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Review Article

Keratitis: An Inflammation of Cornea

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Abstract

Keratitis is an inflammation of the cornea, which has both infectious and non-infectious etiology, among which infectious is more common. Non-infective keratitis may be caused by minor injuries, prolong contact lens usage, hypersensitivity responses, atopic conditions or some autoimmune disorders. Infective keratitis is an infection of the cornea, caused by either bacteria, fungus, virus or protozoa, if not treated earliest can lead to permanent visual impairment. Infective keratitis is commonly associated with several predisposing factors such as ocular trauma, contact lens use, recent ocular surgery, preexisting ocular diseases, dry eyes, lid deformity, compromised corneal sensation, chronic use of topical steroids and prolonged systemic immunosuppression. In spite of advances in clinical diagnosis, molecular laboratory investigations, and the availability of potent antimicrobials, visual morbidity continues to be high in underdeveloped and developing countries of the world. The importance of this disease can be judged by the fact that microbial keratitis remains one of the most common global causes of irreversible blindness among the corneal diseases. Diagnosis and management of microbial keratitis is always challenging in developing and under developed countries.

Keywords: *Keratitis; Infective Keratitis; Inflammation of the Cornea; Infection of the Cornea; Microbial Keratitis*

Abbreviations

AK: *Acanthamoeba* Keratitis; HSV: Herpes Simplex Virus; KOH: Potassium Hydroxide; LPCB: Lactophenol Cotton Blue; DFA: Direct Fluorescent Antibody; IVCM: In vivo Confocal Microscopy; PHMB: Polyhexamethylene Biguanide

Introduction

Cornea is the clear, transparent, dome shaped external covering of the eyes, that plays an important role in visual acuity. Unlike most tissues in the body, cornea contains no blood vessels to nourish or protect it against infection [1]. There are some conditions such as; injuries, allergies, keratitis and dry eyes which affect the cornea [2]. Keratitis is the most serious condition among all these, which has both infectious and non-infectious etiology [2]. Non-infectious keratitis can be caused by either a minor injury or due to a fingernail scratch, or contact lenses use for prolonged period [3]. Infective and non-infective keratitis may overlap each other. Non-infective keratitis may become infective by some microbes and may result in sight-threatening complications [4]. In non-infective keratitis, peripheral ulcerative keratitis (PUK) due to autoimmune diseases is the most common one. Other entities of non-infective keratitis are phlyctenular keratitis due to hypersensitivity response, vernal keratitis due to some atopic conditions and contact lens-related sterile infiltrates [5].

The most common disorders associated with peripheral ulcerative keratitis (PUK) are systemic collagen vascular diseases, of which rheumatoid arthritis (RA) is the most common, accounting for 34% of non-infectious PUK cases. Other than RA, Wegener granulomatosis, systemic lupus erythematosus, relapsing polychondritis, classic polyarteritis nodosa and its variants, microscopic polyangiitis or Churg–Strauss syndrome can be the cause [6]. The main symptoms of PUK for patients are ocular redness, pain, tearing, photophobia, and decreased vision secondary to induced astigmatism or corneal opacity in advanced cases [7].

Infections remains the most common cause of keratitis. The terms 'infective keratitis' and 'microbial keratitis' both are used to describe the suppurative infections of the cornea, caused by either bacteria, fungus, virus, protozoa or parasites, if not diagnosed and treated in the earlier stage may leads to permanent visual impairment [8]. Common risk factors of infectious keratitis includes ocular trauma, contact

lens wear, recent ocular surgery, preexisting ocular diseases, dry eyes, lid deformity, compromised corneal sensation, chronic use of topical steroids and prolonged systemic immunosuppression [8]. Among the contact lens users improper cleaning of contact lens and overuse of old contact lenses are the most common risk factors for infectious keratitis [8]. Minor corneal infections are usually treated with antibacterial eye drops, but if the infection is severe and prolong, it may require more appropriate antimicrobial treatment to eliminate the infections, and to reduce the inflammation [9]. Several parameters determine the clinical outcome of infective keratitis. Epidemiological patterns of infective keratitis varies in different countries of the world and also in different geographical areas of the same country [10].

This article focuses on the key diagnostic modalities and clinical features of the most common organisms causing infective keratitis such as bacteria, fungi, viruses, and Acanthamoeba, in the world. We describe the salient clinical features and diagnostics of microbial keratitis which can help to begin appropriate management of this disease.

Bacterial keratitis

There are several bacteria reported as the causative agents of bacterial keratitis, among them most common includes Staphylococcus aureus, coagulase-negative *Staphylococcus, Pseudomonas aeruginosa, Streptococcus pneumonia*, and *Serratia* spp. Majority of the community acquired cases of bacterial keratitis resolve with empiric treatment and rarely require laboratory diagnosis [11]. It can be acute or chronic, transient or recurrent infection of the cornea and has varying propensity for anatomical and topographical parts of the cornea such as marginal or central [11]. Signs and symptoms of bacterial keratitis include pain, hypopyon, poor vision, and corneal abscesses, which are usually unresponsive to broad spectrum antibiotics. Corneal scrapings remains the most appropriate clinical sample from patients of microbial keratitis for laboratory diagnosis [11]. Bacterial keratitis is easily resolved if diagnosed in the early stage, but may lead to serious visual impairment with late diagnosis and treatment. Spectrum of bacterial keratitis may also be influenced by geographic and climatic factors.

In spite of advances in clinical diagnosis, molecular laboratory investigations, and the availability of potent antibiotics, visual morbidity continues to be high in underdeveloped and developing countries of the world. The importance of this disease can be judged by the fact that bacterial keratitis remains as the most common global causes of irreversible blindness among several corneal diseases [11]. The bacteriological profile in keratitis shows huge disparities amongst populations living in both developed, developing and under developed countries [12]. Some studies from economically different countries of the world reported that, frequency of bacterial keratitis in United States was very less i.e. 11 per 100,000 compared to 799 per 100,000 persons in Nepal [13,14]. *Staphylococcal* species, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* were reported as the major isolates of microbial keratitis in North America [15]. A study from Sweden reported that, *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most common Gram-positive bacteria while *Pseudomonas aeruginosa* was the most common Gram-negative bacteria of bacterial keratitis infections [16]. Factors influencing the etiology and pathogenesis of bacterial keratitis varies such as; contact lens usage, preexisting ocular diseases, corneal trauma, prolonged use of immunosuppressive drugs and postocular surgery especially corneal grafting [11]. A study revealed that among all these above risk factors contact lens use was the most common and predominate for microbial keratitis [13]. A case control study reported, the annual incidence of bacterial keratitis in soft contact lens wearers was 4 - 21 per 10,000 daily wear and extended wear, among whom overnight usage of contact lens was the most important risk factor [17].

Overall clinical signs and symptoms of bacterial keratitis is acute in onset with commonly presenting signs and symptoms related to visual and sensory functions such as lid and conjunctival oedema, reduced vision, pain, redness, photophobia and discharge from eyes [11]. Severity of signs and symptoms depends on the virulence of the organism, the host immune status, history of any preexisting disease of the cornea, history of any prolonged therapy with corticosteroids and the duration of the infection [18]. Microbiological tests and advanced molecular methods remain the critical tool in the diagnosis of bacterial keratitis. Smears, culture and sensitivity to antimicrobial drugs are the most common and fundamental tools for the laboratory diagnosis of bacterial keratitis. Cultures should always be preferred to smears as they are highly specific and information yielding. The culture positive rate in bacterial keratitis is 40 - 73% as compared to 0 - 57% in Gram's staining [19].

Recent studies have shown increasing evidence of resistance of microbes to most of the antimicrobial agents. Microorganisms develop resistance due to chromosomal mutation, expression of latent chromosomal genes by induction or exchange of genetic material via transformation [20]. This may cause continued progression of the infection despite the use of broad spectrum antibiotics.

Fungal keratitis

Fungal keratitis or keratomycosis is a fungal infection of the cornea that primarily affects the corneal epithelium and stroma, although the endothelium and anterior chamber of the eye may get involved in more severe infections [21]. Fungal keratitis is mainly found in tropical climates and rare in temperate zones of the world. Incidence of fungal keratitis is between 6 - 20% of all the microbial keratitis

depending on the geographic locations [10]. In developed countries like US, use of contact lenses is the presumed risk factor in 37 % of patients compared to ocular trauma in 25% of patients [22]. Ocular trauma is a major predisposing factor for fungal keratitis and most cases are reported mainly from developing countries of the world [23]. It is mainly caused by filamentous fungi such as Fusarium and Aspergillus, and some yeast-like fungi, mainly Candida [24]. Of all the microbial keratitis cases, fungal keratitis comprises up to 40% in developing countries [23,25]. Estimated incidence of fungal keratitis was 113 per 100,000 population, as reported in a study from India with Aspergillus spp. was the most common causative agent [26,27].tropical climates and rare in temperate zones of the world. Incidence of fungal keratitis is between 6 - 20% of all the microbial keratitis depending on the geographic locations [6]. In developed countries like US, use of contact lenses is the presumed risk factor in 37 % of patients compared to ocular trauma in 25% of patients [18]. Ocular trauma is a major predisposing factor for fungal keratitis and most cases are reported mainly from developing countries of the world [19]. It is mainly caused by filamentous fungi such as *Fusarium* and *Aspergillus*, and some yeast-like fungi, mainly *Candida* [20]. Of all the microbial keratitis cases, fungal keratitis comprises up to 40% in developing countries [19,21]. Estimated incidence of fungal keratitis was 113 per 100,000 population, as reported in a study from India with *Aspergillus* spp. was the most common causative agent [22,23].

Fungal keratitis should be suspected in cases of vegetative trauma or prolonged contact lens usage and in cases of microbial keratitis that do not respond to any antibacterial agents [24]. Corneal scrapings of these cases are commonly sent to mycology laboratory for identification with KOH or LPCB mount as well as culture on Sabouraud dextrose agar (Figure 1) [21].

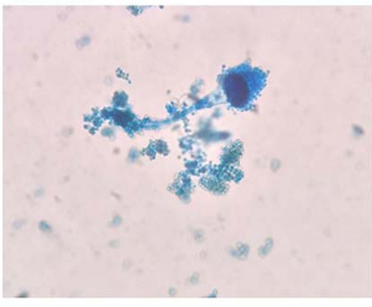

Figure 1: *Aspergillus fumigatus conidiophore and free conidia in LPCB mount (x400).*

The most commonly used antifungal drugs are Voriconazole (1%), Amphotericin B (0.15%), Fluconazole, and Miconazole eye drops. Antiseptics such as Chlorhexidine 0.2% and Povidone iodine (5%) have also been advocated as cheap and easily available alternatives but are not as effective as antifungal drugs [28].

HSV keratitis

Herpes simplex virus (HSV) is endemic throughout the world and humans are the only known natural reservoir. A study examining the presence of HSV-1 DNA in the trigeminal ganglia has reported that, approximately 90% of the world's population is infected with latent HSV-1 by the age of 60 [29]. Chronic infection of the cornea by HSV continues to be an important cause of unilateral corneal blindness. The human herpes viruses are an important source of ophthalmic morbidity worldwide including cytomegalovirus retinitis in AIDS patients. HSV, however, remains the most common cause of unilateral corneal blindness worldwide [30]. Common sign and symptoms of HSV keratitis include redness, discharge, watery eyes, irritation, itching, pain, and photophobia. In most of the patients, symptoms begin to subside after the first 2 weeks [31].

Transmission of HSV-1 occurs mainly through direct contact with infected secretions (saliva, tears) or lesions [32]. Classifications of HSV1 with different parts of the eyes is given in Table 1.

In cases of typical HSV epithelial keratitis (dendritic), clinical diagnosis by slit-lamp microscope is the most important method of examination and laboratory tests are usually not required. Laboratory culture diagnosis is also not so useful in HSV stromal keratitis because, virus usually cannot be cultured routinely, due to lack of expertise and with poor laboratory conditions. In some atypical cases of HSV keratitis, however, advance laboratory tests may also be indicated [32]. Cell culture isolation of HSV-1 is considered as the gold standard in laboratory diagnosis of HSV epithelial keratitis. Direct fluorescent antibody (DFA) detection of HSV antigen is rapid, specific and relatively reliable [32]. Children and some individuals with HSV keratitis may prove relatively difficult to manage and may need relatively higher doses of oral antivirals for treatment [32]. Current treatment for HSV keratitis includes acyclovir, ganciclovir, triflurothymidine, penciclovir, and valacyclovir [33,34].

Corneal Layer	Nomenclature	Alternate Terms
Epithelium	HSV epithelial keratitis	Dendritic epithelial ulcer Geographic epithelial ulcer
Stroma	HSV stromal keratitis without ulceration; HSV stromal keratitis with ulceration	Non-necrotizing keratitis, Interstitial keratitis, Immune stromal keratitis Necrotizing keratitis
Endothelium	HSV endothelial keratitis	Disciform keratitis

Table 1: *HSV keratitis: Classification (White., et al. 2014).*

Acanthamoeba keratitis

Acanthamoeba spp. are the free-living amoeba which cause sight-threatening infection of the cornea commonly known as *Acanthamoeba* keratitis(AK). Initially AK was considered as a rare disease of eye, with only 1.65 to 2.01 cases per million per year [35]. Recently, magnitude of AK is increasing rapidly due the increase in use of contact lenses and their inappropriate unhygienic procedures [35]. In developed countries, majority of the AK infections are due to the use soft contact lens, improper sterilization procedures of contact lens etc [36-38]. However, in developing countries like India, AK infections are observed to be associated with the non-contact lens wearers rather than the contact lens wearers and most reported cases were due to either ocular trauma, fall of dust particles or contaminated water and bad hygienic conditions [39-41]. Signs and symptoms of AK include pain, photophobia, ring-like stromal infiltrate, epithelial defect, eye discharge and lid oedema [42-44]. Earliest diagnosis and treatment of the disease is required for better outcome [45-47].

AK can easily be confused with HSV keratitis in the early stage, while in the advanced stage, the infection resembles features of a fungal keratitis or a corneal ulcer [42]. Provisional diagnosis of AK can often be made by in vivo confocal microscopy (IVCM) in which Acanthamoeba cysts appear as hyper-reflective, spherical structures due to their double wall; but the trophozoites are difficult to distinguish from leukocytes and keratocyte nuclei of host [42,47].

Culture of Acanthamoeba is considered as the gold standard for laboratory diagnosis, but recently several PCR-based techniques are also well established and usually increases sensitivity and specificity of diagnosis significantly [47-51]. Acanthamoeba trophozoites or cysts are commonly recognizable in phase contrast microscopy and cysts exhibit auto-fluorescence [47,49]. Most of the currently used topical agents are effective against trophozoites and cysts of Acanthamoeba such as biguanides, (i) PHMB (polyhexamethylene biguanide), which is effective at low concentrations (0.02%), but is unfortunately toxic to human corneal cells, and (ii) chlorhexidine, which is effective against both forms, and at minimal concentrations is not toxic to corneal epithelial cells. Chlorhexidine 0.02% is often used in combination with aromatic diamidines such as 0.1% propamidine isethionate, hexamidine 0.1% and neomycin, showing good results, if the treatment is applied early during development of the infection [52-54].

Complications

Although most forms of keratitis can be treated successfully, there are a number of possible complications like chronic corneal inflammation, corneal thinning, secondary glaucoma, perforation, chronic or recurrent viral infections of the cornea, corneal ulcers, corneal scarring and swelling, temporary vision loss [55].

Conclusions

Although, corneal ulcers have been described in ancient literatures, but in recent times, despite the availability of advanced diagnostic techniques and wide range of newer antimicrobials, infective keratitis continues to pose a therapeutic challenge. Infective keratitis, is a complex entity with many considerations when it comes to diagnosis and its management. It is mainly a public health problem in developing countries where limited access to care and economic barriers can cause visual disability primarily in young individuals. In all Infective keratitis patients, proper and early identification of microbe and targeted therapy can eradicate the complications. Non-infective keratitis can also be managed well if differentiated earlier with infective one, because treatment modalities of both are different.

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Conflict of Interests

All the authors declare that there are no conflicts of interest related to this review article.

Informed Consent

Consent was obtained from all individual participants included in the presentation of review article.

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