

The approach to diagnosis and management of corneal ulcers

By Benesia Mark Daniel

Abstract

Corneal ulcers are among the major causes of corneal blindness. The cause of corneal ulceration is a variety of infections. The key to improving clinical and visual results in cases of corneal ulcers is an accurate, speedy diagnosis and rapid treatment. However, there are no established standards or guidelines for treating corneal ulcers. Even seasoned eye care professionals occasionally have trouble predicting how the disease will progress in most patients. This article makes an effort to offer a general overview of the diagnosis process and treatment plan for a corneal ulcer.

Introduction

Corneal ulcers are some of the common ocular emergencies seen in eye care practice and are one of the critical causes of ocular morbidity (Merali & Schein, 2020). It is among the common causes of corneal blindness in developing countries, where the eye care services delivery is not well developed. Up to 2 million cases of corneal blindness globally are attributed to cases of corneal ulcers and ocular trauma (Merali & Schein, 2020). In developing countries such as Kenya, the primary cause of corneal ulcers is ocular trauma, while in most developed countries, the leading cause is contact lens wear.

Etiology of corneal ulcers

Infections caused by bacteria, viruses, fungi, or parasites are among the potential causes of corneal ulcers. While autoimmune, neurotrophic, toxic, allergic keratitis, chemical burns,

trichiasis, blepharitis, and lagophthalmos are among the non-infectious causes. Depending on where an individual is, several infections might cause corneal ulcers (Salmon, 2022). *Fusarium* species, *Pseudomonas aeruginosa*, *Aspergillus* spp., *S. pneumoniae*, and *Staphylococcus* spp. are among the common microorganisms. In Kenya, the common types of corneal ulcers are bacterial and traumatic corneal ulcers.

Pathogenesis of different types of corneal ulcers

a. Bacterial Corneal Ulcers

Except for organisms like gonococcus, which can penetrate an intact epithelium to generate ulcers, bacterial corneal ulcers are caused by bacteria penetrating the ocular epithelial barrier after a breach (Mabrouk et al., 2022). The epithelium is susceptible to corneal infection due to corneal edema, extended contact lens wear, dry eyes, and trauma. *Pseudomonas aeruginosa*, the most prevalent bacteria, uses glycocalyx to cling to the epithelium and subsequently invades the stroma through a break in the epithelium.

Tears and limbal veins carry inflammatory cells to the corneal breach site, producing cytokines and interleukins that cause the cornea to invade gradually and the ulcer to enlarge (Mabrouk et al., 2022). The organism undergoes phagocytosis, releasing free radicals and proteolytic enzymes that cause necrosis and sloughing of the stroma, Bowman's membrane, and epithelium.

Proteases, endotoxins, and exotoxins, created by dying organisms and multiplying bacteria, respectively, also aid in the process. Ring infiltrates are caused by endotoxins, polysaccharides found in the cell walls of gram-negative bacteria.

b. Fungal Corneal Ulcers

Fungi are classified as yeast, filamentous septated, pigmented and non-pigmented, and filamentous without septae (Mabrouk et al., 2022). In temperate countries, yeast fungi like candida are widespread, but filamentous fungi like *Aspergillus* and *Fusarium* are more prevalent in tropical regions (Wuletaw et al., 2021). A host inflammatory response is triggered by the invasion of fungal infections, which can also enter the cornea following an epithelial rupture, trauma, or a foreign body in the form of vegetative material or soil particles. In comparison to bacteria, the inflammatory response is slower and less intense (Mabrouk et al., 2022). In order to penetrate deeper into the stroma and break through Descemet's membrane, fungi release proteolytic enzymes, fungal antigens, and toxins. Once in the anterior chamber, they form a mass of fungus, exudate, and iris that covers the pupillary area.

c. Viral Corneal Ulcers

In a viral ulcer, the trigeminal nerve's ophthalmic division's terminal branches are where the virus enters the cornea from within (Byrd & Martin, 2019). According to a theory, herpes simplex causes epithelial swelling due to the involvement of the subbasal nerves. In contrast, herpes zoster causes epithelial swelling due to the involvement of the deep stromal nerves. Therefore, without an epithelial breach, the virus enters the eye through nerve terminals, where it causes nerve inflammation and neurogenic discomfort. The virus replicates in the corneal epithelium (Miller & Cao, 2021). The virus in the epithelium causes a raised lesion that develops into superficial punctate keratitis, sloughs to produce a significant epithelial defect, and ultimately results in stromal ulceration.

d. Parasitic Corneal Ulcers

An excellent example of the causative agent of parasitic corneal ulcers is *Acanthamoeba*. The use of soft contact lenses is most frequently linked to *acanthamoeba* keratitis. Once firmly connected to the contact lens, it lives in the area between the lens and the ocular surface before eventually adhering to the glycoproteins on the corneal villi (Jeang & Tuli, 2022). Contact lens wear causes microtrauma to the corneal epithelial surface, which facilitates an organism's invasion of the epithelium, Bowman's layer, and stroma. Acute inflammation and radial deposits are produced when the infection travels along the corneal nerves (radial keratoneuritis). Metalloproteases are produced by acute inflammation, which digests collagen fibrils and permits deeper penetration into the stroma. The condition may invade the anterior chamber as it worsens and result in endophthalmitis.

Symptoms of corneal ulcers

The common symptoms of corneal ulcers include reduced visual acuity, tearing, discharge, photophobia, and pain (Salmon, 2022). These symptoms vary depending on the cause and the stage of corneal ulcers, whether acute or chronic.

Approach to diagnosis of corneal ulcers

a. Careful patient case history and the history of presenting illness

The TRIAD of ocular trauma lowered immune state (either the ocular surface or the person as a whole), or particularly virulent pathogens that penetrate the intact ocular surface should always be kept in mind. Without ocular trauma, a corneal ulcer cannot form in a healthy person with a healthy ocular surface (Salmon, 2022). In this regard, a thorough history determining the patient's ulcer's underlying etiology is crucial for ensuring optimal care (Wuletaw et al., 2021).

In the absence of trauma, a history of ocular trauma, ocular surgery, long-term ocular medication use (topical steroids, anti-glaucoma medications), contact lens wear (age of the contact lens and lens cleaning solution), and prior ocular infections are crucial. All of these factors alter the ocular surface milieu and encourage the microbial invasion of the cornea (Salmon, 2022). Like opportunistic infections, atypical bacteria, fungi, or viruses, systemic disorders like diabetes, rheumatoid arthritis, hepatitis, autoimmune diseases, and their treatment, tuberculosis, and cancer damage a person's normal immunological condition.

b. Slit lamp biomicroscopy

A comprehensive slit lamp examination should be done keenly. Here are the steps (Salmon, 2022):

- i. Evaluation of the eyelids for blepharitis, malfunction of the meibomian glands, ectropian/entropion, and lagophthalmos.
- ii. Evaluation of trichiasis and distichiasis in the eyelashes.
- iii. Evaluation of the lacrimal apparatus system for punctal anomalies and dacryocystitis
- iv. Assessment of the conjunctiva to look for discharge, inflammation, foreign bodies, papillae, follicles, cicatrization, symblepharon, pseudomembrane, filtering bleb, and tube erosion.
- v. Evaluation of the sclera for any nodules or thinning.
- vi. Epithelial defects, punctate keratopathy, stromal edema, ulceration, thinning, perforation, infiltration features (size, shape, position, depth), foreign bodies, and indications of prior corneal procedures are all evaluated in the cornea. Clinicians can

locate an organism or root cause using fluorescein or rose Bengal staining. For instance, in viral infections, fluorescein and rose Bengal stain dendritic ulcers.

- vii. Examine the anterior chamber for any signs of inflammation, including cells and flares, hypopyon, and hyphema.

c. Signs

Although any particular symptoms cannot identify the causative organisms, a comprehensive slit lamp evaluation combined with clinical expertise can lead to a likely diagnosis (Wuletaw et al., 2021). The aggressiveness of the infection can be determined by several characteristics, including size, shape, location of the infiltrate, involvement of the limbus and sclera, accompanied by an AC reaction, and hypopyon.

Bacterial Corneal Ulcer	Fungal Corneal Ulcer	Viral Corneal Ulcer	Parasitic Corneal Ulcer
<ul style="list-style-type: none"> Gram Positive infection has localized infiltrate with distinct borders, with minimal stromal haze (Chopra et al., 2022). Gram Negative infections have dense stromal suppuration, ring infiltrates, and a hazy ground-glass appearance surrounding the 	<ul style="list-style-type: none"> Dry raised slough with clear corneal surroundings that appear dry (Chopra et al., 2022). Edges of the stromal invasion are feathery. Extensive endothelial exudates and satellite lesions. Presents with a ring infiltrate on occasion. The hypopyon often develops, and it may 	<ul style="list-style-type: none"> Dendritic pattern (linear branching). The branches' tips display a distinctively inflated appearance. Reduced corneal sensitivity A geographical and amoeboid-shaped epithelial defect may develop as a result of progressive centrifugal expansion (Chopra et al., 2022). 	<ul style="list-style-type: none"> Acanthamoeba keratitis may be caused by wearing contact lenses or not (Jeang & Tuli, 2022). Its distinguishing features are epithelium abnormalities, corneal edema, and single or multiple stromal infiltrates with a traditional ring-shaped arrangement.

cornea.	wax and wane.		Diffuse and satellite infiltration, however, are also frequent. Another typical discovery in Acanthamoeba is hypopyon. In advanced situations, the corneal nerves' whitish appearance can be used to diagnose radial keratoneuritis.
---------	---------------	--	--

Table 1: Some classical signs of different infectious corneal ulcers

It is also essential for the clinician to perform corneal scrapping for microscopic culture and microscopy, to identify the exact cause of the corneal ulcer.

Treatment Protocols

Treatment is started based on clinical judgment and staining results and is changed depending on culture results and clinical response (Salmon, 2022). Topical corticosteroids are best avoided because it has been noted that their usage is debatable. The preferred therapies are antibiotic, antifungal, or antiviral eye drops; however, in most cases, antifungal and acanthamoeba therapy is only initiated once there is microbiological evidence (Miller & Cao, 2021). The infiltrate's depth, size, and location determine the course and line of medical treatment (Salmon, 2022). Treatment would need to be more forceful for central infiltrates than peripheral, superficial infiltrates of < 2mm. Injections into the stroma are necessary for deep intrastromal infiltrates because they provide good drug availability at deeper layers.

i. **Bacterial Corneal Ulcers**

In cases of external peripheral infiltrates less than 2mm, topical antibiotics (monotherapy) may be used. A loading dose every 5–15 minutes followed by repeated administrations, such as every hour, is advised for deep stromal involvement or an infiltrate bigger than 2 mm with significant suppuration. In cases of monotherapy, Levofloxacin 1.5% is favored over Gatifloxacin and Moxifloxacin because it is more readily available, and there is increasing resistance to Gatifloxacin and Moxifloxacin (Salmon, 2022). Topical-supplemented antibiotics are chosen in cases of extensive or visually significant infiltrates, severe infection, or hypopyon. Although systemic antibiotics are rarely necessary, they can be considered in severe situations where the limbus and sclera are infected. It is debatable whether corticosteroids should be used to treat bacterial ulcers (Salmon, 2022). The concurrent topical corticosteroid therapy utilizing prednisolone sodium phosphate 1% in conjunction with broad-range topical antibiotics was not proven to be beneficial in the SCUT treatment research (Radhakrishnan et al., 2021). A previous study found no advantages to using corticosteroids to treat corneal scarring (Radhakrishnan et al., 2021).

Gram Positive Cocci

- 4th Generation Fluoroquinolones, higher antibiotics

Gram Negative Cocci

- Ceftriaxone, Ceftazidime, Fluoroquinolone

Gram Positive Bacilli

- Fluoroquinolones, Clarithromycin

Gram Negative Bacilli

- | |
|--|
| - Fluoroquinolones, Higher antibiotics |
|--|

Table 2: Common antibiotics used in the management of bacterial corneal ulcers

ii. Fungal Corneal Ulcers

Fungal ulcers are challenging to treat since the diagnosis might occasionally be delayed. Natamycin has shown a significant clinical improvement compared to voriconazole in the Mycotic Ulcer Treatment Trial (MUTT), which compared the two drugs. In MUTT II, oral voriconazole was compared to an oral placebo, and the former showed promise in treating fusarium ulcers (Cho et al., 2018). Steroids are not recommended for fungal ulcers (Salmon, 2022). Subconjunctival antifungals should be avoided since they cause significant pain and, to some extent, tissue necrosis. Since intrastromal voriconazole has a strong ability for penetration, treating deep and more extensive ulcers may be an option. When topical natamycin is ineffective, intrastromal voriconazole may be administered in addition to it.

iii. Viral Corneal Ulcers

About 50% of active epithelial lesions typically cure on their own without any medical intervention. Antiviral therapy has a 95% cure rate. The majority of the time, healing happens by day 10. After healing has begun, medication should be immediately tapered off and stopped by day 14. In viral ulcers, steroids are contraindicated (Salmon, 2022).

iv. Acanthamoeba Corneal Ulcers

In the beginning, a prescription for polyhexamethylene biguanide 0.02% and propamidine isethionate (Brolene) 0.1% may be given. Additionally, effective treatments include chlorhexidine monotherapy and the combination of Brolene and neomycin (Jeang & Tuli, 2022).

Although steroids should be avoided, they can be used with cysticidal medicines in cases of profound vascularization. Acanthamoebic keratitis may benefit from additional treatment with oral miltefosine.

Cycloplegics as Supplementary Treatment

To minimize ciliary spasm and induce mydriasis, which helps relieve discomfort and prevent synechiae formation, cyclopentolate 1%, atropine sulfate 1%, or homatropine 1% can be prescribed three times per day (Salmon, 2022).

Studies have also pointed out that if IOP is high, there is a need for short-term control (Mack et al., 2022). To reduce IOP, glaucomatous medication might be provided.

The common causes of medical treatment failure have been attributed to wrong diagnosis, antibiotic resistance, and non-compliance of the patient (Syafei & Prajitnob, 2021). In failed medical treatment, surgical interventions are taken to manage the corneal ulcers depending on the size, location, and causes. The standard surgical interventions are corneal gluing in managing the corneal perforations, amniotic membrane transplant (AMT), and other newer treatments such as photoactivated chromophore for infectious keratitis -corneal collagen cross-linking (PACK-CXL) (Schuerch et al., 2020). Raising awareness about eye care is crucial because the condition can impair vision. Using safety glasses while traveling or working helps stop many causes of corneal ulcers. Providing patients with information on contact lens maintenance and care can help reduce ulcers brought on by contact lens use (Salmon, 2022).

References

- Byrd, L. B., & Martin, N. (2019). Corneal ulcer.
- Cho, J., Prajna, N. V., Lalitha, P., Rajaraman, R., Krishnan, T., Ray, K. J., ... & Kidd, C. M. (2018). Therapeutic penetrating keratoplasty button cultures in The Mycotic Ulcer Treatment Trial II: a randomized trial comparing oral voriconazole versus placebo. *American journal of ophthalmology*, 192, 142-145.
<https://doi.org/10.1016/j.ajo.2018.05.007>
- Chopra, A., Solanki, S., Sharma, R., & Gupta, R. K. (2022). Microbial profile of infectious corneal ulcer in a remote Himalayan teaching hospital in Himachal Pradesh (India). *Journal of Clinical Ophthalmology and Research*, 10(3), 101.
<https://www.jcor.in/text.asp?2022/10/3/101/362501>
- Jeang, L., & Tuli, S. S. (2022). Therapy for contact lens-related ulcers. *Current opinion in ophthalmology*, 33(4), 282-289. <https://doi.org/10.1097/ICU.0000000000000861>
- Mabrouk, N. A., Abdelkader, M. F., Abdelhakeem, M. A., Mourad, K. M., & Abdelghany, A. A. (2022). Epidemiology, clinical profile and treatment outcomes of bacterial and fungal keratitis. *International Ophthalmology*, 42(5), 1401-1407.
<https://doi.org/10.1007/s10792-021-02128-x>
- Mack, H. G., Fazal, A., & Watson, S. (2022). Corneal ulcers in general practice. *Australian Journal of General Practice*, 51(11), 855-860.

- Merali, F. I., & Schein, O. D. (2020). Epidemiology of corneal diseases. *In Foundations of corneal disease* (pp. 307-330). Springer, Cham. https://DOI:10.1007/978-3-030-25335-6_26
- Miller, C. G., & Cao, F. (2021). Ocular infections. *In Pediatric Ophthalmology in the Emergency Room* (pp. 147-161). Springer, Cham. https://DOI:10.1007/978-3-030-49950-1_11
- Radhakrishnan, N., Prajna, V. N., Prajna, L. S., Venugopal, A., Narayana, S., Rajaraman, R., ... & Rose-Nussbaumer, J. (2021). Double-masked, sham and placebo-controlled trial of corneal cross-linking and topical difluprednate in the treatment of bacterial keratitis: Steroids and Cross-linking for Ulcer Treatment Trial (SCUT II) study protocol. *BMJ open ophthalmology*, 6(1), e000811.
- Salmon, J. (2022). *Kanksi's Synopsis of Clinical Ophthalmology-E-Book*. Elsevier Health Sciences.
- Schuerch, K., Baeriswyl, A., Frueh, B. E., & Tappeiner, C. (2020). Efficacy of amniotic membrane transplantation for the treatment of corneal ulcers. *Cornea*, 39(4), 479-483. <https://DOI:10.1097/ICO.0000000000002179>
- Syafei, A. R., & Prajitnob, J. H. (2021). Management approach in patient with type 2 diabetes mellitus with bacterial corneal ulcer associated with diabetic keratopathy: a case report. *Management Approach in Patient with Type 2 Diabetes Mellitus with Bacterial Corneal Ulcer Associated with Diabetic Keratopathy: A Case Report*, 88(1), 11-11.

Wuletaw, T., Geta, M., Bitew, A., Mulugeta, W., & Gelaw, B. (2021). Clinical and Microbiological Profile of Bacterial and Fungal Suspected Corneal Ulcer at University of Gondar Tertiary Eye Care and Training Centre, Northwest Ethiopia. *Journal of Ophthalmology*, 2021.
<https://www.hindawi.com/journals/joph/2021/3940151/>