Infectious Keratitis: Management Protocols

Keratitis is an important cause of ocular morbidity worldwide, the outcome of which depends on early diagnosis, prompt and effective treatment. Infective keratitis is the proliferation of microorganisms with associated inflammation and destruction of the corneal tissue (Figure 1). The common causes of infective keratitis include bacterial, fungal, viral, and protozoan, the diagnosis of which is made on clinical examination aided by microbiological demonstration in smears or cultures from corneal tissue. \(^1\,^2\,^3\,^4\).

**Diagnosis**

**Bacterial keratitis**\(^5\)

**Corneal Scraping**

It is done by heat sterilized platinum (kimura) spatula from the margins and base of the ulcer. These specimens are subjected to staining and culture media:

**Staining:**

- Gram’s stain: differentiate into gram positive and negative bacteria.
- Can also identify fungal filaments and amoebic cyst.
- Giemsa stain: can distinguish bacteria from fungi.
- Zeihl-Nelsen acid fast stain: for suspected Mycobacteria, Actinomyces, Nocardia.
- Acridine orange, Calcofluor white stain: fluorochromatic dyes staining for bacteria that fluoresce

**Culture**

usually indicated in cases with large corneal infiltrates, deeper stromal involvement, chronic and unresponsive to therapy and suspected atypical keratitis.
- Blood agar: for most bacteria
- McConkey: for gram negative rods
- Chocolate agar: for Neisseria and Haemophilus
- Thygolycolate broth: for anaerobic bacteria and fungi
- Lowenstein Jenson media: Mycobacteria, Nocardia
- Thayer Martin agar: Neisseria
- Brain heart infusion broth: Anaerobic bacteria

**Conjunctival Swab**

Done when scraping can’t be done like in descemetocoele or unco-operative patients. Calcium alginate swabs

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*Figure 1: Perforated Bacterial Corneal Ulcer*
moistened with trypticase broth can be taken by sweeping through lower cul-de-sac.

**Corneal Biopsy**

Taken in case of deep stromal infiltrates and if cultures are negative. Four mm corneal trephine or blade is used.

**Management**

Empirical therapy in the form of broad spectrum fortified antibiotics combination or fluorquinolones should be immediately started. A loading dose initially as their instillation every minute for 10 minutes, every 5 minutes for 30 minutes, every half an hour for 2 hours and then depending on the severity and response should be initiated (Table 1). Supportive therapy in the form of cycloplegics and antiglaucoma medications should also be prescribed.

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**Infectious Keratitis**

- *Fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin than other fluorquinolones.*
- *Ciprofloxacin 3 mg/ml; gatifloxacin 3 mg/ml; levofloxacin 15 mg/ml; moxifloxacin 5mg/ml; ofloxacin 3 mg/ml, all commercially available at these concentrations.*
- *For resistant Enterococcus and Staphylococcus species and penicillin allergy. Vancomycin and Bacitracin have no gram-negative activity and should not be used as a single agent empirically in treating bacterial keratitis.*
- *Systemic therapy is necessary for suspected gonococcal infection.*

**Table 1: International Council of Ophthalmology Guideline**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Topical Concentration</th>
<th>Subconjunctival Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organism identified or multiple types of organisms</td>
<td>Ceftazolin with Tobramycin or gentamicin or Fluoroquinolones</td>
<td>50 mg/ml 9-14 mg/ml 3 or 5 mg/ml</td>
<td>100 mg in 0.5 ml 20 mg in 0.5 ml</td>
</tr>
<tr>
<td>Gram-positive Cocci</td>
<td>Ceftazolin</td>
<td>50 mg/ml 15-50 mg/ml 10,000 IU</td>
<td>100 mg in 0.5 ml 25 mg in 0.5 ml</td>
</tr>
<tr>
<td>Gram-negative Rods</td>
<td>Tobramycin or gentamicin Ceftazidine Fluoroquinolones*</td>
<td>9-14 mg/ml 60 mg/ml</td>
<td>20 mg in 0.5 ml 100 mg in 0.5 ml</td>
</tr>
<tr>
<td>Gram-negative Cocci***</td>
<td>Ceftaxone</td>
<td>50 mg/ml 50 mg/ml</td>
<td>100 mg in 0.5 ml 100 mg in 0.5 ml</td>
</tr>
<tr>
<td>Non-tuberculous Mycobacteria</td>
<td>Amikacin</td>
<td>20-40 mg/ml 10 mg/ml</td>
<td>20 mg in 0.5 ml</td>
</tr>
<tr>
<td>Nocardia</td>
<td>Sulfacetamide</td>
<td>100 mg/ml 20-40 mg/ml 16 mg/ml</td>
<td>20 mg in 0.5 ml</td>
</tr>
</tbody>
</table>

**Fungal Keratitis**

In India, the most common isolated organism is Aspergillus sp. in north India and Fusarium sp. in South India (Figure 2). Fungal keratitis is usually seen in rural areas and warm climates (Figure 3). Male to female ratio is 1.5:1 to 4.5:1, with higher cases occurring during monsoons and early winter because of high humidity.

**Laboratory Diagnosis**

1. **Corneal Scraping**

**Staining**

- Gram’s stain/Wet KOH (10%) mount
- Geimsa stain
- Gomori Methenamine Silver stain
- Periodic Acid Schiff

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**Figure 2: Various fungi causing keratitis can be grouped**

**Figure 3: Fungal Corneal Ulcer**
Management Protocols

- Calcuoflour white
- Acridine orange
- Lactophenol cotton blue
- Direct immunofluorescence

Culture
- Sabouraud’s dextrose agar incubated at 25 degree centigrade
- Brain heart infusion broth
- Thioglycate broth

2. Corneal Biopsy
3. Anterior Chamber Paracentesis
4. Other Methods:
   - Immunofluorescence staining
   - Electron microscopy
   - Polymerase chain reaction
   - Confocal microscopy

Management

Medical Therapy
Antifungal agents are classified into the following groups:
Polyenes include natamycin, nystatin, and amphotericin B. They are effective against both filamentous and yeast forms.

Amphotericin B is the drug of choice to treat patients with fungal keratitis caused by yeasts.

Although polyenes penetrate ocular tissue poorly, amphotericin B is the drug of choice for treatment of fungal keratitis caused by Candida. In addition, it has efficacy against many filamentous fungi. Administration is every 30 minutes for the first 24 hours, every hour for the second 24 hours, and then is slowly tapered according to the clinical response.

Natamycin has a broad-spectrum of activity against filamentous organisms, particularly for Fusarium. However, because of poor ocular penetration, it has primarily been useful in cases with superficial corneal infection.

Azoles (imidazoles and triazoles) include ketoconazole, miconazole, fluconazole, itraconazole, econazole, and clotrimazole.

Oral fluconazole and ketoconazole are absorbed systemically with good levels in the anterior chamber and the cornea; therefore, they should be considered in the management of deep fungal keratitis. The adult dose of ketoconazole is 200-400 mg/d, which can be increased to 800 mg/d. Itraconazole (200mg/day) for severe yeast keratitis

A new azole antifungal Voriconazole exhibit better penetration and wider spectrum of activity against Candida, Aspergillus and Fusarium.

Others-Fluorinated pyrimidines, such as flucytosine, are other antifungal agents. It is usually administered in combination with an azole or amphotericin B.

Treatment should be instituted promptly with topical fortified antifungal drops, initially every hour during the day and every 2 hours over night.

Subconjunctival injections may be used in patients with severe keratitis or keratoscleritis. They also can be used when poor patient compliance exists.

An oral antifungal (eg, ketoconazole, fluconazole) should be considered for patients with deep stromal infection. Antifungal therapy usually is maintained for 12 weeks, and patients are monitored closely.

Fluconazole has been shown to penetrate better into the cornea after systemic administration compared to other azoles and may be associated with fewer adverse effects.

Surgical Intervention
In cases which are non responsive to medical therapy. Intracameral/ Intracorneal amphotericin B(5-10μg/0.1ml)

References