FUNGAL CORNEAL ULCER

Presented by Dr. Vasu Chaurasia PG student NSCB MCH on 25-4-04 in Hotel Krishna - Conference room. Sponsored by Dey's Medical Ltd. (Also see Infective Keratitis by Dr. Shabbir Hussain)

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. Spiro cheatal
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 keratoconjuctivitis
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. Its necessary to be aware of possibility of such infection and to properly investigate & treat with appropriate drugs.

Etiology-

I. Causative fungi

a. Filamentry fungi - include- Aspergillus, fusarium, cephalosphorium, curvuluria, penicillium.
b. Yeast - Candida, Cryptococcus

II. 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 immunosuppresed hosts.
- Such as patients suffering from dry eye, herpetic Keratitis, bullous keratopathy, Post-operative case of keratoplasty

III. 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 - Fusariam, Acremonium, Gliotoxin, Aspergillous 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 Descement's membrane into the anterior chamber.

Histopathology

Fungal hyphal elements are oriented perpendicular to normal corneal lamellae& tend to penetrate Descement'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 circum-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 Wessley'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.
Filametry 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 remain 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.

1. Sabourauds medium incubated at 25 C
2. Blood agar incubated at 25 & 37 C (fusarium - 37 C)
3. Brain heart infusion broth (Chloramphenicol add)
4. Thioglycolate broth.
5. Chocolate agar substitute for blood agar.

-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 - Flucytocin & 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 with ECCE - may be done if lens is involved.

If vitreous is involved - vitrectomy and intra-vitreal therapy with Amp - B may be done.

Classification of anti-fungal drugs

Name	Action	Dose	Side effects	Activity
Polylene derivatives - 1. Natamycin	Bind with fungal cell membrane causing leakage of cell inclusion and oxidative damage to fungal cells	5% suspension 5 times a day up to 2 weeks	Irritation, burning, punctate keratitis and chemosis	Fusarium, Aspergillus and Candida
2. Amphotericin-B	Same as above	0.15 to 0.25% solution hourly, IV dose 1.5 mg/kg in 5% dextrose, start with low dose. Sub-conjunctival dose 0.5 to 2 mg in 0.5 ml	Nephro-toxicity, bone marrow suppression, anaemia, headaches, vomiting, topical toxicity is minimized by using a diluted preparation	Aspergillus and Candida
3. Nystatin	Same as above	100.000 IU eye ointment 4-5 times a day till healing occurs	Allergic hypersensitivity reaction	Candida
Azole group - Imidazole derivatives 1.Miconazole	Inhibit ergosterol synthesis causing disorganization of fungal cell membrane	1% eye drops hourly, 2% eye ointment, sub-conjunctival 5-10 mg every 48 hours for 2-3 days	Punctate epithelial erosions, pruritis, irritation and erythema	Filamentous fungi, Candida
2.Clotrimazole	Same as above	1% eye drops hourly till healing occurs then taper to 3-4 times per day	Irritation and punctate keratopathy, hepato-toxicity, diarrhea, nausea	Candida and Aspergillus
3. Econazole	Same as above	1% eye drops 4-6 times a day	Local irritation	Aspergillus, fusarium, penicillium
4. Ketoconazole	Increased membrane permeability by inhibiting uptake of precursors of RNA and DNA synthesis	1% eye drops 4 times a day, 200-800 mg/day for 1 week	Gynaecomastia, impotence, abnormal liver function	Candida, Aspergillus, Fusarium and Curvularia
Triozole derivatives 1. Fluconazole	Same as above	0.3% eye drops every 4 hours tapered to 4 times a day for 14-21 days. PO 200 to 600 mg/day in 2 doses for 3 weeks in Candida and 10-12 weeks in Cryptococcus. intra-vitreal dose 100 micrograms	Irritation, burning sensation	Candida and Cryptococcus
2. Itraconazole	Same as above	1% eye ointment one hourly. PO 200 mg BD for 1 week	Dizziness, headaches, pruritis, hypokalemia	Candida and Cryptococcus

3. Terconazole	Selective inhibition of 14 alpha desmethyl sterol synthesis	1% eye ointment one hourly, PO 200 mg/day in divided doses		Candida
Pyramidine 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	Irritation, itching, burning sensation, nausea, vomiting, diarrhea	Candida, cryptococcus, aspergillus, penicillium

Other anti-fungal drugs:

Silver sulfadizine

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 squaline epoxidese, - and corresponding
accumulation of squaline 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 flucytocine 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.