Fungal Keratitis

Dr. N. Bindu MS

Fungal infections of the cornea constitute an important eye problem in outdoor workers in tropical & subtropical countries. Favourable humid climate and large agricultural & manual labourer population makes fungal keratitis common here. 30-50% of culture proved suppurative keratitis of non viral origin is constituted by fungal keratitis.

Globally there has been an increase in number of reported cases of fungal keratitis. Increasing use of antibiotics, injudicious use of steroids, increasing laboratory capability for recovering fungi from infected corneas and an increased awareness all have contributed to this.

Fungi causing human keratitis

A. Hyaline Filamentous fungi
   Fusarium (F.solani,Foxyxsporum)
   Aspergillus (A.fumigatus,A.flavus)
   Scedosporium
   Pencillium(Pspinulosum,Pcetrinum)
   Acremonium(Cephalosporium)
   Paecilomyces

B. Dematiaceous Filamentous fungi
   Curvularia(C.lunata,C.geniulata)
   Bipolaris
   Exserohilum
   Cladosporium
   Coelomycetes

C. Yeast like fungi
   Candida (C.albicans)

Aetiology

Fungal ulcer affects young healthy adults (21-60 yrs) who live in rural areas - agriculture being their main occupation. Males are commonly affected as they do most outdoor works than females. Majority of patients are immunocompetent without any external eye disease.

Epidemiology

Aspergillus species is the most common organism responsible for fungal keratitis world wide.

India

<table>
<thead>
<tr>
<th>Organism</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Aspergillus</td>
<td>27-64 %</td>
</tr>
<tr>
<td>Fusarium</td>
<td>6-32 %</td>
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<tr>
<td>Pencillium</td>
<td>2-29 %</td>
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</tbody>
</table>

In northern India, Nepal & coastal Karnataka Aspergillus is found to be more frequently involved. In Southern India, Fusarium is reported as the leading etiologic agent. Candida is very rare in India as causative organism.

Predisposing factors

- Local
- Systemic

Local

1. Trauma- injury to the cornea with vegetable matter or organic matter is reported in 55-65% of fungal keratitis
2. Contact lenses- In industrialised countries contact lens wear has been identified as a risk factor (29%).
Patients wearing any type of contact lens can get fungal keratitis

3. Iatrogenic – following cataract surgery, refractive surgery, LASIK, penetrating keratoplasty

4. Topical steroid use - 4-30 % has been reported in various studies. Steroid use tend to activate and increase virulence of fungi

5. Other factors-corneal surface disorders, dry eye, bullous keratopathy, exposure keratitis, allergic conjunctivitis are associated with the development of mycotic keratitis

**Systemic factors**-

- Diabetes - 5%
- Malnutrition - 1%
- Alcoholism – rare
- HIV – rare

Chronically ill & intensive care unit patients are prone to develop candida infection.

**Clinical features**

**Symptoms** – may not present as acutely as with other form of microbial keratitis, Usually signs of inflammation is minimal and absence of lid edema is a common feature.

**Signs** – greyish white/yellowish white infiltrates

Ulcer base filled with soft, creamy, raised infiltrates

Feathery borders or hyphate edges – in 70 %

Hypopyon – solid hypopyon with convex upper border- in 55 %

Satellite lesions - 10 %

Demataeaceous fungi keratitis shows black/brown pigmented surface which is dry, rough, leathery and difficult to scrape (fig 1, fig 2, fig 3)

**Other features**

- Immune ring
- Posterior corneal abscess
- Endothelial plaque

Rarely fusarium lead to endophthalmitis.

Depending on aetiological agent each case may vary.

Fusarium species usually produce severe keratitis leading to perforation, deep extension and malignant glaucoma

Aspergillus & curvularia produce less severe ulceration and are more amenable to therapy.

**Microbiological investigations**

Microbiological investigations should always be performed where fungal infections of cornea is suspected, as it is not possible to distinguish between bacterial and fungal keratitis on clinical findings alone. It includes the following

- Smears
- Staining
- Fungal culture
- PCR
- Confocal microscopy

**Direct microscopic evaluation**-

Most valuable and rapid diagnostic tool for detection of fungal elements. Corneal scrapings are obtained by scraping the base and edges of the ulcer with sterile blade or spatula several times. Smears should be made as thin as possible.

**Stains used & their sensitivity**

<table>
<thead>
<tr>
<th>Stain</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram stain</td>
<td>45-73 %</td>
</tr>
<tr>
<td>Giemsa stain</td>
<td>66 %</td>
</tr>
</tbody>
</table>
Lactophenol cotton blue 70-80 %
Grocott's methanamine silver 89 %
Calcoflour white 80-90 %
KOH 10 % wet mount 80-90 %

Calcoflour white
Fungal hyphae and yeast cells are delineated against dark background seen even in thicker preparations also. Acanthamoeba cysts and P. carini can also be detected, but it requires UV microscope.

Culture
Fungal growth usually occurs within 3-4 days (48-72 hrs) but may require incubation up to 4-6 weeks.

Sabo0raud’s dextrose agar is used frequently. It is kept at room temperature. Initial growth occurs within 72hrs in 83% and within 1 week in 97% cultures. (fig 7).

Is a simple, cheap, rapid test and easy to interpret even by ophthalmic technicians. It is an ideal method for practice in developing countries. KOH can be counterstained by India ink, PAS and acridine orange.

Gram stain-
Stains yeast cell and fungal hyphae equally well. It can identify bacteria also.

Lactophenol Cotton Blue (fig 6)- detect all common ocular fungi. It is commercially available and has long shelf life.

Grocotts methanamine silver stain
Fungal cell walls and septa are clearly delineated against pale green background. Can identify acanthamoeba cysts and P. carini.

Blood agar- also yields good positivity
Thioglycollate broth and brain heart infusion are not necessary routinely.

Corneal biopsy
Done if smears and cultures are negative in highly suspicious cases. Done under local anaesthesia using 2-3 mm trephine. Corneal button obtained from therapeutic PKP can also be used. Histopathology reveals the presence of fungal elements (fig. 8).
**Suggested lab workup**

KOH wet mount with or without stain  
Gram staining  
LCB  
Culture in SDA and blood agar

**Other methods**

Impression debridement  
Cellulose acetate filter paper is applied on to the ulcerated part, stained and examined.

**PCR**

Is an effective method of diagnosing fungal keratitis because it offers increased sensitivity and significant reduction in time (4 hrs) to establish diagnosis.

**Confocal microscopy**

Is a non-invasive invivo examination technique. Can reveal hyphal elements and yeast forms. It is more sensitive than culture.

**Medical Therapy**

Therapy of fungal keratitis is unsatisfactory. Antifungal agents available are mostly fungistatic and requires prolonged therapy.

Response to therapy is slow and the result is better in non severe ulcers.

**Drugs available for treatment**

<table>
<thead>
<tr>
<th>Polynenes</th>
<th>Amphotericin B –</th>
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<tbody>
<tr>
<td>Nystatin</td>
<td>Available as systemic preparation (fungizone)</td>
</tr>
<tr>
<td>Natamycin</td>
<td>Topical drops is prepared by diluting with dextrose or distilled water to a concentration of 0.15-0.5 %. Other routes of administration are</td>
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<tr>
<td>Imidazoles</td>
<td>Subconjunctival-10 micrgrams</td>
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<tr>
<td>Clotrimazole</td>
<td>Intracameral – 5-7 micrograms</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Intravitreal – 10 micrograms</td>
</tr>
<tr>
<td>Econazole</td>
<td>Intravenous -0.1 mg/kg bodyweight.</td>
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</table>

It covers Candida and Aspergillus but is not effective against Fusarium. It is used as first line of therapy in Candida.

<table>
<thead>
<tr>
<th>Azoles</th>
<th>Drug</th>
<th>Topical</th>
<th>Oral</th>
<th>Parenteral</th>
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<tr>
<td></td>
<td>%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>1-2</td>
<td>200-600 mg</td>
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<tr>
<td>Miconazole</td>
<td>1-2</td>
<td>200-400 mg</td>
<td>600-1200mg/d</td>
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<tr>
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<tr>
<td>Clotrimazole</td>
<td>1-2</td>
<td>60-100 mg</td>
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<tr>
<td>Fluconazole</td>
<td>1</td>
<td>100-400 mg</td>
<td>2mg/ml</td>
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<tr>
<td>Itraconazole</td>
<td>1-2</td>
<td>200-400 mg</td>
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Available commercially as Auroclot, nistin-(clotrimazole), Aurozole (econazole)

**Treatment protocol**

**Specific antifungal therapy**

Depend on availability of the drugs and the results of lab study and severity of ulcer.

If **hyphae** are seen –natamycin or amphotericin topically

If **yeast**/pseudohyphae seen- amphotericin/ fluconazole/ flucytosine

**Dosage** –topical eye drops hourly during day and 2 hourly at night.

In deep keratitis / endophthalmitis / scleritis / after PKP oral ketoconazole/itraconazole/fluconazole given

Miconazole is the drug of choice in paeciliomyces

Amphotericin and imidazole are antagonistic.

Treatment should be maintained for 6-12 weeks.
Antimicrobial activity of antifungals based on published reports.

<table>
<thead>
<tr>
<th>drug</th>
<th>Aspergillus</th>
<th>Candida</th>
<th>Csporium</th>
<th>Cladosp</th>
<th>Curvulari</th>
<th>Fusarium</th>
<th>Paecilio</th>
<th>Pencillium</th>
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<tbody>
<tr>
<td>Amph-B</td>
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<td>Nystatin</td>
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<td>Natamycin</td>
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<tr>
<td>Clotrimazole</td>
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<tr>
<td>Miconazole</td>
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<td>Econazole</td>
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<td>Flucytosine</td>
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S-susceptible, I- variable, R-resistant

**Surgical therapy**

**a) Frequent corneal debridement**

Mechanical debridement of corneal epithelium helps in debulking fungi and enhances drug penetration.

It is done with spatula/blade using slitlamp under local anaesthesia every 24-48 hrs

**b) Therapeutic keratoplasty**

It is the ideal method to treat nonhealing fungal keratitis threatening perforation. Structural integrity and eradication of sepsis is achieved in 80-90% of cases.

Lens should be left undisturbed as far as possible to prevent posterior extension.

Topical antifungal therapy is to be continued. In addition systemic antifungals to be given for 6-8weeks.

Use of post operative steroids topically is controversial

**Other surgical modalities**

Cyanoacrylate glue
Conjunctival flap
Amniotic membrane transplantation

**Conclusion**

Diagnosis and treatment of fungal keratitis can be quite challenging.

Microbiological investigation is essential for correct diagnosis and treatment.

Prolonged medical treatment and prompt timing of surgical intervention are required to increase chances of cure.

Emphasis on prevention and early diagnosis of this potentially blinding disease.

**References**

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