trophozoite forms of Acanthamoeba [43]. The combination therapy may be of benefit [89]. The earlier the diagnosis, the better the chances of having a good visual prognosis [43]. In the early stage, epithelial debridement and 3 to 4 months of anti-amoebic therapy are enough [45]. Confocal microscopy is the most suitable tool to monitor the keratitis during the course of treatment [62]. However, after a prolonged and maximal medical treatment, recurrence can occur. Topical corticosteroids may mask clinical signs of Acanthamoeba keratitis, encystment, and an increase in number of trophozoites [89]. However, a patient with Acanthamoeba keratitis and severe inflammation may also benefit from this drug [89]. Optical keratoplasty may be considered after 3 to 6 months disease-free interval to avoid the late recurrence [62].

5. Complications of infectious keratitis

Despite timely and appropriate topical antibiotic treatment, surgical interventions such as tectonic or therapeutic keratoplasty may be required to preserve the eye and vision [91]. However, performing keratoplasty in a "hot eye" is associated with

an increased risk of recurrence of the disease and graft rejection/failure [91]. The visual outcomes of infectious keratitis may be poor from various complications such as corneal scarring or perforation, irregular astigmatism, development of glaucoma, cataracts, endophthalmitis, and vision loss [92]. Moreover, the advanced infectious keratitis that required therapeutic keratoplasty had decreased quality of life. The characteristics associated with corneal perforation in infectious keratitis were the lack of corneal vascularization, delay in starting initial treatment, and failure to start fortified antibiotics [42, 93]. Inappropriate use of traditional medicines or topical steroids abuse and delay in referral to an ophthalmologist for diagnosis and treatment are all responsible for unnecessary visual loss [24]. The primary care provider should be aware about complication of infectious keratitis. The standardized referral and treatment guideline for patients with infectious keratitis on their first contact at primary care level is needed [93].

6. Prevention of infectious keratitis

Due to the magnitude of the problem, limited access to treatment, inadequate well-trained medical personnel, costs of treatments, and the often poor visual outcomes, prevention may be one of the feasible public health strategies available [5, 34]. Avoiding or correcting predisposing factors may reduce the risk of keratitis [44]. Patients with risk factors for keratitis should be educated about their risk, made familiar with the signs and symptoms of keratitis, and informed that they have to consult an ophthalmologist promptly if they encounter such warning signs or symptoms to minimize permanent visual loss [44, 94]. In the developed countries, infectious keratitis is usually associated with contact lens wear, but in developing countries, it is commonly caused by trauma during agricultural work [8–10, 13]. Interestingly, data from the recent trial reported that "Up to 50% of contact lens wearer are not compliant with hand washing procedures" [95]. Poor hand hygiene is a risk factor of developing infectious keratitis in contact lens wearers [95]. Developing effective prevention strategy that is circulated to contact lens users is crucial to reduce the incidence of infectious keratitis [40]. Although the use of protective eyewear in industrial and agricultural work can prevent ocular injury, the actual utilization of such protective eyewear has been found to be consistently low, even in industrialized countries with robust workplace safety regulations [34]. The protective eyewear during these works should be compelled. The outcome of corneal injury with secondary infection can be improved by early diagnosis and prompt treatment with appropriate antibiotics at the primary level of eye care [24]. Because most cases of infectious keratitis are the result of corneal trauma, the use of 0.5–1% chloramphenicol eye ointment three times per day for 3 successive days for superficial corneal trauma in primary care is recommended by WHO to prevent the development of infectious keratitis [24].

7. Update of major clinical trials about common pathogens

7.1 Steroids for Corneal Ulcers Trial (SCUT)

The large, randomized, placebo-controlled, double-masked multicenter clinical trial that compared 12 months clinical outcomes in patients receiving adjunctive topical 1.0% prednisolone sodium phosphate or topical placebo in the treatment of bacterial keratitis found that adjunctive topical corticosteroid therapy may improve best spectacle-corrected visual acuity (BSCVA) in bacterial corneal keratitis

not caused by Nocardia species. But no significant difference was identified by treatment for scar size for non-Nocardia ulcers. However, scar size was larger in Nocardia keratitis [96, 97].

7.2 Mycotic Ulcer Treatment Trial (MUTT) I

The double-masked, multicenter trial that compare topical 5% natamycin vs. 1% voriconazole in the treatment of filamentous fungal keratitis showed a benefit of topical natamycin over topical voriconazole for filamentous fungal keratitis, particularly among those caused by Fusarium. Natamycin-treated cases had significantly better 3-month BSCVA, less likely to have perforation or require therapeutic penetrating keratoplasty than voriconazole-treated cases [74].

7.3 Mycotic Ulcer Treatment Trial (MUTT) II

The randomized, placebo-controlled, double-masked multicenter clinical trial showed that adding oral voriconazole to topical antifungal agents in the treatment of severe filamentous fungal keratitis did not improve the rate of corneal perforation, the need for therapeutic penetrating keratoplasty (TPK), microbiologic cure at 6 days, rate of re-epithelialization, BSCVA, and infiltrate and/or scar size. However, oral voriconazole did increase in nonserious adverse events and cost [98].

7.4 The Herpetic Eye Disease Study (HEDS) I

The Herpetic Eye Disease Study (HEDS) was a series of randomized, double-masked, placebo-controlled clinical trials that studied ocular HSV and is still the gold standard for ocular HSV management [86]. HEDS showed a significant benefit of topical corticosteroids and oral acyclovir for HSV stromal keratitis [84, 99].

7.5 The Herpetic Eye Disease Study (HEDS) II

HEDS II showed that oral acyclovir decreased the recurrence rate of any type of HSV keratitis by 50% approximately [88, 100].

8. Recent treatments of infectious keratitis

The mainstay treatment of infectious keratitis is antimicrobial drugs, which is fraught with drug resistance [11]. However, despite appropriate diagnosis and urgent treatment, medical treatment failure may occur and lead to corneal perforation [101] and/or therapeutic keratoplasty. Novel treatment is emerging to expand the armamentarium of tools to manage infectious keratitis and improve treatment outcomes [101]. The interesting managements in recent years are Photo-Activated Chromophore for Keratitis–Corneal Cross-Linking (PACK-CXL) and photodynamic antimicrobial therapy (PDAT) [91, 101–103].

8.1 PACK-CXL

The mechanism of action of PACK-CXL is antimicrobial activity of UV light, which can directly damage the DNA and RNA of various etiologic organisms [91]. Moreover, synergistic effect is derived from reactive oxygen species released from photoactivated riboflavin, which can directly damage DNA and cell membranes of microorganisms [91]. These effects can increase corneal resistance to enzymatic

degradation and increase corneal rigidity. So, it may decrease corneal melting and avoid emergency therapeutic keratoplasty [102, 104]. As microbial resistance to microbicidal therapy increases, CXL might be effective in treating advanced infectious keratitis as an adjuvant and also for treating early-stage bacterial infiltrates as first-line treatment [102, 104]. However, CXL is not routinely used for infectious keratitis because of the uncertainty of its safety and efficacy. A recent systematic review and meta-analysis from Ting et al. demonstrated that adjuvant PACK-CXL could expedite the resolution of bacterial keratitis and potentially fungal keratitis, in terms of size of infiltrates [105, 106]. However, adjuvant PACK-CXL did not shorten the time to corneal healing [107]. Unfortunately, in Acanthamoeba, viral, fungal, and mixed keratitis, treatment outcome was insufficient [91, 103]. However, when rose Bengal was used instead of riboflavin, PACK-CXL was effective against Acanthamoeba [108]. UV radiation in PACK-CXL may exacerbate viral keratitis [109].

8.2 Photodynamic antimicrobial therapy (PDAT)

Since CXL was found to be ineffective against fungal keratitis, potential blinding disease, PDT was proposed as an alternative measure [103]. Photodynamic therapy (PDT) involves the activation of a photosensitizing agent that reacts with oxygen to create reactive oxygen species (ROS). The light using in PDT ranges from ultraviolet-A (UV-A) to near-infrared wavelengths. These ROS react with intracellular components and produce cell inactivation and death [110]. In vitro study demonstrated that Rose Bengal-mediated PDT successfully inhibited the growth of *Fusarium solani*, *Aspergillus fumigatus*, and *Candida albicans* [103]. Moreover, the Rose Bengal- and riboflavin-mediated PDT demonstrated in vitro inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA) [111]. Riboflavin PDAT strengthens the corneal collagen fibers, delays keratolysis, and prevents a corneal perforation in humans [112]. This can be used as an adjunct treatment in bacterial and fungal keratitis with good long-term outcome [112].

9. Conclusion

Infectious keratitis tops the list of the diseases leading to visual impairment and corneal blindness. The precise clinical diagnosis, accurate diagnostic tools, and timely appropriate management are important to reduce the morbidity associated with infectious keratitis. Although most patients improve after medical and surgical management, their vision may be considerably decreased [15]. A few emerging treatments used to manage infectious keratitis show good preliminary outcomes for selected cases of infectious keratitis, although additional research is required before it is accepted as mainstream treatment for this potentially blinding condition. Therefore, the importance of eye protection [18], hygiene education, and contact lens care and hygiene must be strongly emphasized.

Conflict of interest

The authors declare no conflict of interest.

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