Review Article

Preferred practice guidelines and narrative review on infectious keratitis in ocular surface diseases

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Ocular surface disease (OSD) encompasses a variety of additional factors in the natural history of infectious keratitis like disruption of the normal tear film, altered ocular microbiome, adnexal inflammation, de-epithelization of the cornea due to anatomical factors like trichiasis, lid margin keratinization, presence of limbal stem cell deficiency, and other lid related problems. These cases need special attention with respect to lower threshold for inpatient admission and care along with examination and careful corneal scraping to avoid any perforation. The preferable practice patterns in these include documenting epithelial defects using fluorescein stain in the presence of cobalt blue filter, use of preservative-free monotherapy drops in mild to moderate corneal ulcers, quantification of corneal thinning and depth of infiltrate using anterior segment optical coherence tomography, and early tapering of epithelia-toxic drugs with judicious addition of lubricants and steroids. The changes in surgical management involve adopting a lower threshold for procedures that can enhance healing, such as amniotic membrane grafting, electrolysis of trichiasis, and punctal occlusion for severe dry eye disease. Conversely, a higher threshold for therapeutic keratoplasty is preferable as postoperative healing is a major challenge in eyes with OSD. A closer follow-up is vital as healing is slower and risk of reinfection is higher. The long-term management of corneal opacity in OSD is also complex as first-stage ocular surface stabilization is essential prior to keratoplasty.

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The ocular surface functions as a complex immunologic environment. It is similar to other mucosal surfaces with its own defense system. The various defense mechanisms work to protect the eye against numerous pathogens. These include normal resident flora, anatomical barriers, mucus secretion, and chemical agents with antibacterial properties. Additionally, there is local antibody production (such as secretory IgA) and T-lymphocyte responses. Anatomical barriers include protective structure of bony orbit, eyelids, integrity of corneal epithelium, intact ocular coats, blood capillary endothelial cells, tear film, submucosal secretary immunoglobulins, and lymphatic circulation. The epithelium and chemical defense system (lysozyme and defensins) are the first line of protection. The normal resident flora of the eye includes *Staphylococcus aureus, Staphylococcus epidermidis Streptococcus viridians, Chlamydia trachomatis, Chlamydophila pneumoniae, Haemophilus aegyptius, Haemophilus influenzae, Moraxella* sp., and *Neisseria* sp. Routinely, these organisms reside in the conjunctiva and do not incite any inflammatory reaction. However, if there a breach in the ocular barrier, the cell-mediated and humoral immunity are activated. Cellular immunity involves activation of cytotoxic T-cells and release of cytokines, whereas the humoral immunity is mediated by antibodies and complementary proteins. If the infectious agent is able to surpass the ocular defenses, it causes infection. However, an integrated approach by all defense mechanisms ensures that if one defense fails, another can take over, providing robust protection.[1-3]

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The rate of disease progression is influenced by both the virulence of the infecting organism and various host factors. Highly virulent organisms like *Pseudomonas, Streptococcus pneumoniae,* or *N. gonorrhoeae* can cause rapid tissue destruction, whereas other organisms such as nontuberculous mycobacteria and *Streptococcus viridans* typically lead to a more gradual disease course. Bacteria that are normally part of the conjunctival flora, such as *Corynebacterium* sp., can become opportunistic pathogens in compromised eyes, whether due to local ocular conditions.

A significant challenge in managing infectious keratitis within the context of ocular surface disease (OSD) is the need to address both conditions simultaneously. Effective treatment of both the infectious keratitis and the underlying OSD is crucial for optimal ulcer healing and to minimize the risk of recurrence. The management strategies and preferred practice guidelines will be discussed in detail.

Epidemiology and Natural History of Disease

Population-based studies have reported prevalence of OSD symptoms to be present in 8.7% to 65.4%. Women were more commonly affected.[4] OSD has been highlighted as

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a major risk factor for infectious keratitis in many studies across the globe.[5-8] Infectious keratitis associated with ocular surface disease is predominantly caused by Gram-positive bacteria, accounting for approximately 60% to 80% of cases. These bacteria are primarily composed of ocular surface commensals, with coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* identified as the primary pathogens implicated in this condition.[5] The risk factors and etiological agent associated with OSD are enumerated in Table 1.

There are multiple anatomical factors that affect the ocular surface health like entropion, ectropion, trichiatic eye lashes, eyelid margin keratinization, blocked meibomian glands, keratinization of conjunctiva, and underlying subclinical and clinical inflammation in addition to an altered class of microorganisms in the periocular and ocular environment.[14] Infectious keratitis in patients with pre-existing ocular surface disorder creates a major challenge for the treating physician since the healing process starts with initial stabilization of ocular surface. So, addressing both the issues becomes the prime concern.

Approach to a case of infectious keratitis with OSD

Clinical history

The history is usually of a short course (up to 14 days). However, in infections due to atypical microorganisms, the duration may be longer. The patients usually present with pain, watering, blurred visual acuity, and redness in the involved eye. A detailed history of any inciting event, eye rubbing, previous ocular surgery, systemic comorbidity, use of contact lens, exposure to pond water or swimming, previous medical history, allergies, and immune status should be elicited.

Clinical examination

The visual acuity and intraocular pressure should be checked, followed by a thorough ocular examination. Prior cleaning of eyes and use of anesthetic drops may facilitate the examination. The details of corneal ulcer including location, depth, margins, presence of any hypopyon, satellite lesions, infiltrate, and epithelial defects should be documented. The lid and adnexa should be examined carefully. The fellow eye evaluation is essential for clues to etiology and possible similar underlying pathology.

Microbiological testing

Some cases of microbial keratitis can be managed by empirical therapy; however, corneal scraping at presentation may aid in microbiological assessment and interpretation of the clinical course. A corneal scraping can be done on slit lamp. It is advisable for cases with central corneal infiltrate ≥2 mm size or ulcers ≥3 mm, multifocal infiltrates, atypical clinical features, anterior chamber cells ≥1+, and history of corneal surgery.[25] Under the effect of proparacaine 0.5% (least bactericidal anesthetic agent), using a 26-gauge needle or Kimura's spatula, the base and leading margins of corneal ulcer are scraped for good yield. Various instruments like no. 15 blade, sterilized spatula, calcium alginate swab, hypodermic needles, and cotton- or nylon-tipped swabs may be used for sample collection. The collected material may be transferred to glass slides and onto the culture media (blood agar routinely and chocolate agar where a fastidious microorganism is suspected).

The slides may be heat-fixated and examined after Gram's staining or KOH fixation. Culture plates may be handed to a microbiologist for optimum growth of the causative agent. It should be checked for positivity after 48 hours of inoculation. A negative growth after 2 weeks for bacteria and 6 weeks for fungus is considered negative. Polymerase chain reaction (PCR) yields higher positivity; however, it is a costly modality and may not be universally available.

The sensitivity of the microorganisms is usually done using Kirby Bauer disc diffusion method or E-test. It helps

Table 1: Various risk factors associated with a spectrum of diseases in ocular surface disorders

OSD	Anatomical factors	Microbiological Features
Blepharitis	• Inflamed lids and adnexa • Long-term sequalae-trichiasis/ectropion/entropion	• Abundant proteobacteria and actinobacteria and firmicutes were lower in blepharitis.[9] • *Lactobacillus* and *Bifidobacterium* are the biomarkers of posterior blepharitis, and *Ralstonia* is a biomarker of mixed blepharitis[10] • CoNS was most commonly reported etiology, and Aspergillus flavus was associated with recurrent infection[11]
Dry Eye	• Decreased level of mucins causing destruction of epithelial tight junctions[12] • Recurrent epithelial erosions	• Increased *Staphylococcus aureus*, *Corynebacterium*, *Propionibacterium*, *Rhodococcus* and *Klebsiella oxytoca*[13-15] • Gram positive bacteria most common etiology • Ocular Sjogrens 42% bacteria alone, 8% mixed[16]
Meibomian gland dysfunction	• Causes dry eye disease • Disturbed tear film	• MGD with lacrimal dysfunction had more *Pseudomonas azotoformans*, *P. oleovorans*, and *Caballeronia zhejiangensis* compared to MGD and control.[17] • Internal hordeolum: firmicutes 32%, Proteobacteria 26%, Acidobacteria 11%[18] • CoNS most prevalent etiology irrespective of the severity.[19] A strong corelation with Demodex brevis[20]
Chemical injury	• Limbal stem cell deficiency • Persistent epithelial defect	• *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* in chronic LSCD[3] • *Candida dubliniensis* and *Candida albicans* reported[16]
Immunological eye diseases	• Erroneous activation of adaptive immune system results in autoimmune diseases, ocular surface epithelial cells secrete inflammatory molecules[21]	• SJS: 14 types of bacterial isolates identified. *Corynebacteria* 33%, CoNS 28%, *Staphylococcus aureus* 18.2%[22] • Ocular Rosacea: Most common: *Micrococcus luteus* 18%[23] • Behcet's disease: *Staphylococcus aureus*, *Moraxella*, *Streptococcus*[24]

to tailor the treatment according to the microorganism resistance to various drugs. Corneal biopsy is a reserved testing technique for microorganisms that cannot be yielded on routine culture and do not respond to empirical therapy. However, in cases with OSD, it is not preferable due to impaired healing. *In vivo* confocal microscopy is a reserved tool for knowing the microbiological agent as it facilitates diagnosis of atypical corneal infections like acanthamoeba, nocardia, and fungi.

Management

The management in cases of OSD and microbial keratitis aims to treat both the infection and ocular surface condition. To treat the infectious component, empirical therapy is prescribed. Topical cefazolin 5% with tobramycin 1.3% provide wide coverage against Gram-positive and Gram-negative bacteria. In cases of OSD with peripherally located small to medium ulcers, monotherapy with preservative-free formulations may be preferred to avoid epitheliotoxicity.

Based on the response to therapy and microbiological yield, the antibiotic therapy is modified. The ocular surface problem is treated simultaneously. In cases of entropion or ectropion, the lid everting surgeries should be planned along with initiation of medical therapy [Fig. 1]. Trichiatic eye lashes should be removed to avoid constant rub against the corneal stroma. Blepharitis should be treated with oral antibiotics and lid hygiene procedures. Steroids and lubricants should be initiated earlier to avoid scarring and maintain ocular homeostasis. Topical cyclosporine is also a useful adjunct in cases where steroids cannot be prescribed. In cases with severe dry eye disease, lubricants may be initiated early after clinical response to fortified antibiotics. Punctal plugs may be used in these cases. In cases with exposure keratopathy, intermittent taping between the instillation of eye drops is advisable. It provides a temporary means to avoid further exposure. However, in chronic cases, paracentral tarsorrhaphy is preferable.

In cases involving small corneal perforations (less than 3 mm), the application of cyanoacrylate glue followed by the placement of a bandage contact lens is the preferred technique to maintain globe integrity. Therapeutic keratoplasty should be reserved for instances of larger corneal perforations. To enhance graft survival, integration with amniotic membrane grafting or tarsorrhaphy may be employed [Table 2].

Postoperative care

Preservative-free antibiotics and lubricants are preferable options for postoperative management to ensure epithelization of the ocular surface. Topical steroids should be used cautiously since they may increase the risk of infection. All measures to ensure optimization of the ocular surface should be taken to protect the graft. The patients should be advised to adhere to the postoperative antibiotic regimen and follow up regularly.

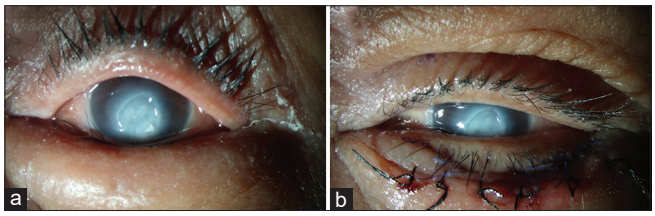

Figure 1: (a) A case with lower lid entropion and corneal ulcer with lashes rubbing the ocular surface; (b) Postoperative image after lid everting procedure and correction of entropion

Dry eye

The global prevalence of dry eye disease is estimated to be 11.59%.[26] The reported prevalence in various geographic zones varies from 8.1% in USA (pooled prevalence), 9.1% in Netherlands population, 22.5% for overall southeast Asia, 26.2% in India, 41.4% in China, 42% in Africa, and 55.7% in Japan.[27-33]

As dry eye is a chronic inflammatory condition, accumulation of inflammatory molecules on the surface leads to decreased tear film stability and destruction of epithelial tight junction integrity that further results in sloughing of surface epithelium. Hence, corneal epithelial barrier gets compromised in dry eye and it becomes easy pathogen colonization onto the corneal surface causing keratitis. Another reason supporting the increased risk of keratitis in dry eye is the reduction in both the quantity and quality of tears, which leads to a decrease in protective tear film proteins.[12] In early stages, epithelial erosions and punctate keratitis are observed; if not treated on time, they may lead to stromal infiltrates, keratitis, neovascularization, limbal stem cell deficiency, and corneal melting.

There is lack of much clinical evidence suggesting the association of keratitis and OSD.[12,34,35] A retrospective observational study was conducted at Australia for 5-year duration to identify clinical features and complications of keratitis that is associated with a poor ocular surface. Gram-positive bacteria were reported in 80%, and Gram-negative bacteria

Table 2: Important points for management for microbial keratitis in case with OSD

Examination Findings	Alteration in Management
Lids	
• Margins: entropion, ectropion, trichiasis • Meibomitis	• Lid correcting procedures to be done first • Warm compresses, lid hygiene and add oral azithromycin/doxycycline
Conjunctiva	
• Symblepharon and ankyloblepharon • Keratinisation and severe dry eye disease • Conjunctival epithelial defects with LSCD	• Symblepharon and ankyloblepharon to be managed after resolution of keratitis • Early tapering of epitheliotoxic drugs and initiation of lubricants and steroids • Use punctal plugs in severe dry eye disease
Cornea	
• Persistent epithelial defects and neurotrophic keratitis • Exposure keratopathy and Bells phenomenon • Filamentary keratitis and dry eye disease	• Prefer preservative free medications (monotherapy), therapeutic bandage contact lens, autologous serum drops, recombinant human nerve growth factors, amniotic membrane graft, oral tetracycline and vitamin C. Avoid topical NSAIDs. • Eye taping or tarsorrhaphy for exposure keratitis • Add topical N-acetylcysteine and lubricants for filamentary keratitis and dry eye disease

were reported in 13% patients.[35] A 10-year retrospective study at an Australian hospital concluded that the presence of dry eye (26%) and rheumatoid arthritis (81%) are the major risk factors for keratitis.[36]

In patients with dry eye, associated either with or without keratitis, artificial tears are the first line of therapy. Most of the artificial tear formulations contain benzalkonium chloride as a preservative which also simultaneously acts as a potent bactericidal and fungicidal agent.[37,38] It causes disruption of the outer membrane of microorganisms, primarily by reducing surface tension. However, with application of an eye drop containing benzalkonium chloride, the detergent effect compromises the lipid layer of the tear film. This disruption is irreversible and affects the aqueous layer, making it prone to rapid evaporation. Furthermore, benzalkonium chloride is toxic to goblet cells, resulting in decreased mucin production, which further contributes to the destabilization of the tear film.[39] Thus, preservative-free artificial tears are preferable modality in healing keratitis with associated dry eye disease.

Topical cyclosporine A 1 mg/ml was approved by European Commission in 2015 to address ocular surface inflammation in keratitis associated with dry eye. It inhibits lymphatic T-cell activation and reduces proinflammatory mediators.[40] As inflammation is the key component of dry eye itself, it is proven to work in improving tear volume and enhancing patient symptoms.[41,42] Additionally, it possesses fungistatic activity.[43]

Punctal plug insertion is a simple, effective, and safe method for treating aqueous tear deficiency and several ocular surface disorders, such as epitheliopathy after penetrating keratoplasty, neurotrophic keratitis, recurrent corneal erosions, and toxic epitheliopathy, that remain unmanageable with preservative-free tear lubrication. However, spontaneous extrusion is one of the limitations of this technique.[44]

In the worst-case scenario, dry eye can lead to nontraumatic corneal perforations. The perforations associated with dry eye are difficult to treat because of unstable tear film dynamics, increased inflammatory cytokines, predisposing systemic disease affecting wound healing, and surface inflammation.[40] Tissue adhesives, amniotic membrane grafts, patch grafts, and penetrating keratoplasty are the most common ways to manage such perforations.[45-47] Keratoplasty should be kept as a reserve option in these cases. The graft survival is poor in cases with OSD, and chances of reinfections are higher. Persistent epithelial defects (PEDs) should be looked for on follow-ups for timely management. Use of preservative-free medications, bandage contact lens, and amniotic membrane graft are unique methods to manage PEDs in these cases.

Other strategies to enhance tear volume include tarsorrhaphy, immunosuppressants, and the management of underlying systemic conditions contributing to dry eye. They promote re-epithelialization and prevent reperforations.[48]

Meibomian Gland Dysfunction (MGD)

Meibomian gland obstruction is the most common form of MGD that is affected by various factors like sex, hormonal disturbances, and age. The prevalence of MGD is two times higher in Asian countries when compared to Caucasian population. Also, it varies geographically because of the difference in diagnostic criteria and a standard definition for MGD.[49,50] Phlyctenular keratitis is a delayed-type hypersensitivity reaction to microbial proteins from pathogens present around meibomian glands. It is characterized by inflammatory corneal nodules with vascularization and meibomitis.[51] Another entity with similar clinical features was proposed by Suzuki *et al*., called MRKC (meibomitis-related keratoconjunctivitis).[52] Warm compresses, self-applied warming devices, LipiFlow (Tear Science Inc., Morrisville, NC) thermal pulsation, intense pulsed light therapy, meibomian gland probing, topical and oral antibiotics, and lipid-containing eye drops were found to be effective from the clinical evidence.[53]

MGD leads to changes in meibum quality and quantity that result in evaporative dry eye and ocular surface disruption. Meibum obstruction causes tear film instability causing all consequences of dry eye, resulting in punctate keratitis, loss of epithelial integrity, and damaging of epithelial junctions. At times, MGD is associated bacterial infection and is called meibomitis.[52,54] Addressing the sequalae like dry eye disease and keratitis will not help in clinical resolution of primary pathology. Hence, treating MGD is of prime importance to avoid or manage corneal complications.

Blepharitis

The common symptoms of blepharitis include redness, pain, irritation, foreign body sensation, crusting of eye lids, watering, light sensitivity, and itching around eyes. If left untreated, the inflammation might be associated with infection and spread across conjunctiva and cornea.[55,56] Based on anatomical location, it is subdivided into two types: anterior and posterior blepharitis. The signs include eye lid margin ulceration, lid margin scarring, discharge, and chalazion, and in some cases, they lead to conjunctivitis, corneal neovascularization, punctate keratopathy, and keratitis.[57,58] Presence of dandruff on the scalp/face, rosacea, oily skin, demodex mites infestation, and allergies on skin are the common risk factors for blepharitis.[59,60] Among bacteria, coagulase-negative *Staphylococci* is the most common pathogen causing blepharitis-associated keratitis, while meager literature is available for fungi causing blepharitis. However, there are a few reports on blepharitis associated with *Aspergillus flavus*.[11,56]

Lid hygiene and topical antibiotics are the mainstay treatment strategies for blepharitis. In the severe cases with phlyctenules and marginal keratitis, use of topical corticosteroids is advisable.[55] In patients where MGD is uncontrolled with lid hygiene and topical antibiotics, oral antibiotics are recommended. Multiple studies concluded that antibiotic/corticosteroid combinations improve ocular signs and symptoms, but the patient needs to be on close follow-up to monitor the intraocular pressure.[61-64]

Chemical injury sequalae

The severe chemical burns can disrupt the integrity of the corneal surface and result in limbal stem cell deficiency (LSCD), predisposing the eye to microbial infections. The incidence of infectious keratitis in patients with LSCD from chemical burns is notably high, with Gram-positive bacteria being the predominant pathogen. The severity of the initial chemical injury plays a crucial role in the likelihood of developing infectious keratitis, with more severe burns (classified as grade III or IV)

showing a higher incidence.[65] Management of PEDs by early amniotic membrane and preservative-free medications are useful modalities to prevent superadded bacterial infections.

The challenge of treating infectious keratitis after chemical injury is compounded by the altered ocular surface environment and the potential presence of multiple pathogens. Various difficult case scenarios with reports of dual fungal infection caused by *Candida albicans* and *Candida dubliniensis* in a young patient following acute chemical injury, with *Pseudomonas* sp. causing early melt and extrusion of intraocular contents, have been described. Targeted treatment strategies to combat infection and hasten epithelial healing in addition to simultaneous management of glaucoma and limbal stem cell deficiency add to the complexity of the situation. Early diagnosis and comprehensive management strategies are vital to address infectious keratitis in cases with ocular chemical injuries.[65,66]

Postocular surgery

Post-keratoplasty infectious keratitis (PKIK) is a significant complication of corneal transplantation with incidence rates varying between 0.02% and 7.9% in developed countries and between 9.2% and 11.9% in developing countries.[67-70] The risk factors associated with poor ocular surface-related keratitis include dry eye disease, MGD, blepharitis, lid-related abnormalities, suture-related infections, dellen formation, and poor epithelial healing. Most infections occur within the first 6 weeks post surgery. Common microbial culprits include *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Acinetobacter* species, and fungi such as *Aspergillus fumigatus*. Bacterial and fungal coinfections and viral reactivation are possible, complicating diagnosis and treatment [Fig. 2]. The management involves use of empirical antibiotic treatment with close follow-up. Removal of any inciting condition like trichiatic lashes or lid abnormalities is vital for optimum healing. Topical corticosteroids should be used judiciously to control inflammation and save the graft without exacerbating infection. The prognosis varies based on the case. Clear grafts are achieved in 23–81% of cases. In extremes of age (under 12 or over 60), there is an association with poorer visual outcomes.[71]

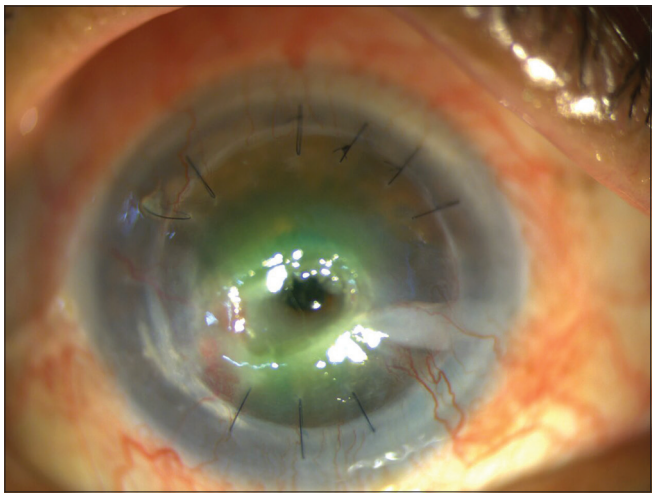

Figure 2: Complicated case of recurrent viral activation and OSD after keratoplasty showing loose suture, two quadrants of deep vascularization, and necrotizing stromal keratitis with descemetocele formation

The incidence of postrefractive surgery infectious keratitis ranges from 0.02% to 1.5%. The major risk factors include pre-existing dry eye, blepharitis, and meibomian gland dysfunction.[72] The use of povidone-iodine solution before surgery and meticulous sterile techniques are critical to reducing the risk of infection. The common pathogens causing post-LASIK keratitis include bacteria such as *Staphylococci* sp., *Streptococci* sp., and *Mycobacteria* sp. Early presentations (<1 week) are typically caused by *Staphylococcus* sp. and *Streptococcus* sp., while late-onset infections (>1 week) often involve slower-growing organisms like *Mycobacteria* sp. and fungi. Most infections resolve with medical management, and approximately 50–75% of patients achieve a final vision of 20/40 or better, with Gram-positive bacterial infections typically resulting in better outcomes than others.[73]

The presence of allergic eye disease has been reviewed as a major risk factor for development of infectious keratitis after collagen cross linking along with other risk factors like bandage contact lens and use of topical steroids. *Staphylococcus* sp. has been the most common pathogen causing collagen crosslinking keratitis.[74,75]

In a study by Vazirani *et al.*,[76] healed microbial keratitis with OSD was one of the indications for which simple limbal epithelial transplantation (SLET) was performed, while in the postoperative phase, 5/68 (7.35%) developed infectious keratitis. SLET may lead to PED, which if not managed promptly may lead to overlay of the infectious agent, thinning, and perforation of the cornea. Additionally, there is a risk of recurring corneal neovascularization. Similarly, in a study exhibiting results of cultivated oral mucosal epithelial transplantation (COMET), 2/40 (5%) eyes developed infectious keratitis after PED development.[77]

In a multicentric study exploring characteristics of microbial keratitis after Boston type-1 keratoprosthesis (Kpro), the incidence of infection was 57/349 (16.3%). It was associated with PED formation and increased risk of Kpro extrusion.[78]

Thus, in postsurgical cases, one has to vigilantly look for PEDs on follow-ups as they are the most common predisposing factor in postsurgical infectious keratitis in cases with OSD. Prompt strategies like preservative-free eye drops, autologous serum eye drops, use of BCL, and early AMG may help to treat PED and thus decrease the risk of infections.

Immunological eye diseases

There is an alteration in normal microbial flora residing in the conjunctival sac in cases of Steven Johnson syndrome (SJS). In a study by Venugopal *et al.*,[22] the culture positivity in cases of SJS was 59% as compared to 12.9% in the control group. In the control group, coagulase-negative staphylococci (CoNS) and *Streptococcus pnemoniae* were observed, while isolates from cases of SJS showed CoNS, *Corynebacteria* sp., and *Staphylococcus aureus.* In 6.7% cases, more than one bacteria were isolated. In another study on cases of SJS in Korean population, CoNS and Corynebacterium were the most common isolated organisms from the conjunctiva. In addition, they showed that culture-positive cases had higher tear matrix metalloproteinase-9 (MMP-9) levels as compared to controls and were not affected by use of cyclosporine, topical steroids, or antibiotics.[79]

The lid margin microbiome was also compared to controls. The phyla were similar between the two groups, but at the genus level, there was an increase in the relative abundance of *Corynebacterium* sp., *Haemophilus* sp., *Azotobacter* sp., and *Afipia* sp., along with a decrease in *Acinetobacter* sp., in SJS compared to healthy lid margins. The microbiota associated with SJS showed lower diversity and greater heterogeneity compared to the healthy controls.[80] Various bacteria are commonly isolated from these cases; however, they do not show high resistance.[81]

The infectious agent isolated from corneal scrapings was not consistent with those isolated from conjunctival swabs marking them to have an association but not direct causal-effect relationship. Severe dry eye disease, use of topical steroids, trichiasis, and lid margin keratinization were most common predisposing factors.[82] It has been studied that microbial keratitis in SJS is different than non-SJS cases in terms of delayed presentation and healing [Fig. 3]. They require supportive treatment modalities in addition to antibiotic therapy like epilation, tissue adhesive application, amniotic membrane graft, tarsorrhaphy, and punctal cautery.[83] These cases require close follow-up even after healing due to high risk of recurrent keratitis, which further deteriorates the visual outcomes.

In vernal keratoconjunctivitis (VKC), ocular surface microbiome has been studied and compared to controls. It was observed that *Staphylococcus* sp. was the most common microorganism predominant in VKC cases. They showed higher resistance to fluoroquinolones.[84] The use of topical steroids beyond 6 months makes these cases susceptible to superadded bacterial infections.[85]

Infectious keratitis has been seen in association with ocular rosacea. Being a chronic inflammatory acneiform condition, it is associated with bilateral chronic blepharitis, meibomitis, and corneal infections. The chronic use of topical steroids has been observed as a risk factor for development for fungal keratitis.[86]

In cases with systemic involvement, it is essential for physicians and ophthalmologists to collaborate on coordinated systemic treatment to prevent relapses. Thus, timely referral plays an important role.

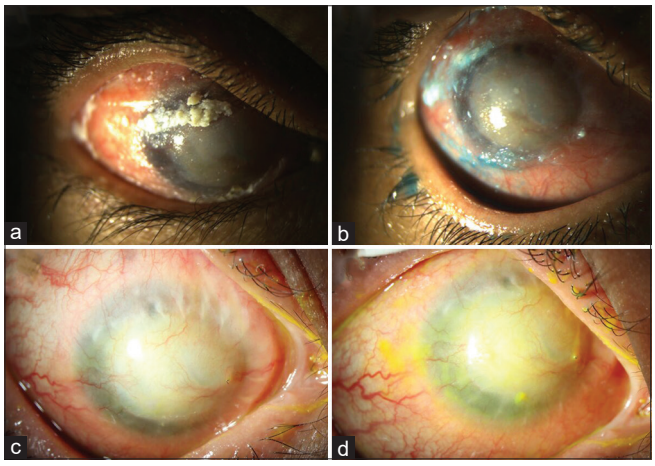

Figure 3: A case of SJS with failed graft with conjunctival keratinization with (a) mucus strands on cornea and *Candida albicans* on conjunctival swab; (b) After fluorescein stain, severe OSD; (c) After 2 weeks of treatment with topical Natamycin and lubricants, an improved ocular surface with an evident exposed suture end (missed at presentation); (d) After fluorescein stain, patchy staining indicating mild–moderate OSD

Conclusion

OSDs have multiple risk factors for developing infectious keratitis, which include lid abnormalities, corneal irritation from trichiatic lashes, abnormal and disrupted tear film, and alteration in the ocular microbiome. These factors not only increase susceptibility to microbial keratitis but also have risks of additional challenges like impaired epithelial healing, rapid stromal melt, and recurrent infections. Consequently, it is crucial to tailor the treatment based on the individual patient's clinical presentation and to maintain vigilant follow-up.

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