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Review Article

The Approach to Diagnosis and Management of Corneal Ulcers

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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 [7]. 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 [7]. 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 [10]. 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

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 [5]. 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 [5]. 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.

Fungal corneal ulcers: Fungi are classified as yeast, filamentous septated, pigmented and non-pigmented, and filamentous without septae [5]. In temperate countries, yeast fungi like candida are widespread, but filamentous fungi like Aspergillus and Fusarium are more prevalent in tropical regions [13]. 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 [5]. 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.

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 [1]. According to a theory, herpes

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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 [8]. 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.

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 [4]. 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 [10]. These symptoms vary depending on the cause and the stage of corneal ulcers, whether acute or chronic.

Approach to Diagnosis of Corneal Ulcers

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 [10]. In this regard, a thorough history determining the patient's ulcer's underlying etiology is crucial for ensuring optimal care [13]. 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 [10]. 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.

Slit Lamp Biomicroscopy: A comprehensive slit lamp examination should be done keenly. Here are the steps [10]:

i. Evaluation of the eyelids for blepharitis, malfunction of the meibomian glands, ectropian/entropian, 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

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 [13]. 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.

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 [10]. 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 [8]. The infiltrate's depth, size, and location determine the course and line of medical treatment [10]. Treatment would need to be more forceful for central infiltrates than peripheral, superficial infiltrates of <2 mm. Injections into the stroma are necessary for deep intrastromal infiltrates because they provide good drug availability at deeper layers.

Bacterial corneal ulcers: In cases of external peripheral infiltrates less than 2 mm, 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 [10]. 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 [10]. 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 [9]. A previous study found no advantages to using corticosteroids to treat corneal scarring [9].

Table 1: Some classical signs of different infectious corneal ulcers.

Bacterial Corneal Ulcer	Fungal Corneal Ulcer	Viral Corneal Ulcer	Parasitic Corneal Ulcer
Gram Positive infection has localized infiltrate with distinct borders, with minimal stromal haze [3]. Gram Negative infections have dense stromal suppuration, ring infiltrates, and a hazy ground-glass appearance surrounding the cornea.	Dry raised slough with clear corneal surroundings that appear dry [3]. 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 wax and wane.	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 [3].	Acanthamoeba keratitis may be caused by wearing contact lenses or not [4]. Its distinguishing features are epithelium abnormalities, corneal edema, and single or multiple stromal infiltrates with a traditional ring-shaped arrangement. 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 2: Common antibiotics used in the management of bacterial corneal ulcers.

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

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 [2]. Steroids are not recommended for fungal ulcers [10]. 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 voriconalzole may be administered in addition to it.

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 [10].

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 [4]. 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 [10].

Studies have also pointed out that if IOP is high, there is a need for short-term control [6]. To reduce IOP, glaucomatous medication might be provided.

The common causes of medical treatment failure have been attributed to wrong diagnosis, antibiotic resistance, and noncompliance of the patient [12]. 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 asphotoactivated chromophore for infectiouskeratitis -corneal collagen cross-linking (PACK-CXL) [11]. 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 [10].

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