e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 1707-1714

Original Research Article

Microbial Keratitis: Understanding Pathogens and Developing Effective Treatments

Shreshth Shanker[1], Varsha Priya[2], Ashok Prasad[3], Bhawna Kumari[4]

[1]Associate Professor, Department of Ophthalmology, MGM Medical College and LSK hospital, Kishanganj, Bihar

[2]3rd Year PGT, Department of Microbiology, MGM Medical college and LSK Hospital, Kishanganj, Bihar

[3]Associate Professor, Department of Microbiology, MGM Medical College & LSK Hospital Kishanganj, Bihar

[4]Assistant Professor, Department of Microbiology, MGM Medical College and LSK Hospital Kishanganj, Bihar

Received: 25-10-2023 / Revised: 23-11-2023 / Accepted: 26-12-2023

Corresponding Author: Dr. Bhawna Kumari

Conflict of interest: Nil

Abstract:

Microbial Keratitis (MK) is a severe eye condition demanding urgent diagnosis and immediate application of targeted antimicrobial therapy to safeguard vision. It results from diverse organisms falling into categories like bacteria, fungi, viruses, and protozoa. The vulnerability of the avascular cornea to microbial invasion heightens the risk of poor visual outcomes, underscoring the necessity for aggressive and precise antimicrobial treatment. Timely identification and intervention are pivotal in managing MK. Treatment initiation often relies on probable organisms prevalent in a particular geographic area, stressing the significance of on-going microbial surveillance to tailor effective empirical therapy. Among bacterial corneal pathogens, Pseudomonas sp. (Gram-negative), Staphylococcus sp. (Gram-positive), Streptococcus sp. (Gram-positive), and other Gram-negative organisms are common. While fungal infections contribute to a small portion of cases in moderate climates, tropical regions may see up to 50% of cases, with prevalent fungal corneal pathogens like Candida sp. (yeast-like), Fusarium sp. (filamentous), and Aspergillus sp. (filamentous).

Keywords: Cornea, Microbial Infection, Microbial keratitis, Pathogens, Ocular Emergency.

Introduction

The severe risk of vision loss caused by microbial keratitis highlights the need for prompt action to avoid further damage. One notable consequence of this disorder is corneal opacities, which are the fourth most common cause of blindness worldwide [1,2]. A crucial step in reducing long-term effects is the prompt administration of tailored antibiotic treatment, which is determined by clinical examinations and testing results.

In the United States [3], there are 11.0 cases of microbial keratitis per 100,000 people per year; however, in poor countries, there are an astounding 799 cases per 100,000 people [4]. Between 1.5 and 2 million instances of ulcerated corneas are recorded in these emerging nations annually [5]. In the case that untreated microbial keratitis is not treated, it may lead to corneal perforation, endophthalmitis, and severe vision loss. The foundation of successful therapy is an accurate identification of the organism responsible. The investigation procedure relies on samples such as biopsy specimens, weeping, and cornea portions. Quick recognition of microorganisms by microscopy using KOH wet mount, staining with Gram, and Giemsa stain allows empirical monitoring while cultured findings are awaited.

In all cases of microbial keratitis, the gold standard—a corneal culture—is recommended [6,7]. Clinical judgment should be used to determine when to begin treatment for suspected instances of herpes simplex virus (HSV) keratitis. Identifying amoebic and fungal keratitis relies heavily on non-invasive approaches, such as in vivo microscopy using confocal microscopes; for the diagnosis of microbial keratitis, the new molecular testing method known as Polymerase Chain Reaction (PCR) shows encouraging signs.

The purpose of this article is to provide insights into the medical signs and symptoms seen in different forms of microbial keratitis [8].

Material and Methods:

A worldwide future registry of systematic literature reviews (PROSPERO) was used to track and map out the steps that this research took. Our study was done with great care, following the detailed instructions provided by Moher et al. in 2009 for recommended report criteria for systematic examinations and meta-analyses. As part of our research, we perused the online halls of prestigious resources such as Google Scholar, Scopus, PubMed, and Web of Science (ISI). We searched these academic terrains using a hand-picked collection of primary keywords, including "fungal keratitis," "keratomycosis," and "mycotic keratitis"—both alone and in cocktail form. The scope of our topic of study and terms like "infectious keratitis" and "microbial keratitis," which could refer to a wide variety of microbes, including bacteria, viruses, fungi, and amoebae, prompted us to implement a thorough search technique. We were pretty specific in selecting parameters in order to get each article and piece of information that was relevant. Papers labelled as "articles" were the only ones we considered, and we only looked at those published in English between January 1, 1990, and May 27, 2020. By using such painstaking measures, we hoped to catch relevant papers and ideas from all corners of the infectious keratitis study spectrum [9].

Epidemiology across the world: Two main findings appear: first, in spite of constraints in research methodology and illness means, there is an association between disease prevalence and GNP modifications; and second, there is an absence of research from unique worldwide areas, impoverished African countries and countries in South America. Insufficient medical care, inadequate incomes, dangerous ecological situations, and a greater likelihood of ocular trauma—especially agricultural injuries—contribute to the higher frequency of infectious keratitis in nations with low incomes. Recent research from lacking resources is scarce, but current statistics do not consistently back the concept that illness prevalence is rising with time, according to certain specialists [10].

The majority of research concentrates on infectious keratitis that is not caused by viruses. For instance, a research conducted in China discovered that 0.192% of the population had either a history of infectious keratitis or a current case of the condition. Of those individuals, 0.11% had viral keratitis, 0.075% had bacterial keratitis, and 0.007% had fungal keratitis [11]. Despite the fact that prevalence does not always correspond to incidence, these data provide us with an understanding of the many factors that contribute to the illness spread across the community. According to a recent study, there are more than one million instances of fungal keratitis each year, the most of which occur in Asia and Africa. The average worldwide incidence of fungal keratitis is around 23.6 occurrences per 100,000 people per year, with the number of cases ranging from 0.02 incidents in Europe to 73 incidents in India [12]. Herpes simplex virus, often known as HSV, is the most common cause of infectious blindness in one eye in the region of cornea, and this is true independent of the degree of development in a nation [11,13,14]. Adenovirus, cytomegalovirus, and varicella-zoster are three more viruses that are associated with viral keratitis, however they are less prevalent.

A comprehensive statistical analysis sheds light on disease frequency estimations, unveiling HSV keratitis incidences ranging from 5.3 to 31.5 cases per 100,000 individuals. Nevertheless, historical records reflecting lower values are prone to underestimating the actual prevalence due to cases managed beyond the audited center [15]. Incidences of new cases fluctuate between 3.2 and 13.2 per 100,000 individuals, with recurrent cases occurring at rates 12 to 1.5 times higher than new cases. Three discrete studies estimating disease prevalence propose figures spanning from 65 to 149 cases per 100,000 individuals [10].

Epidemiology in India: The 3,183 individuals with ulcers of the cornea who were clinically identified between 1999 and 2002 were evaluated in detail at a hospital in the south of India. Out of every single patient studied, 3,186 eyes were found to have corneal ulcers; astonishingly, 3,180 (99.91%) had solitary illness and just 3 (0.09%) had bidirectional participation. Out of 3,183 individuals, 2,247 (70.59%) had microbial colonies revealed by corneal scrapings, whereas 936 (29.41%) showed no development at all. In 1,043 individuals (32.77%), fungi development alone was seen in 1,095 individuals (34.4%), and 33 individuals (1.04%) had Acanthamoeba segregation alone, according to the culture data. There was also evidence of fungal and bacterial development in 76 cases (2.39%) [16].

A striking majority of 1,040 patients (99.71%) with culture-positive keratitis caused by bacteria had unilateral participation, whereas just 3 patients (0.29%) had bilateral disease. In the field of keratitis, 1,122 eyes were examined in detail, and 1,185 bacterial pathogens were isolated. Notably, 1,046 eyes showed no signs of fungal development at all, whereas 76 eyes showed signs of both types of growth at the same time.

Only 63 out of 1,059 eyes showed signs of dual-species bacterial proliferation, whereas 1,059 displayed signs of unifloral bacterial development. With 426 cases (35.95%), Streptococcus pneumoniae was the most common bacterial strain, next to 236 patients (19.92%), and finally,

Pseudomonas aeruginosa. Turning our attention to the realm of fungal isolated compounds, the vast majority, 1,176 to be exact, were collected from 1,171 eyes that had suffered from keratitis. Out of the 1,095 eyes in this group, 1,095 showed fungi developing alone, whereas 76 showed both bacterial and fungal development at the same time. Of the 1,166 cases studied, 1,166 had monospecific fungal isolates, and 5, very rarely, had dual fungal infections. The most common fungus species was Aspergillus spp., found in 294 cases (25% of the total), with Fusarium spp. They came in second with 493 points (41.92%). Surprisingly, only 33 eyes (1.03%) out of 3,186 cultivated corneal ulcers tested positive for Acanthamoeba species [16].

Pathogenesis: Bacteria like Staphylococcus aureus, Streptococcus pneumoniae, and several species of Pseudomonas cause the majority of bacterial corneal ulcers (about 80%). The most common and dangerous of them is Pseudomonas aeruginosa, an eye bacterium that may cause corneal rupture in as little as 72 hours.

The germs that cause keratitis may be either gram-positive or Gram-negative. How well an organism can adhere to the outside or inside of an epithelium defect is the most critical factor in determining its pathogenicity [18, 19, 20]. Adherence allows penetration into the stroma, allowing the pathogen to evade the host's barriers [17,18]. Particularly noteworthy are the invasive characteristics shown by pathogens such as Staphylococcus aureus, Streptococcus pneumoniae, and Pseudomonas aeruginosa [17]. The pathogenic strategies of these bacteria hinge on specialized membrane extensions present in both Gram-positive organisms, like fibrillae, and Gram-negative counterparts, equipped with structures such as fimbriae and glycocalyx. These extensions serve as crucial aids, fostering adhesion to damaged epithelial cells and facilitating penetration into the stroma. However, once they infiltrate the stroma, bacteria undergo the loss of their glycocalyx envelope. Notably, Pseudomonas aeruginosa and Neisseria gonorrhoea exploit the glycocalyx to establish adherence, forming connections between each other, affected epithelial cells, and contact lenses. The adhesive strength of Pseudomonas aeruginosa, distinguished by its capacity for attachment, is primarily attributed to its pili, enriched with calcium and magnesium. Moreover, its biofilm, a protective layer surrounding the organism, serves as a facilitator for attachment to both contact lenses and epithelial breaks [17].

In the context of bacterial corneal infections, a cascade unfolds with the activation of plasminogen into its active form, plasmin. This enzymatic activation sets off proteolytic processes driven by enzymes like chymase and tryptase, leading to microlesions in the epithelium. Consequently, the degradation of adhesive glycoproteins orchestrated by these enzymes significantly impedes the healing process. Certain bacteria bolster their survival and virulence by producing a chemical slime, a defence mechanism against phagocytosis, concurrently reducing their metabolic demands. Proteases and lytic enzymes play pivotal roles in enabling organisms like Neisseria gonorrhoea, Corynebacterium diphtheriae, Listeria, Shigella, and Koch-Weeks bacilli to induce keratitis, even penetrating intact epithelium. Specific bacterial strains, such as Pneumococci, evade ocular lysozyme and phagocytosis by enveloping themselves in protective polysaccharide capsules [17].

Table 1: Organisms causing keratitis

Type	Causative Organisms	Common Risk Factors
Bacterial Keratitis	Pseudomonas sp., Staphylococcus sp., Streptococcus sp. [21]	Contact lens wear, poor hand hygiene, ocular surface disease, ocular trauma or surgery, immune compromise, topical steroid use [21].
Fungal Keratitis	Candida sp., Fusarium sp., Aspergillus sp [22,23].	Trauma involving organic material, contact lens or solution-related, ocular surface disease in immunocompromised patients [22,23]
Parasitic/Amebic Keratitis	Acanthamoeba [24]	Contact lens wear, exposure to contaminated water [24]
Viral Keratitis	Herpes simplex virus [25,26,27,28, 29]	Herpes infection [25,26,27,28, 29]

Signs and Symptoms of microbial keratitis: The signs and symptoms of microbial keratitis can vary depending on the type of microorganism causing the infection—however, common symptoms across various kinds of microbial keratitis include [25,30].

Eye pain: This can range from moderate to severe and usually has an acute onset with rapid progression.

Redness of the eye: This is a common symptom of inflammation [30].

Blurry vision: Vision may become blurred, especially if the lesion is on the visual axis [30].

Sensitivity to light (Photophobia): [25].

Excessive tearing (Lacrimation): [30].

Examination of the eye may reveal additional signs such as [31]:

1. Lid oedema
2. Blepharospasm
3. Matting of eyelashes
4. Purulent discharge
5. Conjunctival chemosis
6. Circumcorneal congestion
7. Hyperemia
8. Epithelial defect
9. Stromal edema
10. Stromal infiltrate
11. Descemet membrane folds
12. Endothelial plaque
13. Hypopyon
14. Exudates in the anterior chamber
15. Anterior uveitis

Diagnosis and Examination of this disease: Slit-Lamp Examination: This non-intrusive device can determine the kind and severity of keratitis, in addition to its potential impact on various ocular frameworks, by using an effective light output and amplification [32,33]. It is commonly used to view the eye under magnification [34].

Cultures of the Cornea: Any ulcer that is large (>2mm), involves the centre to the deep stroma, poses a danger to sight, is chronic, atypical, or does not respond to therapy should have cultures of the cornea made and stained with Gram and Giemsa to identify the causing organisms. When taking a corneal culture, three factors are considered according to the 1-2-3 Rule: 1) At least one cell in the front chamber; 2) two millimetres of infiltration; and 3) the infiltration edge within three millimetres of the cornea's center [34].

One molecular method that may identify trace amounts of microbial DNA in eye samples is polymerase chain reaction (PCR). A substantial number of false positives are produced by it, notwithstanding its susceptibility [35]. Microsporidia DNA in corneal scrapes may be detected using proven PCR-based assays [36]. When diagnosing microsporidia keratitis, pan microsporidian PCR might be a useful addition to smear examination [36].

To quickly diagnose infective keratitis, especially in instances of Acanthamoeba or fungal keratitis, in vivo confocal microscopy (IVCM) is a non-intrusive technique [37,38]. Leukocytes and Langerhans cells are nonspecific indicators of infection that could be hard to differentiate from harmful microbes. Longitudinal patient monitoring for therapy efficacy is another ideal use of IVCM [37].

Current Treatments and Management Strategies: The primary treatment for the care of bacterial keratitis is topically applied antibiotics, particularly fluoroquinolones (gatifloxacin, ciprofloxacin, ofloxacin, and moxifloxacin).

The growing trend of resistance to ciprofloxacin and ofloxacin has led to a change in focus towards moxifloxacin and gatifloxacin, which are more effective in treating this disease, according to recent research. The treatment of gram-positive bacteria that do not produce penicillinase is best accomplished using cephalosporins, especially with fortified topical cefazolin 5%. In contrast, wide varieties of bacterial strains are significantly outcompeted by aminoglycosides such as gentamicin 0.3%, amikacin 1 g/ml injection, or fortified tobramycin 0.3%. Nevertheless, particularly when it comes to fighting pneumococci, individuals show very little responsiveness [39,44].

Table 2:

Type of Keratitis	Treatment	Management Strategy
Bacterial Keratitis infections caused	The main course of therapy is the use of antibiotic eye drops45. Fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin, gatifloxacin) are now recommended as a first line of therapy, with combined or fortified therapy following [46].	Empirical therapy is recommended either in the form of a fluoroquinolone monotherapy or combinations of fortified antibiotics (cephazolin 5% and tobramycin/gentamycin- 1.4%) till sensitivity reports are available [47].
Fungal Keratitis infections caused	Antifungal drops for the eye and oral antifungal medicine are usually used for keratitis caused by fungi [45].	Treatment according to regional patterns, an appropriate dosage of antibacterial agents, and culture-directed therapy with powerful antibiotics are important options [48].
Viral Keratitis infections caused	It is possible to treat infections caused by viruses using antiviral drops for the eyes and dietary medications [46].	Antiviral therapy is used to prevent the causative virus from reproducing [46].
Acanthamoeba Keratitis infections caused	It may be rather difficult to cure keratitis produced by the acanthamoeba worm. Apply antiparasitic eye drops [46].	Medically intense topical therapy with a biguanide, diamidine, or a mix of the two that lasts throughout the day and evening [48].

As a substitute for monotherapy, combo therapy is routinely explored, especially in situations requiring fourth-generation quinolones. This often involves fortified cefazolin and tobramycin. There is significant evidence that reinforced vancomycin 5% is effective against MRSA. Nevertheless, it is crucial to investigate other treatment methods because of on-going problems with medication availability caused by pre-corneal variables and restricted corneal penetration.

In rare cases, such as endophthalmitis, scleritis, or non-resolving progressive bacterial ulcers, a combination of medications like ciprofloxacin and aminoglycosides with cephalosporins may be administered as systemically administered antibiotics as part of the treatment for bacterial keratitis. The primary therapy for bacterial keratitis is antibiotics that are applied topically, although when combined with steroids, there are considerable therapeutic advantages. By reducing the likelihood of scarring, stromal melting, and neovascularization, steroids help minimise damage to tissues. Patients report more comfort, conformity, and effective pain control as a result of its use. There is still debate about using steroids to treat microbial keratitis since they may slow down the recovery of the epithelium and increase the likelihood of bacterial keratitis, which can cause the stroma to weaken and melt [41,42].

Results in bacterial keratitis managed with antibiotic alone vs an amalgam of antibiotics and steroids have been evaluated in research studies, such as the Steroid for Corneal Ulcer Trial (SCUT) along with other comparable investigations [42,43]. Subgroup studies within SCUT revealed substantial visual improvements at three months, especially in those who had impaired vision and those who had aggressive Pseudomonas strains; initial experiments on topical steroid therapy had unclear findings. What's fascinating is that the placebo group had much fewer side effects than the steroid group43. Steroids have complex advantages and hazards when used for managing bacterial keratitis, and our results highlight the need for caution when considering their usage in practical follow [44].

Challenges and Complications: Stromal keratitis may be classified into two main types: necrotizing and caused by the immune system. The immune-related disease is sometimes called non-necrotizing and is mainly caused by the herpes simplex virus (HSV). The immune-mediated subtype may be identified in clinical settings by looking for white or opaque stromal infiltrate free of ulcers and death. The development of neovascularization, corneal thinning, lipid keratopathy, and severe infection are among the frequent consequences that this variation is known to bring about. Stromal infiltration that is greyish-white in colour, ulcers, necrosis, and on-going reproduction of viruses are hallmarks of necrotizing stromal HSV keratitis, which presents a distinct appearance. This specific variation has the potential to cause hypopyon, uveitis, cataracts, glaucoma, retro-corneal membrane formation, and corneal rupture as additional problems. In herpes simplex virus endothelium, disciform keratitis is an easily identifiable characteristic. This condition often manifests itself during slit-lamp exams, accompanied by telltale indications such as stromal oedema and a ground-glass look. Looking more closely, this symptom shows that keratic precipitate (KPs) is hiding beneath the afflicted area. A widespread thickness of the cornea is also apparent, with Descemet's wrinkles and epithelium swelling8.

Results and Discussion

Consistent with previous studies, the research included 200 instances of suspected microbial keratitis and found bacteria in 55% of the patients [50,51,52]. Nevertheless, this rate stands in contrast to the more excellent isolation rates seen in Nepal and Bangladesh, even though they used enriched medium and numerous scrapings for inoculation. Srinivasan et al. (1997) found that the increased accessibility of topical medicines was the reason for the reduced isolation rates. A large percentage of cases (84.5%) were caused by a single microbe, with bacteria being the causative agent in 48% of these instances. The southern areas of Ghana and India have also recorded similar results.

In contrast, bacterial keratitis was found to be more common in Nepal and Hyderabad. Much to previous research in India and elsewhere, the majority of the bacteria in this study were Staphylococcus spp. (33; 47.4%). Staphylococcus spp. was likewise identified as the most prevalent causal agent (56.30%), according to one research conducted in this area, but it was not reported. Pseudomonas aeruginosa was shown to be more common in other places, such as Ghana, Hong Kong, and Bahrain, but Streptococcus pneumoniae was the most common in research conducted in South India [50]. The different accounts highlight different regional trends in the cause of microbial keratitis. According to the study, keratitis is more common in males (61% vs. 39%) than in women. This difference is about 1.5 times larger than the gender gap in women. Previous research on a worldwide scale has shown male predominance ratios between 1.5:1 and 4.5:1, and this tendency supports those results. But other stories mentioned a preference for females, so it seems like there's some regional variation. One possible explanation for the higher incidence rate among males might be the more significant amount of time spent outside that men tend to have in their jobs. Among farmers in particular, there was a strong correlation between

workplace contact and bacterial/fungal keratitis [50].

People under the age of 50 had a much greater incidence of microbial keratitis (73.62%), according to the research. Additionally, 78.5% of cases in this research had corneal damage, which is a prevalent factor in microbiological keratitis. Scratches on the cornea caused by field stems of hay, wheat, maize, or groundnuts were every day in eastern India. In keeping with previous findings from Nepal and India, the research found that 0.5% of cases were related to contact lens usage. The low prevalence might be because those who were evaluated were mostly from disadvantaged backgrounds. Infections with fungi caused almost half (40.9%) of corneal ulcers that tested positive for microorganisms. About 51.8% of corneal ulcers that tested positive for cultures had pathogenic fungi, which is the most common classification for multiple infections when it comes to therapy. This is in good agreement with the fungal separation rates published by Srinivasan et al. (1997) [51] and Hagan et al. (1995) [52]. Although keratitis caused by bacteria can occur all year round, the season from August to December had the highest prevalence of fungal keratitis, which coincided with reaping wheat, maize, and groundnuts, among other tasks related to agriculture. The results of Panda et al. (1997) [53] and Gopinathan et al. (2002) [54] corroborate these tendencies. This research found that the young group, ranging from 20 to 40 years old, had a greater incidence of fungal keratitis (41%), which contradicts prior data that reported the condition to be most frequent in the sixth decade. The financial cost of blindness is magnified since this generation is often the primary breadwinners [49].

Conclusion

Threats to eyesight, such as microbial keratitis (MK) and corneal ulcers, occur at different rates across the globe. Corneal stromal scarring, which may cause extensive opacifications and, in the worst case scenario, legal blindness, is one of the worst consequences that can arise from uncontrolled MK. A person may end up losing an eye due to complications such as corneal thinning, perforation, or endophthalmitis. Proper sample procedures for identifying infectious organisms are essential skills for eye doctors and ophthalmic trainees/residents. This understanding, which is based on the principles of MK as they pertain to microbiology, helps in identifying the infectious agent responsible for the disease, which in turn allows for effective and swift treatment. Early and accurate diagnosis has the potential to decrease the related morbidity by targeting the numerous organisms that cause MK. The clinical manifestations and testing methods relevant to various forms of MK are described in this review article, which acts as a revised fundamental guide. In the end, healthcare providers may use this data to improve MK outcomes by tailoring it to the specific needs of their patients and the assets they have at their disposal.

References

1. Pascolini, D., & Mariotti, S. P. Global estimates of visual impairment: 2010. British Journal of Ophthalmology, 2012; 96(5): 614–618.
2. World Health Organization. Causes of blindness and visual impairment. Accessed December 7, 2016. http://www.who. int/blindness/ causes/en
3. Erie, J. C., Nevitt, M. P., Hodge, D. O., & Ballard, D. J. Incidence of ulcerative keratitis in a defined population from 1950 through 1988. Archives of Ophthalmology, 1993; 111(12): 1665–1671.
4. Upadhyay, M. P., Karmacharya, P. C., Koirala, S., Shah, D. N., Shakya, S., Shrestha, J. K., Bajracharya, H., Gurung, C. K., & Whitcher, J. P. The Bhaktapur eye study: Ocular trauma and antibiotic prophylaxis for the prevention of corneal ulceration in Nepal. British Journal of Ophthalmology, 2001; 85(4): 388–392.
5. Karsten, E., Watson, S. L., & Foster, L. J. Diversity of microbial species implicated in keratitis: A review. Open Ophthalmology Journal, 2012; 6: 110–124.
6. McLeod, S. D. The role of cultures in the management of ulcerative keratitis. Cornea, 1997; 16(4): 381–382.
7. Levey, S. B., Katz, H. R., Abrams, D. A., Hirschbein, M. J., & Marsh, M. J. The role of cultures in the management of ulcerative keratitis. Cornea, 1997; 16(4): 383–386.
8. Alkatan, H. M., & Al-Essa, R. S. Challenges in the diagnosis of microbial keratitis: A detailed review with update and general guidelines. Saudi Journal of Ophthalmology, 2019; 33(3): 268–276.
9. Ahmadikia, K., Aghaei Gharehbolagh, S., Fallah, B., Naeimi Eshkaleti, M., Malekifar, P., Rahsepar, S., Getso, M. I., Sharma, S., & Mahmoudi, S. 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.
10. Stapleton, F.. The epidemiology of infectious keratitis. Ocular Surface. Published online August 2021, 28, 351–363.
11. Song, X., Xie, L., Tan, X., Wang, Z., Yang, Y., Yuan, Y., Deng, Y., Fu, S., Xu, J., Sun, X., Sheng, X., & Wang, Q. A multi-center, crosssectional study on the burden of infectious keratitis in China. PLOS ONE, 2014; 9(12).

12. Brown, L., Leck, A. K., Gichangi, M., Burton, M. J., & Denning, D. W. The global incidence and diagnosis of fungal keratitis. Lancet. Infectious Diseases, 2021; 21(3): e49–e57.
13. Liesegang, T. J. Herpes simplex virus epidemiology and ocular importance. Cornea, 2001; 20(1): 1–13.
14. Labetoulle, M., Auquier, P., Conrad, H., Crochard, A., Daniloski, M., Bouée, S., El Hasnaoui, A., & Colin, J. Incidence of herpes simplex virus keratitis in France. Ophthalmology, 2005; 112(5): 888–895.
15. Norn, M. S. Dendritic (Herpetic) keratitis. 1. Incidence, seasonal variations, recurrence rate, visual impairment, therapy. Acta Ophthalmologica, 1970;48(1): 91–107.
16. Bharathi, M. J., Ramakrishnan, R., Meenakshi, R., Padmavathy, S., Shivakumar, C., & Srinivasan, M. Microbial keratitis in South India: Influence of risk factors, climate, and geographical variation. Ophthalmic Epidemiology, 2007; 14(2): 61–69.
17. Al-Mujaini, A., Al-Kharusi, N., Thakral, A., & Wali, U. K. Bacterial keratitis: Perspective on epidemiology, clinico-pathogenesis, diagnosis and treatment. Sultan Qaboos University Medical Journal, 2009; 9(2): 184–195.
18. Synder, R. W., & Hyndiuk, R. A. Mechanisms of bacterial invasion of the cornea. In W. Tasman & E. A. Jaeger (Eds.), Duane's foundations of clinical ophthalmology. J. B. Lippincott Publishers, and Co. 1990; 11-44.
19. Reichert, R., & Stern, G. A. Qualitative adherence of bacteria to human corneal epithelial cells. Archives of Ophthalmology, 102(9), 1394–1395.
20. Panjwani, N., Clark, B., Cohen, M., Barza, M., & Baum, J. Differential binding of Ps. aeruginosa and staph. aureus to corneal epithelium in culture. Investigative Ophthalmology and Visual Science, 1990; 31(4): 696–701.
21. Zhang, Z., Cao, K., Liu, J., Wei, Z., Xu, X., & Liang, Q. Pathogens and antibiotic susceptibilities of global bacterial keratitis: A meta-analysis. Antibiotics, 2022; 11(2): 238–238.
22. Manikandan, P., Abdel-Hadi, A., Randhir Babu Singh, Y., Revathi, R., Anita, R., Banawas, S., Bin Dukhyil, A. A., Alshehri, B., Shobana, C. S., Panneer Selvam, K., & Narendran, V. Fungal keratitis: Epidemiology, rapid detection, and antifungal susceptibilities of Fusarium and aspergillus isolates from corneal scrapings. BioMed Research International, 2019; 6395840.
23. Sha, X. Y., Shi, Q., Liu, L., & Zhong, J. X. Update on the management of fungal keratitis. International Ophthalmology, 2021; 41(9): 3249–3256.
24. Moran, S., Mooney, R., & Henriquez, F. L. Diagnostic considerations for non-Acanthamoeba amoebic keratitis and clinical outcomes. Pathogens, 2022; 11(2): 219.
25. Durand, M. L., Barshak, M. B., & Chodosh, J. Infectious keratitis in 2021. JAMA, 326(13), 1319–1320.
26. Roongpoovapatr, V., Prabhasawat, P., Isipradit, S., Shousha, M. A., & Charukamnoetkanok, P. Infectious keratitis: The great enemy. http://www.intechopen.com. https://www.intechopen.com/chapters/69696
27. Labib, B. A., & Chigbu, D. I. Clinical management of herpes simplex virus keratitis. Diagnostics, 2022; 12(10): 2368.
28. Chaloulis, S. K., Mousteris, G., & Tsaousis, K. T. Incidence and risk factors of bilateral herpetic keratitis: 2022 update. Tropical Medicine and Infectious Disease, 2022; 7(6): 92.
29. Hu, S., Sun, Y., Li, J., Xu, P., Xu, M., Zhou, Y., Wang, Y., Wang, S., & Ye, J. Automatic diagnosis of infectious keratitis based on slit lamp images analysis. Journal of Personalized Medicine, 2023; 13(3): 519.
30. Urwin, L., Okurowska, K., Crowther, G., Roy, S., Garg, P., Karunakaran, E., MacNeil, S., Partridge, L. J., Green, L. R., & Monk, P. N. Corneal infection models: Tools to investigate the role of biofilms in bacterial keratitis. Cells, 2020; 9(11): 2450.
31. Bharathi, D. N. R., Da, P., & Bhavani, D. M. Indian Journal Of Applied Research. Ophthalmology, 2023; 13(2).
32. Bartolomei, A. (published 2023). Bacterial keratitis – EyeWiki. eyewiki.aao.org.
33. Lee, S., & Kanai, K. An OD's guide to infectious keratitis. Modern optometry. https://modernod.com/articles/2022-apr/an-ods-guide-to-infectious-keratitis?c4src=article:infinite-scroll
34. Seminara, L. (published May 1, 2020). Algorithm for assessing and treating microbial keratitis. American Academy of Ophthalmology. Retrieved January 1, 2024. https:// www. aao.org/ eyenet/article/algorithm-for-assessing-microbial-keratitis
35. Zemba, M., Dumitrescu, O. M., Dimirache, A. E., Branisteanu, D. C., Balta, F., Burcea, M., Moraru, A. D., & Gradinaru, S. Diagnostic methods for the etiological assessment of infectious corneal pathology (Review) [Review]. Experimental and Therapeutic Medicine, 23(2), 137.
36. Joseph, J., Sharma, S., Murthy, S. I., Krishna, P. V., Garg, P., Nutheti, R., Kenneth, J., & Balasubramanian, D. Microsporidial keratitis in India: 16S rRNA gene-based PCR assay for diagnosis and species identification of

Microsporidia in clinical samples. Investigative Ophthalmology and Visual Science, 2006; 47(10): 4468–4473.
37. Charters, L. Confocal microscopy key to diagnosing infectious keratitis. Ophthalmology-Times.https://www.ophthalmologytimes.com/view/confocal-microscopy-key-diagnosing-infectious-keratitis
38. Kumar, R. L., Cruzat, A., & Hamrah, P. Current state of in vivo confocal microscopy in management of microbial keratitis. Seminars in Ophthalmology, 2010; 25(5–6): 166–170.
39. Gokhale, N. S. Medical management approach to infectious keratitis. Indian Journal of Ophthalmology, 2008; 56(3): 215–220.
40. Daniell, M. Overview: Initial antimicrobial therapy for microbial keratitis. British Journal of Ophthalmology, 2003; 87(9): 1172–1174.
41. Ni, Ni, N., Srinivasan, M., McLeod, S. D., Acharya, N. R., Lietman, T. M., & Rose-Nussbaumer, J. Use of adjunctive topical corticosteroids in bacterial keratitis. Current Opinion in Ophthalmology, 2016; 27(4): 353–357.
42. Hirano K, Tanaka, H., Kato, K., Araki-Sasaki, K., Araki-Sasaki, K., Araki-Sasaki, K. Topical corticosteroids for infectious keratitis before culture-proven diagnosis. Clinical Ophthalmology, February 16, 2021; 15: 609–616.
43. 9.Srinivasan M, Mascarenhas, J., Rajaraman, R., Ravindran, M., Lalitha, P., Glidden, D. V., Glidden, D. V., Ray, K. J., Hong, K. C., Oldenburg, C. E., Lee, S. M., Zegans, M. E., McLeod, S. D., Lietman, T. M., Acharya, N. R., & Steroids for Corneal Ulcers Trial Group. Corticosteroids for bacterial keratitis: The steroids for corneal ulcers trial (SCUT). Archives of Ophthalmology, 2012; 130(2): 143–150.
44. Ponniah, L. R. D. R. Alternative treatment approaches in bacterial keratitis. 2023. https://www.intechopen.com/online-first/87929. IntechOpen.
45. Keratitis. Keratitis – Diagnosis and treatment. (published 2022). http://www.mayoclinic.org. https://www.mayoclinic.org/diseases-conditions/keratitis/diagnosis-treatment/drc-20374114. Mayo Clinic Publications.
46. Miller, D., Cavuoto, K. M., & Alfonso, E. C. Bacterial keratitis. Springer eBooks. Published online. (November 28, 2020):85–104.
47. eOphtha. Seven Tips to Treat A Treatment Resistant Microbial keratitis. http:// www.eophtha.com. Retrieved January 1, 2024. https://www.eophtha.com/posts/seven-tips-to-treat-a-treatment-resistant-microbial-keratitis
48. Clinical management. Microbial keratitis (bacterial, fungal). (published 2022). http:// www.college-optometrists.org. https:// www. college-optometrists.org/clinical-guidance/ clinical-management-guidelines/ microbialkeratitis_bacterial_fungal
49. Kumar A, Pandya S, Kavathia G, Antala S, Madan M, Javdekar T. Microbial Keratitis in Gujarat, Western India: Findings from 200 Cases.; 2011. Accessed January 1, 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3290878/pdf/PAMJ-10-48.pdf
50. Hagan, M., Wright, E., Newman, M., Dolin, P., & Johnson, G. Causes of suppurative keratitis in Ghana. British Journal of Ophthalmology, 1995; 79(11): 1024–1028.
51. Srinivasan, M., Gonzales, C. A., George, C., Cevallos, V., Mascarenhas, J. M., Asokan, B., Wilkins, J., Smolin, G., & Whitcher, J. P. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. British Journal of Ophthalmology, 1997; 81(11): 965–971.
52. Hagan, M., Wright, E., Newman, M., Dolin, P., & Johnson, G. Causes of suppurative keratitis in Ghana. British Journal of Ophthalmology, 1995; 79(11):1024–1028.
53. Panda, A., Sharma, N., Das, G., Kumar, N., & Satpathy, G. Mycotic keratitis in children: Epidemiological and microbiologic evaluation. Cornea, 1997;16(3): 295–299.
54. Gopinathan, U., Garg, P., Fernandes, M., Sharma, S., Athmanathan, S., & Rao, G. N. The epidemiological features and laboratory results of fungal keratitis: A 10-year review at a referral eye care center in south India. Cornea, 2002; 21(6): 555–559.