Clinical Practice Module

Quality Assurance in Management of Microbial Keratitis

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PROPHYLAXIS OF OPHTHALMIA NEONATORUM

The innovation of silver nitrate

Carl Siegmund Franz Crede (1819-1892) was Professor of Obstetrics at Leipzig when he introduced the procedure of the instillation of silver nitrate solution into the eyes of the newborn in order to prevent Ophthalmia Neonatorum.

This procedure entitles Dr. Crede to the permanent gratitude of mankind.

**Ophthalmia Neonatorum is a gonococcal infection of the conjunctival sac of babies, contracted as they pass through the birth canal of infected mothers.*

Microbial Keratitis

Disease definition

Microbial keratitis is a suppurative disease of the cornea, predominantly caused by fungi and bacteria.

Epidemiology and Magnitude

The importance of corneal disease as a major cause of blindness in the world today remains second only to cataract, but its epidemiology is complicated and encompasses a wide variety of infectious and inflammatory eye diseases. In addition, the prevalence of corneal blindness varies from country to country and even from one population to another, depending on many factors, such as availability and general standards of eye care[1].

Corneal ulceration in developing countries, like India has only recently been recognized as a silent epidemic[2]. Gonzales et al found that the annual incidence of corneal ulceration in Madurai district in South India was 113 per 1,00,000 people. By applying the 1993 corneal ulcer incidence rate in Madurai district to whole of India, about 8,40,000 people are likely to develop a corneal ulcer in a year. Even this figure is quoted as an under estimation when compared to other SAARC countries. This figure is thirty times more than the number of corneal ulcers seen in the United States[3]. In a prospective study of 434 consecutive patients with corneal ulceration, culture was positive in 68.4% of the patients[4]. Of those with positive cultures, 47% had pure bacterial infection, 46.8% had pure fungal infections, 5% had mixed infections and 1% grew pure culture of Acanthamoeba. The most common bacterial pathogen isolated was Streptococcus pneumoniae (44% of all bacterial cultures) followed by pseudomonas species (14.4%). The most common fungal pathogen isolated was Fusarium species representing 47.1% of all positive fungal cultures, followed by Aspergillus species (16%). In North India, Aspergillus was isolated more frequently than Fusarium.

Natural history

Most of the cases of microbial keratitis results in corneal scarring and partial or total loss of vision. Untreated microbial keratitis may result in corneal perforation with loss of vision. Central corneal ulcers have high significance, since scarring in that location results in marked visual loss, even if the infection is successfully controlled. Since bacterial and fungal corneal ulceration is almost equal in our country, optimal management requires rapid clinical and microbiological recognition and timely institution of specific therapy. Empirical therapy as recommended in developed countries has no role in developing countries especially in India.

The rate of disease progression is dependent on the virulence of the infecting organism and on host factors. Amongst the bacteria, highly virulent organisms such as pseudomonas, pneumococci and gonococcus cause rapid tissue destruction, while other organisms such as staphylococcus species, moraxella, atypical mycobacteriae are usually associated with a more indolent course. Fungal keratitis is more difficult to manage if the ulcer is severe i.e. more than 5-mm and involving deep layers of cornea. So early diagnosis carries better prognosis and lesser morbidity.

Prevention and Early Detection

Avoiding exposure to predisposing factors may minimise the risk of microbial keratitis. The majority of corneal ulcers follow trivial corneal abrasions[5]. The use of Traditional Eye Medicines (TEMs) is an important risk factor for corneal blindness, since they are often contaminated and provide a vehicle for the growth of pathogenic organisms. The common TEMs used in our country includes breast milk, castor oil and leaf extracts. Training traditional healers in asepsis, banning harmful medicines and directing patients to appropriate health care facilities would be the first rewarding approach in preventing corneal blindness due to red eye and corneal injuries. Ocular surface disease such as Trachoma, dry eye, lagophthalmos and Vitamin A deficiency should be treated. Routine use of prophylactic topical antibiotics in this setting is controversial because their efficacy has not been established and may promote growth of resistant organisms. Even though keratomalacia is rare, still children go blind due to Vitamin A deficiency. Proper diet counseling and Vitamin A supplementation will effectively control keratomalacia from our country.

Taking History

Eliciting a proper history with regards to nature of trauma and use of TEM is a crucial step in the management of microbial keratitis. Trauma with vegetable matter such as paddy husks or onions are more likely to cause a fungal keratitis. Contact with contaminated or brackish water is likely to produce Acanthamoeba keratitis. In cases of contact lens wearers, it is imperative to take history of wearing schedule and lens care.

Examination

The physical examination includes recording visual acuity, an external eye examination and slit-lamp biomicroscopy of affected and normal eye.

Visual Acuity

Due to acute infection of the involved eye the recorded vision may not be correct. But an approximate visual acuity with or without correction will give an idea about the seriousness of the lesion and management strategy.

External Examination

An external examination should be performed with particular attention to the following:

- General appearance of the patient
- Facial examination
- Eyelids and lid closure
- Conjunctiva
- Nasolacrimal apparatus
- Corneal sensation

Slit-lamp Biomicroscopy

Should include evaluation of the following:

- Eyelid margins

  Inflammation, ulceration, eyelash, and abnormalities including trichiasis, irregularities, and lacrimal punctal anomalies.
- Conjunctiva

  Discharge, inflammation, morphologic alterations (e.g. follicles, papillae, cicatrisation, keratinization, membrane, pseudomembrane, ischemia, and foreign bodies).
- Sclera:

  Inflammation (e.g. infectious, versus autoimmune), ulceration, scarring / thinning, nodules, ischemia.

- Cornea:

  Epithelium, including defects and punctate keratopathy, edema

  Stroma including ulceration, thinning, perforation

  Infiltrate location, density, size, shape, number, depth, and character of infiltrate margin, edema, endothelium, foreign bodies including sutures.

Clinical features suggestive of bacterial keratitis include dense suppurative stromal infiltrate with distinct edges and edema. The symptoms are typically more prominent than the signs. Fungal keratitis presents with creamy raised surface and feathery in-distinct margins. Accompanying satellite lesions may be present in few cases. Acanthamoeba keratitis usually presents with a ring shaped stromal infiltrate, as a late clinical feature which is commonly misdiagnosed as viral keratitis. It has to be emphasised, however, that all these features are only suggestive of the organism and microbiological confirmation should be sought for proper identification.

Diagnostic Tests

Cultures and Smears

Since bacteria and fungi cause an almost equal proportion of keratitis in our country, it is highly essential to perform at least a smear test in order to initiate the treatment. Corneal infective material is obtained by scrapping after instilling topical anesthetic agent (4% lignocaine) and using a flame sterilised platinum spatula, blade or other similar sterile instrument to obtain material from the advancing borders; ulcer base and edges. Two smears are initially prepared – one with Gram's stain (for identifying bacteria, fungi, and Acanthamoeba) and the other with 10% potassium hydroxide[6] (for fungus).

Cultures are indicated if the smears are non-confirmatory and are also useful to study the microbial pattern in that locality and to evaluate antibiotic sensitivity. Cultures are also helpful to modify therapy in patients showing poor clinical response to empirical treatment. The material collected for culture should be inoculated directly onto appropriate culture media in order to maximise the yield. The initial culture regimen should include blood agar, Sabouraud's dextrose agar or potato dextrose agar and thioglycollate broth. Cultures of contact lens case and solution may be useful when acanthamoeba is suspected.

Table 1: Commonest micro-organisms causing keratitis in India

Common Organisms	Uncommon Organisms
Bacteria	
Strep. pneumoniae	Nocardia species
Pseudomonas	Moraxella
Staph. epidermidis	Mycobacterium
Staph. aureaus	Diphtheria
Enterobacteriae	Neisseria species
Fungal	
Fusarium species	
Aspergillus species	Candida
Pigmented fungi	

Table 2: Recommended Stains and Culture media for Microbial Keratitis

Suspected Organisms	Stain	Media
Aerobic bacteria	Gram's	Blood agar Chocolate agar Thioglycollate broth
Anaerobic bacteria (Rarely involved)	Gram's	Anaerobic blood agar Thioglycollate broth
Mycobacteria	Gram's Acid fast	Blood agar Lowenstein – Jenson
Fungi	10% KOH Gram's Calcofluorwhite	Blood agar Sabouraud's agar Brain heart infusion
Acanthamoeba	10% KOH Gram's Giemsa Calcofluorwhite	——— Non-nutrient agar with E.coli

Note: Acridine orange – GMS – if facilities are available, use it.

Corneal Biopsy

It may be performed in non-healing corneal ulcers with negative culture result, in deep lesions or deep stroma with intact epithelium. Under topical anesthesia, a small trephine or blade is used to excise a small piece of infected stroma, which is large enough to allow bisection so that one portion can be sent for culture and the other for histopathology.

Treatment

Bacterial Keratitis

Topical antibiotics are capable of achieving high tissue levels and are the preferred route in most cases. Ointments may be useful in children and at bedtime. Routine subconjunctival antibiotics are not necessary unless the compliance of the patient is doubtful or poor.

For severe keratitis (ulcer more than 5mm and deep), a loading dose at every 5 to 15 minutes during the first hour, followed by applications every 15 minutes to 1 hour during waking hours is recommended. It is ideal to treat the patient as inpatient. For non-severe keratitis, a regimen with less frequent dosing is appropriate. Cycloplegic agents may be used to prevent synechia formation and to decrease pain. Small ulcers less than 2 mm and away from the visual axis do not need cycloplegics. Chloramphenicol (0.5%) and cefazolin (5 to 10%) are ideal for Gram positive cocci, while Gram negative bacilli respond very well to fluoroquinolones and aminoglycosides. Single drug therapy using a fluoroquinolone has been shown to be as effective as combination therapy utilizing topical antibiotics that are commercially available[8]. But recent reports do not recommend this in view of more drug resistance. S. Pneumoniae, which is the most common bacterial isolate in our country, has variable susceptibility to fluoroquinolones[8] and hence fluoroquinolones may not be the ideal antibiotic for monotherapy in our country. The drug of choice could be 5 to 10% Cefazolin as topical drops.

The treatment of fungal keratitis still remains a challenge. All the available antifungal agents are fungistatic and not fungicidal. The penetration of the drug is poor particularly when the epithelial defect is small. It leads to prolonged treatment, often leading to poor compliance with antifungal therapy. Natamycin (5%) and Amphotericin B (0.1% to 0.5%) are the most efficacious among the available topical antifungal agents against filamentous fungi. Use of systemic anti-fungals like imidazoles and triazoles are reserved for deep keratitis associated with scleritis and endophthalmitis.

Several clinical features suggest the response to antimicrobial therapy.

a. Decreased pain.
b. Consolidation and sharper demarcation of the periphery of the stromal infiltrate.
c. Decreased density of the stromal infiltrate.
d. Reduction of stromal edema and endothelial inflammatory plaque.
e. Dilatation of the pupil.
f. Re-epithelialisation.
g. Reduction in congestion of bulbar conjunctiva.
h. Visual improvement.

Topical therapy is tapered according to the clinical response, taking into account the baseline clinical picture and the virulence of the pathogen. It is better to avoid topical steroids.

Therapy of Bacterial Keratitis

Table 3: Antibiotic Therapy of Bacterial Keratitis

Organism	Antibiotic	Topical Concentration	Subconjunctival Dose
No organism identified or multiple types of organisms	Cefazolin with Gentamycin/ Tobramycin or Fluoroquinolones	50 mg/ml 3-14 mg/ml 3 mg/ml	100 mg in 0.5 ml 20 mg in 0.5 ml
Gram-positive cocci	Chloramphenicol Cefazolin Vancomycin	5 to 10 mg/ml 50 mg/ml 15-50 mg/ml	 100 mg in 0.5 ml 25 mg in 0.5 ml
Gram-negative rods	Gentamicin/ Tobramycin Ceftazidime Fluoroquinolones	3-14 mg/ml 50 mg/ml 3 mg/ml	20 mg in 0.5 ml 100 mg in 0.5 ml
Non-tuberculous Mycobacteria	Gentamicin Amikacin	14 mg/ml 10 mg/ml	20 mg in 0.5 ml
Nocardia	Amikacin Trimethoprim/ Sulphamethoxazole	10 mg/ml 16 mg/ml 80 mg/ml	20 mg in 0.5 ml

Note: Systemic antibiotics are recommended only when the ulcer involves sclera or perforates.

Preparation of fortified antibiotics

This could be done in the hospital pharmacy if possible or by ophthalmologist himself.

Gentamicin and Tobramycin

Add 2 ml of injectable Gentamicin or Tobramycin to 5 ml commercial topical preparation in a sterile set up using disposable syringe.

5 ml commercial has - 15 mg
Added drug - 80 mg
Total in 7 ml - 95 mg

1 cc contains 13.5 mg or 1.35%

Cefazolin

Add 5 ml or 10 ml of distilled water or sterile saline to 500 mg vial of cefazolin to obtain 10% or 5% solution. Use a dropper, available in the pharmacy or other source.

Vancomycin

Add 10 ml distilled water or saline to 500mg vial of Vancomycin and obtain a 5% solution.

Amikacin

1% would be sufficient. Add 10cc distilled water to 100mg of Amikacin. Use a sterile empty Xylocaine vial and place the cap for ready use.

All these solutions could be safely used for a week. If it is applied frequently as recommended it will not last more than a week.

Table 4: Therapy of fungal Keratitis

There is no specific drug as in bacterial keratitis. Try to use broad-spectrum available antifungals. **Never use steroids in any form.**

Organism	Antibiotic	Topical	Systemic
Fusarium	a. Natamycin b. Amphotericin B	5% suspension 0.1 to 0.5%	not available I.V.use rarely
Aspergillus	a. Amphotericin B b. Imidazole	0.1 to 0.5% 1 – 2% (Prepare the suspension)	—— 200 mg to 400 mg daily orally
Candida (rare)	a. Fluconazole b. Nystatin ointment	0.3% 1,00,000 μ	150-200 mg daily

Other Drugs

- Itraconazole – oral – 300 mg daily (only 55 to 60% efficacy)
- Saperconazole – 0.25% drops – 200 mg/day

Systemic Disease

1. Diabetes should be treated with insulin under the supervision of physician till the ulcer heals.
2. Other supportive therapy like vitamins is optional.

Surgical Treatment

Therapeutic keratoplasty has to be performed when the ulcer progresses despite specific anti-microbial therapy leading to descemetocele or perforation. The impending microperforation could be diagnosed by noticing a decrease in the size of the hypopyon, radial folds from the base of the ulcer and relief from pain. Sometimes it may seal spontaneously and healing will be faster. If the anterior chamber is formed within 48 hours with bandage or other supportive therapy therapeutic keratoplasty could be avoided or postponed. The goals of the therapeutic keratoplasty are to eliminate the infection and restore the integrity of the globe. The size of the graft should be decided on the basis of the size of the ulcer and should include the infected edges. Fresh donor corneas give better results in Phakic eyes. Steroid in any form should be avoided post operatively in fungal ulcers.

Follow-up Schedule and Therapy

Frequency of re-evaluation of the patient with microbial keratitis, treated medically, depends on the extent of the disease, but severe cases should be treated as inpatient and evaluated daily at slit-lamp until clinical improvement or stabilization is noticed. Patients, who have undergone therapeutic keratoplasty, should have an adequate information regarding postoperative medications and should ideally be reviewed twice a month for the first two months and then on monthly basis.

Additional Procedures in non-healing ulcers

1. Central tarsoraphy or lateral tarsoraphy.
2. Dacryocystectomy if there is lacrimal sac infection in the same eye.
3. Facility for brief anesthesia to perform minor surgical procedures in children (examination and scraping the ulcer).

Instrumentation and Setting

A. At the ophthalmologists office

1. For better evaluation and collection of material in a case of corneal ulcer, a slit-lamp biomicroscope is essential.
2. a. Kimura's spatula or 15 Bard-Parker blade.
   b. Alcohol lamp.
   c. 10% Potassium hydroxide.
   d. Glass pencil.
3. Glass slides for making smears.
4. Light microscope at the facility or outside the facility to read the smear.

B. Basic ocular microbiology lab equipments

a. Incubator.
b. Light microscope.
c. Basic stains like Gram's, Giemsa, AFB and the slides and jars to stain the smear.
d. Basic media like Blood Agar and Sabouraud's Dextrose Agar.

6. Anaerobic culture station is optional (Since anaerobes rarely cause keratitis).
7. A small autoclave for sterilization of plates and other small instruments.

Treatment Setting

The diagnosis and management of patients with microbial keratitis requires clinical training and experience in an ophthalmologist as the disease has the potential to cause visual loss or blindness. Severe cases or those that fail to respond to treatment may be best managed by an ophthalmologist, who has extensive expertise in treating these patients.

Medical Record Keeping

The significance of medical record keeping is appreciated in teaching institutes and polyclinics where different faculty of the same specialty may involve in treating patients with corneal ulcer. Also it helps for data collection regarding epidemiology, response to treatment and correspondence for referrals. A separate outpatient and inpatient record should be available with adequate space for illustrations, lab reports, systemic diseases and consent forms for minor and major surgical procedures (Attached).

Counseling / Referral

Patients and care providers should be educated about the serious nature of microbial keratitis and the need for strict compliance with the therapeutic regimen. The possibility of permanent visual loss and need for future visual rehabilitation should be discussed. If the diagnosis or management is in doubt, or if the condition is not responding to appropriate treatment, referral to a cornea specialist or a tertiary care centre the correct choice.

Who are the partners in management of Microbial Keratitis?

1. Health personnel at primary care level:
   a. Paramedical Staff
   b. Ophthalmic Assistants
   c. P.H.C. Medical Officers
   d. Other NGO's
2. Secondary health care level
   a. Ophthalmologists in private practice
   b. Medical officers in taluk and district hospitals
   c. Other NGO's – involved in eye care
3. Tertiary care level
   a. Tertiary care centers
   b. Teaching medical institutes
   c. Department of Health at State and Centre

When to refer a case of corneal ulcer and to whom

a. Primary care level

   If the person is trained to recognise red eye and corneal ulcer, he could start treatment with basic broad-spectrum antibiotics mentioned earlier. If the lesion progresses then he or she should refer the patient to a secondary health care facility.

b. Secondary level

   If ophthalmologists are available, he should take the responsibility in managing the referred cases. If not, basic lab procedures like Gram's stain could be recommended by the medical officers, utilizing the lab personnel available in that centre. Systemic work up to ruling out diabetes, leprosy, anaemia and tuberculosis could be performed. Inpatient care should be provided for patients with severe corneal ulcers.

c. Tertiary level

   1. Proper re-evaluation of history and previous treatment. Utilisation of services of a corneal specialist or who has extensive experience in the management of keratitis.
   2. Reconfirmation of diagnosis and performing additional investigations especially culture and sensitivity: Modification of therapy, such as using combination therapy, fortified antibiotics and surgical treatment.
   3. Training, monitoring, publication, and reporting to Department of Health if there is an epidemic of drug resistant pathogens and iatrogenic corneal ulcers (contact lens, refractive surgery related).

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Cornea Case Record

M.R. No. :_____

Cornea No. : _____

Date : _____

Name: _____ Age: _____ Sex: M/F

Address: _____

_____

Diagnosis:

Complaints:

History: Injury/Application of Irritants/Treatment

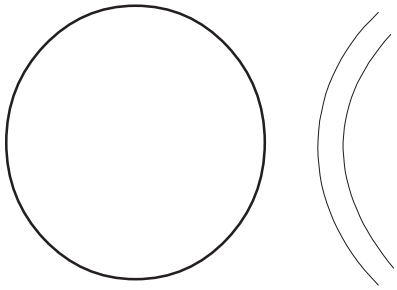
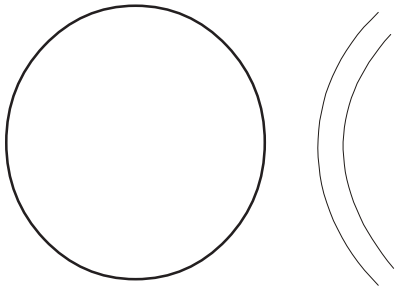
Examination: Details of corneal problem:

Staining:
- Flourescein +ve or -ve
- Rose Bengal

Corneal Sensation - Present
- Abscent

Vision	RE	Without glasses	With glasses	Duct:	RE
	LE				LE

Slit lamp examination: Cornea

Right Eye	Left Eye
	

Keratometry (Not in Active Ulcer)

Pachymetry (Not in Active Ulcer)

Specular Microscopy: (Not in Active Ulcer)

Scraping: KOH:
Gram:

Culture & Sensitivity:

Treatment advised:

- Yellow - Active Infection
- Blue-Oedema
- Red-Vessels
- Green Hatching - Epithelial defect
- Black-Scarring
- Brown-Dystrophic Changes