Understanding host-pathogen interaction in the cornea: Inflammatory response and healing

Literature review

Summary

Microbial keratitis, a serious disease of the cornea, is a major threat to eye health and vision worldwide. It is caused by a variety of microbial invaders, including bacteria, fungi and viruses, making it difficult to diagnose and treat. To combat microbial keratitis, we need to understand the complex network of immune responses and pathogenic pathways behind the infection. In order to develop innovative strategies to treat the disease and improve patient survival, we need to understand the functioning of the immune system, the interaction between hosts and infections and the complexity of pathophysiology. Looking ahead, we are at the dawn of a transformative era in the treatment of microbial keratitis. Innovations in therapeutic technology, such as targeted antimicrobial drugs, immunomodulatory therapies and precision medicine techniques, are poised to revolutionise the field. These advances will make it possible to tailor treatments to specific microbiological causes and patient characteristics. The integration of molecular biology, imaging and artificial intelligence into new diagnostic techniques will improve early diagnosis and personalised treatment programmes, leading to better clinical outcomes and reduced ocular morbidity. Collaboration between clinicians, researchers and industry representatives is essential to accelerate the translation of scientific knowledge into clinical practice. The future of microbial keratitis treatment promises to dramatically improve patient care, increase treatment efficacy and ultimately save the precious sight of people .

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Key words

Microbial keratitis, Bacterial keratitis, Fungal keratitis, Inflammation, Corneal infection, Cytokines

1. INTRODUCTION

The eye is a transparent outer layer of the cornea which plays a crucial role in focusing light onto the retina, which is essential for visual perception. This is the unique structure of the human eye, and exposure to the outside world increases the risk of infections . Damage to the epithelium weakens the body's defences and allows harmful microbes to cause keratitis or inflammation of the cornea [1]. [1]. Although the intact ocular surface effectively suppresses most pathogens, a disruption of the anatomical barriers weakens the host's defences. As a result, an inadequate immune response allows infection to develop, which can lead to visual impairment [2]. Microbial keratitis, also known as infectious keratitis, is a major threat to the visual integrity of the eye. Microbes that invade the cornea create a dangerous situation for the eyes. Corneal irritation is a common manifestation that can lead to serious loss of vision, or even blindness. It is therefore essential to diagnose and treat microbial keratitis immediately to avoid further damage to your vision[3, 4]. The presence of micro-organisms, including bacteria, fungi and viruses, in the cornea leads to an infection that poses a major threat to vision. These microbes set off a chain of physiological reactions in the cornea that can lead to a severe eye infection that seriously jeopardises vision [5]. [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 can cause serious and often permanent damage to the delicate tissue of the eye [6]. If left untreated, microbial keratitis can worsen rapidly and lead to ulcers, holes and, in the worst cases, lifelong vision loss. Because of its ability to threaten vision, it is all the more important to act quickly, make a correct diagnosis and apply the appropriate 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 methods of diagnosis and treatment [9] . [9, 5]. Ocular trauma, poor hygiene and the use of contact lenses all contribute to the current problem of microbial keratitis. Comprehensive efforts focused on prevention, early detection and timely treatment are needed to combat the epidemiological burden of ankylosing spondylitis and limit its adverse effects on ocular health and overall quality of life [8, 10]. [8, 10]. The study highlights the complex physiological responses triggered by microbial invasion of the cornea, leading to

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to microbial keratitis. It also explains the microbial, physiological and immunological dimensions that are important in the treatment of microbial keratitis.

2. SIGNIFICANT INCIDENCE OF MICROBIAL KERATITIS IN INDIA

According to epidemiological data, microbial keratitis is one of the leading causes of eye disease and is still prevalent in India. Microbial keratitis remains one of the leading causes of ocular morbidity [9, 11]. ~~[9, 11].~~ Microbes infect the cornea and pose a major problem for public health and therapeutic practice. This disease, which is a major public health problem, is defined as the infection of the cornea by micro-organisms. In India, the number of cases of microbial keratitis is high due to factors such as a lack of personal cleanliness , accidents in the agricultural sector and lack of access to healthcare [9]. ~~[9].~~ Despite advances in eye care and treatment, microbial keratitis remains the leading cause of blindness and visual impairment in India. Indian researchers from different regions have found that failure of initial treatment or corneal perforation is related to certain factors. In many cases, the ulceration observed and the infiltration or hypopyon of microbes are due to delayed treatment [12]. ~~[12].~~ Lalitha et al. conducted a study of patients with fungal keratitis in South India and found that primary treatment failure or corneal perforation was related to certain factors. These factors included an infiltrate larger 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 patient age as predictors of poor outcome [14, 15]. The authors studied the risk factors for corneal perforation in predominantly bacterial corneal ulcers in northern India. They found that delays in the initiation of antimicrobial therapy or in the administration of fortified antibiotics for bacterial keratitis contributed significantly to the risk of perforation. [15]. Difficulty in diagnosing bacterial keratitis, fungal keratitis or Acanthamoeba keratitis often leads to a delay in initiating treatment. Clinical features such as feathery margins, raised surface, satellite lesions and non-yellow infiltrate in fungal keratitis, annular infiltrates in Acanthamoeba keratitis and well-defined margins in bacterial keratitis provide some guidance. However, the prevalence of

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disease at an advanced stage in India warrants further evaluation of the usefulness of these clinical signs at an advanced stage of the disease [11, 16]. [11, 16].

3. MICROBES INVOLVED IN MICROBIAL KERATITIS

In keratitis, various microbial pathogens provoke an inflammatory reaction leading to infiltration of inflammatory cells throughout the cornea. These organisms, which include bacteria, fungi and viruses, provoke an immunological response characterised by purulent melting of the corneal epithelium and stroma. This process leads to the formation of ulcers in the cornea, which contributes to the progression of the disease. Intrinsic antigens or infectious agents exacerbate the inflammatory cascade, compromising the integrity of the cornea and vision. Effective diagnosis and appropriate therapy are needed to reduce the negative impact of microbial keratitis on eye health. Bacteria, fungi and viruses are the main microbiological pathogens of microbial keratitis, and each poses its own diagnostic and therapeutic problems.

Studies have shown that bacterial keratitis is mainly caused by Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae and other gram-positive or gram-negative bacteria (table 1A). These bacteria can enter the cornea as a result of trauma, contact lens wear or pre-existing ocular surface abnormalities[17] ~~[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 produce exotoxins and enzymes that damage ocular tissues and cause inflammation [18] . ~~[18].~~ Conditions that compromise the integrity of the corneal epithelium are often the cause of bacterial keratitis. A full clinical examination, including slit lamp inspection, corneal scraping with smear and culture analysis, is necessary to establish an accurate diagnosis. The main treatment is antibacterial, although other options include cycloplegics, antiglaucoma drugs and oral anti-inflammatory therapies[19]. [19]. If the situation worsens despite drug treatment, therapeutic keratoplasty may be necessary. The aim is to gain a better understanding of the causes of bacterial keratitis, existing risk factors, its prevalence, how it manifests in individuals, microbiological and histological findings, treatment options, complications, etc.

potential, differentiation between the various diagnoses and prediction of future consequences [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 through 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, particularly in developing countries, are susceptible to fungal keratitis following trauma to the eye [22]. ~~[22].~~ Once the fungi have invaded the cornea, they penetrate the intact Descemet's membrane and can enter the anterior chamber of the eye via proteolytic enzymes. This invasive nature makes fungal keratitis a serious disease, difficult to treat and a frequent cause of unilateral blindness in tropical areas [23]~~ [23]~~ . Non-fungal yeasts such as Candida species often cause keratitis in eyes that already have ocular surface problems or have just undergone topical steroid treatment, making treatment more difficult. Fusarium keratitis has attracted a great deal of attention following an epidemic linked to the use of contact lenses and contamination of the solution. Fusarium species form biofilms on contact lenses and ocular surfaces, leading to long-term infections and complicated treatment options[22, 24]~~ [22, 24]~~ .

Viral keratitis can be caused by herpes simplex virus (HSV), 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 regional ulceration. VZV keratitis is often associated with ophthalmic herpes zoster and presents as a pseudodendritic pattern on the corneal surface [25]. ~~[25].~~ Other less common microbial pathogens associated with microbial keratitis include Acanthamoeba species, Nocardia species and parasites such as Microsporidia and Acanthamoeba [26]. ~~[26].~~ Contact lenses increase the risk of developing Acanthamoeba keratitis, a potentially dangerous disease that requires prompt diagnosis and treatment to avoid severe vision loss. Acanthamoeba, which is generally found in water, can attach itself to the lenses.

contact lenses and invade the cornea, causing an infection that worsens if left untreated. It is imperative to obtain a correct diagnosis immediately, as Acanthamoeba keratitis can resemble other eye diseases and may require special laboratory tests to be sure[27]. [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 effectively fight the infection. If Nocardia keratitis is not recognised and treated quickly, it can lead to serious eye problems and even loss of sight[28]. ~~[28].~~

(A) Bacteria causing keratitis		
Bacteria	***Manifestation and characteristics***	***References***
Staphylococcus aureus	*S. aureus* is a widespread bacterium that lives on the skin and mucous membranes. It can cause keratitis by direct contact or by penetrating contact lenses and their cases and spreading germs.	[19]
Pseudomonas aeruginosa	Serious cases of bacterial keratitis are frequently associated with this opportunistic pathogen, particularly in contact lens wearers. *P. aeruginosa* grows best in damp places and can rapidly penetrate the eye, causing the infection to begin and spread rapidly.	[18]
Streptococcus pneumoniae	*S. pneumoniae* is the main germ responsible for bacterial pneumonia and other respiratory diseases. It can also cause keratitis, particularly in people with a weakened immune system or who already have diseases on the surface of the eye.	[20]
Serratia marcescens	This bacterium is frequently found in soil, water and healthcare. It can cause keratitis, particularly in cases of eye trauma or infection through contact lenses.	[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 linked to ocular trauma or contact lens contamination.	[30]
Species of *Moraxella*	*Moraxella* species, including *Moraxella catarrhalis*, can cause keratitis, particularly in people who	[31]

	suffering from underlying ocular surface disease or weakened immunity.	
Haemophilus influenzae	*H. influenzae* generally causes respiratory infections, but can also affect the eyes and cause keratitis, particularly in children and people who are already ill.	[31]

(B) Fungi causing keratitis

Mushrooms	***Manifestation and characteristics***	References
Fusarium species, for example *Fusarium polyphialidicum*	*Fusarium* species are the fungi most frequently responsible for fungal keratitis in tropical and subtropical climates. These filamentous fungi live in soil, organic matter and plant debris. People who work in the garden or in agriculture often contract Fusarium keratitis when they injure plants, for example when gardening or farming.	[22, 24]
Aspergillus species, for example *Aspergillus fumigatus* and *Aspergillus flavus*	*Aspergillus* species *such as Aspergillus fumigatus* and *Aspergillus flavus* are common moulds found in dirt, dead organic matter and homes. *Aspergillus* keratitis usually occurs when the cornea is damaged, contact lenses are worn or eye surgery is performed. If left untreated, it can quickly and seriously damage your eye.	[32]
Candida species, *for example Candida albicans* and *Candida parapsilosis*	These opportunistic yeasts are often found on the skin and mucous membranes. The people most at risk of contracting candida keratitis are those with diabetes, a weakened immune system or who have been taking corticosteroids for a long time. Keratitis can also occur following an eye injury or when wearing contact lenses.	[33]
Alternaria species, for example *Alternaria alternata*	*Alternaria* species are filamentous fungi that can be found in soil, dead plants and outdoors. Serious damage to the cornea is the most common cause of *Alternaria* keratitis. This is particularly true for people who work in agriculture or spend time outdoors.	[34] [35]
Species of *Curvularia*, for example *Curvularia senegalensis*	*Curvularia* species are dematiaceous fungi generally found in soil, plant material and decaying vegetation. *Curvularia* keratitis is often associated with traumatic lesions of the cornea, particularly in children. agricultural workers or people working outdoors.	[36]

(C) Viral keratitis

Virus	***Event***	***References***
HSV	HSV keratitis manifests itself as dendritic ulcers and more serious forms such as stromal keratitis and necrotising keratitis. It is often associated with ocular or neurological infections. previous systemic HSV infection.	[25, 37, 38]

VZV	VZV keratitis often affects patients who have already had chickenpox or shingles. It takes the form of necrotising keratitis known as acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN).	[25, 39, 40]
Adenovirus	Certain serotypes of adenovirus, in particular serotypes 8, 19 and 37, can cause epidemic keratoconjunctivitis (EKC), a highly contagious form of viral keratitis. Adenoviral keratitis is characterised by symptoms such as conjunctivitis, keratitis and subepithelial infiltration of the cornea.	[41, 42, 43]
CMV	CMV, a herpes virus, can cause keratitis, particularly in immunocompromised individuals. CMV keratitis can present as necrosis or endotheliitis and requires strong antiviral 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]

Table 1: List of microbes involved in microbial keratitis during a corneal infection

4. INFLAMMATORY RESPONSE IN MICROBIAL KERATITIS

In microbial keratitis, the cornea develops a strong inflammatory response to contain and eliminate the invading microbes. The complex interactions between different immune cells, cytokines, chemokines and other inflammatory mediators ultimately determine the course and outcome of the infection [47]. [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 (Figure 1). These cytokines are signalling molecules that ensure that immune cells are sent to the site of an infection and activated [48, 49]. The complexity of the immune response to corneal infections is becoming increasingly apparent. Pattern recognition receptors, such as 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 ocular damage, even leading to blindness. Knowing how the immune system causes this tissue damage could help researchers find therapeutic targets and develop more targeted treatments to reduce ocular damage in infectious keratitis[50]. [50]. Several factors influence vision in infectious keratitis: the way the pathogen interacts with host tissues, the host's natural inflammatory response and the drugs used to treat the disease.

The pathogen and the severity of the infection influence the intensity of this inflammatory response and the damage it causes. We are seeking to better understand how pathogens are recognised and how the host's innate immune system responds. The aim is to find new targets for immunomodulatory treatments [23].

Neutrophils are the first line of defence against micro-organisms that invade the cornea. They move 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 conducted to explore alternative therapeutic strategies, with the clinical prospects of antimicrobial peptides (AMPs) increasingly recognised [51, 52]. [51, 52]. Research into small molecules targeting pathogen virulence factors and the exploration of natural compounds have also gained in importance in response to the growing challenges and demand for effective therapeutic agents [51]. [51]. Macrophages, dendritic cells and other antigen-presenting cells also contribute to the inflammatory response by eliminating harmful microbes and releasing antigenic peptides to T cells, thus triggering the adaptive immune response. However, inflammatory mediators produced during microbial keratitis can also cause tissue damage and inflammation, leading to corneal oedema, infiltration of immune cells and degradation of the extracellular matrix [53, 54] [53, 54]. The balance between pro- and anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) is essential to regulate inflammation and promote tissue healing [55] [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 may contribute to tissue damage and visual impairment in microbial keratitis. Understanding these complex immune mechanisms is essential for developing targeted therapeutic strategies aimed at reducing inflammation, promoting pathogen elimination and preserving corneal integrity and visual function [51, 54, 55]. [51, 54, 55].

Figure 1: Cytokine production during microbial keratitis

A multifaceted immune response aims to eliminate invading pathogens, heal inflammation and promote tissue repair as part of the immunological 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 the production of pro-inflammatory cytokines[56] ~~[56]~~ . The site of infection recruits neutrophils, which phagocytose and eliminate the pathogens. Macrophages and dendritic cells present microbial antigens to T lymphocytes, triggering an adaptive immune response. Helper T 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 in order to restore vision and prevent long-term complications [57, 58]. [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 possibilities for improving patient outcomes and preserving vision.

These advances include innovative diagnostic techniques such as molecular biology tests, imaging techniques and artificial intelligence algorithms to improve the accuracy and efficiency of microbial identification and characterisation. In addition, targeted antimicrobial agents and immunomodulatory therapies are novel ways to treat microbial keratitis that could be more accurate and effective [59, 60] ~~[59, 60]~~ . In addition, personalised medicine approaches tailored to individual microbial aetiologies 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 treatment for microbial keratitis characterised by improved patient care and more effective treatments [59] ~~[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 bioavailability to the eye [61]. Drug-loaded contact lenses offer prolonged drug release and sustained therapeutic effect. In situ gel formulations adapt to the ocular environment and allow controlled release and prolonged duration of drug action. Nanoparticle carriers facilitate targeted drug delivery and improve penetration and efficacy. In addition to these pharmaceutical advances, corneal cross-linking is a promising non-pharmaceutical technique for the treatment of keratitis [62]. By strengthening the collagen bonds of the cornea, corneal cross-linking aims to halt disease progression and promote tissue healing, representing a new therapeutic approach in the treatment of keratitis.

6. PROSPECTS FOR MICROBIAL DERMATITIS AND ITS TREATMENT

Advances in research and technology offer 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 modify drug delivery and increase the efficacy of antimicrobial agents by improving their ocular bioavailability. At the same time, the development of non-pharmaceutical techniques, such as

cross-linking of the cornea, opens up new avenues for the treatment of keratitis, with the aim of preventing the progression of the disease and promoting tissue healing by strengthening the links between the collagens in the cornea. In addition, new diagnostic methods using molecular biology, imaging technologies and artificial intelligence could revolutionise the early detection and accurate diagnosis of microbial keratitis. These advances enable rapid, targeted therapeutic interventions that improve the effectiveness of treatment. Collaboration between clinicians, researchers and industry representatives is essential to translate scientific advances into clinical practice. It fosters the development of personalised therapeutic strategies tailored to individual microbial aetiologies and patient profiles.

7. CONCLUSION

Microbial keratitis triggers a severe inflammatory response in the cornea, which acts as a defence mechanism against invading pathogens. This immune response is essential to contain and eradicate microbial invasion. Ongoing advances in therapeutic strategies involving new pharmaceutical and non-pharmaceutical interventions offer grounds for optimism about more effective treatment of microbial keratitis. These innovative therapeutic approaches aim to optimise drug delivery, reinforce tissue integrity and regulate immune responses in order to fight infection more effectively. By introducing revolutionary treatments and encouraging collaboration between researchers, clinicians and industry representatives, the prospects for improving outcomes in the treatment of microbial keratitis are promising. Ultimately, these advances promise to minimise ocular morbidity, preserve visual acuity and improve the overall quality of life for those affected by microbial keratitis.

ETHICAL APPROVAL

No

Conflict of interest?

References :

1. Bashir H, Seykora JT, Lee V. Invisible shield: review of the corneal epithelium as a barrier to UV radiation, pathogens, and other environmental stimuli. Journal of ophthalmic & vision research. 2017;12(3):305.
2. Shah S, Patel V. Targeting Posterior Eye Infections with Colloidal Carriers: The Case of Ganciclovir. International Journal of Pharmaceutics. 2023 Sep 18:123427.

3. Srigyan D, Gupta M, Ahsan S, et al. Infectious keratitis: an immediate cause for concern. Ophthalmology Research: An International Journal. 2017;7(4):1-6.
4. Shrestha GS, Vijay AK, Stapleton F, et al. Understanding clinical and immunological features associated with Pseudomonas and Staphylococcus keratitis. Contact Lens and Anterior Eye. 2021;44(1):3-13.
5. Ting DS, Ho CS, Deshmukh R, et al. Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. Eye. 202;35(4):1084-1101.
6. Kumar A, Yun H, Funderburgh ML, et al. Regenerative therapy for the Cornea. Progress in retinal and eye research. 2022;87:101011.
7. Anderson CD, Rees N, Koetsie K, et al. Microbial keratitis: Causative organisms, susceptibilities and trends at a tertiary eye hospital in South Africa. African Vision and Eye Health. 2022;81(1):6.
8. Tuft S, Evans J, Gordon I, et al. Antimicrobial resistance in topical treatments for microbial keratitis: protocol for a systematic review and meta-analysis. BMJ open. 2023;13(3):e069338.
9. Koh YY, Sun CC, Hsiao CH. Epidemiology and the estimated burden of microbial keratitis on the health care system in Taiwan: a 14-year population-based study. American Journal of Ophthalmology. 2020;220:152-159.
10. Menassa J, Bou Nassar D, El Naboulsi F, et al. Public Awareness of Rheumatoid Arthritis and Ankylosing Spondylitis in Lebanon. The Open Rheumatology Journal. 2022;16(1).
11. Kusumesh R, Ambastha A, Arya LK, et al. Epidemiological and microbiological profiles of microbial keratitis in a tertiary eye center in Eastern India (Bihar). Indian Journal of Ophthalmology. 2023;71(11):3506-3512.
12. Roongpoovapatr V, Prabhasawat P, Isipradit S, et al. Infectious keratitis: the great enemy. InVisual impairment and blindness - What we know and what we need to know 2019. IntechOpen.
13. Lalitha P, Prajna NV, Kabra A, et al. Risk factors for treatment outcome in fungal keratitis. Ophthalmology. 2006;113(4):526-530.
14. Rautaraya B, Sharma S, Ali MH, et al. A 3½-year study of bacterial Keratitis from Odisha, India. The Asia-Pacific Journal of Ophthalmology. 2014;3(3):146-50.
15. Titiyal JS, Negi S, Anand A, et al. Risk factors for perforation in microbial corneal ulcers in north India. British journal of ophthalmology. 2006;90(6):686-9.
16. Chidambaram JD, Venkatesh Prajna N, Srikanthi P, et al. Epidemiology, risk factors, and clinical outcomes in severe microbial keratitis in South India. Ophthalmic epidemiology. 2018;25(4):297-305.
17. Teweldemedhin M, Gebreyesus H, Atsbaha AH, et al. Bacterial profile of ocular infections: a systematic review. BMC ophthalmology. 2017;17:1-9.
18. Shah S, Wozniak RA. *Staphylococcus aureus* and *Pseudomonas aeruginosa* infectious keratitis: key bacterial mechanisms that mediate pathogenesis and emerging therapeutics. Frontiers in Cellular and Infection Microbiology. 2023;13:1250257.
19. Kumar NM, Mah FS. Bacterial, chlamydial and mycobacterial infections. Principles and practice of ophthalmology by Albert and Jakobiec. 2022:281-307.
20. Keller LE, Robinson DA, McDaniel LS. Unencapsulated Streptococcus pneumoniae: emergence and pathogenesis. MBio. 2016;7(2):10-128.
21. Ahmadikia K, Aghaei Gharehbolagh S, Fallah B, et al. Distribution, prevalence, and causative agents of fungal keratitis: a systematic review and meta-analysis (1990 to 2020). Frontiers in Cellular and Infection Microbiology. 2021;11:698780.

22. Hoffman JJ, Burton MJ, Leck A. Mycotic keratitis-a global threat from the filamentous fungi. Journal of Fungi. 2021;7(4):273.
23. Lakhundi S, Siddiqui R, Khan NA. Pathogenesis of microbial keratitis. Microbial pathogenesis. 2017;104:97-109.
24. Guarro J, Rubio C, Gené J, et al. Case of keratitis caused by an uncommon Fusarium species. Journal of clinical microbiology. 2003;41(12):5823-6.
25. Labetoulle M, Boutolleau D, Burrel S, et al. Herpes simplex virus, varicella-zoster virus and cytomegalovirus keratitis: Facts for the clinician. The ocular surface. 2023 Apr 1;28:336-50.
26. Cabrera-Aguas M, Khoo P, Watson SL. Infectious keratitis: A review. Clinical & Experimental Ophthalmology. 2022;50(5):543-62.
27. Fanselow N, Sirajuddin N, Yin XT, et al. Acanthamoeba keratitis, pathology, diagnosis and treatment. Pathogens. 2021;10(3):323.
28. Lalitha P, Srinivasan M, Rajaraman R, et al. Nocardia keratitis: clinical course and effect of corticosteroids. American journal of ophthalmology. 2012 Dec 1;154(6):934-9.
29. Pifer R, Harris V, Sanders D, et al. Evaluation of serratia marcescens adherence to contact lens materials. Microorganisms. 2023;11(1):217.
30. Jan-Roblero J, Cruz-Maya JA, Barajas CG. Kosakonia. InBeneficial Microbes in Agro- Ecology 2020; 213-231. Academic Press.
31. Deepthi KG, Prabagaran SR. Ocular bacterial infections: pathogenesis and diagnosis. Microbial pathogenesis. 2020;145:104206.
32. Niu L, Liu X, Ma Z, et al. Fungal keratitis: Pathogenesis, diagnosis and prevention. Microbial pathogenesis. 2020;138:103802.
33. Sun RL, Jones DB, Wilhelmus KR. Clinical characteristics and outcome of Candida keratitis. American journal of ophthalmology. 2007;143(6):1043-5.
34. Hsiao CH, Yeh LK, Chen HC, et al. Clinical characteristics of Alternaria keratitis. Journal of Ophthalmology. 2014;2014.
35. Leite J, Romano J, Lopes V, et al. Case report: Alternaria alternata keratitis. International Medical Case Reports Journal. 2023:59-64.
36. Narula H, Meena S, Jha S, et al. Curvularia lunata causing orbital cellulitis in a diabetic patient: An old fungus in a new territory. Current Medical Mycology. 2020;6(1):51.
37. Kapoor D, Sharma P, Shukla D. Emerging drugs for the treatment of herpetic keratitis. Expert opinion on emerging drugs. 2024:1-4.
38. Musa M, Enaholo E, Aluyi-Osa G, et al. Herpes simplex keratitis: A brief clinical overview. World Journal of Virology. 2024;13(1).
39. Kalogeropoulos CD, Bassukas ID, Moschos MM, et al. Eye and periocular skin involvement in herpes zoster infection. Medical Hypothesis, Discovery and Innovation in Ophthalmology. 2015;4(4):142.
40. Julian K, Bodaghi B. Varicella-zoster virus. InIntraocular Inflammation 2016:1227-1238. Berlin, Heidelberg: Springer Berlin Heidelberg.
41. Zhou X, Robinson CM, Rajaiya J, et al. Analysis of human adenovirus type 19 associated with epidemic keratoconjunctivitis and its reclassification as adenovirus type
64. Investigative ophthalmology & visual science. 2012;53(6):2804-11.
42. Wright KW, Spiegel PH, editors. Pediatric ophthalmology and strabismus. Springer Science & Business Media; 2013.
43. Chigbu DI, Labib BA. Pathogenesis and management of adenoviral keratoconjunctivitis. Infection and drug resistance. 2018:981-93.
44. Venugopal A, Christy J, Raut V, et al. Viral Keratitis, Surgical Intervention in Viral Keratitis, Challenges in Diagnosis and Treatment of Viral Keratitis, HSV, HZV. InSeminars in Ophthalmology 2024:1-13. Taylor & Francis.

45. Stewart MW. Herpetic retinal infections (without cytomegalovirus) in patients with acquired immunodeficiency syndrome. Current HIV Research. 2013;11(3):210-9.
46. Feng Y. Virus Infection and Ophthalmic Diseases from the Perspective of Integrated Medicine. Integrative Ophthalmology. 2020:191-197.
47. Das S, D'Souza S, Gorimanipalli B, et al. Ocular Surface Infection Mediated Molecular Stress Responses: A Review. International Journal of Molecular Sciences. 2022 Mar 14;23(6):3111.
48. Björkström NK, Strunz B, Ljunggren HG. Natural killer cells in antiviral immunity. Nature Reviews Immunology. 2022;22(2):112-23.
49. Thakur A, Xue M, Stapleton F, et al. Balance of pro-and anti-inflammatory cytokines correlates with outcome of acute experimental Pseudomonas aeruginosa keratitis. Infection and immunity. 2002;70(4):2187-2197.
50. Zhang Y, Wu J, Xin Z, et al. Aspergillus fumigatus triggers innate immune response via NOD1 signaling in human corneal epithelial cells. Experimental eye research. 2014;127:170-178.
51. Nuti R, Goud NS, Saraswati AP, et al. Antimicrobial peptides: a promising therapeutic strategy in tackling antimicrobial resistance. Current medicinal chemistry. 2017;24(38):4303-14.
52. Jadi PK, Sharma P, Bhogapurapu B, et al. Alternative therapeutic interventions: antimicrobial peptides and small molecules to treat microbial keratitis. Frontiers in Chemistry. 2021;9:694998.
53. Germic N, Frangez Z, Yousefi S, et al. Regulation of the innate immune system by autophagy : monocytes, macrophages, dendritic cells and antigen presentation. Cell Death & Differentiation. 2019;26(4):715-27.
54. Fortingo N, Melnyk S, Sutton SH, et al. Innate immune system activation, inflammation and corneal wound healing. International journal of molecular sciences. 2022;23(23):14933.
55. Torrecilla J, del Pozo-Rodriguez A, Vicente-Pascual M, et al. Targeting corneal inflammation by gene therapy: Emerging strategies for keratitis. Experimental Eye Research. 2018;176:130-40.
56. Taube MA, del Mar Cendra M, Elsahn A, et al. Pattern recognition receptors in microbial keratitis. Eye. 2015;29(11):1399-415.
57. Appelberg R. Neutrophils and intracellular pathogens: beyond phagocytosis and killing. Trends in microbiology. 2007;15(2):87-92.
58. Punt J. Adaptive immunity: T Cells and Cytokines. InCancer immunotherapy 2013:41-53). Academic Press.
59. Ting DS, Gopal BP, Deshmukh R, et al. Diagnostic armamentarium of infectious keratitis: A comprehensive review. The Ocular Surface. 2022;23:27-39.
60. Shannon AH, Adelman SA, Hisey EA, et al. Antimicrobial peptide expression at the ocular surface and their therapeutic use in the treatment of microbial keratitis. Frontiers in Microbiology. 2022;13:857735.
61. Ali ZJ. A Review of Current and Novel Approaches for Treatment of Keratitis 2021 (Doctoral dissertation, University of Pittsburgh).
62. Mandal P, Khan MI, Shah S. Drugs-do we need them? Applications of non-pharmaceutical therapy in anterior eye disease: a review. Contact Lens and Anterior Eye. 2017;40(6):360-6.

There are enough articles to limit to 12 or a maximum of 15 articles.

~~62.~~ Indicate in the title that this is a review of the literature carried out by the authors.

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