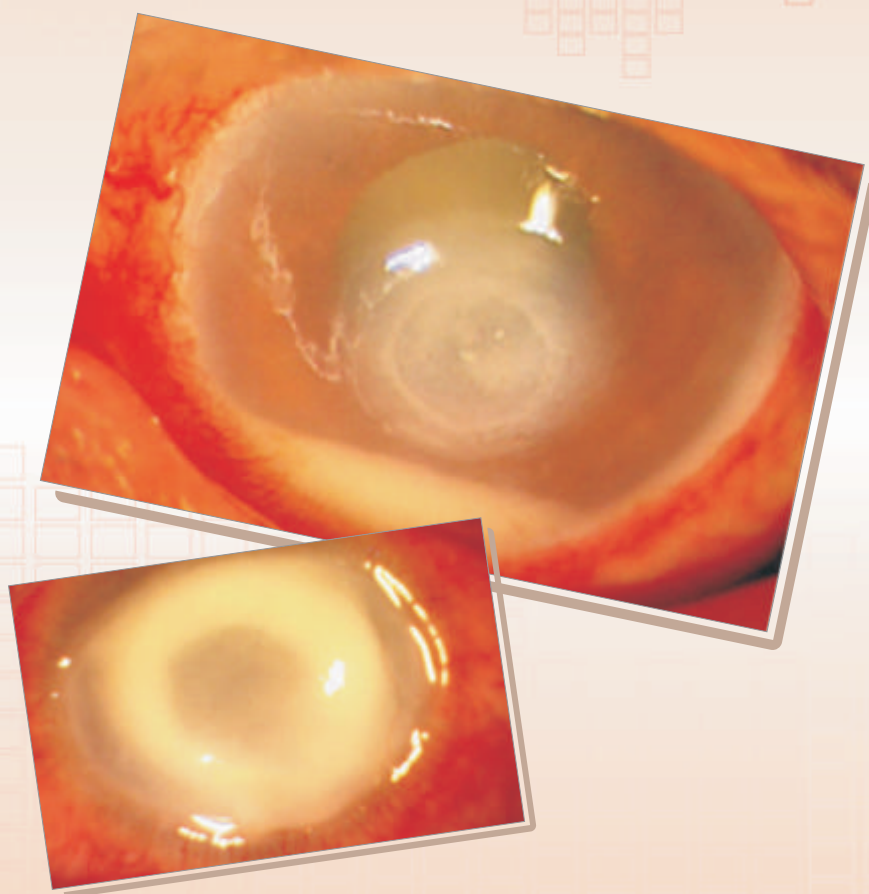
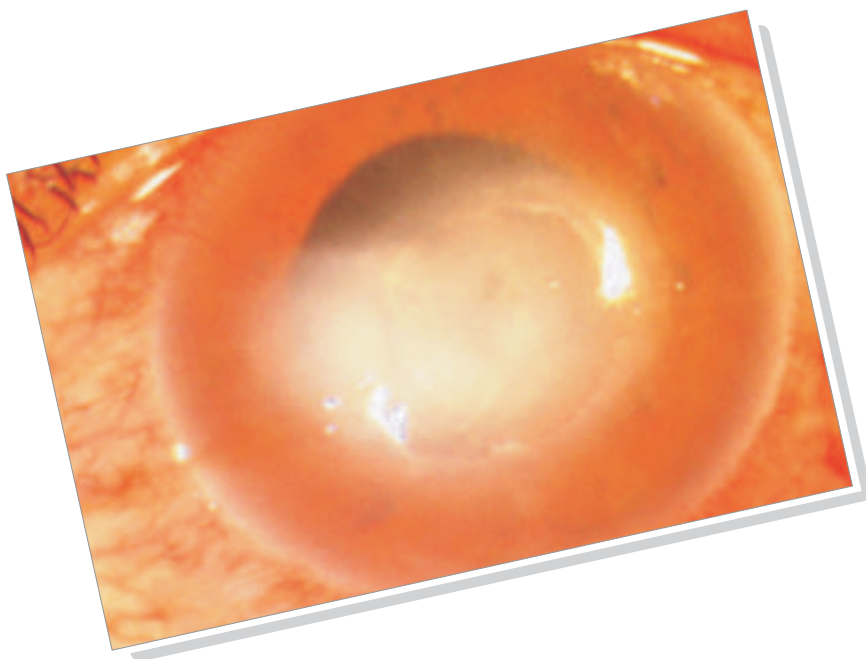


AIOS Guidelines for Diagnosis and Management of Microbial Keratitis



Joint Initiative of
All India Ophthalmological Society & Cipla





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All India Ophthalmological Society

Room No. 111, OPD Block

Dr. R.P. Centre, AIIMS, New Delhi-110029 - India

Ph. : 011-26588327

E-mail : aiossecreteriate@yahoo.co.in, lalitverma@yahoo.com

For any suggestions please write to

Hony. General Secretary

AIOS

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Foreword

Corneal Ulcer is one of the very common clinical problems, all of us face in our day-to-day practice.

Each one of us has our own approach, follow our own treatment protocols - despite a lot of text book and internet data being available.

All India Ophthalmological Society (AIOS) conducted a workshop to evolve a consensus on “Diagnosis and Management of Microbial keratitis” with special reference to our country. Dr. Namrata Sharma, Associate Professor at Dr. R.P Center, AIIMS, conducted this one day workshop on 16th July 2010. Corneal experts from across the country met, debated, argued and ultimately came to a consensus. This booklet, conceived, written, checked and cross-checked by Dr. Namrata and Dr. Shveta Jindal is the synopsis of that workshop and has been brought to you by generous educational grant by M/S Cipla.

For Comments and Suggestions, please write to Dr Namrata at namrata.sharma@gmail.com

Happy Reading !!

Dr. R.V. Azad
President

Dr. Lalit Verma
Hony. Secretary

Management at Primary level

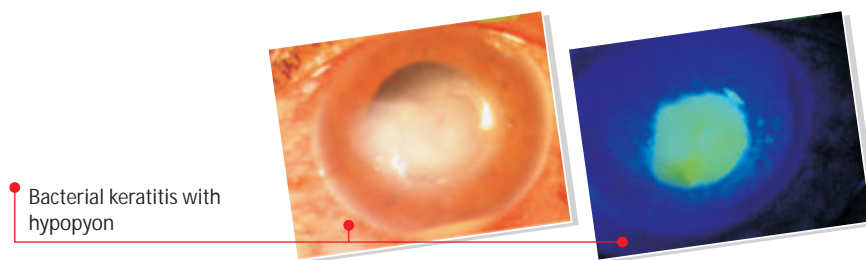
It is important to distinguish between corneal abrasions and corneal infections.

History

Evaluate for history of trauma, use of self medication, predisposing systemic conditions like diabetes mellitus.

Symptoms

Typical symptoms include pain, redness, photophobia and/or a foreign body sensation.



Examination

Examination includes:

- Torch light examination
- Fluorescein staining of the ocular surface

Treatment

- Prescribe chloramphenicol eye ointment (0.5 - 1% 3 times a day)/ antibiotic drops
- Do not prescribe steroids
- Do not allow any self medication by the patient

Refer to an ophthalmologist without delay if:

- Pain and redness persist for >24 hrs
- There is an increase in the symptoms
- A white mark on cornea is present along with the red eye

Management at Secondary level

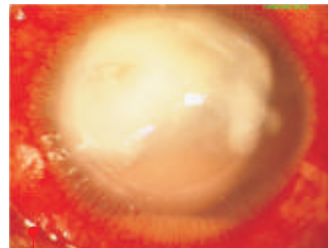
Confirm diagnosis of microbial keratitis

A detailed history should be elicited for evaluation of:

- Risk factors including contact lens use/ use of steroids
- Use of ocular medications including antibacterials/antifungals/antivirals
- Compliance to the antibiotic regimen previously prescribed if any

A good clinical examination includes a record of following parameters:

- Visual Acuity
- External examination
 - Status of eyelids for entropion, trichiasis, lagophthalmos
 - Adnexal examination for dacryocystitis
- Slit lamp exam
 - Fluorescein staining
 - Area and density of infiltration
 - Size and depth of ulceration
 - Size of epithelial defect
 - Degree of stromal edema
 - Scleral involvement
 - AC reaction
 - Examine for specific features of fungal etiology: feathery margins, satellite lesions, immune rings, fixed hypopyon, dry looking infiltrates, pigmentation with some fungi
- Corneal sensation
- Documentation: drawing/ clinical photograph



Satellite lesions in Fungal keratitis

Investigations

Ocular

It is recommended that in all the cases of microbial keratitis, a smear examination should be done. All the smears should be examined under the microscope for detection of fungal hyphae using a 10% KOH wet mount preparation. Gram staining should also be done if facilities are available.

Procedure for scraping

- Scraping should be done under slit lamp/operating loupe/operating microscope.
- Instil 1-2 drops of topical anaesthetic agent.
- Wait for 1 min. Keep 2 clean glass slides having 1cm circle with glass pencil on reverse side of slide.
- Scrape base and edges of corneal ulcer with flame sterilized kimura spatula or sterile 15# BP blade.
- Streak over glass slide within circle: KOH, Gram stain.
- Apply KOH, cover with cover slip.
- Examine under Light Microscopy (LM).

The corneal scrapings and related material like contact lens, lens case and solution should be subjected to culture if facilities are available.

Culture

Culture and sensitivity should be done in all cases of microbial keratitis if the facilities are available. The ideal culture media recommended for identification of pathogenic organisms include blood and chocolate agar along with Sabaroud's Dextrose Agar (SDA). If the facilities are limited, then either blood agar or chocolate agar along with SDA should be used for the same. Direct plating is recommended.

It is of note here that conjunctival swab does not correlate with the etiological agent for keratitis, and so has no role in the microbiological workup for a patient with corneal ulcer.

Ultrasonography

An ultrasound examination of the eye must be conducted if there is a suspicion of endophthalmitis.

Systemic

Systemic work up should include a fasting/random blood sugar test to rule out diabetes mellitus.

Treatment

If smear examination reveals fungal hyphae, the patient should be started on intensive antifungal therapy with Natamycin 5% (Natadrops) eye drops given 1 hourly round the clock. The dosage should be tapered to a 2 hourly dose after 24-48 hours if a positive clinical response is seen. The same may be started in cases with a strong clinical suspicion of fungal etiology.

If the smear examination reveals gram positive or gram negative organisms, combination therapy with broad spectrum fortified antibiotics should be started. The same regimen should be given in patients when no organism is seen on the smear or a smear examination is not possible.

The treatment may include any of the following combinations of antibiotics.

- Conc. Cefazolin 5 % + Conc. Tobramycin 1.3 %
- Conc. Cefazolin 5 % + Conc. Gentamicin 1.3 %
- Conc. Cefazolin 5 % + Ciprofloxacin 0.3%

Dosage

Initial loading dose is every 5 minutes for an hour followed by 1 hourly round the clock. If a positive clinical response is seen at 24-48 hrs, the dose can be tapered to 2 hourly. Further tapering of the dose should be done subsequently depending on the clinical response of the patient.

Monotherapy with fourth generation flouroquinolones (commercially available moxifloxacin 0.5% (Moxicip e/d) or gatifloxacin 0.3% (Gatiquin e/d) can be considered in cases where the ulcer is small (<3mm), involves the superficial layers of the cornea, and the visual axis is spared. The choice of flouroquinolone antibiotic should be guided by the sensitivity pattern prevalent in the region.



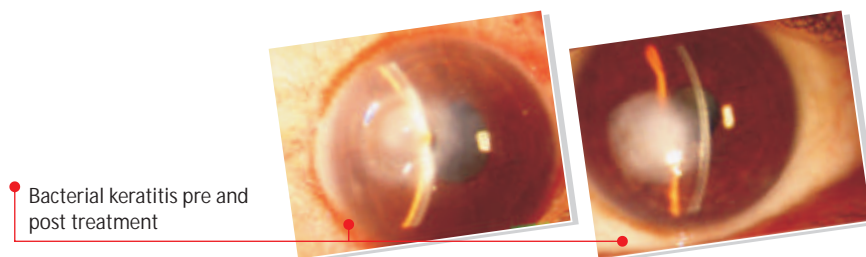
Bacterial keratitis responding to therapy

Adjunctive therapy

Cycloplegics and analgesics should be added to relieve ciliary spasm and associated pain. Anti-glaucoma medication can be added in the treatment regimen if indicated.

There is no role of topical anti-inflammatory medications in the management of corneal ulcer. Topical steroids are contraindicated in the management of corneal ulcer at a secondary level.

Subconjunctival injection of antibacterial agents can be considered as an adjunct in cases likely to be non-compliant with topical treatment regime like elderly patients, patients with physical disability.



Oral antibiotics are indicated in cases with;

- Impending perforation
- Actual perforation
- Post perforating injury
- Scleral involvement
- Or if the cultures reveal agents like *Neisseria*, *Haemophilus* species

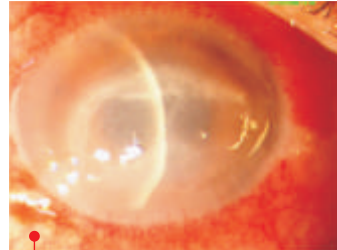
Recommended oral antibiotics include Tablet ciprofloxacin 500 mg twice a day or Tab. levofloxacin 750 mg once a day.

Indications for starting oral antifungals in cases of fungal keratitis include:

- Large ulcers
- Severe deep keratitis
- Scleritis
- Post Keratoplasty
- Endophthalmitis

- Patients with diabetes mellitus
- Immunosuppressed individuals

Recommended oral antifungals include ketoconazole (200mg bd)/ fluconazole (200mg bd)/ itraconazole (100mg bd)/ voriconazole (200mg bd) for 4-6 weeks. All the patients being started on oral antifungal therapy should be monitored for hepatotoxicity. A baseline liver function test report should be followed by repetition of these tests every 2 weeks.



Fungal keratitis

Follow-up

Patient should be regularly followed up every 24 hrs till there is improvement in the signs and symptoms. Signs of improvement include:

- Reduced pain, discharge, eyelid, edema, congestion
- Consolidation, sharper demarcation of stromal infiltrate
- Decreased density of stromal infiltrate
- Reduced stromal edema, endothelial inflammatory plaque
- Reduced anterior chamber cells or hypopyon
- Initial re-epithelialization
- Cessation of progressive corneal thinning

Following patients should be promptly referred to a tertiary centre:

- One eyed patient
- Pediatric patient
- Impending perforation
- Actual perforation
- Recalcitrant/ non-healing ulcers
 - Bacterial keratitis not responding after 3 days
 - Fungal keratitis not responding after 5-7 days

Management of Microbial Keratitis at a Tertiary Level

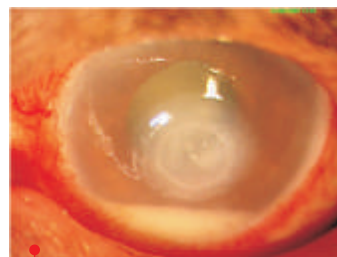
Management of microbial keratitis at a tertiary level requires a thorough evaluation of the patients. A detailed history should be sought and a thorough clinical examination should be done to look for the etiology of a non-responding corneal ulcer.

Possible reasons for failure of the therapeutic regimen include:

- Improper antimicrobial agent or dosage
- Non-compliance with the treatment regimen
- Uncommon causative organisms
- Medication toxicity

Patient work-up

A repeat scraping should be done for all cases of microbial keratitis presenting to a tertiary care centre. Ziehl Neelsen staining should be performed in addition for suspected mycobacterial organisms. For culture positive cases, the therapeutic regimen should be altered on the basis of culture sensitivity report. If the organism is sensitive to the current treatment regimen, inadequate dosage or non compliance should be suspected.



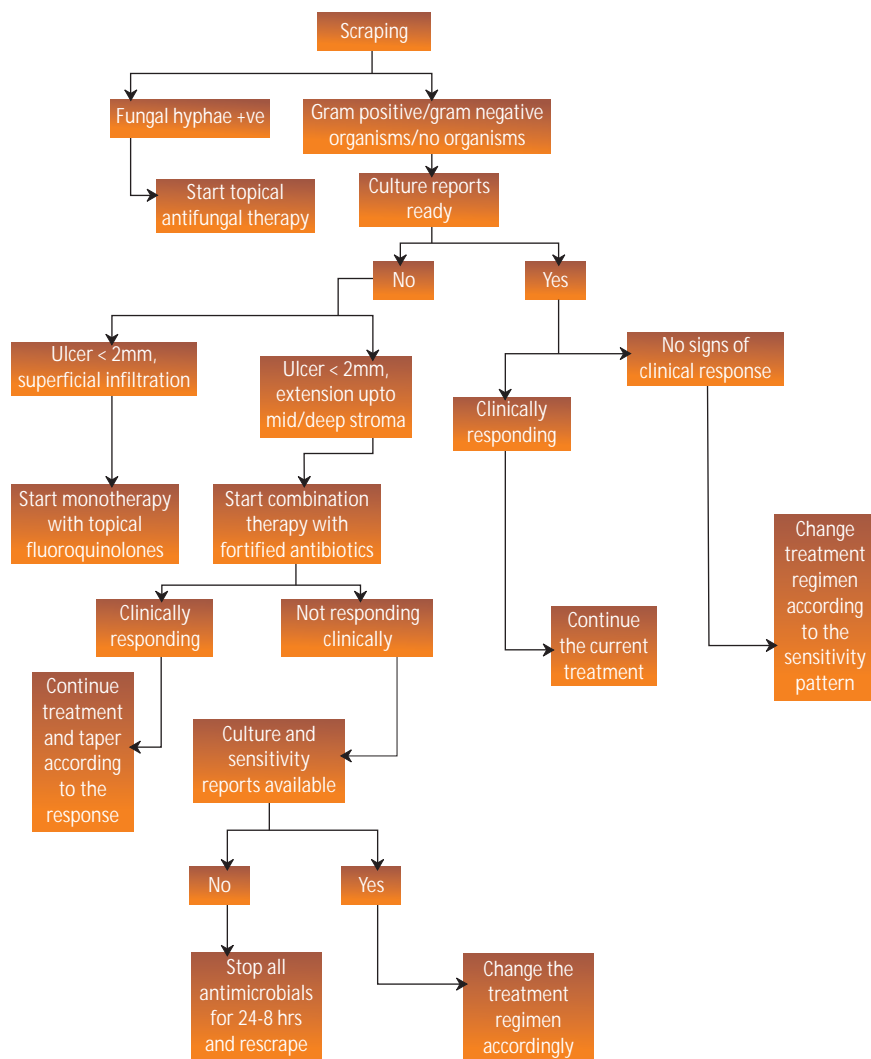
Staphylococcal infective keratitis

In addition to blood agar, chocolate agar and Sabaroud's agar, selected media capable of supporting the growth of atypical microorganisms may also increase the culture yield and should be considered, e.g., Lowenstein-Jensen media for atypical mycobacteria. Additionally, plating on non-nutrient agar with *E.coli* overlay should be done for suspected cases of *Acanthamoeba*. Stains like calcofluor white 0.1%, methanamine silver, periodic acid schiff can be used to identify the typical polygonal and double walled cysts of *Acanthamoeba*.

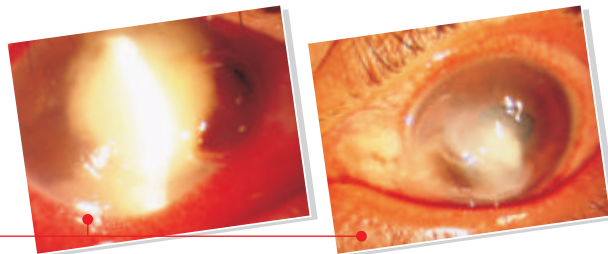
In cases with no clinical improvement and where the smear and culture reports fail to reveal the causative pathogen, a corneal biopsy should be performed. The procedure is performed under topical anaesthesia under an operating microscope. A partial thickness trephination, with a dermatology punch, of the anterior corneal stroma (preferably avoiding the visual axis) is followed by enbloc resection of the tissue with a crescent blade or Bard Parker knife. The tissue should be divided into sections and subjected to smear examination, cultures and histopathological examination.

Confocal microscopy is particularly useful for demonstrating the cyst and trophozoite forms of *Acanthamoeba* in suspected cases. Presence of hyphae in cases of filamentous fungi and pseudohyphae in cases of *Candida* keratitis can also be sometimes demonstrated on confocal microscopy.

The choice of drugs to be used has been discussed in the previous section.



Corneal ulcer with perforation



Role of steroids in the management of microbial keratitis at a tertiary level

Steroid therapy has a role in the management of microbial keratitis at a tertiary level. Along with the combination therapy, it may decrease the amount of inflammation and reduce chances of scarring. The prerequisites for starting the patient on steroid therapy include:

- The case should be a proven bacterial keratitis identified in culture. Fungal infection should have been ruled out.
- The ulcer should be stabilized with antibiotic treatment for the first 48 hours or till epithelium heals.
- The patient should be admitted and evaluated every day.

1% prednisolone phosphate should be given for three weeks in a tapering dose under the cover of 1 hourly instillation of topical antibiotics. The dosage schedule is four times a day for the first week, twice a day for the next week and once a day for the last week.

Adjuvant therapeutic measures

1. Intracameral injections in cases with proven fungal etiology.

They can be considered in situations like:

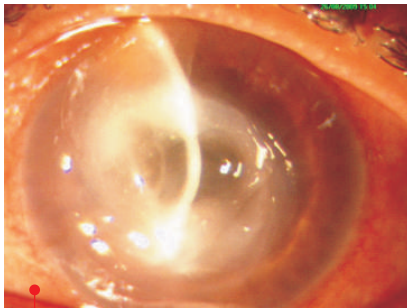
- Ulcers non-responsive to medical therapy
- Thick hypopyon
- Endothelial exudates
- Deep anterior chamber exudates

The recommended antifungals and their dosage for the above therapy are as follows:

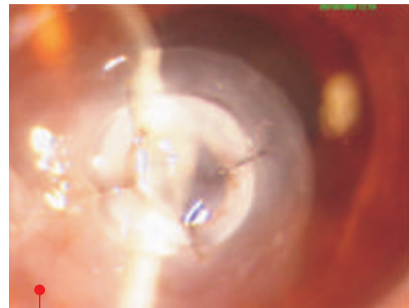
- Amphotericin B: 5-7.5 g /0.1ml
- Voriconazole: 50 mg/0.1 ml

2. Debridement involves surgical removal of corneal epithelium without injury to the basement membrane. In cases of microbial keratitis, this procedure should be used to enhance penetration of drugs especially antifungals.

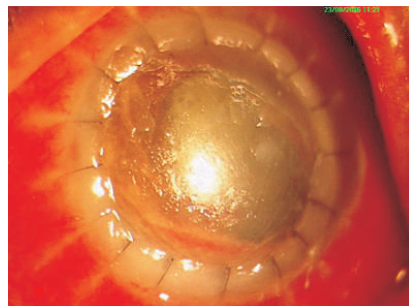
3. Tarsorrhaphy should be employed in cases of corneal exposure and neuroparalytic keratitis.
4. Tissue adhesives can be used in cases with a small perforation. The bed should be dry and free of epithelial cells. Adequate time should be given for complete drying of the adhesive.
5. Patch grafts and penetrating keratoplasty should be considered for larger perforations.



Descemetocèle formation



Operated Patch graft secured with 10-0 Monofilament nylon sutures and fibrin glue



Post-Therapeutic Keratoplasty

Special Situations

Non-tuberculous mycobacteria

Non-tuberculous mycobacteria are the emerging causes of keratitis especially after surgical procedures such as laser-in-situ keratomileusis. Clinically, the bed of the ulcer has a cracked windshield appearance with minimal changes in the surrounding cornea or the anterior chamber. The choice of treatment for the same includes topical amikacin (2-4%) one drop every hour. Systemic clarithromycin should be added for all the cases infected with atypical mycobacteria. Steroids are contraindicated in these cases.

Nocardia

For *Nocardia* keratitis, combination therapy with trimethoprim (16mg/ml) and sulfamethoxazole (80 mg/ml) or topical amikacin (2-4%) is the treatment of choice. Systemic cotrimoxazole or systemic ampicillin should be added in these cases along with the topical antibiotic therapy.

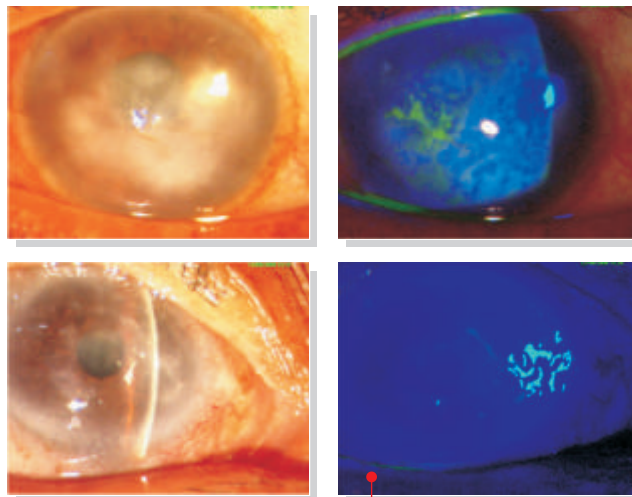
Management of Viral Keratitis

Clinical features

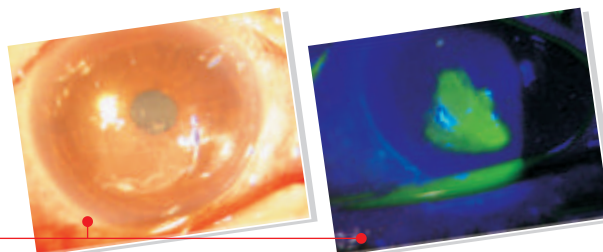
The typical clinical features of viral keratitis include recurrent episodes of pain, redness, watering, decreased vision in a young patient. Presence of a trigger factor like fever, surgery, menstruation, minor local trauma, immunocompromised status adds to the clinical diagnosis of viral keratitis.

Examination

A careful slit lamp examination should be done for signs of epithelial keratitis, stromal keratitis, or combined epithelial and stromal disease. Diminution of corneal sensation further adds to the diagnosis of herpetic keratitis.



Dendritic ulcer in
Herpes epithelial keratitis



Geographic ulcer in
Herpes epithelial keratitis

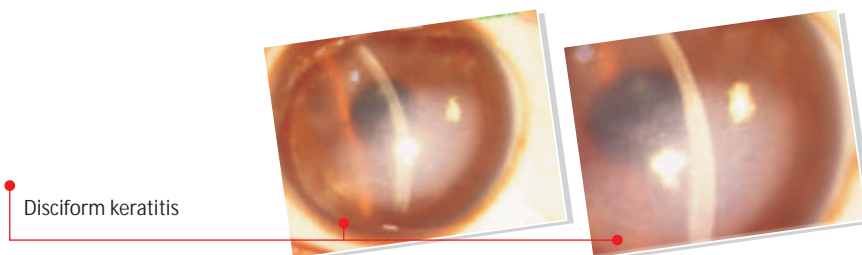
Epithelial keratitis

Earliest stages present as a cluster of small, discrete, clear vesicles in the corneal epithelium. The vesicles may coalesce within 24 hours to form dendritic ulcers.

True Herpes Simplex virus (HSV) dendrites have a branching, linear pattern and form true ulcers with positive fluorescein staining of the ulcer bed. The dendrites have terminal bulbs in cases of HSV keratitis. The terminal bulbs are absent in pseudodendrites seen in Herpes Zoster virus (HZV) epithelial keratitis.

Management of HSV epithelial keratitis:

- Epithelial debridement: by rolling a cotton swab over the affected area.
- Topical antiviral therapy: Topical ointment acyclovir 3% five times a day for 14-21 days.
- Cycloplegics can be added if the patient complains of excessive pain, photophobia.
- Steroids are contraindicated in cases with epithelial keratitis.



Stromal keratitis

Non necrotizing stromal keratitis: Clinically, the disease is characterized by presence of stromal infiltrates, immune ring, stromal vascularisation.

Necrotizing stromal keratitis: Corneal necrosis, ulceration and dense infiltration of stroma with an overlying epithelial defect are the classical clinical features of this disease.

Endothelitis

Herpetic endothelitis: It is clinically recognized by the presence of keratic precipitates on the endothelium along with overlying stromal edema.

Management of stromal keratitis and endothelitis: The treatment regimen for the above includes: topical corticosteroids (1% prednisolone acetate suspension, 4 times a day) along with 3% acyclovir ointment (5 times a day).

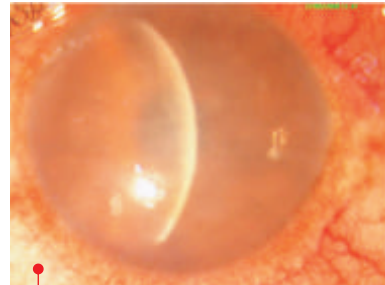
Cycloplegics, and antiglaucoma therapy (if indicated) should be added in these cases.

Combined epithelial and stromal keratitis

Epithelial lesions should be treated first in such cases. Steroids should only be started after the epithelial lesions have healed.

Indications of Systemic Acyclovir in HSV keratitis:

1. Herpetic iridocyclitis
2. Recurrent attacks of viral keratitis
3. Prophylaxis after penetrating keratoplasty
4. Immunocompromised patients



Herpetic endothelitis

Management of HZV epithelial keratitis:

All cases of Herpes Zoster Ophthalmicus should be treated with oral acyclovir 800 mg five times daily. The recommended duration of therapy is 10-14 days.

Metaherpetic keratitis

Clinical findings in these cases include recurrent corneal erosions, persistent non-healing sterile ulceration present in interpalpebral region with shallow, clean margins. The management options for the same includes:

Medical

- Withdrawal of Epitheliotoxic Drugs
- Intensive Lubricants
- Cycloplegics

Surgical

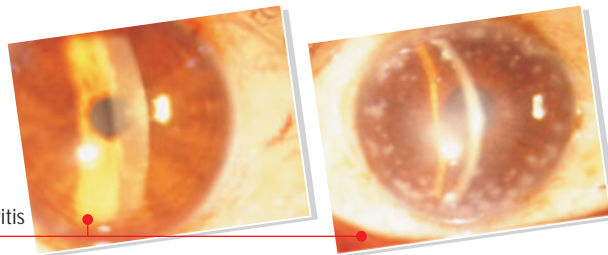
- Conjunctival Flap
- Amniotic membrane graft
- Glue for small perforations
- Patch graft
- Tectonic graft

Adenoviral infections

Early stages manifest with superficial punctate keratopathy. The later stages are characterized by nummular subepithelial lesions.

- Acute stage
 - Cold Compresses
 - Lubricants
 - Prophylactic antibiotics
- Nummular opacities
 - Lubricants
 - Topical steroids: Topical steroids are indicated in acute stages with pseudomembrane formation and should be given in a tapering doses in central opacities affecting vision.

• Subepithelial infiltrates in Adenoviral keratoconjunctivitis



Acanthamoeba keratitis

Risk factors for developing *acanthamoeba* keratitis include trauma with vegetable matter, contact lens usage, use of homemade saline as contact lens solution, history of exposure to contaminated or swimming pool water. *Acanthamoeba* keratitis should be suspected in cases who fail to respond to antibacterial, antiviral or antifungal treatment.

Severe pain is one of the characteristic features in these cases. The examination findings may reveal:

- Epithelial irregularities (punctate, linear or pseudodendritiform)
- Patchy stromal infiltrates
- Radial perineural infiltrates (pathognomonic)
- Ring infiltrates
- Satellite lesions
- Stromal thinning

Management

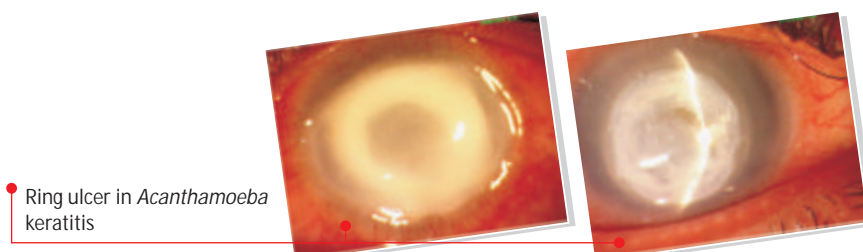
The recommended treatment regimen includes a combination therapy of a biguanide and a diamidine. However, due to lack of free availability of diamidines in India, biguanides can be used as monotherapy.

- Biguanide: PHMB 0.02% or Chlorhexidine 0.02%
- Diamidine: Propamidine 0.1% or hexamidine 0.1%

The drugs should be given one hourly for 48 hours round the clock, tapered to hourly drops by day for 72 hours, 2 hourly after 5 days for 3 to 4 weeks. The treatment should be given for 6 months-12 months in a 4 hourly dosage after one month of healing of the ulcer.

Low potency topical steroids are recommended in qid dosage after 2 weeks of biguanide therapy in cases with severe pain or anterior scleritis.

Penetrating keratoplasty can be considered for severe cases with impending actual perforation. There are high chances of reinfection or severe inflammation in cases undergoing surgery in acute stages of the disease.



Addendum

Tarsorrhaphy

- Types : Lateral, Central
- Indication
 - Exposure keratitis (Bells palsy)
 - Neuroparalytic keratitis
- Technique
- Local infiltration with 2% lidocaine at lid margins
- Shave off 1-2 mm of inter-marginal strip upto dermis and appose with 4 "0" silk suture and anchor with bolsters.

Tissue Adhesives

- Indicated for perforations < 3mm
- Dry the surface and bed of the perforation
- Apply a thin film of adhesive applied using a small gauge disposable needle, micro capillary applicator
- Allow to dry
- Place BCL

Preparation of Fortified Drops

Cefazolin 50 mg/ml or Ceftazidime 50 mg/mL

- Add 9.2 mL of artificial tears to vial of cefazolin 1 g (powder for injection)
- Dissolve and take 5 mL of this solution and add to 5 ml of artificial tears
- Refrigerate and shake well before instillation

Tobramycin 14 mg/mL or Gentamicin 14 mg/mL

- Withdraw 2 mL of tobramycin or gentamicin injectable vial (40 mg/mL)
- Add this to vial of commercially available Tobramycin or Gentamicin eye drop 5 mL (0.3%)
- Final Concentration achieved is 1.4% (14 mg/mL)

Vancomycin 25-50 mg/ml

- Add 20 mL of 0.9 % NaCl or artificial tears to produce 25 mg/ mL , Add 10 mL of 0.9 % NaCl or artificial tears to produce a solution of 50 mg/mL

Intracameral/Intrastromal Amphotericin B

- 50 mg powder, Fungizone, in 5 % dextrose
- 10 ml of dextrose + vial----5.0 mg/mL
- 1.0 mL of this added to 4.0 mL of dextrose -----1.0 mg/mL
- Of this conc, 1.0 mL is diluted with 9.0 mL of dextrose -----100 µg/mL
- 0.1 mL of this contains 10 µg
- Similarly, 0.5 and 0.75 ml of this diluted drug contains 5 and 7.5µg, respectively

Intrastromal/Intrastromal Voriconazole 50 µg/0.1 ml

- Injection voriconazole is available as 200 mg of white lyophilized powder
- 19 ml of ringer's lactate (RL) solution added to the vial gives 20 ml of clear concentrate containing 10 mg/ml of voriconazole
- 1 ml aliquot of the above solution further diluted with 20 ml of RL to give 0.5mg/ml (50 µg/0.1 ml)

The reconstituted fortified drop should be refrigerated. The shelf life of the refrigerated reconstituted fortified drops is 5 days.



Notes



Workshop Participants (16th July 2010)



S.No.	Name of Dr.	Place	Mob.No.
1	Dr. Rishi Mohan	Delhi	9811107007
2	Dr. Namrata Sharma	Delhi	9810856988
3	Dr. Ajay Dave	Delhi	9811111169
4	Dr. Rajib Mukharjee	Delhi	9810192903
5	Dr. M. Srinivasan	Madurai	9043103773
6	Dr. A.K. Jain	Chandigarh	9316131944
7	Dr. Asish Bansal	Hyderabad	9393357807
8	Dr. Samar Kumar Basak	Kolkata	9830323013
9	Dr. Prashant Garg	Hyderabad	9849593572
10	Dr. Nikhil Gokhale	Mumbai	9820154362
11	Dr. Paras Mehta	Barodra	9898836933
12	Dr. Sunil Singh	Lucknow	9935030062
13	Dr. Shreesha Kumar	Coimbatore	9443317795
14	Dr. Ashish Nagpal	Ahmedabad	9879440210
15.	Dr. Shveta Jindal	Delhi	

Terms of Use

Aim of these guidelines is to assist the ophthalmic surgeon in diagnosis and management of Microbial Keratitis.

These guidelines are mere suggestions and cannot be used in court of law to safeguard against or for any legal proceedings. AIOS has no financial or any other interest in formulation of these guidelines.

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