Bacterial Keratitis

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Introduction

Microbial keratitis is due to proliferation of any of the microorganisms on the cornea. Bacterial Keratitis is the most common cause of suppurative corneal ulceration. It is the duty of the clinicians to identity both the systemic and local risk factors and to find out the aetiology of each case. Laboratory investigations have to be considered in selected cases and treatment plan may be implemented accordingly. The therapeutic plan has to be changed if there is no response. The outcome depends on the proper treatment and the virulence of the organism. Surgery should be considered if medical therapy fails to stop the progress of the ulcer or vision is lost due to scarring and opacity.

Risk Factors

Cornea is normally protected by the natural defense mechanisms. They are eye lids, tear film, corneal epithelium, and normal ocular flora. Eye lids protect the cornea by providing a physical barrier and by resurfacing the pre-corneal tear film due to blink. Normal amount of tear secretion is 1 to 2 microlitres per minute and it protects the cornea due to the presence of enzymes like lysozyme, bactoferrin, betasins and ceruloplasmin. Intact corneal epithelium is another normal defense barrier. Only few organisms like Coryne bacterium diphtheriae, Nisseria gonorrhoeae, Haemophilus aegyptius and Listeria monocytogenes can invade the normal corneal epithelium. If epithelium is destroyed due to injury, contact lens wear or any surgery, there is possibility for bacterial infections. Inappropriate use of topical antibiotics may change the normal conjunctival flora, and may cause opportunistic organisms to attack the cornea.

Local risk factors for keratitis are bullous corneal oedema from corneal injury or surgery, absence of corneal sensation from herpetic corneal infection or topical anaesthesia abuse and local immunosuppression due to prolonged use of topical steroids. Other factors are use of contaminated water for eye wash, and, contaminated eye drops. Various lid problems like lagophthalmos, entropion, ectropion, trichiasis, dry eye, and contact lens wear are other local risk factors for bacterial keratitis. All type of contact lenses like hard, gas permeable, soft, disposable, and cosmetic lenses may predispose for microbial keratitis. Aphakes, patients with a corneal transplant, and patients wearing a bandage contact lens for chronic keratopathy are at high risk for bacterial keratitis. Ocular pemphigoid, Steven-Johnson syndrome, atopic keratoconjunctivitis, chemical injuries, and Vitamin-A deficiency may produce ocular surface disorders and hence can cause bacterial keratitis. After keratoplasty, and LASIK, there is possibility for bacterial corneal infection. (Fig 1-8 explain the various risk factors for corneal ulcer)

Aetiologic Agents

Bacterial keratitis may be due to any organism, and from the clinical features the organism cannot be identified, but we can keep a strong suspicion based on various clinical presentations. In an uncompromised cornea, the microorganism may be Pseudomonas aeruginosa, Streptococcus pneumoniae, Moraxella, Beta Haemolytic Streptococcus, and Klebsiella pneumoniae.
Fig 1: Acute conjunctivitis

Fig 2: Spring catarrh (palpaberal type)

Fig 3: Spring catarrh (bulbar type)

Fig 4: Blepharitis

Fig 5: Chronic dacryocystitis

Fig 6: Hordeolum internum lower lid

Fig 7: Corneal abrasion

Fig 8: Lagophthalmos
In a compromised cornea, the organisms which can be suspected are Staphylococcus aureus, Streptococcus epidermidis. Alpha Haemolytic Streptococci, Beta Haemolytic Streptococci, Proteus, Enterobacter Aerogenes, Escherichia and Nocardia. If a patient wearing contact lens develops keratitis the suspected organisms are Pseudomonas aeroginosa, Staphylococcus aureus, Staphylococcus epidermidis, E. coli, Klebsiella, and Proteus.

**Clinical Examination**

Detailed history and clinical examination is necessary for proper diagnosis. Most important is the history of any injury and any previous surgery, or chronic use of any topical steroids and antibiotics. History of unilateral watering and discharge is a clue to chronic Dacryocystitis. Contact lens wear has to be enquired and if present, further details like what type of lens and duration of the wear has to be enquired. History for symptoms of dry eye also has to be evaluated. Examination should not be restricted to the eye only and systemic orientation should be there. Basic illness like diabetes and infectious diseases or malignancy has to be suspected. Incidence of CP angle tumour presenting with intractable corneal ulcer has been reported.

Ocular examination should include visual acuity, torch light examination and slit lamp biomicroscopy. Visual acuity testing may be difficult due to photophobia, chemosis and oedema of lids, but it has to recorded for further evaluation of prognosis. Vision and posterior segment examination in the unaffected eye also has to be assessed. Torch light examination is for evaluation of the eye lids, conjunctiva, sclera, lacrimal sac, ulcer proper, anterior chamber, iris, pupil and lens. Position of the ulcer on the cornea, and condition of the surrounding area also has to be examined. Using slit lamp look for the depth, width, floor, and margin of the ulcer. By retroillumination, presence of oedema and the endothelial aspect of the ulcer has to be evaluated. Presence of microperforation, small hypopyon, and signs of early iritis also has to be looked for. Condition of the surrounding cornea is examined for corneal oedema and satellite lesions.

**Clinical Presentation**

Clinical presentation and symptoms are variable and they depends on virulence of the organism, duration of infection, pre-existing corneal conditions, immune status of the patient, previous use of antibiotics or corticosteroids. If the virulence of organism is more and the immune status of the patients is poor, the clinical signs will be severe and acute. Another factor which decide the clinical presentation is contact lens wear. Infection associated with contact lenses are multifocal. Epithelial and stromal infiltration is more diffuse. Usual clinical signs are conjunctival congestion, chemosis, lid oedema, decreased vision, pain, tearing, photophobia, and purulent discharge. Conjunctival reaction will be close to the limbus. Corneal epithelium becomes ulcerated and there will be infiltration which may be grayish white and necrotic. Infiltration and oedema of cornea may be seen away from the main lesion. Stromal abscess may be seen with deep infiltration with relatively clear stroma and intact epithelium. Anterior chamber reaction may leads to hypopyon, and fibrin plaques may be seen on the endothelium. The ulcer is considered to be severe, if the lesion progresses rapidly, has an infiltration dimension larger than 6 mm, involve deeper than one-third of corneal thickness and presents with impending perforation, or has scleral involvement. The organisms that produce severe and rapidly progressive ulcers include S. Aureus, S. Pneumoniae, Beta Haemolytic Streptococcus and P. Aeruginosa. Less severe and slowly progressive ulcers are usually caused by organisms such as coagulase negative Staphylococcus, S. Viridans, Actinomyces, Nocardia, Moraxella, and Serratia.

Hypopyon is due to outpouring of fibrin and polymorpho nuclear leukocytes from the vessels of iris and ciliary body. Usually hypopyon is sterile as long as Descemet's
membrane is intact. Hypopyon may be there in any of the bacterial infections but it will be severe and more common in infection with S. Pneumoniae and Pseudomonas.

Specific Bacterial Ulcers
From the clinical presentation we can suspect the presence of some organisms, but it has to be confirmed by laboratory investigations.

Ring Ulcer
It is severe form of ulcer seen around the cornea. It may be due to haematogenous spread or penetrating injury. The organisms like Pseudomonas, Streptococcus, Listeria, and Proteus has to be suspected.

Infectious Crystalline Keratopathy
The organisms responsible for this condition are S.Pneumoniae, S. Epidermidis, Haemophilus, Peptostreptococcus, and Candida. The stromal opacity is crystalline in appearance, resembling a snowflake, and not associated with cellular infiltrate or other sings of inflammation. Infection usually occurs within a corneal graft in the midstroma with clear stroma superficial to it. The epithelium will be intact.

Staphylococci
They produce acute purulent infection. Severe pain, photophobia, and decreased vision are seen in early cases. There is tendency to spread towards the centre of cornea. The edge of the ulcer may be undermined and covered by over hanging tissue.

Streptococci
Ulcer due to S. Pneumoniae occurs after corneal trauma, chronic dacryocystitis, or filtering bleb infection. The ulcer will be acute, purulent, and rapidly progressive with deep stromal abscess. Anterior chamber reaction will be severe with marked hypopyon and retrocorneal fibrin coagulation. Perforation secondary to ulcer is common.

Nocardia
Nocardia asteroides produce indolent ulcer after minor trauma with exposure to contaminated soil. Ulcer usually waxes and wanes. The characteristic features of Nocardia keratitis include raised, superficial pin head like infiltrates in a wreath like configuration. Keratitis may simulate mycotic infection.

Non Tuberculous Mycobacteria
They produce slowly progressive keratitis usually after removal of corneal foreign body, trauma, or following corneal surgery particularly after LASIK. The symptoms are delayed in onset and severe ocular pain develops 2 to 8 weeks after exposure to the organism. Lesion can be solitary or multifocal with variable anterior chamber reaction. Lack of response to conventional antibiotic therapy is usually a clue to the diagnosis.

Pseudomonas Aeruginosa
It causes a rapidly spreading ulcer which can extend to twice its size in 24 hours and perforation can occur within 2-5 days. Ulcer will be either central or paracentral. Dense stromal infiltration and necrosis are characteristic. There will be oedema of surrounding cornea, posterior corneal stromal folds, endothelial plaques and hypopyon. Diffuse epithelial graying or a “ground glass” appearance is noted in the nonulcerated area of the cornea. A copious mucopurulent discharge with a greenish colour is seen. Early desemetocele formation, melting and perforation may occur. Ulcer may spread to sclera and in those cases prognosis will be bad.

Moraxella
They cause corneal ulcer in compromised hosts, particularly alcoholics, diabetics, malnourished and other debilitated patients. Ulcer is indolent paracentral or peripheral, usually oval in shape and localized with an undermined necrotic edge. It progresses deep into stroma and in untreated cases may perforate. Hypopyon may be present and the anterior segment is highly inflammed.

Neisseria
N. Gonorrhoea and N. Meningitides can invade the cornea and conjunctiva through an intact epithelium and cause an ulcer. They are dangerous especially in newborns because they may lead to perforation. Marked purulent discharge, congestion and chemosis usually are present.

Laboratory Investigations
Laboratory investigations include corneal scraping for culture and sensitivity. Majority of cases will resolve
with empirical therapy and managed with out smears or cultures. Cultures are indicated in severe cases with corneal infiltrate that is large and extends to middle stroma, is chronic in nature or unresponsive to broad spectrum antibiotic therapy. It is also indicated to exclude the presence of fungus, amoeba, and mycobacteria. Cultures are useful for the modification of the therapy in patients with poor clinical response to empirical treatment.

**Culture**

Scraping for corneal material is performed after putting local anaesthetic drops. Proparacaine hydrochloride 0.5% is preferred because of it’s minimal inhibitory effect on microorganisms. Specimen is collected using a heat sterilized spatula (Kimura spatula), No. 15 Bard Parker blade, large gauge disposable needle or sterile cotton swab. If deep stroma is involved a small trephine can be used to get adequate specimen. Multiple samples has to be collected from the advancing margins of the ulcer. Specimen should be directly inoculated into the culture media. Blood agar, chocolate agar and thyoglycollate broth are the standard medias used for bacterial keratitis.

**Stains**

By examining the stained smears of corneal scraping various organisms can be identified. Gram stain is the one routinely used and it can confirm the presence of microorganisms with a sensitivity of 55-79 %. It can also distinguish bacteria from fungi. Giemsa stain also is useful to distinguish bacteria, fungi and Acanthamoeba. Chlamydia inclusion bodies can be identified with Giemsa stain. Cabolfusin, or Ziehl-Neilsen acid fast stains are for identification of Mycobacterium, Actinomyces, or Nocardia.

**Other Diagnostic Methods**

**Corneal Biopsy**

It is indicated in partially treated or unresponsive corneal ulcers or if culture negative for more than one occasion. It is also indicated if the infiltrate is in the mid or deep stroma with normal overlying tissue. Under topical anaesthesia, a small trephine or blade is used to excise a small piece of stromal tissue. The specimen should be at least 1-2 mm in diameter, and the edge of the ulcer should be included. One portion may be taken for biopsy and another for culture. In cases of deep corneal abscess with overlying clear cornea the biopsy should be taken from below a lamellar flap.

Impression cytology, polymerase chain reaction (PCR), and confocal microscopy are other rare diagnostic tools. Confocal microscopy is a new and non invasive procedure in which four dimensional view of internal structures are possible at cellular level.

**Specific Therapeutic Agents**

**Cephalosporins**

Cephalosporines contains betalactum ring that is necessary for bactericidal activity. Cefazolin with an excellent activity against grampositive organisms and minimal toxicity after topical administration is a widely used first generation cephaplorin.

**Glycopeptides**

Vancomycin is a glycopeptide antibiotic with activity against penicillin resistant Staphylococci. It is active against gram positive organisms.

**Aminoglycosides**

They have bactericidal action against aerobic and gram negative bacilli. Tobramycin, gentamycin and amikacin are the commonly available aminoglycosides. They are active against pseudomonas.

**Macrolides**

They are Erythromycin, azithromycin, clarithromycin and roxithromycin. They have broad spectrum of activity against gram positive and gram negative organisms.

**Fluoroquinolones**

The second and third generation fluoroquinolones ciprofloxacin, ofloxacin and levofloxacin are commercially available for ophthalmic use. Now the fourth generation fluoroquinolones like gatifloxacin and moxifloxacin also are available. They are active against aerobic gram negative and gram positive bacteria.

**Strategies for Initial Management**

Antibiotics can be used as either drops or ointments. Subconjunctival injection has to be considered if the ulcer is severe and extends to sclera. Systemic antibiotics are not necessary in routine cases. It has to
be considered if the infection spread to intraocular structures. Soft contact lenses soaked in antibiotics may sometimes be useful. For severe ulcers a loading dose every 5 to 15 minutes for first hour followed by application every 15 minutes to 1 hour can be considered. For less severe cases dose can be decided in each case. For selection of antibiotics any of the following approach can be considered.

**Culture Guided Approach**

Corneal scraping for staining and microbiological culture are performed in all cases and treatment will be started only after that. This option can be implemented only where cornea sub specialities are functioning and they deal with only referred patients. Those patients may have severe presentation caused by unusual organisms. Major inconvenience of this approach is cost. If the patient is on treatment with antibiotics it should be stopped for 12 to 24 hours before taking the specimen for culture.

**Empirical approach**

Treatment is started based on pre-existing culture and sensitivity data without obtaining corneal specimens from the patient. Broad spectrum antibiotics has to be started. Either single drug or fortified preparations can be considered.

**Case based approach**

In selected severe cases only culture and sensitivity is tested. In routine cases treatment will be started with broad spectrum antibiotics. Culture will be taken for ulcers affecting visual axis, large and deep ulcers, and those ulcers developed after trauma with contaminated vegetable materials. For small and peripheral ulcers treatment is started without any investigations. This approach is more practical in the management of corneal ulcer.

**Selection of Antibiotic and Initial Management**

Based on any of those approach the antibiotics can be selected. The frequency of instillation of the medicines has to decided based on the severity of each case. For more severe ulcers topical preparations should be given every 15 to 30 minutes and then hourly for 6 hours for adequate loading dose. After the loading therapy frequent and regular administration is necessary to reach a sustained therapeutic level. If the ulcer is responding the dose can be gradually tapered to reduce the medication induced complications. Prolonged intensive therapy may induce epithelial toxicity and delay corneal healing. Subconjunctival infection has to be considered in those ulcers spreading to sclera and cases of impending perforation. Systemic antibiotics are indicated if there is either intraocular or scleral spread of infections. In severe cases with impending perforation or frank perforation also systemic antibiotics has to be considered. Cycloplegic agents should be used to reduce pain, congestion and to decrease the formation of synechiae. Single drug therapy with either third or fourth generation fluoroquinolone is as effective as combinations therapy. Fortified preparations can be considered if there is no positive response with commercially available preparations.

**Modification of therapy**

The clinical response after 48 hours has to be evaluated, and modification of therapy if necessary should be done. Signs of improvement are reduction of pain, consolidation and sharp demarcation of the ulcer, decrease in density of the infiltration, reduction of stromal oedema, reduction in the anterior chamber inflammation and re-epithelialization. If there is no positive response therapeutic regimen may be modified based on the results of culture and sensitivity. If there is signs of improvement with initial therapy it need not be modified based solely on culture and sensitivity results.

**Follow up**

After one week the response has to be evaluated and if the ulcer completely heals, medication can be discontinued. If the ulcer is still progressive the medication should be stopped at least for 24 hours and microbiological work up may be repeated. Special staining or culture media or corneal biopsy may be required in those cases. Non infectious causes or rare organisms like mycobacteria, Nocardia, or Acanthamoeba should be suspected. If there is no response with antibiotics other reasons like drug toxicity, and possibility of local and systemic risk factors has to be considered. Non healing ulcers sometimes can be improved by debridement of necrotic corneal stroma, frequent lubrication and temporary tarsorrhaphy.
Adjunctive therapy

Additional treatment is necessary if there is impending or frank perforation or if there is signs of endophthalmitis. Impending perforation is suspected if there is thinning of the cornea and descematocele. Frank perforation is suspected if the anterior chamber depth is suddenly reduced and a black discolouration is seen at the base of the ulcer. Black discolouration may be due to incarceration, iris or pigments, in the base of the ulcer. Sudden relief of severe pain is the clinical symptom of frank perforation. Pressure bandage, cyanoacrylate tissue adhesives, or bandage contact lens application are the modifications to be introduced at this stage.

Surgical Management

Conjunctival flap

This is to save the eye ball and is indicated in non-healing corneal ulcers. In peripheral ulcers flap can be placed without compromising vision. Flap can bring blood vessel to the infected area promoting healing and provide a stable surface covering.

Penetrating keratoplasty

If the ulcer is not responding to any type treatment this surgical option is indicated. It is also indicated in ulcers involving limbus with scleritis, impending and frank perforation. Intensive antibiotic administration for 48 hours before surgery will minimize the risk of recurrence and endophthalmitis.

Summary and Conclusions

One of the major cause for corneal blindness is contributed by Microbial keratitis. The incidence of corneal blindness can be reduced if the disease is identified and managed early. Evaluation of each case should start with history of any trauma, and mode of onset. All the system has to be closely examined to exclude or establish the presence of any systemic risk factors. Then search for any local risk factors and closely observe the ulcer for a clinical diagnosis. At this stage the surgeon should built a clinical conclusion that he is dealing with Bacterial, Fungal, Viral or Parasitic keratitis. Laboratory confirmation is not required in all cases but in severe and selected cases specimen is collected for further investigations. Based on clinical evaluation a broad spectrum topical antibiotics has to be started, which could either be one commercially available or fortified. If there is no positive response to treatment, modification of the regimen should be considered. Surgical intervention is the ultimate way out in non-healing ulcers.

References