Infectious Keratitis

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7.1 Introduction

Corneal infection or microbial keratitis is a common cause of ocular morbidity and visual loss. Microbial keratitis may be caused by viruses, bacteria, fungi, and parasites. The most common causative agent of corneal infection is viral, followed by bacteria, fungi, and parasites.

7.2 Pathogenesis of Corneal Infections

The viruses and parasites usually do not require breach of the corneal surface to establish an infection. On the other hand, bacteria and fungi require a break in the integrity of the epithelium barrier to gain entry and adhere to establish an infection. A few bacteria, however, such as *Neisseria, Corynebacterium, Haemophilus*, *and Listeria*, can invade the intact cornea and establish infections. The ocular surface is equipped with both specific and nonspecific defense mechanisms that prevent offending agents. Several systemic and local factors may predispose to corneal infections.

The main barrier to microorganisms that invade the cornea is the epithelial surface. The epithelium of the cornea serves as a physical and functional barrier to infections preventing entry of microbes and interfering with their growth through productions of microbial and antimicrobial agents. If the epithelium is breached and an organism gained access to the underlying tissue, the organism would encounter defense mechanisms of innate immunity which are designed to react rapidly against microbes. The ocular surface tear film contains substances that are effective in killing the organisms including lysozyme, lactoferrin, secretory immunoglobulin IgA, and other defense mechanisms. Neutrophils and macrophages ingest microbes and destroy them by producing substances that are microbiocidal. In addition, macrophages produce cytokines that recruit, activate, and upregulate immunocytes. On the other hand, natural killer cells kill virus-infected cells and produce cytokines including interferon gamma. Many forms of proteins are involved in the host defense including proteins of the complement system, the complement agent by microbes or by antigen antibody complexes. The complement system is aimed at

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killing microbes and lead to opsonization for the phagocytosis by macrophages and neutrophils. In addition to combating infections, innate immune responses stimulate subsequent adaptive immunity providing symptoms that are essential for initiating responses of antigen-specific T and B lymphocytes. Innate immunity works in concert with adaptive immune responses leading to the control of infection.

Antibodies bind to extracellular microbes blocking their ability to infect the host cells. The phagocytes ingest organisms and kill them, while helper T lymphocytes enhance the microbial killing of the phagocytes. Cytotoxic T lymphocytes, on the other hand, destroy cells that have been infected by microbes that are inaccessible to antibodies. The main goal of the adaptive response is to activate the defense mechanisms against microorganisms that invade the cornea.

Microorganisms that invade the epithelial cells of the cornea may be captured and processed by macrophages and dendritic cells that are residents in the epithelial surface and migrate from the limbus. Protein antigens of these microorganisms are processed by the antigen-presenting cells to generate peptides that are discreet on the surface of the antigen-presenting cells and then bind to the major histocompatibility complex molecules. Naive T cells recognize MHC complexes, and the T lymphocytes start to respond. Protein antigens are recognized by T lymphocytes, while polysaccharides and other nonprotein antigens are captured in the lymphoid organs.

The epithelial surface represents a barrier to infections and innate immunity provides the first line of defense against the offending organisms. There are multiple strategies of innate recognition of infection. The most common of which is recognition of molecules, highly characteristic of large groups of microbes or viruses. In the corneal epithelium, there are innate immune receptors known as Toll-like receptors (TLRs). Toll-like receptors recognize bacterial cell-wall components or cell membrane receptors. Their main function is to induce production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL-1) 1, whereas the intracellular TLRs cause production of type 1 interferon. Both TNF and IL-1 are the main inflammation-inducing cytokines. This helps in the fighting against infections but at the same time may lead to damage of the tissue leading to corneal scarring and, therefore, decrease in vision.

Toll-like receptors recognize pathogens on the epithelial surfaces. TLRs recognize the variety of molecules including bacterial cell-wall components and pathogen-derived nucleic acids. Nucleotide-binding oligomerization domain-containing protein 1 (NOD1) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) recognize proteoglycan substructures and promote innate immune responses as well. NOD1 and NOD2 are innate immune components found in the cytoplasm of cells. They recognize small fragments of bacterial cell-wall peptidoglycans which are transported across the host cell. NOD1 and NOD2 are synergistic with TLR signaling and bind to certain ligand to induce inflammatory cytokines.

Table 7.1 shows the factors that may predispose to ocular infections [1].

7.3 Bacterial Keratitis

Bacterial keratitis is a devastating infection of the cornea that may lead to rapid insult and loss of vision. Early diagnosis and prompt treatment are essential in minimizing the damage and improving the visual outcome. There are numerous bacteria that may cause bacterial keratitis. The most frequent causative organisms of bacterial keratitis include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *and Pseudomonas aeruginosa.* Other organisms that may cause bacterial keratitis include *Moraxella*, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *and Neisseria* species. In rare cases of bacterial keratitis, multiple organisms may be isolated.

This section covers the clinical findings of bacterial keratitis, diagnostic workup, and management.

Patients with bacterial keratitis usually present with history of pain, redness, photophobia,

Table 7.1 Predisposing factors for ocular infections

Exogenous factors	Endogenous local conditions	Systemic factors
Contact lens wear	Lid disorders	Alcoholism
Topical corticosteroids	1. Lagophthalmos	Allergies
Topical antibiotics	2. Entropion	Blood dyscrasias
Trauma	3. Ectropion	Collagen-vascular disease
Glaucoma medication	4. Blepharitis	Coma
	Lacrimal disorders	Dementia
	1. Keratitis sicca	Diabetes mellitus
	2. Dacryocystitis	Immune disorders
	Conjunctival disorders	Prematurity
	1. Vernal catarrh	Systemic steroids
	2. Trachoma	Nutritional deficiency
	3. Ocular pemphigoid	Psychosis
	4. Stevens-Johnson syndrome	
	5. Xerophthalmia	
	Corneal disorders	
	1. Neurotrophic keratitis	
	2. Penetrating keratoplasty	
	3. Bullous keratopathy	
	4. Herpetic eye disease	

tearing, irritation, foreign-body sensation, purulent discharge, and blepharospasm. Symptoms of lid swelling may be present.

7.3.1 Clinical Findings

Patients with bacterial keratitis present with hyperemia of the conjunctiva, ciliary injection, and purulent discharge. Biomicroscopy of the cornea reveals an epithelial defect with creamy-white infiltration surrounded by ground-glass appearance. The ulcer may be small or large. The cornea may show folds in Descemet's membrane with edema and keratic precipitates found on the endothelium. The anterior chamber demonstrates varying degrees of cells and flare. Fibrin or hypopyon may be present. It is important to examine the stroma carefully to assess the amount of necrosis that may lead to thinning of the cornea. This is true in patients with *Pseudomonas* infection where thinning of the stroma may be marked and sometimes a descemetocele may form which carries a poor prognosis. The descemetocele may lead to corneal perforation and iris adhesion to the cornea. Central corneal ulcers are usually infectious in nature, while noninfectious infiltrates may appear as single or multiple peripheral corneal infiltration ulcer secondary to immune-mediated reactions. Marginal ulcers that extent to the center may be infectious in nature. *Staphylococcus* corneal ulcers are usually round, well circumscribed with an epithelial defect and corneal infiltration. In some patients with *Staphylococcus* ulcer, multiple deep stromal infiltrates may be seen together with small infiltrates adjacent to the corneal ulcer. The surrounding cornea may show minimal edema. *Streptococcus pneumoniae* may appear as serpiginous ulceration that moves across the cornea with infiltration. On the other hand, *Pseudomonas aeruginosa* causes an aggressive and fulminant corneal ulcer which is rapidly progressing and may lead to corneal perforation if not treated early. The corneal ulcer is usually extensive with necrosis and yellow-green purulent discharge adherent to the surface. The corneal surrounding of the ulcer shows edema with ground-glass appearance and loss of its transparency. A hypopyon is usually present. Certain bacterial ulcers are indolent and insidious in nature such as *Moraxella*, *Nocardia*,

and nontuberculous *Mycobacteria*. The corneal ulcers show a localized epithelial defect with infiltration. The ulcer tends to be round or oval, and the cornea surrounding the ulcer appears to be relatively clear unlike cases with *Pseudomonas* corneal ulcer. In cases of traumatic penetrating corneal laceration, the patient may be infected with *Bacillus* species or *Clostridium* species which may produce gas in the anterior chamber or corneal stroma. On the other hand, *Serratia marcescens* corneal ulcer may produce red pigment that appears in the stroma.

7.3.2 Diagnostic Laboratory Investigation

Simple corneal ulcers should always be scraped for cytological evaluation with Gram and Giemsa stains and for cultures. The corneal scrapings should be performed at the area of corneal infiltration obtaining adequate specimens. Part of the scraping specimen is placed on two slides for Gram and Giemsa staining, and another specimen should be placed onto culture plates, blood agar, and chocolate agar. Other media may be used, as indicated, such as Löwestein-Jensen medium, cooked meat, or brain-heart infusion medium. Corneal cultures are obtained in the office utilizing topical anesthetic such as proparacaine 0.5 %, tetracaine 0.1 %, or benoxinate 0.4 %. The corneal scrapings are obtained with the slit-lamp magnification using either Kimura spatula or a 25 g needle. The scrapings should be done aggressively in the bed of the ulcer as well as the leading edge of the infiltrate. Mucopurulent discharge should be avoided. A wire lid speculum may be used to prevent blinking during the procedure. Thioglycolate medium is use for anaerobic cultures. If fungi are suspected, Sabouraud's dextrose agar should be used. An additional slide may be prepared for periodic acid-Schiff (PAS) or Grocott-Gomori methenamine-silver nitrate stain. The corneal specimen should be cultured even in patients who are on antibiotics. Media with antibiotic removal device may be used. Molecular diagnostic techniques are available such as polymerase chain reaction (PCR). Molecular diagnostic tests may not be readily available in every institution but may prove to be helpful.

7.3.3 Management

Clinical severity of corneal ulcers is divided into three grades: mild, moderate, and severe. Mild corneal ulcers are those that are less than 2 mm in size, and the depth of the ulcer is less than 20 % or 100 μm of the corneal thickness. The infiltrates may be superficial next to the base of the ulcer. In cases with moderate corneal ulcers, the size of the ulcer is 2–5 mm, the depth of the ulcer is 20–50 % (100–275 μm) of the cornea, and the infiltrate is dense extending to the midstroma. In severe corneal ulcers, the ulcer size is more than 5 mm in size, the depth of the ulcer is more than 50 % (>275 μm) of corneal thickness, and the infiltration is dense reaching the deep layers of the corneal stroma. The sclera may be involved in patients with severe peripheral bacterial keratitis. After obtaining the corneal scrapings for culture and cytology, the patient should be started on combination of topical antibiotics to cover the most commonly encountered organisms while the patient is still in the office. The mainstay of treatment includes frequent aggressive administration of topical antibiotics. Certain antibiotics may have to be compounded and made available for the patient. Mild and moderate bacterial keratitis may be treated on an out-patient basis whereas patients with severe bacterial keratitis may have to be admitted to the hospital for the intensive in-patient management.

The patient should be treated with topical antibiotics every hour in addition to the pulse therapy which should be given three times a day and consists of one drop every minute for 5 min.

In moderate and severe corneal ulcers, treatment should be aggressive, and antibiotic eye drops should be administered every 15 min around the clock with an initial pulse therapy. It is of great importance to monitor the corneal thin-

ning and stromal necrosis in cases of imminent perforations, shallowing of the anterior chamber, or sudden appearance of the hypopyon.

In patients with small perforations, tissue adhesive may be applied. In patients where there is rapid reepithelialization, it is recommended to rescrape the cornea in order to increase the corneal penetration of the antimicrobial agents where the infiltration is persistent. Antibiotic therapy is modified when the culture is available. When the infiltration subsides and the epithelial defect heals, frequency of the antibiotics may be tapered. The size of the infiltration and the ulcer should be measured by slit beam. Optical coherence tomography (OCT) and external photography are helpful. The size of the infiltration and the epithelial defect are recorded and followed up closely. The size of the epithelial defect is usually smaller than the infiltration. Cycloplegic agents such as cyclopentolate 0.1 % eye drops may be given twice daily to minimize pain and blepharospasm. Oral analgesics may be required in patients with severe ocular pain. It is always recommended not to patch the infected eye, but a plastic clear shield may be applied.

Patients may be started on empirical therapy consisting of tobramycin 14 mg/ml and vancomycin 50 mg/ml eye drops. These can be given 5 min apart initially in the first hour followed by every hour. A pulse topical therapy may be given every 1 min for 5 times 3 times daily. Commercially available fluoroquinolones such as gatifloxacin, moxifloxacin, and besifloxacin may be used as initial empiric therapy in mild cases. Ciprofloxacin is approved for use in bacterial keratitis and has demonstrated clinical efficacy and safety in a large clinical trial [2]. Ciprofloxacin is potent against Gram-negative organisms such as *Pseudomonas* but has limited efficacy against staphylococci and streptococci.

The treatment for bacterial keratitis is the topical administration of commercially available antibiotics or fortified compounded antibiotics. Increasing the concentration of antibiotic solutions creates a larger diffusion grading across the cornea, and this serves to increase the corneal penetration of the antibiotic. Subconjunctival or subtenon injection of antibiotics is occasionally used in patients with moderate to severe corneal ulcers, ulcers with imminent perforation, patients with scleral extension of the corneal ulcers, and patients with associated endophthalmitis. Subconjunctival injection may also be indicated in patients who are not compliant. Repeated injections must be administered to maintain appropriate drug loads.

Intravenous administration of antibiotics is rarely indicated in patients with bacterial keratitis. *Neisseria* species and *Haemophilus* species are treated with systemic as well as topical antibiotics because of the possibility of systemic infection, particularly, in the pediatric age group.

The severe inflammation associated with bacterial keratitis may lead to damage to the corneal tissue, and this inflammatory reaction should be taken into consideration. Topical corticosteroids are contraindicated in the initial therapy of bacterial keratitis but once the infection is under control and the epithelium has healed, corticosteroids may be used with care. Clinical trials have shown that topical corticosteroids given 2 days after initiation of topical antibiotic therapy did not worsen the course of the disease. Topical corticosteroids, however, may inhibit the immune mechanisms of the ocular surface leading to persistence of the infection. The risks and benefits of topical corticosteroids should be weighed carefully.

7.4 Viral Keratitis

There are many viruses that lead to keratitis in man. Both DNA and RNA viruses may cause keratitis. The severity of keratitis varies from mild superficial punctate epithelial keratitis with or without conjunctivitis to severe form of stromal keratitis leading to scarring and loss of vision. Viruses that cause keratitis include herpes virus and varicella-zoster virus, adenovirus, human immunodeficiency virus, smallpox, vaccinia, *Molluscum contagiosum,* measles, mumps virus, mucacin disease virus, enterovirus, rubella virus, flaviviridae and myxoviridae group of viruses (Table 7.2).

Table 7.2 Non-herpetic viral keratitis

Virus	Ocular manifestations	
DNA viruses		
Adenovirus	Follicular conjunctivitis, epithelial keratitis, subepithelial nummular opacities	
Small pox (variola virus)	Corneal ulcers, corneal perforation	Skin vesicles, scars fever, death
Vaccinia virus	Corneal scars, keratitis, conjunctivitis blepharitis, superficial punctate keratitis (SPK)	Vesicles
Molluscum contagiosum	Lid umbilicated lesion, follicular conjunctivitis	
Papilloma virus	Limbal keratitis, conjunctival papilloma	Warts of lid margin
RNA viruses		
Measles virus	SPK, conjunctivitis secondary to bacterial infections	Koplik's spots
Mumps virus	SPK, acute conjunctivitis	Dacryoadenitis
New castle disease virus	SPK, follicular conjunctivitis	Parotiditis
Enterovirus 70 virus	Subconjunctival hemorrhage	
Coxsackie virus	Follicular conjunctivitis, subconjunctival hemorrhage	
Rubella virus	Congenital cataract, retinopathy, microphthalmia, iris atrophy Acquired follicular conjunctivitis, SPK	
Flaviviridae		
West Nile virus	Multifocal choroiditis, retinal vasculitis	
Dengue virus	Chorioretinitis, vasculitis	
Chikungunya virus		
Bunyaviridae	Subconjunctival hemorrhage	
Rift Valley fever	Retinitis, retinal vasculitis, optic neuritis, optic atrophy retinal hemorrhages	

7.5 Herpes Keratitis

Herpes simplex virus (HSV) and herpes zoster virus (HZV) are the most serious infections of the cornea that may lead to devastating complications and loss of vision. HSV is the most common infectious cause of unilateral visual loss from corneal disease [3]. Herpetic infections are common and afflict between 50 and 95 % of the population. HSV type 1 is transmitted by direct contact with infected secretions. Humans are the only known natural reservoir. The disease can be primary infection in an immunized individual or secondary disease due to recurrence of HSV which has been dormant in the trigeminal ganglion. Nearly 95 % of individuals older than 60 years of age harbor HSV in their trigeminal ganglia at autopsy. The majority of cases of herpetic infections are subclinical, and HSV has been isolated from tears and saliva of patients with no active disease [4]. Following a primary infection, the virus stays dormant in the trigeminal ganglion in cases of ocular surface infection. The ocular involvement is most commonly associated with type 1 HSV which causes disease in the distribution of the trigeminal ganglion: *Herpes keratitis*, *Herpes labialis*, *and Herpes gingivostomatitis*. HSV type 2, on the other hand, is associated with disease and in the distribution of the sacral ganglion leading *to Herpes vulvovaginitis* and *Herpes progenitalis.* Reports of HSV type 2 ocular disease have been shown in adults and suggest an oculogenital transmission of the virus. In neonates, HSV-2 is responsible for the 80 % of the herpetic infections. If the herpes virus is found in the birth canal, the risk of infection to a newborn is 40 %, and therefore, a cesarean section is preferable for delivery in such cases [5].

The most common manifestation of ocular herpes is herpetic keratitis. The newborn becomes susceptible to an infection with HSV at 6 months at the time of decline in maternal antibodies to the herpes virus. The initial episode of herpetic infection is referred to as primary infection and can occur between the ages of 1 and 5 years but is subclinical in the majority of cases. The primary

infection may affect the eyelids, conjunctiva, and cornea presenting as lid swelling and edema with initial erythematous papular lesions progressing rapidly into vesicular eruptions and ulcerative stage 1. The conjunctiva may show follicular conjunctivitis, and the cornea reveals epithelial keratitis. The primary infection gives more severe symptoms than recurrent disease. The virus may be cultured from the conjunctiva. In patients who are immunologically compromised, a severe generalized infection may occur. Patients who are immunocompromised such as newborns, malnourished children, pregnant women in their last trimester, patients with atopic dermatitis, tuberculosis-acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, leukemia or lymphoma, severe burns, and patients on systemic immunosuppressive agents are susceptible to severe herpetic infection. The site of the primary infection determines the pathway of viral spread and site of viral latency. The most common site for the establishment of the latent infection is the trigeminal ganglion. Latency of HSV in the corneal nerves has been suggested [6].

7.6 Epithelial Disease

Following the primary infection, HSV stays latent in the trigeminal and sacral ganglia. Certain triggers have been shown to reactivate the herpetic infection. These triggers include fever, sunlight, cold wind, surgery, infection, menstruation, stress, cutting the root of the ganglion, trauma, and immunosuppression. Recurrent ocular disease may lead to herpetic dermatitis of the lids which tend to recur in the same geographic location where vesicle ulcerates leaving an erythematous base. Recurrent conjunctivitis leads to hyperemia and sometimes chemosis of the conjunctiva. The most common form of recurrence of the ocular disease is the cornea. Recurrent herpetic keratitis may lead to epithelial dendrites, geographic ulceration, and stromal invasion of the cornea by herpes virus [7]. Recurrent herpetic stromal disease may lead to infiltration and edema of the corneal stroma leading to stromal necrosis and melting. In severe cases, stromal keratitis may be associated with uveitis. Trauma to the trigeminal nerve of the cornea may induce viral recurrences in the peripheral tissue. HSV reactivation occurs in 90 % of patients after trigeminal root section, but not after trauma to previously denervated tissue. Herpetic disease may lead to dendrite formation in the cornea and geographic epithelial ulceration which if treated early may lead to minimal superficial corneal haze. Scrapings of the dendrites may show intra- and intercellular edema of the corneal epithelium with necrosis in the area of ulceration. Multinucleated epithelial cells and intranuclear eosinophilic inclusions may be seen. Virus may be isolated on culture from the smears, and PCR is usually positive. In the postinfectious period, epithelial defect may become indolent and the ulceration showing poor tendency towards healing. Viral replication does not occur in such lesions. Abnormal tear film function and decreased corneal sensation as well as antiviral toxicity may contribute to the development persistent postinfectious epithelial defect. Disciform keratitis may occur in some patients with recurrent herpetic keratitis. This is immune reaction to viral antigen.

Histologically, one may find lymphocytes and plasma cells within the stromal edema but usually no live virus. In some cases, herpes simplex viral particles may be seen in the corneal endothelium in cases of endotheliitis. Patients typically have well-circumscribed stromal edema with minimal infiltration and keratic precipitates.

Corneal immune rings and interstitial keratitis are also seen in herpetic keratitis. Uveitis and trabeculitis may occur, and some patients with keratouveitis may have an increase in the intraocular pressure which can be acute or chronic (Table 7.3).

Table 7.3 Causes of dendritic corneal lesions [8]

Herpes simplex virus
Varicella-zoster virus
Healing of epithelial defect
Richner-Hanhart syndrome (tyrosinemia type II)
Autoimmune polyendocrine syndrome type 1 (APS-1)
Keratosis follicularis
Thygeson's superficial punctate keratitis
Soft contact lens wear

Table 7.4 Differentiation between herpetic peripheral infiltration and staphylococcal peripheral infiltration

	Herpetic peripheral infiltrate	Staphylococcal peripheral infiltrate
Pain and photophobia	–	+
Early epithelial defect	+	–
Lucid interval	–	+
Decreased corneal sensation	+	–
Blepharitis	–	+
Cytology	Multinucleated cells	Polymorphonuclear cells

Patients with herpetic keratitis may present with unusual clinical presentation of peripheral corneal infiltration or a marginal ulcer. In these patients, differentiation from *Staphylococcus* marginal ulcer has to be made. Table 7.4 shows the differentiation between herpetic peripheral infiltration and staphylococcal peripheral infiltration [8].

The aftermath of interstitial herpetic keratitis is corneal scarring and vascularization with loss of vision. In patients who have been given topical steroids, secondary infection may occur or corneal descemetocele or perforation may ensue.

7.6.1 Laboratory Diagnosis

Corneal scrapings in corneal herpetic epithelial disease may be subjected to cytologic examination, PCR, culture, and electron microscopy. Giemsa-stained corneal scrapings may show multinucleated epithelial cells. Giemsa stain obscures nuclear details, and therefore, intranuclear inclusions typical of HSV infection cannot be seen. Specimens fixed with 95 % ethanol and stained with Papanicolaou (PA) method may demonstrate intranuclear inclusion bodies. Fluorescent antibody staining of the corneal scrapings can be done and may demonstrate the presence of herpetic antigens. Cultures taken from epithelial disease are usually positive, while cultures from geographic stromal or disciform lesions are much less likely to be positive. This denotes that the number of virus particles is low in such lesions. Cultures for bacteria and fungi should be obtained from patients with stromal infiltration where secondary infection is suspected.

7.6.2 Management of Epithelial Keratitis

The treatment epithelial dendrites or geographic corneal ulcers consists of applying topical anesthesia in the form of tetracaine 1 % or benoxinate 0.4 % and sweeping the epithelium with a sterile cotton applicator followed by topical application of acyclovir 3 % ophthalmic ointment 5 times daily or ganciclovir 0.15 % gel 5 times daily [9]. Antiviral therapy should be continued for a period of 7–10 days after. Antiviral agents such as idoxuridine, adenine arabinoside, and trifluridine are all toxic to the corneal epithelium and should be avoided [10]. An alternate therapy is trifluridine 1 % solution administered every 2 h. This dosage is used in the initial treatment period for 2–4 days and later decreased to 5 times daily. If there is lack of response or increase in the size of the ulcer, the therapy should be discontinued. Topical trifluridine may cause toxicity to the corneal epithelium.

7.7 Stromal Keratitis

In herpetic stromal keratitis, there is evidence of inflammatory response which requires the use of topical corticosteroids under antiviral coverage. Topical steroids can decrease the inflammation and minimize the damage to the stromal lamellae. At the same time, topical steroids may compromise the local immune response and may lead to viral replication. It is recognized from the study that delaying topical steroids did not have an adverse reaction on the corneal inflammation. It is, therefore, reasonable to start with antiviral agents initially and later add topical

corticosteroids in the form of prednisolone acetate 1 % eye drops 4 times daily to be tapered over a period of 4–6 weeks [11, 12].

Patients with corneal thinning and perforation can complicate the stromal disease, and topical steroids may aggravate the corneal melting. It is, therefore, recommended to minimize the use of corticosteroids. One may shift from prednisolone acetate 1 % eye drops to fluorometholone 0.1 % eye drops to be used 3 or 4 times daily.

Soft contact lenses may promote epithelial healing and stop melting. If perforation occurs, cyanoacrylate glue may be used to seal small defect and reform the anterior chamber. Severe corneal scarring or corneal perforation may require tectonic graft or penetrating keratoplasty (PKP).

7.8 Disciform Keratitis

Disciform keratitis is an immune-mediated reaction to viral antigens [13]. The corneal epithelium is intact with central round corneal stromal infiltration and edema. Keratic precipitates may be present. Treatment of disciform keratitis includes topical prednisolone acetate 1 % eye drops 8 times daily for 3 days and later to be tapered to 4 times daily after 2–3 days. Steroids are given with appropriate topical or systemic antiviral therapy [13]. Topical therapy may consist of acyclovir 3 % ophthalmic ointment or ganciclovir 0.15 % gel. The corticosteroids and antiviral agents may later be tapered and adjusted according to the response of the corneal lesion. Disciform keratitis responds promptly to topical corticosteroids.

7.9 Penetrating Keratoplasty (PKP) in Herpetic Keratitis

Herpetic keratitis leads to upregulation of many cytokines and inflammatory response leading to upregulation of Class II antigens on the keratocytes and endothelial cell increasing the rate of graft rejection in patients undergoing PKP. The rate of rejection of the corneal graft in a patient with herpetic keratitis is high. Herpes virus in the trigeminal ganglion allows periodic shedding of the virus onto the cornea that may lead to recurrences of the herpetic disease in the corneal graft. Recurrence of herpetic keratitis in the corneal graft will increase the chances of corneal graft rejection because of the upregulation of many forms of cytokines and the expression of the HLA Class II antigen on the surface of the endothelial cells. It is estimated that 40–50 % of the corneal transplant cases may end up in corneal graft rejection. We have previously found out that preoperative oral valacyclovir at a dosage level of 500 mg orally twice daily for 2 days before the procedure and continued for up to 1 month after the procedure with topical ganciclovir 0.15 % gel given 4 times daily is safe and effective in the prevention of recurrences of herpetic disease *in* the corneal graft [14]. We had several cases that were kept on topical ganciclovir 0.15 % gel up to 2 years after the corneal transplantation with no evidence of recurrence or graft rejection [15]. Oral valacyclovir and topical ganciclovir 0.15 % are effective therapy for acute herpes simplex keratitis. Antiviral oral therapy and long-term prophylaxis is indicated in patients with keratitis and uveitis.

Herpetic keratitis is a recurrent disease, and prevention is essential in ameliorating the damage that occurs following recurrences of herpetic keratitis. Prophylactic therapy in herpetic keratitis consists of using valacyclovir 500 mg orally twice daily or topical ganciclovir 0.15 % gel twice daily. Sozen and associates [16] compared the efficacy of oral valacyclovir and topical acyclovir in the treatment of herpes simplex keratitis in a randomized prospective clinical trial. They found that systemic antiviral therapy is more effective in herpes simplex keratitis than topical acyclovir ointment.

7.10 Herpes Zoster Keratitis

Varicella-zoster virus is the cause of chicken pox and herpes zoster "shingles." The virus (*Herpesvirus varicellae*) is a distinct virus related to *Herpes* virus family. Other members of the

Herpes group include Herpes simplex, Cytomegalovirus (CMV), and Epstein-Barr virus (EBV). They are all morphologically similar and have icosahedral symmetry surrounding a spherical core of DNA. The initial infection of varicella-zoster virus leads to systemic varicella or chicken pox. Patient has a spontaneous recovery and sometimes the disease is asymptomatic. The virus remains latent in the body indefinitely and may reactivate later in life. Varicella occurs usually in childhood and is characterized disseminated cutaneous vesicular eruption that occurs after the onset of fever and flu-like illness.

7.11 Varicella Keratitis

Varicella-zoster virus may rarely cause keratitis in the primary form of the disease. It is characterized by conjunctivitis with watery discharge. A phlyctenule-like lesion may be seen at the limbus with punctate keratitis. Varicella may also cause dendritic keratitis [17]. The dendrites are fine linear and slightly elevated and nonulcerative. Disciform keratouveitis may occur occasionally [18].

7.11.1 Herpes Zoster Ophthalmicus

It is estimated that 20 % of unvaccinated adults develop disease at one time or another. Herpes zoster ophthalmicus (HZO) is much less common than varicella. It is postulated that with age there is decrease in the immunity to the varicella-zoster virus and this may lead to reactivation of the latent virus [19]. Other triggers to reactivation of latent varicella zoster are trauma, stress, systemic disease, surgery, immunosuppression, or disease such as leukemia and lymphoma.

Herpes zoster begins with a localized pain, tingling sensation, dysesthesia in the affected dermatome associated with fever and malaise. A cutaneous eruption occurs 3–4 days after with edematous and maculopapular eruption which becomes vesicular followed by ulceration and scarring [20]. The ophthalmic branch of the trigeminal nerve is involved and lead to swelling of the lids, conjunctival hyperemia. Involvement of the tip of the nose also known as, Hutchinson's sign, is evidence of nasociliary nerve distribution, and the ocular structures may be involved in 85 % of the cases. The cutaneous eruptions in Hutchinson's sign are *on* the tip of the nose [21]. The side of the midportion of the nose may also be involved. It should be kept in mind that herpes simplex dermatitis may have a dermatomal distribution and should be in the differential diagnosis of HZO. Recurrences of HZO is extremely rare but has been reported. The possible ocular manifestations of HZO are numerous. Herpes zoster can cause blepharitis, canaliculitis, episcleritis, conjunctivitis, keratitis, iridocyclitis, uveitis, retinal vasculitis, retinal necrosis, choroiditis, papillitis, and optic neuritis.

Herpes zoster keratitis may have variable ocular manifestations. The corneal epithelium shows punctate keratitis and fine with no terminal bulbs dendritic epithelial lesions and sometimes progress to geographic or neurotrophic corneal ulcerations. The corneal stroma may be involved showing disciform keratitis or nummular opacities. The nummular opacities are more frequently seen at the periphery. The lesions may cause corneal necrosis and melting, and corneal perforation may occur [22]. Lid corneal scarring and vascularization with lipid deposition in the cornea are seen. Zoster dendrites do not have terminal bulbs and are usually small, linear, and less ulcerative than herpetic keratitis caused by herpes simplex. The dendrites are softer and less branching than the herpes simplex dendrites. They tend to be small and in starfish configuration. Corneal sensation is diminished. Herpes zoster may cause disciform keratitis and sometimes keratouveitis [23]. The anterior uveitis may be associated with sector iris atrophy.

7.11.2 Laboratory Investigations

Corneal scrapings of the epithelial dendrites do not show viral particles. Multinucleated epithelial cells may be seen on Giemsa-stained corneal scrapings. Several predisposing diseases including leukemia and lymphoma and Hodgkin's disease as well as other neoplastic diseases, tuberculosis, syphilis, immunodeficiency syndrome,

and systemic immunosuppression have been associated with HZO. Most patients with ophthalmic zoster are otherwise healthy.

Systemic evaluation should be done in patients who are young or in patients who have history suggestive of existing systemic diseases.

7.11.3 Management

Topical management of herpes zoster keratitis consists of ganciclovir 0.15 % gel given initially 8 times daily for 1 week and later decreased to 5 times daily for another 2 weeks. Skin lesions may be treated with topical 5 % acyclovir skin ointment to be applied 5 times daily [24]. In patients with zoster keratitis, there is element of inflammatory reaction. Systemic steroids are indicated for vision-threatening lesions such as retinitis or optic neuritis. Dosage for oral prednisone for adults is 40–60 mg daily followed by quick tapering to lower levels adjusted according to the clinical response. The treatment with systemic steroids should also be combined with valacyclovir 1,000 mg 3 times daily for 1 week tapered to 1 g orally twice daily after 1 week.

Systemic antivirals are initiated for anterior and posterior uveitis especially in vision-threatening conditions like retinitis, optic neuritis [25], and glaucoma. Since authors advised to treat retinal neurosis in herpes zoster with intravitreal injection of ganciclovir and dexamethasone.

Nonhealing postzoster epithelial defects are secondary to neurotrophic ulceration and should be treated with artificial tears and lubricating ointments, patching, and soft contact lenses. Topical preservatives such as benzalkonium chloride should be avoided [26]. Tarsorrhaphy or conjunctival flap may be indicated in cases with exposure keratitis. Amniotic membrane transplantation [27], topical autologous serum, and topical Cocicol eye drops may help in the healing of a persistent epithelial defect. Topical corticosteroids should be given in chronic stromal inflammation and anterior uveitis [26]. Autologous serum, topical exogenous nerve growth factor can also be used.

Corneal perforation of the cornea is treated with cyanoacrylate adhesive and soft contact lens. Keratoplasty may be considered at a later stage following complete healing and decrease in the inflammatory reaction.

Postzoster neuralgia [28] is a condition that may cause severe pain, tingling sensation, numbness, and paresthesias. The condition may be treated with oral analgesics or neuroleptics such as chlorpromazine, amitriptyline, gabapentin, or Lyrica. Because depression coexists with postzoster neuralgia, antidepressive therapy may enable the patients to tolerate the pain. Topical capsaicin 0.025 % dermatologic cream (Zostrix) or 8 % patch is reported to alleviate postzoster neuralgia in some cases. Capsaicin is applied 4 times daily to the skin of the affected dermatome. Lidocaine 5 % patch is more efficient than capsaicin topically [29].

7.12 Varicella-Zoster Vaccine (Zostavax)

Varicella-zoster vaccination is recommended for individuals over the age of 50 years. Vaccination helps in the prevention of herpes zoster ophthalmicus and postherpetic neuralgia.

Zostavax is a life-attenuated varicella-zoster virus that has been demonstrated to decrease the incidence of herpes zoster infection by 51 % over a period of 3 years. A total of 38,546 patients who were 60 years of age or older were enrolled prospectively in the study. The group clearly demonstrated that in the short term the vaccine can dramatically reduce the burden of HZV infections. The effects of this vaccine on children remain to be elucidated. It has postulated that decreasing the incidence of primary infection among children would effectively reduce the burden of herpes zoster. Vaccine may also be of help in patients with latent infection and may decrease the incidence of HZO [30].

7.13 Epstein-Barr Virus Keratitis

Epstein-Barr (EB) virus keratitis is another member of the *Herpesviridae* group. It is the most common cause of infectious mononucleosis syndrome characterized by lymphadenopathy,

fever, pharyngitis, headache, hepatitis, skin rash, and sometimes arthritis and hepatomegaly and splenomegaly.

7.13.1 Clinical Findings

EB virus may cause nummular keratitis or well-circumscribed disciform lesions in the cornea. The lesions appear late in the course of the infectious mononucleosis syndrome. The disease may be associated with mild nonspecific conjunctivitis. EB virus also can cause dryness, oculograndular syndrome, uveitis, and choroiditis. Occasionally, patients may develop optic (disk) nerve head edema (papillitis) and paresis of the oculomotor nerves [31].

7.13.2 Laboratory Investigations

Laboratory investigations include blood smears to determine the presence of atypical lymphocytes in the blood smears and positive neutrophil antibody response. PCR can be positive for an EB virus in case of uveitis, and EB virus and specific antibodies and core and capsid antigens may be detected [32].

7.13.3 Management

EB virus keratitis lesions may be treated with topical corticosteroids in the form of fluorometholone 0.1 % eye drops 4 times daily. The lesions may show spontaneous recovery and decrease in the redness and photophobia. No systemic therapy is indicated.

7.14 Cytomegalovirus Keratitis

Recent studies have shown that cytomegalovirus (CMV) can cause keratitis and anterior uveitis in immunocompetent hosts. The disease is usually unilateral and characterized by history of redness, photophobia, and decrease in vision. Patients develop increased intraocular pressure and endotheliitis with evidence of corneal edema and large keratic precipitates in a triangular fashion. No epithelial disease is noted in the cornea. Anterior corneal edema is observed. The anterior chamber shows cells and flare with evidence of iritis and cyclitis [33].

7.14.1 Laboratory Diagnosis

Aqueous specimens obtained from such patients may show CMV nucleotides by PCR [33].

7.14.2 Management

Patients with CMV (anterior) keratitis and uveitis may be treated with topical ganciclovir 0.15 % gel applied 8 times daily. The treatment is continued for 1 week and later decreased to 5 times daily or with systemic and intraocular ganciclovir [34]. Systemic valganciclovir and intravitreal ganciclovir has been used in some patients with CMV (retinitis) uveitis and keratitis [35].

Topical steroids in the form of prednisolone acetate 1 % eye drops 4 times daily may help the inflammatory reactions in the anterior chamber and decrease the corneal edema.

The intraocular pressure should be treated with beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues. Oral therapy with valganciclovir (Valcyte) can be given at a dosage level of 450 mg tablets orally twice daily for 2 weeks. In severe cases like necrotizing retinitis, ganciclovir 0.5 mg/kg can be given intravenously every 12 h. Intravitreal ganciclovir can be given at a dosage level of 2 mg one injection twice a week for 2 weeks. Foscarnet can also be given. Formiversin was approved by the Food and Drug Administration (FDA) in 1998 for intravitreal injection. Ganciclovir intraocular implant was also used to treat CMV retinitis [36].

7.15 Fungal Keratitis

Fungal infection of the cornea, fungal keratitis or keratomycosis, is a serious ocular condition. It may eventuate in serious complications. Early diagnosis and prompt treatment are mandatory

for arresting the disease process and inducing rehabilitation of the ocular surface. Fungal keratitis occurs in eyes with preexisting ocular surface disease. Fungal keratitis is difficult to diagnose and may present with a clinical picture similar to some bacterial infections or herpetic corneal disease. In such patients, a high index of suspicion is required, and laboratory identification of the fungal corneal pathogen is essential. Incomplete and inadequate therapy and inaccurate or delay in diagnosis may lead to poor outcome and visual loss. It is, therefore, conceded that successful management of fungal keratitis requires early diagnosis, prompt treatment, and close follow-up.

The use and abuse of corticosteroids may promote fungal replication and corneal invasion and lead to poor outcome. Fungal keratitis may be caused by filamentous fungi or by yeast. The disease is common in tropical climate and warm weather [37]. The disease is associated with outdoor activities and occupations. The most frequently encountered causes of fungal keratitis include *Fusarium* species, *Aspergillus* species, and *Candida* [37, 38]. Other causes of fungal keratitis include *Acremonium*, *Alternaria*, *Fusarium*, *Cephalosporium*, *Curvularia*, *Penicillium*, *Sporothrix*, *Mucor*, *Rhizopus*, and other fungi that are rarely seen. Predisposing factors to fungal keratitis include a compromised ocular surface, atopic disease, long-term use of topical corticosteroids, exposure keratopathy, keratoconjunctivitis sicca, neurotrophic keratitis, immunosuppression, agricultural occupation, vernal keratoconjunctivitis, trauma, older patients, herpetic keratitis, and soft contact lens use [38]. *Fusarium* is the most common genus of filamentous fungi responsible for fungal keratitis in the southern part of the United States, while *Aspergillus* species are more common in India [39] and Saudi Arabia [37].

7.15.1 Clinical Findings

Fungal keratitis is commonly found in patients who sustained superficial corneal trauma. The incubation period of the fungus may take 2–21 days depending on the type of organisms and the size of the inoculum as well as the immune status of the host. It should be kept in mind that there are no pathognomonic features of fungal keratitis. Certain findings, however, may suggest the presence of fungal keratitis. Fungal keratitis is an insidious slowly progressive ulceration of the cornea associated with corneal infiltration. The corneal infiltration consists of intrastromal abscess or discrete elevated plaque on the corneal epithelium. The fungal infiltration is characterized by feathery edges [40]. The ulcer base is usually dry, gray, or white texture. There is thickening and elevation of the borders with hypertrophic corneal epithelium. Stromal infiltration may radiate from the ulcer edge leading to small round satellite lesions [40]. A ring infiltration may be adjacent to the ulcer representing an immune response. The ulcer borders are irregular and elevated with fine branching infiltration. Folds in Descemet membrane may be seen, and stromal inflammation is observed. In some patients, an endothelial plaque composed of fibrin may be visualized over the endothelium. The plaque may be present in the absence of a hypopyon. The hypopyon is frequently observed in the anterior chamber and may contain fungal elements in contrast to bacterial keratitis which is usually sterile. The presence of keratoconjunctivitis sicca, neurotrophic keratitis, or herpetic keratitis should be ruled out in the absence of trauma. The fungal keratitis is usually an indolent form of keratitis that may last for days or weeks.

7.15.2 Laboratory Diagnosis

The clinical diagnosis of fungal keratitis should be confirmed by laboratory investigation. Following instillation of topical unpreserved anesthetic such as benoxinate 0.4 % or proparacaine hydrochloride 0.5 %, corneal scrapings are obtained for cytologic evaluation and cultures. Corneal scrapings are placed on precleaned glass slides, and one slide is immediately fixed in absolute methanol for 5 min. Corneal biopsy specimens are usually fixed in 10 % formalin solution for light microscopy and glutaraldehyde for electron microscopy. One slide is kept as reserve, while the other slides are stained with Gram stain, Giemsa

stain, Grocott-Gomori methenamine-silver stain, and periodic acid-Schiff (PAS) stain. An anterior chamber paracentesis may be obtained in patients with suspected fungal endophthalmitis. Corneal scrapings are inoculated on blood agar, chocolate agar, thioglycolate broth, and Sabouraud's agar. A modification of Sabouraud (Emmond's medium) consisting of pH7.0 without cycloheximide may be used. Blood agar can support the growth of many fungi. Sabouraud's agar contains 50 μg of gentamicin to inhibit bacterial contamination. Sabouraud's agar plates are maintained at room temperature (25 °C). Liquid-infusion medium may be used as an adjunct to solid fungal media. The Grocott-Gomori methenamine-silver stain is a stain to identify fungi. PAS stain is useful for identifying fungal elements in tissue and cytological preparation. The carbohydrates in the fungal cell wall react with PAS and stain magenta. With this stain, the fungi appear pink with dark blue against the yellow background. Both Giemsa and Gram stains may also selectively stain fungi. The proteinaceous debris, however, may reduce the contrast between fungi and the background. Most fungi appear to be Gram positive. The use of potassium hydroxide 10 or 20 % is unreliable because of the presence of very few hyphae in the slides. Calcofluor white is another method of staining fungi. It makes the living and dead fungi visible under fluorescent microscope.

Fungal cultures should be checked daily. Growth may appear within 2–3 days. Delayed growth is unusual, and negative cultures do not rule out fungal keratitis. Keratectomy specimens or corneal biopsies may be obtained for histopathologic evaluations and staining with hematoxylin and eosin (H & E), Grocott-Gomori methenamine-silver stain and PAS stain. Confocal microscopy seems to be accurate and reliable diagnostic modality in the etiologic diagnosis of fungal keratitis [41].

7.15.3 Management

Fungal keratitis should be treated with topical agents that can penetrate the corneal tissue and reach the fungi in the stroma. Superficial yeast infection in the cornea such as *Candida* species may be treated with nystatin which is a polyene antifungal agent. It is found in a dermatologic preparation (Mycostatin ointment) containing 100,000 units per gram which is well tolerated when applied topically every 4–6 h. Nystatin, however, is a large molecular weight and, therefore, penetrates the cornea poorly.

Natamycin is a macrolide antibiotic produced by *Streptomyces natalensis* and is currently the only topical ophthalmic antifungal agent available commercially. Natamycin is a broad spectrum antifungal agent and has been used effectively in the treatment of fungal keratitis caused by *Fusarium*, *Cephalosporium*, *Aspergillus*, and *Candida* species [42]. Natamycin is poorly soluble in water but does form a stable microsuspension and adheres to the cornea at the site of epithelial defects. Natamycin demonstrates poor penetration and is less effective in the treatment of fungal keratitis with deep stromal infiltrates [43]. Natamycin 5 % ophthalmic suspension should be applied topically every hour. Intensive topical antifungal therapy is continued until clinical improvement is noted. Signs of improvement and resolution of the infection are demonstrated by rounding up the ulcer margin, decrease in the infiltrate, disappearance of the satellite lesions, healing of the epithelial defect, decrease in the corneal edema, and absorption of the hypopyon. Pain is decreased and the ocular inflammation subsides. Amphotericin B can be compounded as topical drops at the concentration level of 0.15 % eye drops. Amphotericin B is prepared in sterile water. Initial therapy may include topical administration every hour, and the medication may be gradually tapered after a favorable clinical response [44]. Amphotericin B is toxic to the tissues and can cause irritation and, therefore, should not be given subconjunctivally. Subconjunctival injection may lead to necrosis of the conjunctiva. Fluconazole (2 mg/ml) is available for injection and is well tolerated eye drops [45]. The intravenous injection can be prepared as topical and can be given subconjunctivally at the same concentration.

Fluconazole is effective in the treatment of *Candida* keratitis. Fluconazole may also be given

orally 200 mg as loading dose than 150 mg/daily and 2 % subconjunctivally [46].

Voriconazole is effective against *Fusarium* [47], *Aspergillus*, and *Candida.* The drug can be prepared as 1 % eye drops and may be given every hour as initial loading dose and later shifted to every 2 h [48]. The drug is well tolerated. Voriconazole can be given subconjunctivally and also intravenously. Voriconazole 25 μgm in 0.1 ml can be given as an intrastromal injection at the site of the corneal infiltrates using a 30 g needle [49]. This can be done under topical anesthesia. Intrastromal injection has to be given every three days. Voriconazole 1 % eye drops can be prepared from the intravenous preparation (V Fend Pfizer, Inc.). Other imidazoles are miconazole which is available for injection 10 mg/ml and may be given topically and subconjunctivally 10 mg in 1 ml. Other imidazoles include ketoconazole and itraconazole. Ketoconazole can be given 200 mg orally per day but may cause hepatotoxicity, and liver function tests should be obtained. Miconazole may demonstrate good ocular penetration following topical, subconjunctival, or intravenous administration with no ocular or systemic toxicity. Miconazole may be helpful for deep fungal keratitis especially *Aspergillus*. Topical miconazole should be given 10 mg/ml eye drops every hour and subconjunctivally 10 mg in 1 ml.

In general, imidazole compound should not be combined with polyenes like amphotericin B because of their drug interaction. The imidazoles decrease the ergosterol synthesis which is the target of amphotericin B.

Corneal scrapings during treatment can help in debridement and also allow the antifungal agent to penetrate the corneal stroma. Corneal scraping can remove the dead cells and the necrotic tissue. Superficial keratectomy may be performed for small ulcers especially when they are covering the visual axis.

Conjunctival flap or amniotic membranes may be required in indolent fungal corneal ulcers not responsive to medical therapy. The conjunctiva flap should be thin and avascular and sutured with minimal tension to prevent retraction. Penetrating keratoplasty (PKP) may be performed at a later date following resolution of the infection and the ocular inflammation. Therapeutic PKP may be indicated in deep keratomycosis with impending corneal perforation [50]. Although PKP may be successful in eliminating residual infection and restoring the anatomic integrity of the globe, prognosis for visual recovery is poor [50]. Good visual outcome may be achieved with PKP in central corneal ulcers without hypopyon or significant anterior chamber reaction. Postoperative complications following PKP include peripheral anterior posterior synechiae, pupillary membranes, macular edema, retinal detachment, secondary glaucoma, cataract formation, as well as corneal graft rejection [50]. If there is no impending perforation, PKP may be performed several months after the conjunctival flap has healed and after dissecting away the flap from the cornea. Therapeutic keratoplasty is most successful when surgery is performed early enough to remove all the corneal pathology. Corneal cross-linking has been shown to be safe and effective in small early superficial fungal keratitis in experimental animals [51]. Finally, excimer laser lamellar keratectomy has been performed in experimental *Candida* keratitis and achieved sterilization on culture and histopathologically in all corneal tissues. These therapeutic modality should, however, be carried out early in superficial fungal keratitis.

7.16 Parasitic Keratitis

The most frequently encountered causes of parasitic keratitis include *Acanthamoeba*, *Leishmania*, *Microsporidia*, *and Onchocerca.*

7.16.1 Acanthamoeba Keratitis

Acanthamoeba species may cause an indolent form of parasitic keratitis. The organism has been identified as an important cause of ocular morbidity and has been increasing in prevalence over the past two decades [52]. *Acanthamoeba* is a free-living protozoa which is ubiquitous in nature and is found in soil, drinking water, stagnated water, swimming pools, and hot tubs. The most common species of *Acanthamoeba* that have been reported to cause

Acanthamoeba keratitis include *Acanthamoeba polyphaga*, *Acanthamoeba castellanii*, and *Acanthamoeba hatchetti.* It has also been isolated from animal feces. *Acanthamoeba* exists in two forms – the trophozoites form which is active motile and the dormant original double-walled structure which allows the amoeba to survive in hostile environment. The encysted form is triggered by food deprivation and desiccation. Several predisposing factors may lead to *Acanthamoeba* keratitis including poor hygiene with soft contact lens wearing, trauma, exposure to stagnated water, and immunocompromised patients. The majority of cases of *Acanthamoeba* keratitis have been reported in contact lens wearer [53, 54].

7.16.2 Clinical Findings

Patients with *Acanthamoeba* keratitis give history of pain, discomfort, irritation, tearing, and blurring of vision. In some patients, pain may be severe and much worse than what is expected in the clinical findings.

Biomicroscopy shows an indolent keratitis and may have variable clinical manifestations. Patients with *Acanthamoeba* keratitis may be mistaken for herpetic keratitis. Dendrite-like lesions may be seen or localized circumscribed geographic ulcer. In addition, patients may have infiltration of the cornea with peripheral ring infiltrates and severe inflammation with stromal keratitis which may lead to corneal stromal melting and descemetocele formation and perforation [55]. One characteristic finding in *Acanthamoeba* keratitis is the finding of perineuritis of the corneal nerves referred to as radial keratoneuritis. Satellite subepithelial infiltrates may be seen similar to those seen in patients with viral keratitis. The corneal epithelium may be irregular and elevated in the edges with recurrent erosions. The corneal infection may be associated with concurrent bacterial infections.

7.16.3 Laboratory Diagnosis

Corneal scrapings may be obtained and placed in liquid medium which can be centrifuged and examined by microscopy without staining. Occasionally, trophozoites are seen on the slide prepared from the sediment after centrifugation of corneal scrapings placed in Page's solution. *Acanthamoeba* can survive on cultured corneal epithelium and stromal keratocytes and can maintain its growth by nutritional support. In mixed infections, *Acanthamoeba* can thrive on bacteria, and it has been suggested that initial infections from contaminated soil or water may induced a mixed infection of *Acanthamoeba* and bacterial infection leading to the initial support of *Acanthamoeba* [56]. Corneal scrapings may be stained with Giemsa stain, Gram stain, and Wright stain. For patients with deep stromal involvement, corneal biopsy is necessary to make the diagnosis of *Acanthamoeba* keratitis. Hematoxylin-Eosin-stained sections of corneal biopsy specimens may show *Acanthamoeba* organisms both in trophozoites and the cysts. Trichrome stain, periodic acid-Schiff reagent, and Gomori methenamine-silver stain may also show the organism. Indirect fluorescent antibody staining techniques may be utilized to show the *Acanthamoeba* in the tissues [57]. Calcofluor white, a chemofluorescent stain is absorbed by the cellulose components of the cyst wall of *Acanthamoeba* and can highlight the organism in tissues [58]. *Acanthamoeba* may be cultured on blood agar, chocolate Agar, Sabouraud's agar, and Löwestein-Jensen agar at 25C or 37C. On the other hand, optimal recovery of the organism can be achieved by the inoculation of the corneal scrapings specimens on non-nutrient agar coated with a bacterial overlay of *Escherichia coli* (*E. coli*) which provides nutrition for the *Acanthamoeba*. The culture is positive when wavy cracks are seen on the surface of the agar plate indicating motile trophozoites that are engulfing the bacteria. *Acanthamoeba* may be stored in Page's solution if culture material is not available. Electron microscopy can show the trophozoites and the cyst of *Acanthamoeba.*

Confocal microscopy has also been helpful in the diagnosis of in vivo *Acanthamoeba* and in the diagnosis of corneal stromal cysts and trophozoites in vivo [59].

7.16.4 Management

Corneal debridement and removal of necrotic tissue can help in the healing of the ulcers, and the material can be used for diagnosis of *Acanthamoeba* keratitis. The debridement of *Acanthamoeba* keratitis should be with combination therapy of topical neomycin ointment, propamidine isethionate and one of the imidazoles (such as miconozole, fluconazole, ketoconazole or intraconazole); and polyhexamethylenebiguanide (PHMB) [60] or chlorhexidine 0.02% eyedrops. Bang and associates [61] have reported successful treatment of three eyes with resistant *Acanthamoeba* keratitis with 1 % voriconazole. Voriconazole can be given 25 µgm/0.1 ml intrastromally with a 30 g needle. Voriconazole has to be compounded for topical use at a dosage level of 1 or 2 % eye drops.

In patients with severe *Acanthamoeba* keratitis, corneal scarring may occur, and patients may require PKP at a later stage when the eye has no evidence of inflammation.

7.17 Microsporidia Keratitis

Microsporidium is a unicellular parasite that may cause disease in man. *Microsporidia* are primitive eukaryotes that lack mitochondria, initially recognized as protozoa and now regarded as fungi. Several intestinal organisms have shown to cause keratitis and keratoconjunctivitis. Immunocompetent and immunodeficient individuals may acquire the disease. *Microsporidia* are small, oval, obligate intracellular organisms widely distributed among both vertebrates and invertebrates [62]. They were believed to be protists under *Archezoa*, but now they are classified as fungi. They are opportunistic organisms. The ocular manifestations of microsporidiosis include superficial diffuse punctate keratitis, conjunctivitis, and stromal keratitis. Immunocompromised individuals may develop keratoconjunctivitis [63, 64]. The most commonly encountered genus is *Encephalitozoon encephalae dejune* while stromal keratitis is caused by *Nosema and Microsporidia.* The disease starts in the corneal epithelium with diffuse epithelial keratitis and later may progress to cause stromal keratitis. In *Nosema* keratitis, the deep stromal layers of the cornea may be involved and patients may show evidence of folds in Descemet membrane [65]. Extensive inflammatory reactions are noted in the cornea and patients may have marked decrease in vision.

7.17.1 Laboratory Diagnosis

Corneal scrapings are obtained from patients with keratitis, while patients with keratoconjunctivitis conjunctival scrapings may be obtained. Corneal scrapings are placed onto clean slides and stained with Giemsa and Gram stains and Acid-Fast stain [66]. Scrapings are also cultured to rule out bacterial or fungal infections. *Microsporidia* cannot be cultured but can be seen by special stains including 1 % acid-fast stain, modified trichrome stain, Gram stain, and Gomori methenamine-silver stain. The organism appears as small, oval bodies that are Gram negative. The corneal scrapings may be fixed with 2 % glutaraldehyde for electron microscopy and blood test for HIV 1 and 2 should be performed. PCR and indirect immunofluorescent antibody (IFA) staining method can also be used.

7.17.2 Management

Patients with *Microsporidia* keratitis should be given albendazole 400 mg orally twice daily for a period 4–6 weeks, and liver function test should be monitored. Patients may be treated with topical fumagillin 0.113 mg/ml eye drops initially every 2 h for a period of 2 weeks and later decreased in frequency to 4 times daily for a period of 6 weeks [67]. In addition, compounded fluconazole or voriconazole eye drops may be given [68].

7.18 Leishmaniasis

Leishmania species may cause systemic or cutaneous disease in man. *Leishmania donovani* causes visceral leishmaniasis kala-azar and patients

with fever and hepatosplenomegaly [69], while *Leishmania tropica* causes localized papule (oriental sore) that becomes ulcerative over a few weeks or months at the site of inoculation by the insect vector, sand fly, *Phlebotomus* genus. Spontaneous healing ensues following the development of immunity to the parasites. Scarring may occur.

7.18.1 Clinical Finding

The sandfly bites occur on exposed areas of the skin and for this reason, the face is frequently affected, and consequently ulceration of the cheeks or eyelids may occur. The main ocular manifestations include the lesions on the eyelid which may lead to cicatricial ectropion and exposure keratopathy. Patients may develop nummular keratitis. The keratitis is due to the hypersensitivity to the parasite. Cicatricial and nummular keratitis have been observed in patients with cutaneous leishmaniasis. Intraretinal hemorrhages have been described by some authors following visceral leishmaniasis [70].

7.18.2 Laboratory Diagnosis

Microscopic examination of the skin scrapings from the base of the ulcer may reveal the presence of the *Leishmania* parasites. The slide may be stained with Giemsa and examined by light microscope.

7.18.3 Treatment

Treatment of cutaneous and mucocutaneous leishmaniasis is with sodium stibogluconate or meglumine antimoniate 20 mg/kg/day for 10 days; amphotericin B is the treatment of choice for visceral leishmaniasis [71]. Patients who have one single cutaneous lesion due to *Leishmania tropica* and the lesion is of no cosmetic damage may be treated with localized cryotherapy. On the other hand, these patients who developed generalized leishmaniasis may be given pentamidine isethionate with daily dose of 4 mg/kg body weight for a period of 2 weeks.

7.19 Keratitis Due to Onchocerciasis

Onchocerciasis is a disease caused by *Onchocerca volvulus*. This is a filarial parasite. Onchocerciasis is also known as African river blindness, and the vector is the blackfly *Simulium damnosum*, *yahense*, and other subspecies of the genus *Simulium*. The disease is common in sub-Saharan Africa and Latin America. Onchocerciasis is a common cause of infectious blindness worldwide [72]. The disease can be transmitted transplacentally from an infected mother to her fetus.

7.19.1 Clinical Findings

Infected individuals with *Onchocerca volvulus* develop subcutaneous nodules of the adult form of male and female *Onchocerca*, and the female produces millions of microfilaria, but the nodules are on the head, and the microfilariae migrate in the skin and may reach the eye. The microfilariae cause conjunctivitis and keratitis. The keratitis is usually nummular at the site of the death of the microfilariae resulting from localized inflammatory reaction which is well circumscribed. The microfilariae may reach the anterior chamber and can be seen easily with a slit lamp. The death of the microfilariae in the eye leads to an inflammatory reaction and may cause uveitis. In the cornea, it causes punctate keratitis with localized infiltration that appears as ill-defined (snowflakes) feathery round opacity measuring 0.5 mm or less. The inflammation may lead to sclerosing keratitis, anterior uveitis, secondary glaucoma, cataract, and the microfilaria may migrate to the posterior segment leading to chorioretinitis with optic atrophy with pigmented chorioretinal lesions [73].

7.19.2 Laboratory Diagnosis

Skin snip for specimens can be taken to identify the *Onchocerca volvulus*. Serological tests like ELISA and Western blot for antigen detection can also be used. PCR, ultrasound of the nodules, and sclerocorneal biopsy are also helpful.

7.19.3 Treatment

The treatment of choice for onchocerciasis is ivermectin 0.2 mg/kg orally once daily. Ivermectin has no effect on the adult worm and has narrow therapeutic window and is a good prophylactic agent for *Onchocerca volvulus* [74]. Other therapeutic modalities include suramin diethylcarbamazine, doxycycline, rifampin, and azithromycin. Excision of the nodules may help in decreasing the load of the microfilaria. Patients with *Onchocerca* keratitis may require topical use of corticosteroids in the form of fluorometholone 0.1 % eye drops 3 times daily and cycloplegics during the treatment with ivermectin. This will reduce the photophobia and corneal inflammation. The ocular pressure should be monitored. Patients with secondary glaucoma may be treated with topical beta-blockers and carbonic anhydrase inhibitors. PKP can be considered if vision is compromised from corneal scarring.

Compliance with Ethical Requirements

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent No human studies were carried out by the authors for this article.

Animal Studies No animal studies were carried out by the authors for this article.

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