Updates in different types of keratitis: A simple review article

Abstract:

Keratitis is the medical tenure for inflammation of the cornea. The cornea is the dome-shaped opening in the front of the eye. When looking at a person's eye, one can see the iris and pupil through the typically clear cornea. Making a diagnosis of keratitis is not difficult; however, finding the etiology is not always easy. Many periods the direct microscopy and culture reports are unremarkable, and the patient has to be pickled based on clinical findings. Treatment of infectious keratitis diverges, contingent on the cause of the infection. Bacterial keratitis;For mild bacterial keratitis, sterile eyedrops may be all you need to effectively treat the infection. If the infection is reasonable to severe, you may need to take oral antibiotics to become rid of the infection. Fungal keratitis; Keratitis caused by fungi typically needs antifungal eyedrops and oral antifungal medication. Viral keratitis; If a virus is causing the contagion, antiviral eyedrops and oral antiviral medications may be effective. Other viruses need only helpful care such as artificial tear drops. Acanthamoeba keratitis; Keratitis that's caused by the minute parasite acanthamoeba can be difficult to luxury. Antibiotic eyedrops are used, but some acanthamoeba infections are resistant to medicine. Severe cases of acanthamoeba keratitis may require a cornea transplant.

Key words: corneal ulcer, ,keratitis, keratoplasty, vericonazole, posaconaole.

Introduction:

Keratitis is an inflammation of the cornea, characterized by corneal edema, inflammatory cell penetration, and ciliary bullying. It is associated with both infectious and non-infectious diseases and may be systemic or confined to the ocular surface. Of the above types of keratitis, "microbial keratitis" accounts for the majority and is a source of great concern, primarily in developing countries. However, non-communicable keratitis cannot be underestimated, especially in developed countries. Our first line of defense is powerful enough to dissipate most

of the infection and triggers an attack. However, there are some organisms that can circumvent this line and cause infection. The corneal epithelium is one such barrier. Biological records cannot penetrate the intact epithelium and will not cause keratitis without cell damage. Neisseria meningitides, N. gonorrhea, Corynebacterium diphtheria, Haemophilus influenzae and Listeria spp. Is a toxic organism that can invade even intact epithelium and cause keratitis (1). This article describes the etiology of different types of keratitis and the current and future treatment options available. Keratitis is a medical term for inflammation of the cornea. The cornea is a dome-shaped window in front of you. When you look at the human eye, you can usually see the iris and pupil through the clear cornea. Due to its curved shape, the cornea bends the rays, accounting for about two-thirds of the total optical effect of the eye, and the lens of the eye provides the remaining one-third. Only a wafer-thin tear film lies between the anterior surface of the cornea and our environment. Corneal opacity is the fifth most common cause of blindness in the world, accounting for about 3.2% of all suitcases (2). According to the latest World Health Organization (WHO) report, corneal blindness or moderate / severe visual impairment affects approximately 6 million people worldwide, including 2 million affected by trachoma. It is emphasized that there is (2). In addition, corneal opacity is estimated to be responsible for 1.5 to 2 million cases of unilateral blindness each year, highlighting the constant and uncontrolled burden on human health (3,4).

Etiology

There are many possible causes for keratitis, a condition of the eye that causes the cornea to become inflamed. Different types of infections, dry eye, eyelid abnormalities, injuries, and various underlying medical conditions can all cause keratitis. Some cases of keratitis result from unknown factors. Based on the etiology, keratitis can be classified as follows:

Infectious keratitis

Bacterial keratitis such as Pseudomonas, Staphylococcus, Streptococcus, Moraxella, Nocardia, Atypical Mycobacteria. Protozoan keratitis, including Acanthamoeba. Keratitis caused by the oomycete Pythium keratitis. Morphologically very similar to a fungus. However, unlike fungi,

the cell wall here contains (13 and 16) beta-D-glucan (5,6). Fungal keratitis These include infections caused by Aspergillus, Fusarium, Candida (yeast), Cladosporium, Alternaria, Carbularia, and microsporidia. Viral keratitis This includes infections caused by herpes simplex virus (HSV), shingles virus (HZV), adenovirus, and more. Onchocerca volvulus keratitis (sclerotic keratitis). Non-infectious keratitis.

Local causes include trichiasis, giant papillae, foreign body in the inferior groove. Peripheral ulcerative keratitis.

Rheumatoid arthritis, polyarteritis, polyarteritis nodosa, relapsing polychondritis Collagenal vascular diseases such as chondritis and systemic erythematosus.

Neurotrophic corneal ulcer (herpes zoster trichiasis followed by surgery or tumor damage to the trigeminal nerve(7). Xerophthalmia is also considered a type of keratitis.

Epidemiology

In an epidemiological education in California, the incidence of ulcerative keratitis was found to be 27.6/100000 person-years.(8)Ulcerative keratitis was significantly developed among contact lens wearers.(8)

As per a study showed in South India, middle-aged males were more likely to get corneal ulcers compared to females.(9) Farmers are at great risk on account of their occupation. Fungal corneal ulcers are very common in developing nations. However, HSV is a chief concern in developed nations(10) In an epidemiological study at Rochester, Minnesota, the occurrence of epithelial disease was 15.6/100000 person-years, and for stromal keratitis, it was 2.6/100000 person-years.(11)

Autoimmune disorders related to keratitis accounts for an estimated incidence of 3 per million per year.(12)The prevalence of xerophthalmia was almost 21% in a study in rural Ethiopia and was mostly associated with other features of comprehensive malnutrition(13).For xerophthalmia, the population at risk is basically young children who are malnourished.

Risk factors

Major risk factors for the expansion of keratitis include any break or disruption of the surface layer (epithelium) of the cornea.The use of contact lenses increases the risk of emerging keratitis, especially if hygiene is poor, improper solutions are used to stock and clean the lenses, or if contact lenses are worn improperly or in the presence of persistent irritation.A decrease in the superiority or quantity of tears predisposes the eye to the expansion of keratitis.Disturbances of immune function through diseases such as AIDS or the use of medications such as corticosteroids, both in the form of eyedrops or systemically, or chemotherapy also rise the risk of developing keratitis.

Differential diagnosis

The diagnosis of keratitis is made by an ophthalmologist (a surgeon who specializes in diseases and surgery of the eye) through a history and a physical examination. The past consists of questions recording a past medical and ocular history and the symptoms specific to the current visit. The eye inspection will consist of checking your vision and careful inspection of the corneas using a slit lamp, which is a microscope with brilliant illumination and magnification to view the entire ocular surface, with the cornea in detail. A special dye containing fluorescein in the form of eyedrops may be positioned in the eyes to assist with the examination.

In cases in which infection is supposed, a culture may be taken from the surface of the eye for specific identification of the bacteria, virus, fungus, or parasite producing the keratitis. Blood tests may also be done in convinced patients with suspected underlying disease.

Making a diagnosis of keratitis is not difficult; however, discovery the etiology is not always easy. Many times the direct microscopy and culture reports are ordinary, and the patient has to be treated based on clinical results. In early-stage, *Acanthamoeba keratitis* and *HSV* stromal keratitis are often blurry; however, late stages of *Acanthamoeba* keratitis may simulate fungal keratitis. Atopic keratoconjunctivitis, Bacterial endophthalmitis, Band keratopathy, Blepharitis, Corneal ulcer, Entropion, Epidemic keratoconjunctivitis, Fungal keratitis, Herpes simplex virus keratitis, Herpes Zoster, Interstitial keratitis, Neurotrophic keratitis, Nasolacrimal duct obstruction, Ocular rosacea, Pseudophakic bullous keratopathy, Scleritis and Viral conjunctivitis

Different types of keratitis

Bacterial keratitis

Keratitis by gram-positive organisms: Staphylococcal keratitis can be whichever because of direct invasion of the organism or since of staphylococcal antigen. Staphylococcal antigen-induced keratitis is usually touching the peripheral cornea and hence the name 'marginal keratitis.' Marginal keratitis is invariably related with staphylococcal blepharitis. The corneal lesions usually start at 10, 2, 4, and 8' o'clock positions, where the lid boundary is in contact with the limbus. There is always a clear area amid the limbus and the ulcerative lesion, unlike HSV marginal keratitis. The most common source of Streptococcal keratitis is a blocked nasolacrimal duct. So, lacrimal duct patency or regurgitation on pressure done the lacrimal sac (ROPLAS) should be evaluated in corneal ulcer suitcases. In early-stages of Gram-positive infection, the cuff of cellular infiltration is renowned around the corneal focus of infection and is not diffuse, unlike Pseudomonal keratitis.

Pseudomonas keratitis: In early-stage, diffuse and condensed corneal cellularity is noted much yonder the focus of infection. Pseudomonas is a gram-negative bacteria with principally greenish-yellow corneal infiltrate and extensive collagenolysis. The symptoms are more acute and rapidly progressive. Corneal melt might progress to corneal puncture or endophthalmitis if not taken care of in the early phases. Nocardia keratitis: Nocardia is a feebly acid-fast bacteria (Modified Kinyoun stain)(14)There may be a past of either trauma or intraocular surgery with corneal infiltrates usually starting adjacent to the surgical incision site. The infiltrates are granular, insincere to mid-stromal with the wreath-like design often in the mid-peripheral cornea(15)

Atypical mycobacteria: The Atypical mycobacteria are acid-fast bacilli producing keratitis with a protracted course. There may be a antiquity of trauma with corneal foreign bodies or a history of corneal surgery (LASIK).(16)The onset of keratitis in trauma cases can differ from days to weeks; however, the post-LASIK cases usually have an usual time of presentation of 3.4 weeks.(17) The disease has a waxing and waning sequence.(18) The corneal infiltrate has a

typical cracked windshield arrival with radiating lines in the middle one-third of the corneal stroma.(19).

Pathogenesis

The pathogenesis of ocular contagious disease is determined by the intrinsic virulence of the microorganism, the fauna of the host response, and the anatomical features of the site of the infection(20).The avascular clear anatomical erection of the cornea with its specialized microenvironment predisposes to potential modification and destruction by invading microorganisms, virulence factors, and host response influences. The intrinsic virulence of organism relates to its capability to invade tissue, resist host defense mechanisms, and produce tissue damage(21). Diffusion of exogenous bacteria into the corneal epithelium typically requires a imperfection in the surface of the squamous epithelial layer. By virtue of specialized enzymes and virulence features, a few bacteria, such as *Neisseria gonorrhea*, *N. meningitidis*, *Corynebacterium diphtheriae*, *Shigella* and *Listeria* may directly penetrate corneal epithelium to initiate stromal suppuration.

Bacteria colonize host cells by engaging adhesins at their external with receptors on the host cell surface. Specific receptors are often required by many adhesins to accomplish binding. Besides adherence, microbial adhesins also contribute to ensuing interactions. Virulence factors may initiate microbial invasion or secondary effector molecules may contribution the infective process. Upregulation or downregulation of host defense mechanisms may be complicated. Adhesins may also be toxins(22). Consequently, receptor recognition is only the first step in the pathogenesis of infection absorbed by microbial adhesin molecules(23).

Many bacteria display several adhesins on fimbriae (pili) and nonfimbriae constructions. Such adhesive proteins may recognize carbohydrates on host cells, or otherwise protein–protein interactions can also occur.Certain bacteria exhibit discrepancy adherence to corneal epithelium. The observance of *Staphylococcus aureus*, *S. pneumoniae*, and *Pseudomonas*

aeruginosa to ulcerated corneal epithelium is meaningfully higher than other bacteria and may account in part for their recurrent isolation(24).

Treatment

In general, because of the probable rapid destruction of corneal tissue that may accompany bacterial keratitis, if there is a clinical suspicion redolent of a bacterial pathogen, the patient should be treated properly for bacterial keratitis until a definitive diagnosis is established. The objective of therapy in bacterial keratitis is to eradicate the infective organism in a rapid fashion, reduce the inflammatory response, avert structural damage to the cornea, and promote healing of the epithelial shallow(25).

With suspected infectious keratitis, the clinician has the option grounded on the clinical impression and severity of the keratitis of initiating specific focused or broad-spectrum antimicrobial therapy, or complying treatment pending the results of laboratory investigation, or monitoring clinical signs(26,27). The initial therapy selection is based on the quantifiable features, antecedent risk factors, and familiarity with the most likely accountable corneal pathogen(s) and their respective antimicrobial vulnerability patterns(28).

Fungal keratitis

Microsporidial keratitis: Microsporodial spores stain fine with Grams, silver, and 10% potassium hydroxide (KOH) with 0.1% calcofluor white. The keratoconjunctivitis different has a self-limiting course. (29) Topical lubricants can be additional to palliate the foreign body sensation. Epithelial debridement is also a valid option for the initial resolution of corneal lesions.(30) endazole (400 mg twice daily for 3-4 weeks) and up-to-date fumagillin (topical, 70 mcg/ml, 2 drops every 2 h for 4 days and then 2 drops 4-times daily)(31,32) Therapeutic penetrating keratoplasty is the conduct of choice.(33)

Filamentous fungal keratitis: Routine microscopy with 10% KOH alone or 10% KOH with 0.1% calcofluor white reveal hyaline/ pigmented, septate (Aspergillus, *Fusarium*)/ aseptate

(*Mucor, Rhizopus*) fungal filaments. Preferred culture media for fungal growing are Saboraud's and potato dextrose agar. Current natamycin (5%) is the drug of choice for filamentous fungal keratitis.(34) Current voriconazole (1%) is added as an adjunct to natamycin in *Aspergillus* keratitis, not responding to natamycin alone. Voriconazole is not agreed as a primary drug for fungal keratitis.(34) Systemic anti-fungal is extra for large and deep corneal ulcers.

Pathogenesis

The occurrence of a fungal infection implies an modification in one or more of the cornea's anti-infectious defense schemes (epithelial barrier, tear film, blinking). The inflammatory response to the infection depends on fungal imitation, mycotoxins, secreted proteolytic enzymes and fungal antigens (80). Fungi may infiltrate the stromal lamellae, attack Descemet's membrane, spread into the anterior chamber and aggravate endophthalmitis.

Treatment

Topical treatments

Treatment of fungal keratitis is usually initiated by the current administration of antifungal drugs. Natamycin is an effective drug to treat corneal infection produced by fungal species, it is the first effective line of the treatment; but, due to its poor penetration into the corneal stroma(42) and several reports of handling failure by this drug, other antifungal medications are suggested to treat fungal keratitis. Current amphotericin B 0.3% to 0.5% and voriconazole 1% are recommended as alternatives. One of the compensations of topical administration of voriconazole is its excessive ocular penetration.(43)

Oral voriconazole

Although topical voriconazole is substandard to topical natamycin, oral administration of voriconazole may be an effective treatment for particular cases of fungal keratitis. Thiel et al(43) found that the concentration of voriconazole in human aqueous is highly adjustable during the topical administration of this drug and it may be lower the minimum inhibitory

concentration (MIC) required to indulgence some fungal infections. Oral voriconazole, however, results in intraocular drug concentration well above the MIC compulsory for most fungal corneal pathogens. Jhanji et al(44) described a case of fungal keratitis with Fusarium at the site of cataract surgery wound. The corneal ulcer was not receptive to topical natamycin 5%, amphotericin B 0.15%, and intracameral amphotericin B. After altering the therapeutic regimen to topical and oral voriconazole, significant development was noted.

Intracameral amphotericin B

Intracameral amphotericin B can be measured in the management of deep fungal corneal ulcers or impervious cases. Kuriakose et al(45) reported complete resolution of three of four cases of deep fungal keratitis with 3 to 13 intracameral inoculations of amphotericin B as adjuvant therapy. Successful managing of severe fungal keratitis by intracameral amphotericin B has also been reported in an earlier cases sequences of three patients who did not respond to topical natamycin 5%, amphotericin B 0.15%, and oral itraconazole.(46)

Intrastromal voriconazole

Intrastromal injection of voriconazole has also been stated to be effective in cases of recalcitrant and deep fungal corneal ulcers.(47-48) However, the indication is still lacking regarding the use of this technique and further studies are desirable to determine its benefit in the administration of fungal keratitis.

Corneal collagen crosslinking (CXL)

Corneal collagen crosslinking (CXL) has been used to halt the evolution of keratoconus by strengthening the chemical ties between collagen bundles in corneal stroma.(49) Over the last few years, CXL has gained popularity amongst researchers to treat infectious keratitis. The term photoactivated chromophore for contagious keratitis (PACK)-CXL was coined in 2013 to differentiate this method from CXL used to treat corneal ectasia.(50)CXL may have a direct antifungal effect. Moreover, it might slow down the melting of the cornea, suspending the need for emergency keratoplasty.(51-52)

Viral keratitis

Adenoviral keratitis: Adenoviral keratitis regularly has related conjunctivitis, so the meticulous terminology could be Epidemic adenoviral keratoconjunctivitis (Human adenovirus kinds 8,19,37 and 54). Presentation is commonly unilateral to begin with; however, it will become bilateral later. A predominantly follicular response is noted. (53) It can also additionally or might not be associated with conjunctival hemorrhages. (54) At instances the infection may be unembellished enough, ensuing withinside the formation of pseudomembranes. Clinically, corneal epitheliopathy advances manifesting as punctate corneal erosions, which over per week develops into several, punctate to nummular anterior stromal infiltrates.(54,55)

Preauricular lymphadenopathy is an huge locating in adenoviral keratoconjunctivitis. In the pharyngoconjunctival irregular (human adenovirus kinds 3,four and 7), the affected person can also additionally have systemic effects like pharyngitis and fever. The corneal effects withinside the early-degree (subepithelial to anterior stromal infiltrate) are taken into consideration to be because of lively viral replication; but, withinside the persistent degree, the infiltrates are the final results of an immunological response.(54) In the persistent degree, symblepharon also can be visible(56,57) The sufferers at this degree frequently grumble of photophobia, glare, and haloes.

Herpes simplex keratitis: HSV keratitis can present day as epithelial ailment, stromal keratitis, and endotheliitis.(58) HSV epithelial ailment manifestation can also additionally diverge from a couple of punctate erosions to dendritic ulcers and geographical ulcers. The untimely vesicular degree is frequently missed, due to not on time overall performance to the ophthalmic clinic. The ruptured vesicles coalesce collectively to shape dendrites with a terminal bulb.(59) Unfortunate and indiscriminate use of topical steroids can also additionally bring about geographical ulcer establishment. In epithelial ailment, the virus is actively worried withinside the causality of the ulcer. (60) HSV epithelial ailment is commonly unilateral, however the bilateral ailment is greater regularly visible in immunodeficient and sufferers with a records of atopy. (61) HSV stromal keratitis can whichever be secondary to epithelial ailment because of adjoining spread, or immune-mediated. If stromal keratitis develops secondary to epithelial

ailment, an overlying epithelial disorder is existing. However, the number one stromal involvement manifests as localized stromal edema without or with symptoms and symptoms of previous comparable episodes. On resolution, those effect in scar formation. These scars with vascularization are the telltale symptoms and symptoms and also are called `footprint scars' with or disadvantaged of superficial or deep vascularization. HSV endotheliitis demonstrates as localized or diffuse stromal edema with number one keratic precipitates.

Pathogenesis

If it is the stratagem of the virus to infect the majority of the population, then it is an extraordinarily successful pathogen and one that is essentially benign. Participation of the brain or eye is relatively rare; severe belongings of encephalitis or keratitis must surely be seen as aberrations as they serve the virus poorly. They occur, however, as a significance of a key property namely the virus' ability to establish dormant infection not only in neurones supplying the lips, but also in a number of other sites inside the nervous system that are reached during primary contagion(62).

Management

A more rational approach to treatment is facilitated by a comprehensive classification of various symptoms of anterior ocular lesions by HSV (63, 64). The HEDS publication clearly shows that properly used steroids play an important role in the management of interstitial keratitis (65). The evaluation was performed using a 1%, then 0.125% prednisolone phosphate reduction regimen. This shows that weak steroids are effective with minimal handling errors. The HEDS publication also reports the value of oral acyclovir for treatment and prevention (66, 67, 68), which determines the sectors of increasing use today, including the treatment of children. (69).

Protozoal keratitis

Acanthamoeba keratitis: Contact with soil or contaminated water is very common in Acanthamoeba keratitis in developing countries. However, in developed countries, wearing contact lenses has been found to be strongly associated with Acanthamoeba keratitis. The range of medical features can range from superficial punctate keratitis, pseudodendrites to early stage perineuritis. (70) Ring infiltration is very common in Acanthamoeba keratitis. However, this does not exist in all cases. (70) As the disease progresses, the infiltrates spread anteriorly from the middle to all layers, making them indistinguishable from bacterial and fungal keratitis. (71)

Pathogenesis

The devastating nature of Acanthamoeba keratitis and the difficulties associated with its diagnosis and successful treatment suggest the need for a complete understanding of its pathogenesis and pathophysiology in order to find surrogate therapeutic interventions. Another major concern in the course of treatment is the ability of Acanthamoeba to transform into a resting cystic morphology that can withstand any stage of antibacterial chemotherapy. The ability of Acanthamoeba to induce infection requires the ability to resist specific adhesins, toxin formation, and immune / environmental factors and chemotherapeutic mediators that may allow this pathogen to induce infection. .. For convenience, the information is divided into factors that directly and indirectly contribute to the pathogenicity of Acanthamoeba (72). process

Treatment of Acanthamoeba keratitis has progressed since the first medical treatment was reported in 1985 (73-79). Early diagnosis and aggressive medical treatment have improved the management of this difficult infection. Other factors that may promote effective medical treatment and improved outcomes include early epithelial debridement (to eliminate most organisms) and inclusion in medically resistant cases. Corneal transplant is included. To date, no chemotherapeutic agent has been identified as the single effective treatment for AK, regardless of the isolate or genotype that causes AK. This is because there are many factors, including the different pathogenic personalities of different isolates, making it nearly impossible to establish a link between in vitro and in vivo potency. However, it is not easy to determine the most

effective treatment regimen for several reasons: B. A relatively small number of reported cases of AK, adjustable pathogenicity of different strains, and endemic variable flora of disease processes (72).

Conclusion

IK places an ongoing burden on human health in both established and developing countries. Incidence of IK is likely to be underestimated in recent studies, so a well-designed prospective study using all types of microorganisms (bacteria, fungi, protozoa, viruses, etc.) IK outbreaks And necessary to truly judge the impact. Considering the key risk factors for IC in different regions, especially after CL wear, trauma, OSD, and eye surgery, promotes more effective public health involvement in correcting and reducing IC risk. .. Elevated AMR in eye infections in many countries, including the United States, China, and India over the past period, has led to careful use of antibiotics, tighter control of over-the-counter antibiotics, and new antibiotics and treatment strategies. Emphasizes the need for development. Better guidance on the proper use of future antimicrobial therapies by improving the diagnostic rate of microbiological studies from IK using new know-how such as next-generation sequencing and platforms supported by artificial intelligence. You can provide and ultimately reduce the risk of lowering AMR.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References

1-Tjia KF, van Putten JP, Pels E, Zanen HC. The interaction between Neisseria gonorrhoeae and the human cornea in organ culture. An electron microscopic study. Graefes Arch Clin Exp Ophthalmol. 1988;226(4):341-5. [PubMed]

2-Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e1221–e34.

3-Whitcher JP, Srinivasan M. Corneal ulceration in the developing world-a silent epidemic. Br J Ophthalmol. 1997;81:622–3.

4-Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. Bull World Health Organ. 2001;79:214–21.

5- Mendoza L, Hernandez F, Ajello L. Life cycle of the human and animal oomycete pathogen Pythium insidiosum. J Clin Microbiol. 1993 Nov;31(11):2967-73. [PMC free article] [PubMed]

6- Tondolo JSM, Ledur PC, Loreto ÉS, Verdi CM, Bitencourt PER, de Jesus FPK, Rocha JP, Alves SH, Sassaki GL, Santurio JM. Extraction, characterization and biological activity of a (1,3)(1,6)-β-d-glucan from the pathogenic oomycete Pythium insidiosum. Carbohydr Polym. 2017 Feb 10;157:719-727. [PubMed]

7- Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. Curr Opin Ophthalmol. 2000 Dec;11(6):468-71. [PubMed]

8- Jeng BH, Gritz DC, Kumar AB, Holsclaw DS, Porco TC, Smith SD, Whitcher JP, Margolis TP, Wong IG. Epidemiology of ulcerative keratitis in Northern California. Arch Ophthalmol. 2010 Aug;128(8):1022-8. [PubMed]

9- Srinivasan M, Gonzales CA, George C, Cevallos V, Mascarenhas JM, Asokan B, Wilkins J, Smolin G, Whitcher JP. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. Br J Ophthalmol. 1997 Nov;81(11):965-71. [PMC free article] [PubMed]

10- Hill GM, Ku ES, Dwarakanathan S. Herpes simplex keratitis. Dis Mon. 2014 Jun;60(6):239-46. [PubMed]

11- Liesegang TJ. Epidemiology of ocular herpes simplex. Natural history in Rochester, Minn, 1950 through 1982. Arch Ophthalmol. 1989 Aug;107(8):1160-5. [PubMed]

12- Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007 Nov;33(4):835-54, vii. [PMC free article] [PubMed]

13- Moore DB, Shirefaw W, Tomkins-Netzer O, Eshete Z, Netzer-Tomkins H, Ben-Zion I. Prevalence of xerophthalmia among malnourished children in rural Ethiopia. Int Ophthalmol. 2013 Oct;33(5):455-9. [PubMed]

14- DeCroos FC, Garg P, Reddy AK, Sharma A, Krishnaiah S, Mungale M, Mruthyunjaya P., Hyderabad Endophthalmitis Research Group. Optimizing diagnosis and management of nocardia keratitis, scleritis, and endophthalmitis: 11-year microbial and clinical overview. Ophthalmology. 2011 Jun;118(6):1193-200. [PubMed]

15- Sridhar MS, Gopinathan U, Garg P, Sharma S, Rao GN. Ocular nocardia infections with special emphasis on the cornea. Surv Ophthalmol. 2001 Mar-Apr;45(5):361-78. [PubMed]

16- Ko J, Kim SK, Yong DE, Kim TI, Kim EK. Delayed onset Mycobacterium intracellulare keratitis after laser in situ keratomileusis: A case report and literature review. Medicine (Baltimore). 2017 Dec;96(51):e9356. [PMC free article] [PubMed]

17- John T, Velotta E. Nontuberculous (atypical) mycobacterial keratitis after LASIK: current status and clinical implications. Cornea. 2005 Apr;24(3):245-55. [PubMed]

18- Moorthy RS, Valluri S, Rao NA. Nontuberculous mycobacterial ocular and adnexal infections. Surv Ophthalmol. 2012 May-Jun;57(3):202-35. [PubMed]

19- Kheir WJ, Sheheitli H, Abdul Fattah M, Hamam RN. Nontuberculous Mycobacterial Ocular Infections: A Systematic Review of the Literature. Biomed Res Int. 2015;2015:164989. [PMC free article] [PubMed]

20- O'Brien TP, Hazlett LD . Pathogenesis of ocular infection. In: Pepose JS, Holland GN, Wilhelmus KR (eds). *Ocular Infection and Immunity*, Chap 15. Mosby: St Louis, MO, 1995.

21- Jones DB . Pathogenesis of bacterial and fungal keratitis. *Trans Ophthalmol Soc UK* 1978; 98: 367.

22- Baker NR . *Pseudomonas aeruginosa* exoenzyme S is an adhesin. *Infect Immun* 1991; 59(9): 2859.

23- Hoepelman AIM, Tuomanen EL . Consequences of microbial attachment: directing host cell functions with adhesins. *Infect Immun* 1992; 60: 1729.

24- Reichert R, Stern GA . Quantitative adherence of bacteria to human corneal epithelial cells. *Arch Ophthalmol* 1984; 102: 1394.

25- Jones DB . Initial therapy of suspected microbial corneal ulcers II. Specific antibiotic therapy based on corneal smears. *Surv Ophthalmol* 1979; 24: 97.

26- Jones DB . Polymicrobial Keratitis. *Trans Am Ophthalmol Soc* 1981; 79: 153.

27- Baum JL, Jones DB : Initial therapy of suspected microbial corneal ulcers. *Surv Ophthalmol* 1979; 24: 97.

28- Wilhelmus KR . Bacterial corneal ulcer. *Int Ophthalmol Clin* 1984; 24: 1.

29- Sanjay S. Clinical trial of 0.02% polyhexamethylene biguanide versus placebo in the treatment of microsporidial keratoconjunctivitis. Am J Ophthalmol. 2011 Jan;151(1):183; author reply 183. [PubMed]

30- Das S, Wallang BS, Sharma S, Bhadange YV, Balne PK, Sahu SK. The efficacy of corneal debridement in the treatment of microsporidial keratoconjunctivitis: a prospective randomized clinical trial. Am J Ophthalmol. 2014 Jun;157(6):1151-5. [PubMed]

31- Font RL, Samaha AN, Keener MJ, Chevez-Barrios P, Goosey JD. Corneal microsporidiosis. Report of case, including electron microscopic observations. Ophthalmology. 2000 Sep;107(9):1769-75. [PubMed]

32- Didier ES, Maddry JA, Brindley PJ, Stovall ME, Didier PJ. Therapeutic strategies for human microsporidia infections. Expert Rev Anti Infect Ther. 2005 Jun;3(3):419-34. [PubMed]

33- Vemuganti GK, Garg P, Sharma S, Joseph J, Gopinathan U, Singh S. Is microsporidial keratitis an emerging cause of stromal keratitis? A case series study. BMC Ophthalmol. 2005 Aug 17;5:19. [PMC free article] [PubMed]

34- Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, Raghavan A, Oldenburg CE, Ray KJ, Zegans ME, McLeod SD, Porco TC, Acharya NR, Lietman TM., Mycotic Ulcer Treatment Trial Group. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol. 2013 Apr;131(4):422-9. [PMC free article] [PubMed]

35-Srinivasan M. Fungal keratitis. Curr Opin Ophthalmol. 2004;15(4):321-327.

36-Ghosh AK, Gupta A, Rudramurthy SM, Paul S, Hallur VK, Chakrabarti A. Fungal keratitis in North India: spectrum of agents, risk factors and treatment. Mycopathologia. 2016;181(11-12):843-850.

37-Shah A, Sachdev A, Coggon D, Hossain P. Geographic variations in microbial keratitis: an analysis of the peer-reviewed literature. Br J Ophthalmol. 2011;95(6):762-767.

38-Kredics L, Narendran V, Shobana CS, Vágvölgyi C, Manikandan P. Filamentous fungal infections of the cornea: a global overview of epidemiology and drug sensitivity. Mycoses. 2015;58(4): 243-260

39-Thomas P, Kaliamurthy J. Mycotic keratitis: epidemiology, diagnosis and management. Clin Microbiol Infect. 2013;19(3):210-220.

40-. Ng JK, Fraunfelder FW, Winthrop KL. Review and update on the epidemiology, clinical presentation, diagnosis, and treatment of fungal keratitis. Curr Fungal Infect Rep. 2013;7(4):293-300.

41-Nielsen SE, Nielsen E, Julian HO, et al. Incidence and clinical characteristics of fungal keratitis in a Danish population from 2000 to 2013. Acta Ophthalmol. 2015;93(1):54-58. 43. Bharathi MJ, Ramakrishnan R, Vasu S, Meen

42-O'day DM, Head WS, Robinson RD, Clanton JA. Corneal penetration of topical amphotericin B and natamycin. Curr Eye Res. 1986;5(11):877-882.

43-Thiel MA, Zinkernagel AS, Burhenne J, Kaufmann C, Haefeli WE. Voriconazole concentration in human aqueous humor and plasma during topical or combined topical and systemic administration for fungal keratitis. Antimicrob Agents Chemother. 2007;51(1):239-244.

44-Jhanji V, Sharma N, Mannan R, Titiyal JS, Vajpayee RB. Management of tunnel fungal infection with voriconazole. J Cataract Refract Surg. 2007;33(5):915-917.

45-Kuriakose T, Kothari M, Paul P, Jacob P, Thomas R. Intracameral amphotericin B injection in the management of deep keratomycosis. Cornea. 2002;21(7):653-656.

46-Kaushik S, Ram J, Brar GS, Jain AK, Chakraborti A, Gupta A. Intracameral amphotericin B: initial experience in severe keratomycosis. Cornea. 2001;20(7):715-719.

47-Sharma N, Agarwal P, Sinha R, Titiyal JS, Velpandian T, Vajpayee RB. Evaluation of intrastromal voriconazole injection in recalcitrant deep fungal keratitis: case series. Br J Ophthalmol. 2011;95(12):1735-1737

48-Kalaiselvi G, Narayana S, Krishnan T, Sengupta S. Intrastromal voriconazole for deep recalcitrant fungal keratitis: a case series. Br J Ophthalmol. 2015;99(2):195-198.

49-Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg. 2011;37(1):149-160.

50-Said DG, Elalfy MS, Gatzioufas Z, et al. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. Ophthalmology. 2014;121(7):1377-1382.

51-Li Z, Jhanji V, Tao X, Yu H, Chen W, Mu G. Riboflavin/ultravoilet light-mediated crosslinking for fungal keratitis. Br J Ophthalmol. 2013;97(5):669-671.

52-. Sauer A, Letscher-Bru V, Speeg-Schatz C, et al. In vitro efficacy of antifungal treatment using riboflavin/UV-A (365 nm) combination and amphotericin B. Invest Ophthalmol Vis Sci. 2010;51(8):3950-3953.

53-Omari AA, Mian SI. Adenoviral keratitis: a review of the epidemiology, pathophysiology, clinical features, diagnosis, and management. Curr Opin Ophthalmol. 2018 Jul;29(4):365-372. [PubMed]

54-Mader TH, Stulting RD. Viral keratitis. Infect Dis Clin North Am. 1992 Dec;6(4):831-49. [PubMed]

55-Bialasiewicz A. Adenoviral keratoconjunctivitis. Sultan Qaboos Univ Med J. 2007 Apr;7(1):15-23. [PMC free article] [PubMed]

56-Akkaya S, Ozkurt YB. Persistent Symblepharon in an Infant Following Epidemic Keratoconjunctivitis. Med Hypothesis Discov Innov Ophthalmol. 2016 Fall;5(3):74-77. [PMC free article] [PubMed]

57- Hammer LH, Perry HD, Donnenfeld ED, Rahn EK. Symblepharon formation in epidemic keratoconjunctivitis. Cornea. 1990 Oct;9(4):338-40. [PubMed]

58-Shoji J, Sakimoto T, Inada N, Kamei Y, Matsubara M, Takamura E, Sawa M. A diagnostic method for herpes simplex keratitis by simultaneous measurement of viral DNA and virus-specific secretory IgA in tears: an evaluation. Jpn J Ophthalmol. 2016 Jul;60(4):294-301. [PubMed]

59-Chang EJ, Dreyer EB. Herpesvirus infections of the anterior segment. Int Ophthalmol Clin. 1996 Summer;36(3):17-28. [PubMed]

60-Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015 Jan 09;1:CD002898. [PMC free article] [PubMed]

61-Souza PM, Holland EJ, Huang AJ. Bilateral herpetic keratoconjunctivitis. Ophthalmology. 2003 Mar;110(3):493-6. [PubMed]

62-Labetoulle M, Kucera P, Ugolini G, Lafay F, Frau E, Offret H *et al*. Neuronal propagation of HSV 1 from the oral mucosa to the eye. *Invest Ophthalmol Vis Sci* 2000; **41**: 2600–2606.

63-Liesegang TJ . Classification of herpes simplex virus keratitis and anterior uveitis. *Cornea* 1999; **18**: 127–143.

64-Holland J, Schwartz GS . Classification of herpes simplex virus keratitis. *Cornea* 1999; **18**: 511–531.

65-Wilhelmus KR, Gee L, Hauk WW *et al*. Herpetic eye disease study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology* 1994; **101**: 1883–1895.

66-Herpetic Eye Disease Study Group. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994; **101**: 1871–1882.

67-Barron BA, Gee L, Hauck WW, Kurmij N, Dawson CR, Jones DB *et al*. Herpetic eye disease study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994; **101**: 1871–1882.

68-Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med* 1998; **339**: 300–306.

69-Shwartz GS, Holland EJ . Oral acyclovir for the management of herpes simplex virus keratitis in children. *Ophthalmology* 2000; **107**: 278–282.

70-Maycock NJ, Jayaswal R. Update on Acanthamoeba Keratitis: Diagnosis, Treatment, and Outcomes. Cornea. 2016 May;35(5):713-20. [PubMed]

71-Lorenzo-Morales J, Khan NA, Walochnik J. An update on Acanthamoeba keratitis: diagnosis, pathogenesis and treatment. Parasite. 2015;22:10. [PMC free article] [PubMed]

72-lorenzo-Morales,J'' . Khan, N. A., and Walochnik, J., (2015): An ubdate on acanthamoeba keratitis: diagnosis, pathogenesis and treatmentParasite. 2015; 22: 10.

Published online 2015 Feb 18. doi: 10.1051/parasite/2015010

73- Khan NA. 2009. *Acanthamoeba – Biology and Pathogenesis*. Caister Academic Press: Norfolk, Great Britain, 290 p. [Google Scholar]

74- Lorenzo-Morales J, Martín-Navarro CM, López-Arencibia A, Arnalich-Montiel F, Piñero JE, Valladares B. 2013. *Acanthamoeba* keratitis: an emerging disease gathering importance worldwide? *Trends in Parasitology*, 29(4), 181–187. [PubMed] [Google Scholar]

75- Roberts CW, Henriquez FL. 2010. Drug target identification, validation, characterisation and exploitation for treatment of *Acanthamoeba* (species) infections. *Experimental Parasitology*, 126, 91–96. [PubMed] [Google Scholar]

76-Trzyna WC, Legras XD, Cordingley JS. 2008. A type-1 metacaspase from *Acanthamoeba castellanii*. *Microbiology Research*, 163, 414–423. [PubMed] [Google Scholar]

77-Turner NA, Russell AD, Furr JR, Lloyd D. 2004. Resistance, biguanide sorption and biguanide-induced pentose leakage during encystment of *Acanthamoeba castellanii*. *Journal of Applied Microbiology*, 96(6), 1287–1295. [PubMed] [Google Scholar]

78-Visvesvara GS, Moura H, Schuster FL. 2007. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. *FEMS Immunology and Medical Microbiology*, 50(1), 1–26. [PubMed] [Google Scholar]

79- Visvesvara GS. 2010. Amebic meningoencephalitides and keratitis: challenges in diagnosis and treatment. *Current Opinion in Infectious Diseases*, 23(6), 590–594. [PubMed] [Google Scholar]

80-.Bourcier.T.,.SauerA.,.DoryJ.A., .Sabou.M.D.,(2017): Fungal keratitisJournal Français d'Ophtalmologie Volume 40, Issue 9, November 2017, Pages e307-e313