**Corneal Ulcer** - It is a discontinuation of normal epithelium of cornea associated with necrosis of surrounding corneal tissue and characterized by edema & cellular infiltration.

**Etiology classification of corneal ulcers**

1. **Infective Keratitis** -
   - a. Bacteria
   - b. Viral
   - c. Fungal
   - d. Spirocheatal
   - e. Chlamydial
   - f. Protozoal

2. **Allergic Keratitis** -
   - a. Phlyctenular
   - b. Vernal

3. **Trophic**
   - a. Exposure

4. **Associated with**
   - a. Skin-diseases
   - b. Atopic
   - c. Neuroparalytic
   - d. Mucous membrane diseases

5. **Associated with systemic collagen disorder**

6. **Traumatic:**
   - a. Mechanical trauma
   - b. Chemical trauma
   - c. Thermal burn

7. **Idiopathic**
   - a. Mooren’s Corneal Ulcer
   - b. Superior limbic keratoconjunctivitis
   - c. Superficial punctate keratitis of Thygeson

**Stages of corneal ulcers**

1. Stage of progressive infiltration
2. Stage of active ulceration
3. Stage of regression
4. Stage of cicatrization

**FUNGAL CORNEAL ULCER**

It is climatic specific. Fungi are opportunistic agents of infection, 70 different types of fungi are implicated as a cause for fungal corneal ulcers.

Filamentary fungi are predominant in tropical & subtropical climates (fusarium & aspergillus) while candida & aspergillus appear more important in temperate and colder climates.

Incidence of suppurative corneal ulcer caused by fungi has increased in recent year due to injudicious use of antibiotic & steroid. Morbidity of fungal infection tends to be greater than that of bacterial keratitis because of delay in diagnosis. It’s necessary to be aware of possibility of such infection and to properly investigate & treat with appropriate drugs.

**Etiology** -

1. **Causative fungi**
   - a. Filamentry fungi - include- Aspergillus, fusarium, cephalosphorium, curvularia, penicillium.
   - b. Yeast - Candida, Cryptococcus

2. **Mode of infection**
   - 1. Injury by vegetative materials. (Common sufferers are field workers specially in harvesting season)
   - 2. Injury by animal tail
   - 3. Secondary fungal ulcer - is commonly found in immunosuppressed hosts.
     - Such as patients suffering from dry eye, herpetic Keratitis, bullous keratopathy, Post-operative case of keratoplasty

3. **Role of antibiotics & steroids**
   - Antibiotic disturb symbiosis between bacteria & fungi, Steroid makes the fungi facultative pathogens.

**Pathogenesis**
Fungi thrive in hot & humid environment, rich in vegetable matter & organic decay. Fungi do not infect the cornea easily - they require trauma, immunological compromised state & tissue devitalization. Virulence of fungi, relate to their ability to proliferate within corneal tissue, resists host defense & produce tissue damage. After penetration fungi causes direct damage by invasion and growth of fungal elements & damage resulting from infiltrating leukocyte, fungal toxin & enzyme. In fungal corneal infection clinical manifestation in may occur as quickly as 24-48 hrs or may be delayed for 10-20 days. Fungi secrete various toxin substance - protease, haemolysin, Exotoxin Tricothene - Fusarium, Acremonium, Gliotoxin, Aspergillus penicillium, Candida albicans Phospholipase.

These toxin elicit an inflammatory response in low dose and destruction of cell type at higher concentration. Fungal corneal infections tend to spread deep into the corneal stroma, where the organisms are inaccessible to the usual diagnosis and therapeutic measure. Fungi even may penetrate an intact Descemet's membrane into the anterior chamber.

**Histopathology**

Fungal hyphal elements are oriented perpendicular to normal corneal lamella & tend to penetrate Descemet's membrane. Localized inflammatory reaction at limbus is characterized by a collection of round cell & plasma cells.

**Clinical features**

- Pain, Watering - reflex hyperlacrimation, Photophobia - Stimulation of nerve ending, Redness - Congestion of cillum-corneal vessels,
- Dry eye, grayish white with elevated rolled out margins, Feathery figure like extension surround the stroma under intact epithelium, Yellow line demarcation (sterile immune ring) known as Waxley's ring due to deposition of immune complex and inflammatory cell around the ulcer
- Multiple small satellite lesions may present around the ulcer
- Hypopion - Big, thick, immobile, not sterile may be present, Perforation - rarely
- Corneal vascularisation are conspicuously absent. Filamentary fungal infection - slow onset
- History of Previous trauma with vegetable matter
- Persistent infiltration gradually increase with time at site of previous superficial trauma.
- Cornea slightly thickened and satellite lesions peripheral to focal area at infiltration.
- Multiple micro abscess may present surround main lesion.
- Saprophytes that grow in decaying vegetation & also in stem, root, leaves, fruits, cultivated plant.
- Large banana shaped macro conidia that are produced on short lateral hyphae.

In *Fusarium*

- Aspergillus :
- Common contamination in hospital air
- Hyphae of Aspergillus are separate & characteristically branch dichotomously.
- If patients is left untreated - Inflammatory sign gradually progress. . Yeast Infection
- Permanently break down of epithelium and stromal ulceration - Formation of descematocele
- Neovascularization - Association of Hypopion with fungal endophthalmitis may be seen following fungal corneal ulcer.
- It mostly occurs in immuno-suppressed patients
- Infections are superficial, appearing as white raised colonies in previously ulcerated areas
- Most case remains superficially but deep infection may be occur
- Eye can be quickly lost unless appropriate treatment

**Diagnosis**

I. Proper history
- Associated with vegetative injury, be suspect when condition of chronic ulcer worsen in spite of most efficient treatment

II. Smear

III Culture

1. Wet KOH
2. Direct smear immediately fixed with methyl alcohol.
3. Giemsa stain - Show ghosting of fungal wall and yeast budding is may be noted.
4. Gomori methanamine Silver technique - Delineate the hyphae as sharp black structure against a pale green background.
5. Gram stain - fungus can be seen directly
6. Periodic acid schiff (PAS)
7. Calco fluor white.

- Fusarium Colonies are white in early stage, when colonies mature pigmentation occur from yellow to red then red to purple
- Aspergillus Colonies are white at first but as spore are produce they become velvet green.
- Candida Colonies are white to tan and Opaque with a smooth, flat, round, contour. Pasty soft consistency.

**Management**

In case of septate hyphal elements (filaments) the drug of choice natamycin 5% suspension 5 time/day.
If natamycin is not available - Amphotericin - B 0.150/0 every 5 minute for 1 hour then 1 hourly for first 24 to 48 hours

If Pseudohyphae or budding yeast are seen on smear - Doc - Amp- B 0.15% in distilled water, every 5 minute for 1 hour and then 1 hourly for several days.

For systemic yeast infection - Fluocytocin & Amp-B can be given.

If Amp- B is not available - then - Miconazole - 1 % eye drops in arachis oil

The other alternative Fluconazole ointment or eye drops

Treatment for Initial stage Natamycin + Amp - B can be given.

For prolonged topical therapy 8-10 time per day for one week then tapering the dose 4 to 6 times/day 6-8 wks

If therapy is not effective - discontinuation of therapy for 24 hours. Take another specimen for culture.

**Treatment for Intraocular complication following fungal keratitis**

**Surgical Management**

If invasion of sclera, A/c & deeper ocular structures has occurred - Then - anterior chamber washout with Amp-B 5-10/microgram - this process repeated & systemic anti fungal (fluconazole ) should be given.

If conservative management does not succeed; Then Penetrating keratoplasty done with A/c washout with Amp - B

If significant corneal scar present - Therapeutic penetrating keratoplasty will be done.

If perforation or scleral invasion occur - penetrating keratoplasty.

Or lamellar patch graft may be required.

Large cornea & corneoscleral graft that encompasses the area of inflammation effective in combating the infectious process & restoring integrity of globe. Anterior and posterior chamber lavage - may be done if lens is involved.

If virettous is involved - virectomy and intra-vitreal therapy with Amp - B may be done.

**Classification of anti-fungal drugs**

<table>
<thead>
<tr>
<th>Name</th>
<th>Action</th>
<th>Dose</th>
<th>Side effects</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polylene derivatives - 1. Natamycin</td>
<td>Bind with fungal cell membrane causing leakage of cell inclusion and oxidative damage to fungal cells</td>
<td>5% suspension 5 times a day up to 2 weeks</td>
<td>Irritation, burning, punctate keratitis and chemosis</td>
<td>Fusarium, Aspergillus and Candida</td>
</tr>
<tr>
<td>2. Amphotericin-B</td>
<td>Same as above</td>
<td></td>
<td>Nefro-toxicity, bone marrow suppression, anemia, headaches, vomiting, topical toxicity is minimized by using a diluted preparation</td>
<td>Aspergillus and Candida</td>
</tr>
<tr>
<td>3. Nystatin</td>
<td>Same as above</td>
<td></td>
<td>Allergic hypersensitivity reaction</td>
<td>Candida</td>
</tr>
<tr>
<td>Azole group - Imidazole derivatives - 1 Miconazole</td>
<td>Inhibit ergosterol synthesis causing disorganization of fungal cell membrane</td>
<td>1% eye drops hourly, 2% eye ointment, sub-conjunctival dose 5-10 mg every 48 hours for 2-3 days</td>
<td>Punctate epithelial erosions, pruritis, irritation and erythema</td>
<td>Filamentous fungi, Candida</td>
</tr>
<tr>
<td>2. Clotrimazole</td>
<td>Same as above</td>
<td></td>
<td>Irritation and punctate keratopathy, hepato- toxicity, diarrhea, nausea</td>
<td>Candida and Aspergillus</td>
</tr>
<tr>
<td>3. Econazole</td>
<td>Same as above</td>
<td></td>
<td>Local irritation</td>
<td>Aspergillus, fusarium, penicillium</td>
</tr>
<tr>
<td>4. Ketoconazole</td>
<td>Increased membrane permeability by inhibiting uptake of precursors of RNA and DNA synthesis</td>
<td>1% eye drops 4 times a day</td>
<td>Gynecomastia, impotence, abnormal liver function</td>
<td>Candida, Aspergillus, Fusarium and Curvularia</td>
</tr>
<tr>
<td>Triazole derivatives - 1. Fluconazole</td>
<td>Same as above</td>
<td></td>
<td>Irritation, burning sensation</td>
<td>Candida and Cryptococcus</td>
</tr>
<tr>
<td>2. Itraconazole</td>
<td>Same as above</td>
<td></td>
<td>Dizziness, headaches, pruritis, hypokalemia</td>
<td>Candida and Cryptococcus</td>
</tr>
</tbody>
</table>
3. Terconazole
Selective inhibition of 14 alpha desmethyl sterol synthesis
1% eye ointment one hourly, PO 200 mg/day in divided doses

Pyrimidine derivatives
Flucytosine
Interferes with nucleic acid synthesis
1% eye drops one hourly, then 4 times a day for 3 weeks. PO 50-150 mg/kg/day in divided doses for 1 week

Candida
Irritation, itching, burning sensation, nausea, vomiting, diarrhea

Candida, cryptococcus, aspergillus, penicillium

Other anti-fungal drugs:

Silver sulfadiazine
Fungistatic, active against candida, aspergillus and fusarium.
Doses:
1 % eye drops hourly initially then tapering QID. Adverse effect - irritation, FB sensation, itching.

New Anti-fungal drug:

Terbinafine (Lamisil) - Allylamine derivatives, lipophilic, fungicidal
Mode of Action - inhibiting squalene epoxidase, - and corresponding accumulation of squalane which causes cell death.
Dose:
1 % e/oint. Oral dose 250 mg/day for 2-4 wk adverse effect local redness, itching, stinging, and dryness, systemic - gastrointestinal dysfunction

Under trial new anti-fungal drugs
1. Posaconazole
2. Ravuconazole
3. Voriconazole

Drug interactions
1. Amphotericin - B - penetration of flucytosine into the fungus
2. Aminoglycoside and vancomycin increased renal impairment cause by AMB 3. Rifampicin and cimetidine decrease efficacy of fluconazole

Summary
During the past 10 years there has been a major change in outlook for fungal infection of cornea. Better diagnostic methods, more effective & less toxic antifungal agent, an enhanced awareness of pathogenic mechanism involved in corneal inflammation have been responsible for improvement in outcome.