Understanding Host-Pathogen Interaction in the Cornea: Inflammatory response and Cure

Abstract

Microbial keratitis, a severe corneal disease, significantly threatens global eye health and vision. It is caused by various microbial invaders, including bacteria, fungi and viruses, making it difficult to diagnose and treat. Combating microbial keratitis requires understanding the intricate web of immune responses and pathogenic pathways that cause the infection. To develop innovative strategies to treat the disease and improve patient survival, we need to understand how the immune system works, how hosts and infections interact and how complicated the pathophysiology is. Looking to the future, we are on the cusp of a transformative era in treating microbial keratitis. Innovations in therapeutic technology, such as targeted antimicrobial drugs, immunomodulatory therapies and precision medicine techniques, are set to revolutionise the field. These advancements will enable customised treatments for specific microbiological causes and patient characteristics. Integrating molecular biology, imaging and artificial intelligence into novel diagnostic techniques will enhance early diagnosis and personalised treatment programmes, leading to better clinical outcomes and reduced ocular morbidity. Collaboration between clinicians, researchers, and industry representatives is critical to accelerating the translation of scientific knowledge into clinical practice. The future of microbial keratitis treatment promises to significantly improve patient care, increase treatment efficacy and ultimately save people's precious sight.

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Keywords

Microbial keratitis, Bacteria keratitis, Fungi keratitis, Inflammation, Corneal infection, Cytokines

1. INTRODUCTION

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The eye is transparent outer layer of corneais crucial in focusing light on the retina, which is essential for visual perception. It is the unique structure of the human eye, and exposure to the outside world increases the likelihood of infection. Damage to the epithelium weakens the body's defences and allows harmful microbes to cause keratitis or inflammation of the cornea[1].Although the intact ocular surface effectively suppresses most pathogens, a breach of the anatomical barriers weakens the host's defences. As a result, an inadequate immune response allows infection to develop, which can lead to impaired vision[2]. Microbial keratitis, also known as infectious keratitis, poses a significant threat to the visual integrity of the eye. Microbes invading the cornea cause a hazardous situation for the eyes. Corneal irritation is a common manifestation that can lead to severe vision loss or even blindness. It is, therefore,essential to diagnose and treat microbial keratitis immediately to prevent further damage to your vision[3,4]. The presence of microorganisms, including bacteria, fungi and viruses, in the cornea leads to infection, which poses a significant threat to vision. These microbes trigger a chain of physiological reactions in the cornea that can lead to a severe eye infection that severely jeopardises vision[5]. When these infections penetrate the corneal epithelium, they reach the underlying layers of the cornea, where they can multiply and cause inflammation. This disease risks the delicate eye tissue severe and often permanent damage[6]. If left untreated, microbial keratitis can worsen quickly and lead to ulcers, holes and, worst cases, lifelong vision loss. Because of its ability to threaten vision, it is even more important to act quickly, diagnose correctly, and apply the proper treatment methods to protect your vision and reduce the long-term impact on your health [7, 8]. Visual impairment and blindness are among the many adverse effects of microbial keratitis that persist worldwide despite improved diagnosis and treatment methods[9, 5]. Eye trauma, poor hygiene and contact lens use all contribute to the ongoing problem of microbial keratitis. Comprehensive efforts focusing on prevention, early detection and timely treatment are necessary to combat the epidemiologic burden of ankylosing spondylitis and limit its detrimental effects on eye health and overall quality of life [8, 10]. The study highlights the complex physiological responses triggered by microbial invasion in the cornea, leading to microbialkeratitis. It also explains the microbial, physiological and immunological dimensions important for treatingmicrobial keratitis.

2. SIGNIFICANT INCIDENCE OF MICROBIAL KERATITIS IN INDIA

According to epidemiological data, microbial keratitis is one of the significant causes of eye diseases and is still prevalent in India. Microbial keratitis remains one of the leading causes of ocular morbidity[9, 11].Microbes infect the cornea and pose a significant problem for public health and therapeutic practice. This disease, a major national health problem, is defined by microorganisms infecting the cornea. In India, microbial keratitis is high due to factors such as lack of personal cleanliness, occupational accidents in agriculture and lack of access to health care[9].Although there have been advances in eye care and treatment, microbial keratitis is still the leading cause of blindness and visual impairment in India. Some

Indian researchers from different regions have found that failure of initial therapy or perforation of the cornea correlates with certain factors. In many cases, the observed ulceration and infiltration or hypopyon of microbes are due to delayed treatment [12]. Lalitha et al. conducted a study on patients with fungal keratitis in South India and found that failure of primary treatment or corneal perforation correlated with certain factors. These factors included an infiltrate size greater than 14 mm2, a hypopyon at presentation, or a positive culture for Aspergillus sp[13]. Similarly, Rautaraya et al. studied bacterial keratitis in eastern India. They identified larger ulcer size (>25 mm2), poor visual acuity at presentation and advanced age of the patient as predictors of poor outcomes [14, 15] investigated the risk factors for corneal perforation in predominantly bacterial corneal ulcers in northern India. They found that delays in initiating antimicrobial treatment or administering fortified antibiotics for bacterial keratitis contributed significantly to the risk of perforation[15].The difficulty in diagnosing bacterial keratitis, fungal keratitis or Acanthamoeba keratitis many times leads to delayed initiation of treatment, with clinical features such as feathery margins, a raised surface, satellite lesions and a non-yellow infiltrate colour in fungal keratitis, ring infiltrates in Acanthamoeba keratitis and well-defined margins in bacterial keratitis providing some guidance. However, the prevalence of advanced disease in India warrants further evaluation of the utility of these clinical signs in late-stage disease[11, 16].

3. MICROBES INVOLVED IN MICROBIAL KERATITIS

In keratitis, various microbial pathogens cause an inflammatory reaction leading to inflammatory cell infiltration throughout the cornea. These organisms, which include bacteria, fungi and viruses, cause an immunological response characterised by purulent melting of the corneal epithelium and stroma. This process leads to ulcers in the cornea, contributing to the disease's progression. Intrinsic antigens or infectious agents exacerbate the inflammatory cascade and jeopardise corneal integrity and vision. Efficient diagnosis and tailored therapy are required to reduce the negative consequences of microbial keratitis on the eye's health. Bacteria, fungi and viruses are the primary microbiological pathogens of microbial keratitis, and each of them has its own diagnostic and therapeutic problems.

Studies found that Bacterial keratitis is caused mainly by Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae and other gram-positive or gram-negative bacteria (Table: 1A). These bacteria can enter the cornea through trauma, contact lens wear or pre-existing ocular surface abnormalities[17]. Pseudomonas aeruginosa, for example, is known for its tendency to rapidly invade the cornea, leading to severe infections characterised by corneal melting and perforation. Gram-positive bacteria such as Staphylococcus aureus frequently create exotoxins and enzymes that cause ocular tissue and cause inflammation[18]. Conditions compromising the corneal epithelium's integrity often led to bacterial keratitis. A complete clinical examination, including slit lamp inspection, corneal scraping with smear and culture analysis, is necessary to make an accurate diagnosis. The primary treatment is antibacterial, although other options include cycloplegics, antiglaucoma medications and oral anti-inflammatory therapies[19]. If the condition worsens despite drug treatment, therapeutic keratoplasty may be required. The goal is to gain a deeper understanding of the causes of bacterial keratitis, existing risk factors, its prevalence, manifestations in individuals, microbiologic and histologic findings, treatment options, potential complications, differentiation between various diagnoses, and prediction of future outcomes[17, 20].

Fungal keratitis is mainly caused by filamentous fungi such as *Fusarium* sp., *Aspergillus* sp. and *Candida* sp. (Table: 1B). These fungi are widespread in the environment. They can enter the cornea via corneal trauma, agricultural damage or contact lens wear [21].Fungal spores invade the cornea through epithelial defects caused by trauma, contact lens wear or previous eye surgery. Agricultural workers, especially in developing countries, are susceptible to fungal keratitis as a result of eye trauma[22]. Once the fungi have invaded the cornea, they penetrate the intact Descemet's membrane and can enter the eye's anterior chamber via proteolytic enzymes. This invasive nature makes fungal keratitis a severe disease that is difficult to treat and a common cause of unilateral blindness in tropical areas[23]. Non-fungal yeasts such as Candida species often cause keratitis in eyes that already have problems with the eye surface or have just undergone topical steroid treatment, making treatment more difficult.Fusarium keratitis attracted much attention following an outbreak linked to contact lens use and contamination of the solution. Fusarium species form biofilms on contact lenses and eye surfaces, leading to long-term infections and complicated treatment options[22, 24].

Viral keratitis can be caused by the herpes simplex virus (HSV), the varicella-zoster virus (VZV) and other herpes viruses (Table: 1C). HSV keratitis, in particular, is the most common cause of infectious corneal blindness worldwide. HSV can establish latency in the trigeminal ganglion and be reactivated, leading to recurrent corneal infections with dendritic or regionalulceration. VZV keratitis is often associated with herpes zoster ophthalmicus and presents as a pseudo-dendritic pattern on the corneal surface[25]. Other less common microbial pathogens associated with microbial keratitis are Acanthamoeba species, Nocardia species and parasites such as Microsporidia and Acanthamoeba[26]. Contact lenses increase your risk of developing Acanthamoeba keratitis, a potentially dangerous disease requiring prompt diagnosis and treatment to prevent severe vision loss. Acanthamoeba, typically found in water, can attach to contact lenses and invade the cornea, causing an infection that worsens if left untreated. It is imperative to get a correct diagnosis immediately as Acanthamoeba keratitis can look like other eye diseases and may require special tests in a laboratory to be sure[27]. People with weak immune systems often develop Nocardia keratitis, characterised by corneal infiltrates in the cornea. This unique lecture shows the importance of knowing the patient's immune system and applying personalised treatment plans to fight the infection effectively. If Nocardia keratitis is not recognised and treated quickly, it can lead to serious eye problems and even loss of vision[28].

(A) Bacteria causing keratitis		
Bacteria	***Manifestation and features***	***References***
Staphylococcus aureus	*S. aureus* is a widespread bacterium that lives on skin and mucous membranes. It can cause keratitis through direct contact or by penetrating contact lenses and lens cases and spreading the germs.	[19]
Pseudomonas aeruginosa	Severe cases of bacterial keratitis are frequently associated with this opportunistic pathogen, especially in contact lens wearers. *P. aeruginosa* grows best in moist places and can quickly enter the eye, causing the infection to start and spread rapidly.	[18]
Streptococcus pneumoniae	*S. pneumoniae* is the primary germ that causes bacterial pneumonia and other respiratory diseases. It can also cause keratitis, especially in people with weakened immune systems or who already have diseases on the eye's surface.	[20]
Serratia marcescens	This bacterium is frequently found in soil, water and healthcare. It can cause keratitis, especially in eye trauma or contact lens infections.	[29]
Enterobacteriaceae e.g. *Klebsiella*sp., *Enterobacter* sp., *Citrobacter* sp., *Salmonella* sp., *Escherichia coli*, *Shigella*, *Proteus*, *Serratia*sp. and other species	Certain members of the Enterobacteriaceae family, such as *Escherichia coli* and *Klebsiella pneumoniae*, have been associated with microbial keratitis, which is often associated with eye trauma or contact lens contamination.	[30]
Moraxella species	*Moraxella* species, including *Moraxella catarrhalis*, can cause keratitis, especially in individuals with underlying ocular surface disease or weakened immunity.	[31]

Haemophilus influenzae	*H. influenzae* usually causes respiratory infections but can also affect the eye and cause keratitis, especially in children and people who are already ill.	[31]
	(B) Fungi causing keratitis	
Fungi	***Manifestation and features***	References
Fusarium species, e.g. *Fusarium polyphialidicum*	*Fusarium* species are the most common fungi responsible for fungal keratitis in tropical and subtropical climates. These filamentous fungi live in soil, organicmaterial and plant debris. People working in the garden or agriculture often get Fusarium keratitis when they injure plants,e.g., gardening or farming.	[22, 24]
Aspergillus species, e.g. *Aspergillus fumigatus* and *Aspergillus flavus*	*Aspergillus* species such as *Aspergillus fumigatus* and *Aspergillus flavus* are common moulds found in dirt, dead organic material, and homes. *Aspergillus* keratitis usually occurs when the cornea is damaged, contact lenses are worn, or surgery is performed on the eye. If you do not treat it, it can quickly and severely damage your eye.	[32]
Candida species e.g. *Candida albicans* and *Candida parapsilosis*	These opportunistic yeastsare often found on the skin and mucous membranes. People who are more likely to get candida keratitis have things like diabetes, a weak immune system or have been taking corticosteroids for a long time. It can also occur after an injury to the eye or after wearing contact lenses.	[33]
Alternaria species, e.g. *Alternaria alternata*	*Alternaria* species are filamentous fungi that can occur in soil, dead plants and outdoors. Severe corneal injury is the most common cause of *Alternaria* keratitis. This is particularly true for people who work in agriculture or spend time outdoors.	[34][35]
Curvularia species, e.g. *Curvularia senegalensis*	*Curvularia* species are dematiaceous fungi commonly found in soil, plant material and decaying vegetation. *Curvularia* keratitis is often associated with traumatic corneal injuries, particularly in agricultural workers or people who work outdoors.	[36]
	(C) Virus-causing keratitis	
Virus	***Manifestation***	***References***
HSV	HSV keratitis manifests as dendritic ulcers and more severe forms such as stromal and necrotising keratitis. It is often associated with previous ocular or systemic HSV infections.	[25, 37, 38]
VZV	VZV keratitis often affects patients who have already had chickenpox or shingles. It presents as a type of necrotising keratitis called acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN).	[25, 39,40]
Adenovirus	Specific adenovirus serotypes, particularly 8, 19, and 37, can cause epidemic kerato-conjunctivitis (EKC), a highly contagious form of viral keratitis. Adenoviral keratitis is characterised by symptoms such as conjunctivitis, keratitis, and sub-epithelial infiltration of the cornea.	[41,42,43]

CMV	CMV, a herpes virus, can cause keratitis, especially in immunocompromised people. CMV keratitis can present as necrotising or endotheliitis and requires antiviral solid treatment.	[25,44]
EBV	EBV, another member of the herpesvirus family, has been associated with viral keratitis, particularly in people suffering from infectious mononucleosis or other EBV-related diseases.	[45,46]

Table1 : List of microbes involved in microbial keratitis during corneal infection

4. INFLAMMATORY RESPONSE DURING MICROBIAL KERATITIS

In microbial keratitis, the cornea develops a robust inflammatory reaction to contain and eliminate the invasive microbes. The complicated interactions between different immune cells, cytokines, chemokines and other inflammatory mediators ultimately determine the course and outcome of the infection[47]. In response to microbial infections, pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) are released by corneal epithelial cells and resident immune cells (Figure1). These cytokines are signalling molecules that ensure that the immune cells are sent to the site of an infection and switched on[48, 49].The complex immune response to corneal infections is becoming increasingly apparent. Pattern recognition receptors such as the Toll-like and Nod-like receptors are essential to the corneal defence system. When they recognise a pathogen, they trigger inflammatory processes. These pathways, including the inflammasome, can cause significant tissue and eye damage, leading to blindness. Knowing how the immune system causes this tissue damage could help researchers find therapeutic targets anddevelop more targeted treatments to reduce eye damage in infectious keratitis[50]. Several factors influence vision in infectious keratitis: how the pathogen interacts with the host tissue, the host's naturalinflammatoryreaction and thedrugs used to treat the disease. The pathogen andthe severity of the infectioninfluence how strong thisinflammatoryreaction is and how much damage it causes. We are working to learn more about how pathogens are recognised and how the host's innate immune system responds. Theaim is to find new targets for immunomodulatory treatments[23].

Neutrophils are the first line of defence against microorganisms that invade the cornea. They move there in response to chemotactic signals and devour pathogens that come into contact with them. These cells also release antimicrobial peptides, reactive oxygen species (ROS) and cytotoxic molecules to help eliminate pathogens. While antibiotics and antifungals are frequently used to treat corneal infections, a remarkable escalation of antimicrobial resistance is emerging. Extensive research has been made to explore alternative therapeutic strategies, with the clinical prospects of antimicrobial peptides (AMPs) increasingly recognised[51, 52]. Small molecule research targeting the virulence factors of pathogens and the exploration of natural compounds have also gained importance in response to the increasing challenges and demand for effective therapeutic agents[51].Macrophages, dendritic cells and other antigen-presenting cells also aid in the inflammatory response by removing harmful microbes and releasing antigenic peptides to T-cells, triggering the adaptive immune response. However, the inflammatory mediators produced during microbial keratitis can also cause tissue damage and inflammation, leading to corneal oedema, immune cell infiltration and extracellular matrix degradation[53, 54]. The balance between pro-inflammatory and anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) is critical for regulating inflammation and promoting tissue healing[55].Dysregulation of these cytokines can prolong inflammation and delay wound healing[51]. While the inflammatory response is essential for host defence against microbial pathogens, its dysregulation can contribute to tissue damage and visual impairment in microbial keratitis. Understanding these complex immune mechanisms is critical to developing targeted therapeutic strategies to reduce inflammation, promote pathogen clearance, and preserve corneal integrity and visual function[51, 54, 55].

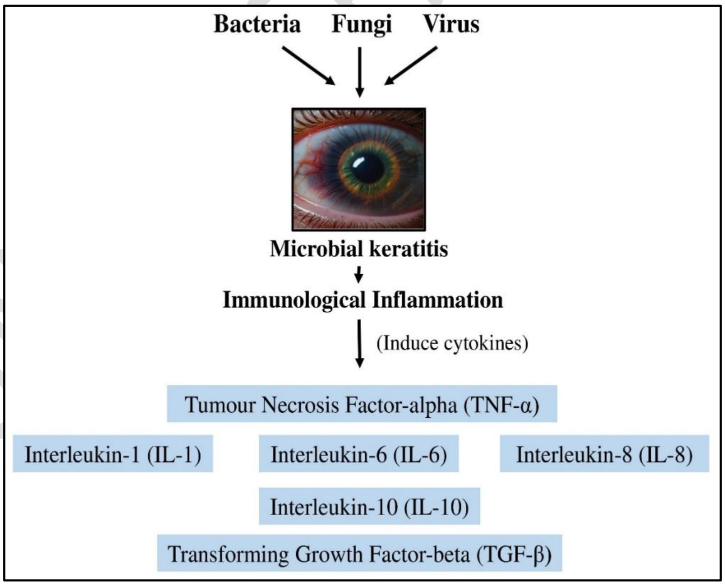

Figure 1: Production of Cytokines during microbial keratitis

A multifaceted immune response aims to eliminate the invading pathogens, heal the inflammation, and promote tissue repair as part of the immunologic mechanism that heals microbial keratitis. Following microbial invasion, corneal epithelial cells and resident immune cells recognise pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs), which trigger pro-inflammatory cytokine production[56]. The site of infection recruit neutrophils that phagocytose and eliminate the pathogens. Macrophages and dendritic cells present microbial antigens to the T-cells, triggering an adaptive immune response. T helper cells release cytokines that increase inflammation and activate cytotoxic T-cells that eliminate infected cells. Regulatory T-cells modulate the immune response to prevent excessive tissue damage. Therapeutic measures aim to modulate the immune response, improve pathogen elimination and promote corneal healing to restore vision and prevent long-term complications[57, 58].

5. NEW ADVANCES IN THE DIAGNOSIS AND TREATMENT OF MICROBIAL KERATITIS

New advances in the diagnosis and treatment of microbial keratitis offer promising opportunities to improve patient outcomes and preserve vision. These advances include innovative diagnostic techniques such as molecular biology testing, imaging techniques and artificial intelligence algorithms to enhance microbial identification and characterisation accuracy and efficiency. In addition, targeted antimicrobial agents and immunomodulatory therapies are new ways to treat microbial keratitis that could be more precise and effective[59, 60]. In addition, personalised medicine approaches tailored to individual microbial etiologies and patient profiles are becoming increasingly important. Collaboration between clinicians, researchers and industry representatives is driving the translation of these scientific discoveries into clinical practice, ushering in a new era of microbial keratitis treatment characterised by improved patient care and greater treatment efficacy[59].

Novel pharmaceutical strategies, including drug-loaded contact lenses, in situ, gel formulations and nanoparticle carriers, are innovative ways currently being explored to deliver drugs. These methods investigate the delivery of conventional antimicrobial agents, such as nucleosides, fluoroquinolones, and steroids, to improve the eye's bioavailability[61]. Drug-loaded contact lenses offer prolonged drug release and provide a sustained therapeutic effect. In situ gel formulations adapt to the ocular environment and provide a controlled release and prolonged duration of drug action. Nanoparticle carriers facilitate targeted drug delivery and improve drug penetration and efficacy. In addition to these pharmaceutical advances, corneal cross-linking is a non-pharmaceutical technique promising in treating keratitis[62]. By strengthening the collagen bonds of the cornea, corneal cross-linking aims to halt the progression of the disease and promote tissue healing, representing a new therapeutic approach in the treatment of keratitis.

6. PROSPECTS OF MICROBIAL KERATITIS AND ITS CURE

Advances in research and technology are opening up promising prospects for the future of microbial keratitis and its treatment. Innovative pharmaceutical approaches such as drug-loaded contact lenses, in situ gel formulations and nanoparticle carriers will change the delivery of drugs and increase the efficacy of antimicrobial agents by improving their ocular bioavailability. At the same time, the development of non-pharmaceutical techniques, such as corneal cross-linking, opens up new avenues for treating keratitis to prevent disease progression and promote tissue healing by strengthening corneal collagen bonds. Also, new diagnostic methods using molecular biology, imaging technologies and artificial intelligence have the potential to revolutionise the early detection and accurate diagnosis of microbial keratitis. These advances enable prompt and targeted therapeutic interventions that improve treatment efficacy. Collaboration between clinicians, researchers and industry representatives is critical in translating scientific breakthroughs into clinical practice. It drives the development of personalised treatment strategies tailored to individual microbial etiologies and patient profiles.

7. CONCLUSION

Microbial keratitis triggers a severe inflammatory reaction in the cornea, which serves as a defence mechanism against invading pathogens. This immune response is critical in containing and eradicating the microbial invasion. With continued advances in therapeutic strategies involving novel pharmaceutical and non-pharmaceutical interventions, there is some optimism about the potential for more effective treatment of microbial keratitis. These innovative therapeutic approaches aim to optimise drug delivery, strengthen tissue integrity and regulate immune responses to fight infection more effectively. By introducing breakthrough treatments and fostering collaboration between researchers, clinicians and industry representatives, the prospects for improved outcomes in treating microbial keratitis are promising. Ultimately, these advances promise to minimise ocular morbidity, preserve visual acuity and improve the overall quality of life for people affected by microbial keratitis.

ETHICAL APPROVAL

None

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