Emergencies in Microbial Keratitis

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7.1 Introduction

Microbial keratitis frequently presents as corneal emergency in clinical practice. It necessitates well-timed appropriate therapeutic interventions to salvage visual function and structural integrity. Small-sized corneal ulcers are amenable to treatment by broad-spectrum antibiotics. Whereas, while dealing with a large-sized corneal ulcer ophthalmologists are faced with dilemma of mixed microbial aetiology as a result of long duration, already instated cocktail of treatment and rapidly progressing damage. In such a case despite initiation of treatment, ulcer may show suboptimal response with progressive damage. Visual and structural loss can be devastating in such cases. This chapter intends to discuss clinical features, diagnostic differentiators, investigations and treatment, of microbial keratitis (MK) most likely to require emergent care.

7.2 Incidence

The incidence and type of MK largely vary with factors related to geography, ethnicity and trends in antibiotic usage [1]. Bacterial keratitis is reported to be more prevalent in developed countries as opposed to mycotic keratitis in the developing world. This variation is largely attributed to the organic matter-related ocular trauma as one of the most common risk factors for mycotic keratitis in the developing

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world. The incidence of MK varies from 10/lakh persons/year in the United States to 799/lakh persons/year in developing countries [2, 3]. Moreover, bacterial keratitis is the most common form of MK, accounting for 90–95% cases with highest reported cases in temperate climate regions [1].

Fungal keratitis is a common cause of corneal infection in developing nations owing to tropical climate with higher temperature and humidity. In sub-Saharan Africa and Asia, filamentous fungi account for more than 40% of cases of MK. In the United States, *Candida* and *Aspergillus* are regarded as most common cause of fungal keratitis while *Fusarium species* is predominant in the southern United States [4]. However, *Aspergillus* remains the most common cause of mycotic ulcers all over the world including India [4].

7.3 Aetiology

The variable aetiological agents in different types of MK are an important determinant of severity of lesion and corneal emergencies associated with it. In bacterial keratitis, the most common causative pathogen has been reported to be Gram-positive cocci which include *Staphylococcus aureus and Streptococcus pneumonia* [5, 6]. Gram-negative bacilli like *Pseudomonas aeruginosa*, *Haemophilus influenzae and Serratia* species are other less common causative agents [7]. *Staphylococcus epidermidis and Fusarium species* are the most common organisms seen in polymicrobial keratitis. Among viral keratitis, Herpes simplex virus (HSV) is one of the leading and emerging causes of corneal blindness worldwide. Stromal necrotising HSV keratitis may lead to severe stromal necrosis and neurotrophic ulcer but rarely perforates. Rare pathogens causing microbial keratitis includes the protists, *Acanthamoeba* spp., *Pythium* and *Microsporidia*.

The aetiology of fungal keratitis varies depending on geographical region, climatic condition and socio-economic status [6]. The common fungal agents associated with infectious keratitis include filamentous as well as yeast variants. Filamentous fungi are responsible for more than 70% of cases [6]. Mycotic keratitis carries a significantly higher potential for corneal perforation in comparison to other infective aetiologies [8]. *Aspergillus* keratitis shows a higher tendency for descemetocele formation and perforation in comparison to *Candida* and *Fusarium* keratitis. In addition, up to 20% cases of mycotic keratitis (mainly candidiasis) are complicated by bacterial coinfection [9].

Pseudomonas is the commonest pathogen identified in contact lens-associated bacterial keratitis and subsequent sloughing in such cases. It is also the most common bacterial organism detected in cases with corneal perforation [1]. While *Staphylococcus aureus* also exhibits considerable propensity towards corneal abscess, sloughing and perforation [10]. Incidence of secondary glaucoma is observed to be more in cases of *Pneumococcal*, mycotic and advanced stage of *Acanthamoeba* keratitis. *Acanthamoeba* keratitis may lead to corneal perforation in advanced cases, especially when initially misdiagnosed and inappropriately managed.

7.4 Approach to Diagnosis

7.4.1 History

The relevant history together with the evaluation of clinical features is an important step towards formulating a clinical diagnosis. Identification of predisposing factors along with characteristic onset of symptoms can be indicative of causative organism (Table 7.1). Important predisposing factors that should be elicited during pre-treatment workup should comprise ocular trauma, conjunctivitis and subsequent use of over-the-counter medications, contact lens wear (including type and duration of lens used, time since last change to a new pair of lenses, cleaning regimen and frequency of use) and whether the patient was engaged in activities such as sleeping or swimming with contact lenses in place, tear film abnormalities, use of topical steroids, ocular surgery, neurotrophic keratopathy, systemic diseases and immune compromised states.

7.4.2 Clinical Examination

A meticulous clinical examination is an important step towards further management of the case. Patients presenting with microbial keratitis-related corneal emergencies should be first assessed for visual acuity in the involved eye. The extent of deterioration in visual acuity is indicative of severity of the lesion and provides a useful guide to the prognosis and potential response to treatment. Careful slit lamp aided ocular examination is important for presumptive diagnosis of the causative pathogen by determining the morphology of lesion, growth pattern within the cornea and other unique clinical signs (Table 7.2).

Slit lamp photography is a useful tool to monitor the clinical progress and is a strong aid in counselling the patient for improved compliance. Ultrasound B-scan (USG B-scan) should be employed to assess the posterior segment in severe cases where endophthalmitis is suspected and visualisation of fundus is not possible. Clinical grading of ulcer is indicative of extent and severity of disease and is further helpful in treatment and prognosis of the case. Corneal ulcer can be graded into mild moderate and severe depending on the extent of involvement [11] (Table 7.3). Documenting the clinical features as a colour-coded diagram and/or a clinical photograph can serve as an important guide for prognosis and follow-up (Fig. 7.1).

7.4.3 Microbiological Evaluation

Microbiological evaluation for identification of causal organism is undoubtedly the most important step towards proper management of corneal ulcer. Cultures are helpful to guide in modification of therapy in patients with a poor clinical response and to decrease toxicity by eliminating unnecessary medications (Table 7.4). Obtaining a corneal culture is a means of identifying the causative organism(s) and the only

Table 7.1 Pre-disposing factors and corneal emergencies associated with various pathogens

Sr. no.	Predisposing factor	Indolence	Perforation	Sloughing	Descemetocele	Secondary glaucoma	Toxic epitheliopathy	Neurotrophic ulcer	Corneal abscess	Corneal fistula
Bacterial										
Staphylococcus	Diseased corneas like PBK, DED, viral keratitis, exposure keratopathy	Common	In advanced cases and in suboptimal treatment	In advanced cases an in suboptimal treatment	Progressive corneal thinning leads to descemetocele formation	Common	Common with long term treatment	Common with long-standing cases	Hallmark feature	Associate with central perforation
Pseudomonas	Corneal trauma	–	Most common cause of corneal perforation in microbial keratitis	Rapidly progressing	Severe ulceration leads to descemetocele formation	Longstanding severe inflammation leads to rubeotic glaucoma	–	–	Suppuration and abscess are very common	Rare
Pneumococcal	Corneal trauma; Coexistent dacryocystitis, persistent epithelial defects consequent to lid abnormalities	Common	Common with 'Ulcus Serpens'	Seen in advanced inadequately treated cases	Common	Can be seen with a long duration	Common	–	Common	Associate with central perforation
Herpes simplex virus (HSV)										
Epithelial	Active viral replication	Untreated and recurrent cases are commonly associated with PED	Uncommon	Not seen	Chronic recurrent cases may lead to descemetocele	Not seen	Seen commonly	Chronic recurrent cases may lead to neurotrophic ulcer	Uncommon	Not seen
Stromal necrotising	Active viral replication; when topical steroids are given without antiviral cover	Common	Perforation in advanced cases	Sloughing in advanced cases	Common	Common	Seen commonly	Necrosis with decreased corneal innervation leads to neurotrophic ulcer	Uncommon	Associate with central perforation

Immune stromal	Type III hypersensitivity to viral antigen	Rare	Very rare	Not seen	Rare	Secondary trabeculitis may lead to secondary glaucoma	Common with chronic cases	Common with chronic cases	Not seen	Rare
Disciform	Type IV hypersensitivity to viral antigen	Rare	Rare	Not seen	Rare	Secondary trabeculitis may lead to secondary glaucoma	May be seen in chronic cases	Common with chronic cases	Rare	Rare
Mycotic										
Aspergillus	Trauma with vegetative matter; contact lens wear; prolonged topical steroids/antibiotic usage	Very common, especially in steroid-treated cases	Very common	In advanced cases	Progressive thinning leading to descemetocele	In long-standing and steroid-treated cases	Common		Suppuration and abscess	Associate with central perforation
Fusarium	Contact lens wear; trauma with vegetative matter	Common	Very common		Progressive thinning leading to descemetocele	In long-standing and steroid-treated cases	Common		Suppuration and abscess	Associate with central perforation
Candida	Diseased cornea like DED, chronic HSV keratitis; Immunosuppression; contact lens wear	Common	Very common	Uncommon	In advanced cases	In long-standing and steroid-treated cases	Common		Common	Rare
Acanthamoeba										
	Contact lens wear; trauma with agricultural matter; contaminated water bodies	Commonly seen	Common	Common		Very common		Radial keratoneuritis and neurotrophic ulcer	Common	Associate with central perforation
Pythium										
	Exposure to aquatic flora and soil, especially in rainy season	Common; Response to medical treatment is poor	Common	Common	Causes rapid perforation	Common		Common		

Table 7.2 Morphological pattern of different pathogens causing microbial keratitis

Sr. no.	Pathogen	Subtype	Morphology	Associated findings	Corneal emergency
1	Bacterial		Greyish white infiltrates at epithelium and stromal level with associated stromal oedema and overlying epithelial defect	Papillary and ciliary congestion with conjunctival chemosis Anterior chamber reaction with or without hypopyon	Descemetocele; Perforation Sloughing Fistula
		Staphylococcus	Centrally located oval greyish white opaque ulcer with distinct margins and mild oedema of surrounding cornea	Mild AC reaction Long-standing cases Stromal abscess	Corneal abscess Hallmark is 'suppuration' Secondary glaucoma
		Pseudomonas	Spreads concentrically and symmetrically to involve increasing depth of cornea forming 'Ring ulcer' with greenish-yellow discharge. Marked surrounding stromal oedema	Severe AC reaction; Hypopyon Rapidly progressing ulcer; secondary glaucoma	Stromal necrosis and corneal liquefaction progressing to descemetocele; perforation and sloughing
		Pneumococcal	Greyish white or yellowish disc-shaped ulcer near centre of the cornea Starts at periphery and spreads towards centre	Hypopyon Severe AC reaction and anterior uveitis Tendency to creep over the cornea in serpiginous manner	'Ulcus Serpens' leading to corneal perforation

Table 7.2 (continued)

Sr. no.	Pathogen	Subtype	Morphology	Associated findings	Corneal emergency
2	Mycotic		Elevated branching ulcers with feathery irregular margins; associated overlying epithelial defect and satellite lesions Advanced stage might be associated with ring infiltrates, endothelial plaques and corneal perforation	Hypopyon in advanced cases Secondary glaucoma	Persistent epithelial defect Perforation; sloughing ulcer
		Filamentous fungi	Dry looking ulcer with irregular feathery extensions into normal cornea	Fixed hypopyon	Perforation and sloughing. *Fusarium* species typically have a severe course with rapid perforation
		Candida	Elevated yellowish-white plaque-like lesion with surrounding infiltration and oedema	Fixed hypopyon	Perforation in advanced cases or immunocompromised subjects

(continued)

Table 7.2 (continued)

Sr. no.	Pathogen	Subtype	Morphology	Associated findings	Corneal emergency
3	Acantham-oeba	Early phase	Punctate lesions, pseudo-dendrites, subepithelial and perineural infiltrates	Ring infiltrates Symptoms disproportionate to clinical signs	Radial keratoneuritis Secondary glaucoma
		Advanced phase	Advanced stages show multiple large stromal infiltrates associated with thinning of stroma and corneal melting	Hypopyon Anterior Uveitis	Corneal perforation
4	Viral	Epithelial	Superficial punctate keratitis which coalesce to form dendritic ulcer, terminal bulbs and swollen borders	Loss of corneal sensations Symptoms may be less than clinical signs	Persistent epithelial defect Dendritic ulcer Neurotrophic ulcer
		Stromal Non-necrotising	White opaque stromal infiltration, without ulceration	Anterior Uveitis Secondary glaucoma	Neurotrophic ulcer
		Necrotising	Grey-white stromal infiltration with ulceration and necrosis	Anterior Uveitis; Secondary glaucoma	Corneal thinning leading to corneal perforation, necrosis Neurotrophic ulcer
		Disciform	'Ground glass appearance' Stromal oedema not associated with infiltration or vascularization Thickening of all layers of the affected cornea with Descemet's folds	Keratic precipitate (KPs) just behind the involved area	Secondary trabeculitis leading to secondary glaucoma

Table 7.3 Grade of ulcer and stage-wise treatment

S. No	Grade of ulcer				Treatment	Regimen
		Size (mm)	Depth of involvement (%)	Features		
1	Mild	<2	< 20	Superficial involvement No scleral involvement	Monotherapy • Ciprofloxacin 0.3% • Gatifloxacin 0.3% • Moxifloxacin 0.5%	• 4–6 times • Asses the response • Improvement—continue for 7 days and taper over another 7 days
	Moderate	2–5	20–50	Mid-stromal infiltrates No scleral involvement	Combination therapy • Fortified Cefazolin5% +Tobramycin 1.3% Or • Fortified Cefazolin 5%+Gatifloxacin 0.3%or Moxifloxacin 0.5% Cephalosporin for Gram +ve cocci and AG/FQ for Gram – ve bacilli	• 2 hourly day time, 4 hourly night time for 2 days • Taper over next 1 week, later 4 times for another 1 week
	Severe	>5	>50	Deep stromal, scleral involvement	Combination therapy • Fortified Cefazolin5% +Tobramycin 1.3% OR • Fortified Cefazolin 5%+Gatifloxacin 0.3% or Moxifloxacin 0.5% Cephalosporin for Gram +ve cocci and AG/FQ for Gram – ve bacilli Systemic antibiotics	• Loading dose Every 5 min for half-hour; every 15 min for 2 h; every half to 1 h for 24 h • Assess the clinical response • Improvement: 2 hourly day time 4 hourly night time for 2 days and taper over next 1 week; 4 times for another 1 week
2	Perforated ulcers or Impending perforation				Systemic antibiotic—oral or intravenous Ciprofloxacillin 500–1000 mg BD Tab Doxycycline 100 mg BD along with topical therapy as described	1–2 weeks

(continued)

Table 7.3 (continued)

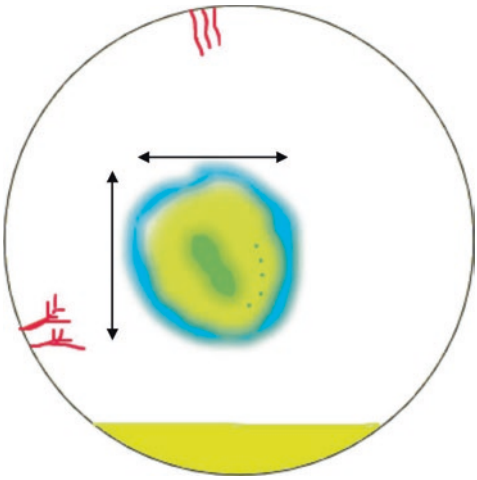
S. No	Grade of ulcer				Treatment	Regimen
		Size (mm)	Depth of involvement (%)	Features		
3	Scleral involvement *Neisseria, Corynebacterium* and *Haemophilus* infection				Systemic antibiotic—oral or intravenous Ciprofloxacillin 500–1000 mg BD	1–2 weeks
4	Descemetocele				BCL; Tissue glue; AMT	
5	Perforation <2 mm				BCL; tissue glue; AMT	
6	Perforation >2 mm				Patch graft Therapeutic keratoplasty	
7	Sloughing				Therapeutic keratoplasty	
8	Corneal Fistula				Patch graft	
9	Endophthalmitis				I/V antibiotics	

AG/FQ: Aminoglycosides/Fluroquinolones
BCL: Bandage contact lens
AMT: Amniotic membrane transplantation

method to determine antibiotic sensitivity. However, with the advent of broad-spectrum antibiotics many ophthalmologists tend not to culture the microbe. Small peripheral ulcers may not require culture but central ulcers and ulcers more than 2 mm, should be cultured prior to initiating therapy to prevent progression, indolence and relapse. If access to the culture media is not available, valuable information can still be achieved from Gram stain. The site should be cultured even in patients already on antibiotics as, there always remains a possibility to get conclusive result. In event of inconclusive microbiological report of non-responding ulcers, patients should be evaluated for non-bacterial aetiology. Samples of the eyelids/conjunctiva, topical eye medications and contact lens solutions should also be cultured wherever deemed necessary.

Indications for Culture Sensitivity

- A corneal infiltrate which is central, more than 2 mm and/or associated with significant stromal involvement or melting.
- Infection is chronic in nature or unresponsive to broad-spectrum antibiotic therapy.
- History of corneal surgeries.
- Atypical clinical features suggestive of fungal, amoebic, or mycobacterial keratitis.
- Infiltrates in multiple locations over the cornea.



Epithelial defect - Size mm × mm
Infiltrates – Size and depth of involvement
Maximum thinning in mm & depth of involvement

Other findings:

- Epithelial and Stromal edema
- Epithelial and Stromal necrosis
- Descemetocele – Size and sector of involvement
- Hypopyon - Size and mobility
- Vascularisation - Type, sector and extent of involvement
- Satellite lesions - Number, size and sector of involvement
- Immune ring

Fig. 7.1 Colour-coded diagram for documentation

Table 7.4 Microscopy and microbial culture in microbial keratitis

	Microscopy (smear)	Culture media
Bacterial	Gram's stain Giemsa stain	Chocolate agar (*Haemophilus* and *Neisseria* spp.) Blood agar (aerobes) Thioglycollate broth Roberson cooked meat media (anaerobes)
Fungal	KOH mount (10%) Calcofluor white Gram's stain Periodic acid-Schiff (PAS)	Sabouraud dextrose agar without chlorhexidine Brain heart infusion agar with chloromycetin
HSV keratitis	–	Tube culture isolation—traditional gold standard Cell culture (cell lines—human foreskin fibroblasts, MRC-5)
Acanthamoeba	Calcofluor white	Non-nutrient agar with seeded *Escherichia coli*
Mycobacteria/ Acid-fast bacilli	Ziehl-Neelsen (ZN) stain	Lowenstein-Jensen (LJ) media Middlebrook media
Pythium	Acridine orange hydrochloride, Lactophenol blue	Potato dextrose agar Sabouraud dextrose agar, and Chocolate agar

7.4.4 Response to Treatment

Response to treatment should be assessed after 24 and 48 h. Stable clinical features after initiation of treatment without any worsening, even if not showing any improvement on clinical parameters is indicative of resolving infection. Subsequently, the ulcer should start consolidating with progressive healing of epithelial defect, decrease in infiltration and stromal oedema. Other clinical signs also, should noticeably be decreasing. However, the visual acuity is the last to improve in majority of cases. Consequent to signs of healing, gradually reduce the frequency of topical treatment and follow up over 2 weeks. If morphological looking and culture-proven bacterial ulcers fail to show any improvement even after 7 days it is reasonable to consider methicillin-resistant *Staphylococcus aureus* (MRSA).

7.4.5 When to Refer?

Referral guidelines largely depend on the level of health care delivery system, where the patient reports for the first time. Decision to refer the patient for further management is dependent on multiple factors like onset and duration of symptoms, severity of disease and associated complications if any.

At Primary Centre
With limited resources and lack of skilled care at primary centre urgent referral to higher centre is mandatory along with prescription of broad-spectrum antibiotic eye drops for hourly instillation, until they are seen at the referral centre.

At Secondary Centre
Management of mild-to-moderate grades and uncomplicated corneal ulcers can be effectively done at secondary eye care centres. In cases of severe grades and complicated variants, the decision to refer the case can be taken as per the guidelines (Fig. 7.2).

At Tertiary Centre
Different tertiary eye care centres have their own protocols for management of corneal ulcer. However, the WHO recommended guidelines to be followed at eye care facilities are as follows [12]:

- Careful history, background examination findings and treatment history.
- Meticulous corneal scraping.
- Hospitalisation to ensure adequate treatment and regular follow-up.
- Documentation.

If the keratitis responds to treatment, instituted therapy should be continued for 1–2 weeks in a bacterial aetiology and at least 2–3 weeks in fungal. In cases with

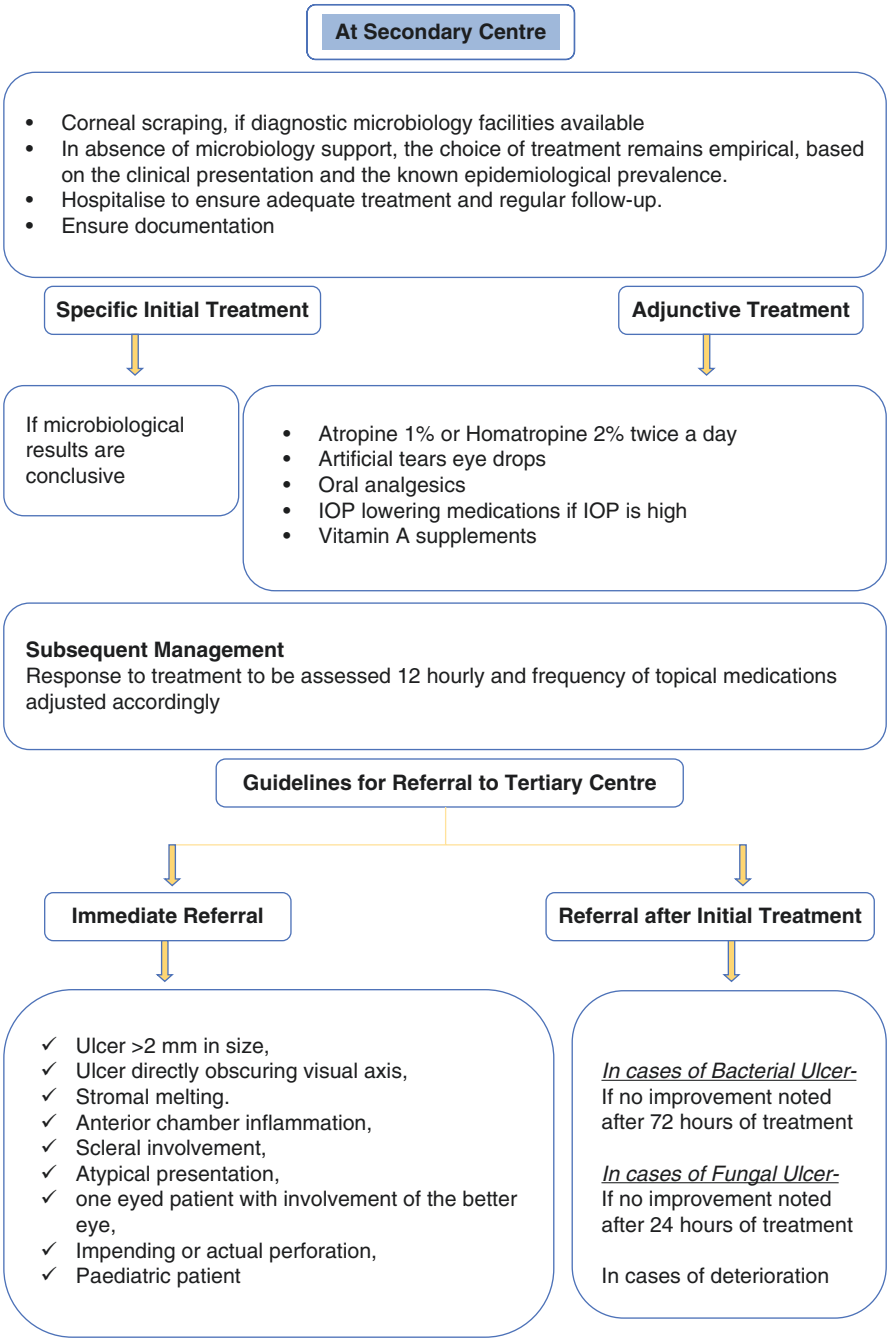


Fig. 7.2 Management and referral guidelines for secondary centre

poor response manifested as increase in size of epithelial defect, increase in infiltrations, AC reaction and hypopyon, progressive thinning and perforation, it is prudent to re-evaluate the case for possible cause of indolence.

7.5 Bacterial Keratitis

Bacterial keratitis is the most common cause of microbial keratitis and accounts for more than 85% of all microbial keratitis cases [12]. It is a corneal emergency which if not managed properly, can lead to vision threatening complications such as perforation, sloughing, endophthalmitis and/or corneal scarring/opacification [12]. Since it is characterised by rapidly progressing clinical course, an early diagnosis and treatment are paramount to minimising visual deterioration. The clinical features and morphological appearance of important causes of bacterial keratitis are described below.

7.5.1 Diagnostic Differentiators

Patients presenting with bacterial keratitis exhibit distinct morphological patterns amenable to be correlated to particular pathogen which is immensely helpful in initiating an appropriate and timely treatment. However, in advanced cases the morphological distinction is not discernible. Lid oedema, conjunctival and circumciliary congestion, epithelial defect, stromal infiltration, surrounding oedema and endotheliitis associated with anterior chamber reaction with or without hypopyon are some of the important clinical signs that help differentiate bacterial corneal ulcer from other aetiologies.

7.5.1.1 Staphylococci

Staphylococcus being a commensal of conjunctival flora is seen to be a cause of keratitis more frequently in compromised corneal surface (Table 7.1). Corneal lesions are usually pale white, round or oval disc-shaped ulcer with dense deep surrounding infiltration. Presence of stromal oedema, folds in Descemet's membrane along with moderate-to-severe AC reaction and hypopyon are indicative of deeper involvement. Abscess formation may be seen in long standing cases with suboptimal treatment (Fig. 7.3).

7.5.1.2 Streptococci

Streptococcus pneumoniae usually presents with rapidly progressing lesion with severe mucopurulent discharge. Typical morphology being round or oval central or paracentral ulcer with formation of deep stromal abscess. It is accompanied by severe fibrinous AC reaction and hypopyon formation. Rest of the cornea is usually clear (Fig. 7.4).

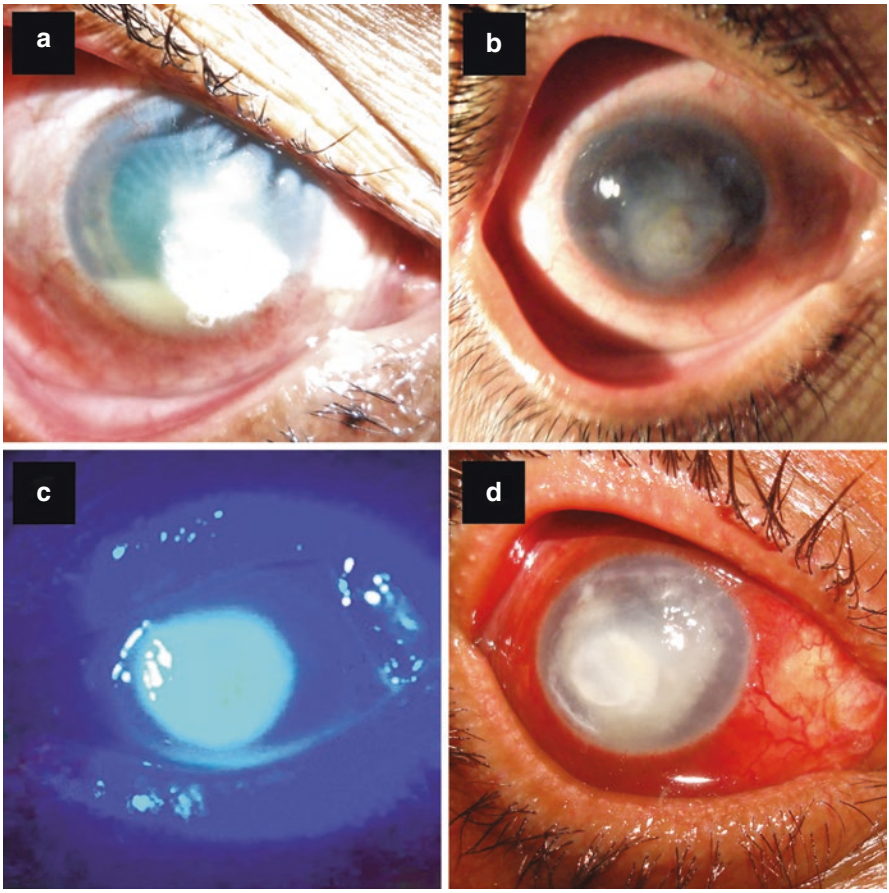


Fig. 7.3 (**a**) Pale white disc-shaped ulcer with dense deep surrounding infiltration, stromal oedema, folds in Descemet's membrane and hypopyon indicative of *Staphylococcus*. (**b**) Status post healing with the formation of leucomatous corneal opacity. (**c**, **d**) Larger pale white Staphylococcal central ulcer with surrounding infiltration

7.5.1.3 Pseudomonas

Pseudomonas aeruginosa typically presents with rapidly progressing ulcer both in size and in depth with dense deep stromal infiltrate and oedema, intense necrosis and greenish-yellow mucopurulent discharge (Fig. 7.5). Rest of the cornea has steamy inflamed ground glass appearance. In event of suboptimal treatment, the aggressive pathological course of *Pseudomonas* causes rapid descemetocele formation and subsequent corneal perforation or sloughing. Immune ring may be seen in a slowly progressing lesion.

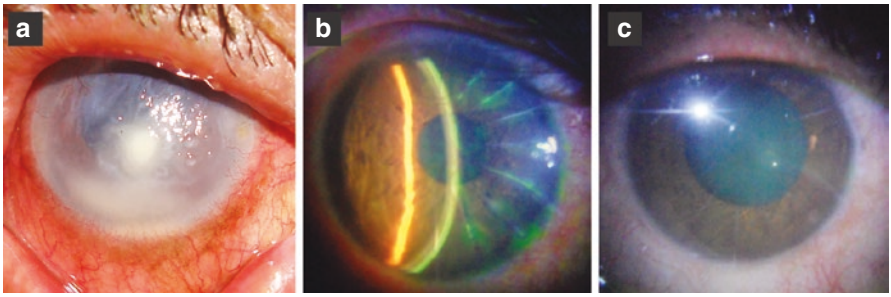


Fig. 7.4 (**a**) Round paracentral ulcer with formation of deep stromal abscess with hypopyon (**b**) *Streptococcus* keratitis status post radial keratotomy, and (**c**) Healed keratitis at follow up of 7 days

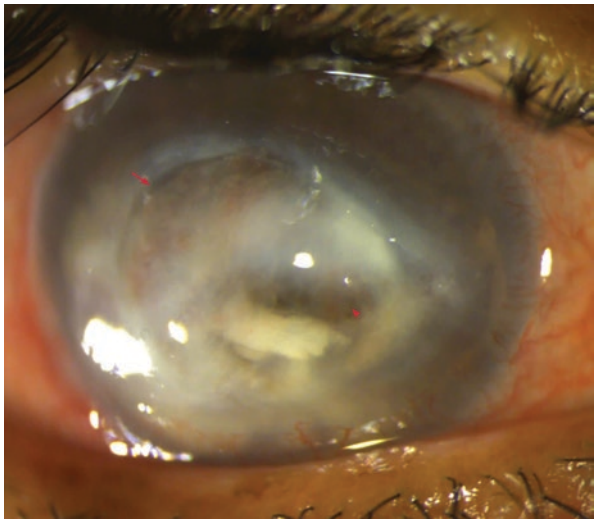


Fig. 7.5 Slit lamp picture showing Grade III corneal ulcer with dense stromal infiltrates, liquefactive necrosis and intense yellow exudates, causative organism being *Pseudomonas*. Note the marked thinning with peripheral gutter formation (arrow) and perforation sized 2 × 3 mm (arrowhead)

7.5.2 Management

Empirical therapy should be started in cases of mild keratitis, obviating the need for corneal scraping, especially in centres where laboratory facilities may not be readily available for plating and inoculation. However, in moderate and severe grades of ulcers microbiological workup and antibiotic sensitivity should necessarily be done. Subsequently, empirical treatment should be started with broad-spectrum antibiotics in accordance with the sensitivity report (Table 7.5) [12]. Corneal biopsy could be considered in cases with deep stromal infiltrates, particularly in setting of negative culture and poor clinical improvement.

Bacterial keratitis is effectively managed (including severe cases) using fortified antibiotics, tobramycin (14 mg/mL) one hourly alternating with cefazolin or vancomycin (50 mg/mL). General guidelines for antibiotic usage in the management of

Table 7.5 Antimicrobial therapy for the management of bacterial keratitis

Organism	Antibiotic	Topical concentration	Subconjunctival dose
No organism identified or multiple types of organisms	Cefazolin or vancomycin with Tobramycin or gentamicin or Fluoroquinolones[a]	50 mg/mL 9–14 mg/mL Various[b]	100 mg in 0.5 mL 20 mg in 0.5 mL
Gram-positive cocci	Cefazolin Vancomycin[c] Bacitracin[c] Fluoroquinolones[a]	50 mg/mL 15–50 mg/mL 10,000 IU Various[b]	100 mg in 0.5 mL 25 mg in 0.5 mL
Gram-negative rods	Tobramycin or gentamicin Ceftazidime Fluoroquinolones	9–14 mg/mL 50 mg/mL Various[b]	20 mg in 0.5 mL 100 mg in 0.5 mL
Gram-negative cocci[d]	Ceftriaxone Ceftazidime Fluoroquinolones	50 mg/mL 50 mg/mL Various[b]	100 mg in 0.5 mL 100 mg in 0.5 mL
Nontuberculous mycobacteria	Amikacin Clarithromycin Azithromycin Fluoroquinolones	20–40 mg/mL 10 mg/mL 10 mg/mL Various[b]	20 mg in 0.5 mL
Nocardia	Sulfacetamide Amikacin Trimethoprim/ sulfamethoxazole: Trimethoprim Sulfamethoxazole	100 mg/mL 20–40 mg/mL 16 mg/mL 80 mg/mL	20 mg in 0.5 mL

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[a]Fewer Gram-positive cocci are resistant to gatifloxacin, moxifloxacin and besifloxacin than other fluoroquinolones

[b]Besifloxacin 6 mg/mL; ciprofloxacin 3 mg/mL; gatifloxacin 3 mg/mL; levofloxacin 15 mg/mL; moxifloxacin 5 mg/mL; ofloxacin 3 mg/mL, all commercially available at these concentrations

[c]For resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy. Vancomycin and bacitracin have no Gram-negative activity and should not be used as a single agent in empirically treating bacterial keratitis

[d]Systemic therapy is necessary for suspected gonococcal infection

bacterial keratitis are illustrated in Table 7.5. Adjunctive treatment of cycloplegics, tear supplements and antiglaucoma medication should be instituted along with antibiotics. Less-severe forms of keratitis can be effectively managed by monotherapy with fourth-generation fluoroquinolones such as moxifloxacin or Gatifloxacin. MRSA should be considered in a culture-proven bacterial ulcer, if it fails to show any improvement in 24–48 h [13]. Ocular surface disease should be ruled out in such cases. Figure 7.6 summarises the treatment approach to bacterial keratitis at a tertiary level facility.

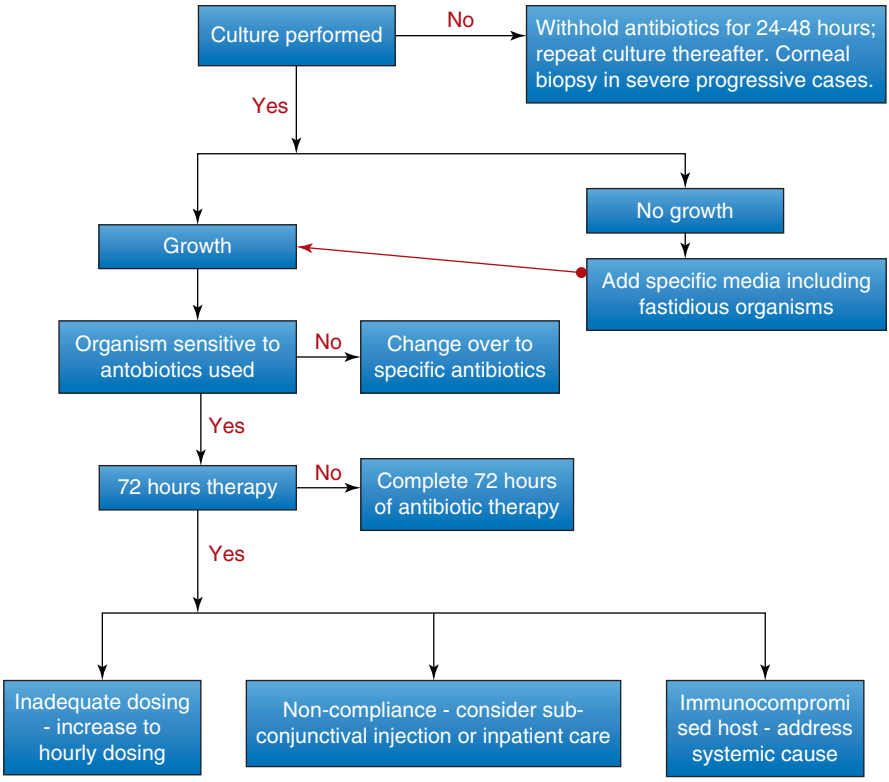

Fig. 7.6 Treatment approach to bacterial keratitis at a tertiary level facility

7.6 HSV Keratitis

HSV keratitis is by far the most underdiagnosed and an equally challenging entity in clinical practice both from diagnostic and from therapeutic perspective. It can affect all the layers of cornea individually or as mixed variants. The diagnostic dilemma and therapeutic concerns can be challenging for the ophthalmologist, because HSV keratitis often masquerades as *Acanthamoeba* keratitis, mixed microbial keratitis, toxic epitheliopathy and neurotrophic keratitis [14]. Thus, it warrants an emergent intervention to alleviate symptoms minimise visual loss and prevent complications. As opposed to other types of microbial keratitis, HSV keratitis can have clinical manifestations ranging from infectious to immunological variants requiring varied treatment in diverse circumstances.

It can be broadly categorised as epithelial disease, caused by active virus replication, stromal disease, usually caused by immunologic mechanisms in addition to active viral replication and endotheliitis (Table 7.6). The commonest cause of corneal emergency in HSV keratitis which necessitates emergent intervention is

Table 7.6 HSV keratitis

	Morphology	Corneal emergencies	Symptoms	Complications	Treatment	Outcomes	Etiopathogenesis
Epithelial infective	Superficial punctate keratitis: branching epithelial dendrites	Persistent epithelial defect Toxic epitheliopathy	Pain, photophobia, redness, watering	Epithelial and faint anterior stromal opacities	Topical antiviral; Surface debridement	Self-limiting in immune-competent hosts; Ghost scarring; footprints	Active virus replication in epithelial cells, causing cell destruction
Stromal necrotising	Grey-white stromal infiltration with ulceration and necrosis	Persistent epithelial defect Corneal thinning and perforation	Pain, photophobia, redness, watering diminution of vision	Anterior chamber inflammation; Iritis; Thinning and Progressive corneal scarring	Topical and systemic anti-viral followed by topical corticosteroid therapy	Stromal opacity and neovascularisation; thinning and scarring leading to visual impairment	Active Virus proliferation within the stroma
Immune stromal	Stromal infiltration with intact epithelium Punctate Stromal opacities and haze Immune ring	Stromal oedema	Pain, photophobia, diminution of vision	Anterior chamber inflammation; iritis; Mid-to-deep stromal neovascularisation Corneal scarring	Topical /systemic corticosteroids with systemic anti-virals	Stromal opacity and neovascularisation; ghost vessels; lipid keratopathy leading to visual impairment	Antibody complement cascade against retained herpes antigens in stroma

(continued)

Table 7.6 (continued)

	Morphology	Corneal emergencies	Symptoms	Complications	Treatment	Outcomes	Etiopathogenesis
Endotheliitis	Stromal oedema not associated with infiltration or vascularisation epithelial microcysts; keratic precipitate, Descemet's folds	Stromal oedema; endothelial decompensation	Pain, photophobia, decreased vision	Anterior chamber inflammation; Iritis	Topical and or systemic corticosteroids	Corneal decompensation in severe cases and in absence of treatment	Cell-mediated immune reaction to stromal tissue
Neurotrophic ulcer	Greyish white oval ulcer with rolled and smooth borders; Inter-palpebral location	Corneal perforation	Non-specific	Corneal thinning Neovascularisation	Discontinuation of potentially toxic eye drops; Artificial tear supplements soft corticosteroid eye drops; Bandage contact lens		Decreased tear secretion consequent to impaired corneal innervation; toxic epitheliopathy

necrotising stromal keratitis. However, it is imperative to have knowledge of all types of clinical presentations, their morphology and treatment.

7.6.1 Diagnostic Differentiators

7.6.1.1 HSV Epithelial Keratitis

Infective epithelial keratitis is the most common manifestation and generally presents as dendritic and geographic ulcers in addition to marginal keratitis in infrequent cases [15]. Raised clear epithelial vesicles which later coalesce to form the typical dendritic or geographical ulcers are the hallmark of disease (Fig. 7.7a). The patient presents with symptoms of photophobia, pain, foreign body sensation and serous discharge. Blurring and diminution of vision may be seen in cases of central involvement.

The typical dendritic ulcer is a central or paracentral branching, linear lesion with terminal bulbs and swollen epithelial borders containing live viruses. However, immune compromised subjects may fail to show a typical dendrite and may have only vesicles.

The fluorescein-stained lesion is an important differentiator from other branching lesions of the corneal epithelium often regarded as pseudo dendrites particularly of varicella-zoster virus (VZV). Psuedodendrites are raised lesions usually peripherally located and arranged in cluster of cells without break in surface epithelium and hence do not stain with fluorescein. Coalescent and enlarged dendrites with scalloped borders are referred to as geographic ulcer (Fig. 7.7b). It has swollen epithelial borders that contain live viruses while staining brightly with fluorescein. If treatment is not initiated promptly the disease can progress to stromal necrotising keratitis, immune stromal keratitis or neurotrophic keratopathy [15].

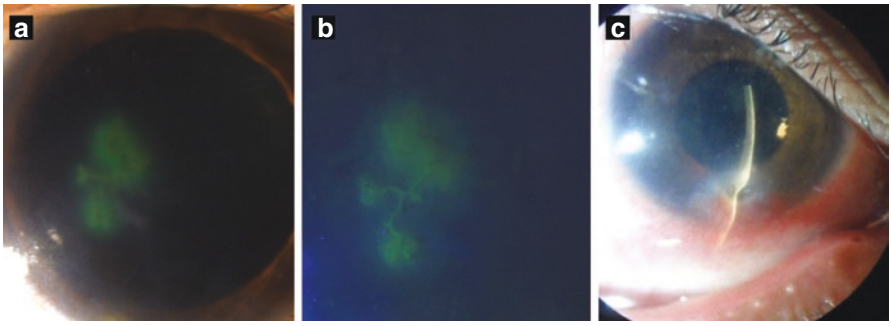

Fig. 7.7 (**a**) Slit lamp picture showing herpetic dendritic ulcer. (**b**) Slit lamp picture showing herpetic dendritic ulcer with dichotomous branching as visualised on cobalt blue filter with fluorescein staining. Broad terminal end pattern is indicative of progression to geographical ulcer. (**c**) Corneal thinning consequent to marginal keratitis of HSV associated with superficial and deep vascularisation extending up to the lesion

Treatment

Epithelial keratitis is a self-limiting disease with resolution in more than 50% of cases within 2 weeks [15, 16]. However, it is prudent to initiate timely treatment to promote healing, prevent progression and subsequent subepithelial scarring. It is advisable to do debridement of ulcer by a cotton-tipped blunt applicator which facilitates shedding of virus thereby decreasing the viral load. This is to be followed by topical antiviral agents in adequate doses.

Recommended treatment agents comprise of ganciclovir gel 0.15%, trifluridine 1% ophthalmic suspension, every 2–4 h [17]. Acyclovir 3% or vidarabine 3% ointment five times a day can also be used. To prevent drug-induced epithelial toxicity dosing frequency can be reduced over the next 2 weeks. Ganciclovir/ trifluridine can be reduced to 4–6 times and acyclovir/ vidarabine to 3 times per day and can be discontinued completely by 3 weeks. There is no role of topical corticosteroids in management of HSV epithelial keratitis. Supportive treatment in the form of topical cycloplegics (homatropine acetate 1%/ cyclopentolate 2%), broad-spectrum antibiotic (ofloxacin 0.3%/ moxifloxacin 0.5%) and preservative-free tear substitutes (HPMC 0.3%/ CMC 0.5%) are initiated to prevent iritis, ciliary spasm and superimposed secondary infection. Systemic antivirals are indicated in infants, immunocompromised patients, and patients not responsive or not compliant to topical therapy. They can shorten the course of disease, reduce the chances of complications and recurrences.

7.6.1.2 Marginal Ulcer of HSV

Marginal ulcer of HSV is a frequently misdiagnosed entity which is characterised by severe inflammation, anterior stromal infiltrates and accompanying vascularisation as a sequel to active viral replication and resultant immune response (Fig. 7.7c). It has to be differentiated from marginal keratitis of bacterial origin which is purely an immune response to bacterial antigen and presents with an intact overlying epithelium with a clear zone between the lesion and corresponding limbus. The HSV lesion rarely progresses centrally even in advanced stage. In event of confounded diagnosis of bacterial marginal keratitis with initiation of topical corticosteroids without antiviral cover, the lesion can rapidly progress to larger size and central extension [15]. Treatment involves topical antiviral agents followed by topical corticosteroids once the infiltrates start to decrease and epithelial lesion is healed.

7.6.1.3 Stromal Keratitis

Is representative of true corneal emergency in HSV keratitis and presents either as primary or secondary affection (Table 7.6). Secondary involvement may occur as a complication of endotheliitis, epithelial keratitis or neurotrophic keratopathy. Stromal keratitis manifests as two major entities:

- *Necrotising stromal keratitis*—which involves active viral replication in stroma
- *Immune stromal keratitis*—sequel of an immune reaction to viral antigen within the stroma

Necrotising Stromal Keratitis

Necrotising stromal keratitis occurs as a result of direct viral invasion of the corneal stroma. Clinical features include intense infiltration of the stroma, stromal necrosis and ulceration with an overlying breached epithelium (Fig. 7.8). If untreated it rapidly progresses to thinning and perforation. The condition needs to be differentiated from other types of microbial keratitis mainly bacterial and mycotic (Fig 7.9).

Treatment

Treatment is more complex in necrotising keratitis, in which both live virus and immune response are present and depend on severity of disease. For mild-to-moderate cases prednisolone 1% ophthalmic suspension 4 times and in severe grades 2 hourly dosing is started which can be tapered over a period of 8–10 weeks

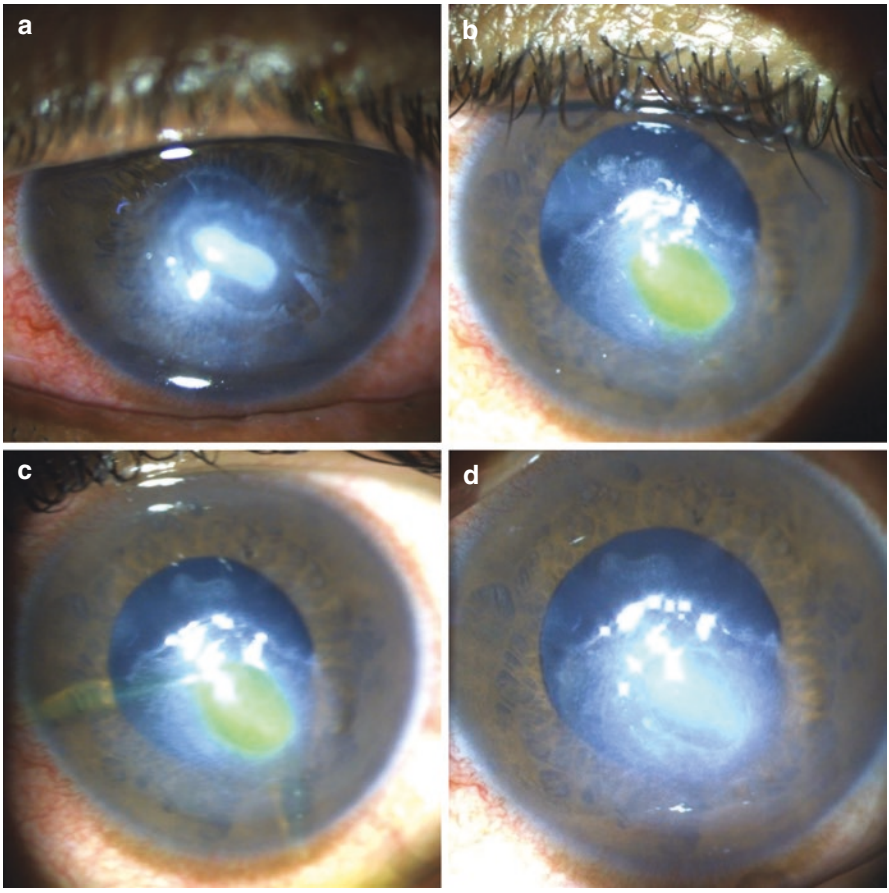

Fig. 7.8 (**a**) Stromal necrotising keratitis as visualised with fluorescein stain showing dense stromal infiltrates and epithelial defect sized 4 × 4 mm. (**b**, **c**) Subsequent pictures show progressive healing with decrease in size of ulcer, infiltrates and healing epithelial margins

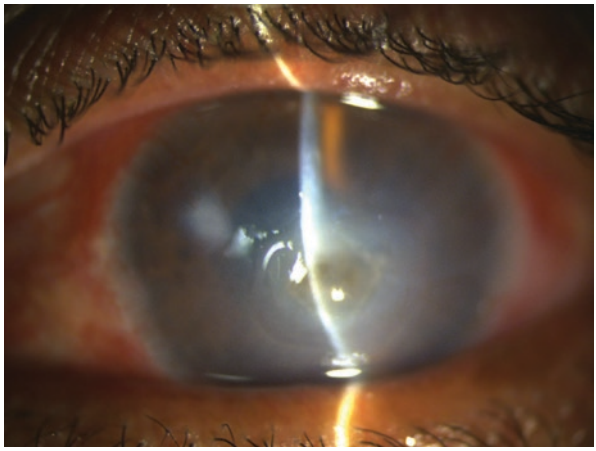

Fig. 7.9 Slit lamp picture showing necrotising viral keratitis with super-added bacterial infection (image courtesy—Prof. Namrata Sharma; Dr. R. P. Centre for Ophthalmic Sciences, All India institute of Medical Sciences, New Delhi)

[17]. It should always be supplemented with topical and systemic antiviral agents, cycloplegics and surface lubricants (Table 7.6).

Immune Stromal (Interstitial) Keratitis

It involves immune-mediated inflammation to retained viral antigen within the stroma. The viral antigen is thought to trigger an antigen-antibody-complement (AAC) cascade that results in intrastromal inflammation [18]. Stromal involvement occurs in the form of infiltration and stromal oedema with an intact overlying epithelium accompanied with anterior chamber inflammation. The lesion heals by varying grades of stromal opacification depending on virulence of organism and host immune response. Wessely immune ring is seen as a consequence of AAC precipitate in mid stroma of central or paracentral cornea.

Immune stromal keratitis may lead to stromal neovascularisation and intense inflammation as a response to ongoing inflammation. The neovascularization may range from sectoral in less inflamed cases to complete involvement in severe inflammation. It can be a cause of visual impedance if not managed timely. Emergent treatment of inflammation can result in resolution of blood vessels. Visual deprivation may occur consequent to stromal scarring, lipid keratopathy, corneal neovascularisation and ghost vessels. Such lesions may show reactivation after a period of quiescence which may range from weeks to months necessitating long-term topical corticosteroids to suppress the ongoing inflammatory reaction.

Treatment

Topical corticosteroids used in conjunction with systemic and topical antivirals are the mainstay of treatment in HSV immune stromal keratitis [19]. Dosing schedule largely depends on severity at the time of presentation. For mild-to-moderate disease prednisolone acetate 1% ophthalmic suspension four times a day and for severe cases 2 hourly regimen is to be instated. Topical antiviral agents should always be supplemented with topical steroids. Acyclovir 3% ointment, trifluridine 1%

suspension or ganciclovir 0.15% gel 3–5 times a day should be started. Mydriatic cycloplegic drops of HA 2% /cyclopentolate 1% 2–3 times a day are to be given for ensuing iritis. Additionally, systemic antivirals like oral acyclovir 400 mg five times for 1 week and then three times for 1 week should be started. They shorten the course of the disease and reduce the chances of complications and recurrences.

Topical steroids work by reducing inflammation, scarring and neovascularisation. However, injudicious use of topical steroids can be a cause of perforation, secondary infection and secondary glaucoma. Systemic corticosteroids are to be reserved for severe stromal keratitis with endotheliitis and iritis. They should be given for long term up to 6 months till complete resolution occurs, otherwise, there is a risk of continuing inflammation and sequel.

7.6.1.4 HSV Endotheliitis

HSV endothelitis is characterised by immune-mediated inflammation of corneal endothelium manifesting as moderate to severe stromal oedema associated with keratic precipitates (KP) and overlying epithelial oedema in severe cases. Oedema is clearly demarcated from surrounding uninvolved cornea with or without presence of immune ring. Ongoing inflammation can be a cause of moderate-to-severe iritis. Characteristically the KP's are always present along the line of endothelial, stromal and epithelial oedema and absent over the rest of cornea. Initiation of timely treatment results in complete resolution of lesion. However, if untreated stromal oedema may persist leading to bullous keratopathy, scarring and secondary neovascularisation. Most agreed upon aetiology is immune mediated, however, some studies have demonstrated live virus in the lesion [20]. HSV endotheliitis can be classified as disciform, diffuse, and linear based on their morphology. Disciform endotheliitis is by far the most common variant present in central or paracentral area and typically with round configuration (Fig. 7.10). Patient presents with photophobia foreign body sensation with mild-to-moderate ocular discomfort. Clinical signs composed

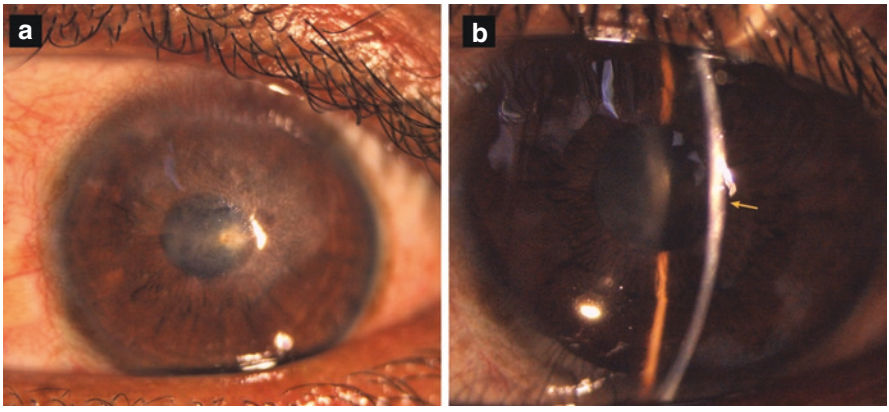

Fig. 7.10 Slit lamp picture showing disciform keratitis of HSV. Note the central circular 3 × 3 mm lesion (**a**) with stromal oedema (arrow) seen on slit beam (**b**)

of varying grades of visual acuity impairment, circumciliary congestion and the typical morphological lesion (as described above) with or without iritis. Secondary open-angle glaucoma may be seen in advanced cases and in severe involvement.

Diffuse endotheliitis is a rare form of HSV endotheliitis. Lesion typically is of diffuse distribution with diffuse stromal oedema and KP over the entire cornea. Severe cases may show epithelial bullae and hypopyon due to intense inflammation. Linear endotheliitis typically presents as a line of stomal oedema with KP and secondary iritis that progresses centripetally from the limbus [21–23].

Treatment

It necessitates aggressive treatment with both corticosteroids and antiviral agents. Oral acyclovir may have a beneficial role and should be considered in all cases. Adjuvant therapy with hyperosmotic agents, anti-glaucoma medication and lubricating eye drops are to be given as per the clinical requirement.

7.6.1.5 Neurotrophic Ulcers

Neurotrophic ulcers are oval ulcers with smooth scalloped borders accompanied by lack of corneal lustre and decreased corneal sensations. They are formed consequent to piling up of epithelial cells over the margin of ulcer mainly as a sequel to corneal nerve involvement, toxic epitheliopathy due to overtreatment with topical antiviral drugs and resultant decreased tear secretion. Neurotrophic ulcers can complicate stromal ulceration and resultant perforation in absence of appropriate treatment [24].

Treatment

Treatment aims to promote epithelial regeneration thereby healing the ocular surface. All topical antivirals, antibacterial and cycloplegic agents should be discontinued. Soft bandage contact lens can be supplemented to prevent shedding of regenerating epithelium. Frequent use of preservative-free artificial tears promotes epithelial healing. In non-responsive cases debridement of the epithelium from the margin of ulcer is advisable to facilitate migration of new epithelial cells thereby facilitate healing. Temporary tarsorrhaphy or eyelid stay suture can be employed as temporary measures to promote epithelisation and healing.

7.7 Fungal Keratitis

The incidence of fungal keratitis has increased over the years owing to frequent use of corticosteroids and antibiotics. Corticosteroids suppress the host immune response and antibiotics provide a non-competitive environment for the fungi to grow. Of the several agents known to cause fungal keratitis, two are important, namely—yeast (*Candida* spp.) and filamentous fungi (septate and aseptate). Former causes secondary fungal keratitis in already compromised corneas following use of

topical steroids or preexistent ocular surface disease while the latter overall, constitutes the most common cause of fungal corneal ulcer. Few if any, fungi can penetrate intact corneal tissue. Risk factors for invasion and infection have been summarised in Table 7.1.

7.7.1 Diagnostic Differentiators

The clinical picture combined with relevant history makes for a good diagnostic differentiator in isolating fungal aetiology among other causes of infectious keratitis. Although the most frequently presented signs of fungal keratitis are similar to other microbial keratitis, an intact epithelium over deep stromal infiltrate should alert the examiner in favour of fungal aetiology. Certain characteristic findings such as greyish white elevated ulcer with hyphate or branching edges, dry rough texture, satellite lesions, immune ring, endotheliitis/ endothelial plaque and fixed hypopyon with convex upper edge can be helpful in narrowing down the cause of keratitis to filamentous fungi (Fig 7.11). *Fusarium* species show a more aggressive course with deeper involvement and rapid perforation (Fig. 7.12). Corneal ulcer caused by yeast is a cheesy white elevated plaque-like lesion with small central ulcer and wider deep stromal infiltrates in a collar stud configuration. Dematiaceous fungi, such as *Curvularia lunata* are identified by the presence of gross brown pigmentation in the region of keratitis.

7.7.2 Treatment

Topical antifungal therapy is the mainstay of treatment of fungal keratitis. However, topical antifungal agents have poor corneal penetration; hence it is advisable to perform epithelial debridement at the time of initiating treatment. Topical 5% Natamycin eye drop being a wide-spectrum antifungal agent, is the drug of choice for most cases of mycotic keratitis. It is given in hourly dosing at daytime, and 2 hourly at bedtime with tapering over 4–7 days if improvement is seen. The treatment should be continued preferably for a period of 3–4 weeks or until complete resolution. Adjunctive treatment in the form of topical fluoroquinolone, Gatifloxacin, cycloplegics, tear supplements and antiglaucoma medication should be continues as per the clinical condition. In event of worsening of clinical features, it is advisable to introduce 0.15% Amphotericin B or 2 % Voriconazole eye drops. Systemic treatment with oral Fluconazole 100–150 mg BD, oral Voriconazole 200 mg BD or oral Itraconazole 200 mg BD for 1–2 weeks is indicated in large-sized ulcers >5 mm, deep keratitis with more than 2/3rd involvement, scleritis, post-PK and in impending endophthalmitis.

Targeted therapy with intracameral or intrastromal antifungal agents can be given in severe cases which are non-responsive to medical therapy, have endothelial

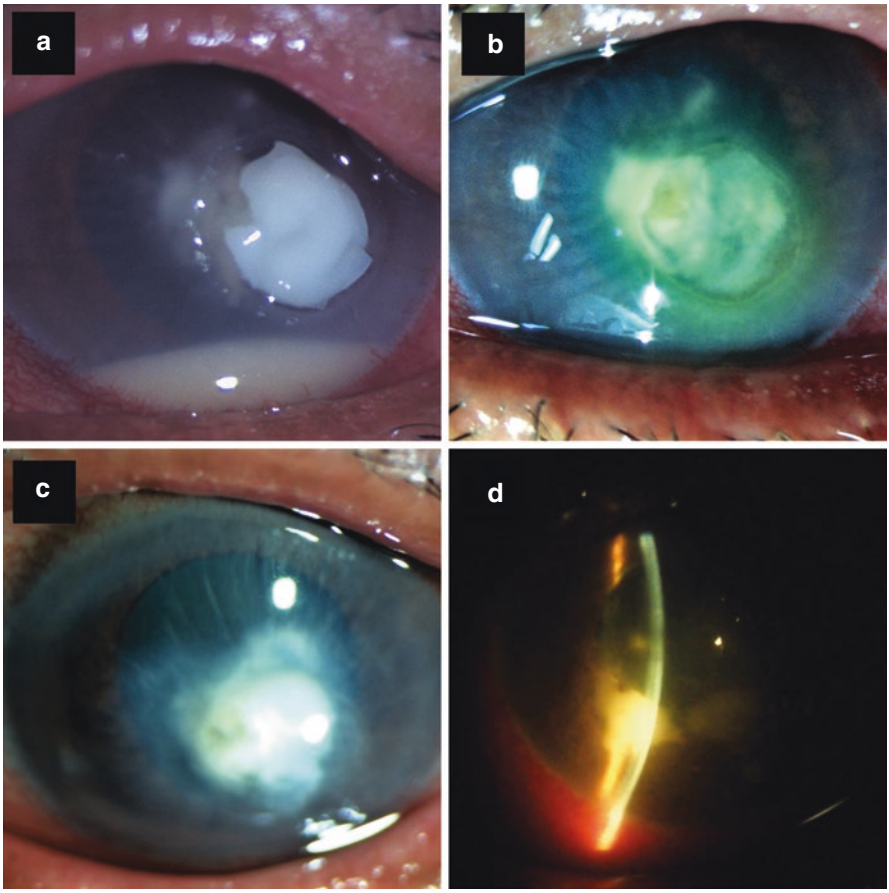

Fig. 7.11 (**a**–**d**) Mycotic corneal ulcer with deep stromal abscess, endothelial plaque formation and fixed hypopyon. Large-sized corneal ulcer with satellite lesion and endothelial plaque is seen after removal of epithelial debris

exudates and severe AC reaction. Amphotericin B 5–7.5 µgm/0.1 mL of 5% dextrose or Voriconazole 50–100 µgm/0.1 mL of 5% dextrose can be given. Repeat dose can be given after 1 week. In severe cases such as deep infections, associated scleritis, anterior chamber infiltration—systemic therapy combined with intracameral or intrastromal injections should be considered. Collagen cross-linking and cryotherapy have also been proposed as a useful adjunct to medical therapy [25].

Advanced cases involving the stroma often require prolonged and intensive topical and systemic antifungal therapy [26, 27]. Failure with medical management alone is common. Surgical interventions (therapeutic keratoplasty (TKP), penetrating keratoplasty (PK), conjunctival flap, lamellar keratoplasty or cryotherapy) are required for visual rehabilitation and control [28, 29].

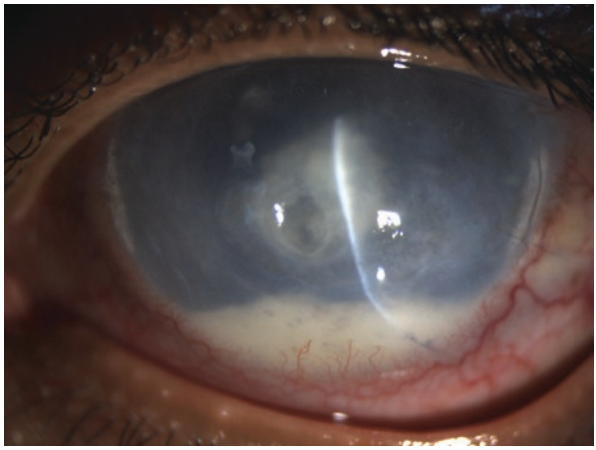

Fig. 7.12 Slit lamp picture of mycotic corneal ulcer with hypopyon, surrounding dense infiltration, marked thinning in centre and impending perforation

7.8 Acanthamoeba Keratitis

It is a fairly uncommon cause of infective keratitis caused by a protozoa—*Acanthamoeba* which is found ubiquitously in water and soil. The patient typically presents as a chronic case of contact lens wear with history suggestive of improper hygiene, exposure to contaminated water bodies or an organic matter-related trauma [30]. In patients with indolent features, leading history of previous use of topical steroids should be elicited. Predominant symptoms of severe pain, photophobia, watering, foreign body sensation even in milder looking lesions should alert the ophthalmologist about *Acanthamoeba* as a possible causative agent.

7.8.1 Diagnostic Differentiators

It primarily presents as ulcer with features similar to herpes simplex. Morphological features consist of epithelial microcysts and erosions, pseudo dendrites, stromal infiltrates and ulceration, radial keratoneuritis and immune ring formation [31] (Fig. 7.13). The pseudo dendrites are raised above the surface with symptoms disproportionate to signs. Presence of satellite lesion is indicative of replicating trophozoites. In advanced case with stromal ulceration disease may be indistinguishable from HSV.

Confocal microscopy is a useful, non-invasive imaging technique for diagnosis, and treatment of *Acanthamoeba* keratitis. *Acanthamoeba* cysts are identified as high contrast round configuration with double-walled structure of the ectocyst surrounding the endocyst, while trophozoites as more irregular structures. Radial keratoneuritis can be demonstrated, as irregularly swollen nerve fibres. Identification and subsequent resolution of these lesions are important to evaluate the response to treatment and can serve as prognosis indicators.

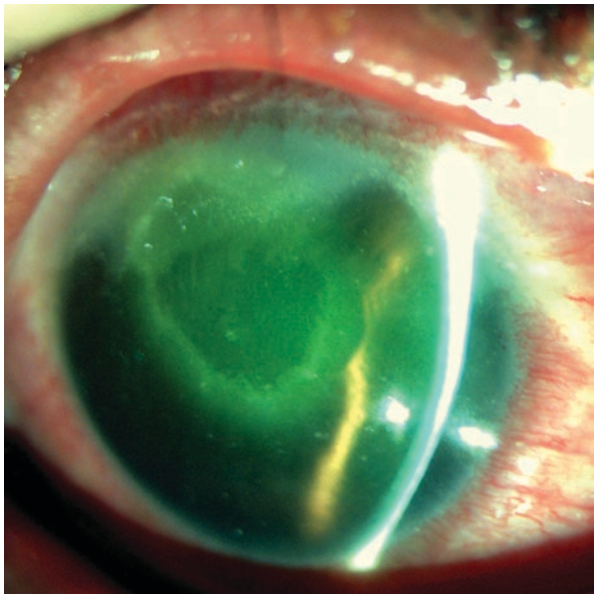

Fig. 7.13 Corneal ulcer sized 5 × 5 mm with deep stromal infiltrates and immune ring formation caused by *Acanthamoeba*

It should be differentiated from mycotic keratitis when a similar history of trauma with vegetative matter is present. However, clinical signs of radial keratoneuritis, pseudo dendrites and epithelial erosions are important differentiating features. Advanced cases present as deep stromal infiltrate and abscesses which can progress to descemetocele and perforation. Uncontrolled infection can be a cause of scleritis, iridocyclitis, secondary glaucoma and complicated cataract.

7.8.2 Treatment

Microbial keratitis due to *Acanthamoeba* is difficult to treat requiring treatment for longer duration up to 6–12 months. Combination therapy includes cytocidal drugs like Propamidine isethionate 0.1%, Chlorhexidine 0.02%, polyhexamethylene biguanide 0.02%, hexamidine and miltefosine (65.12 μg/mL) are effective when given for prolonged period [30]. Chlorhexidine 0.02% is given 1–2 hourly for 2–4 weeks, which can later be tapered to 4–6 times for 6–12 months. Adjuvants like mydriatic cycloplegic agents, surface lubricants and broad-spectrum antibiotics can be supplemented. Recommended dosing frequency varies, but they are initially used hourly for the first several days and tapered slowly over 4−6 weeks to four times a day. The maintenance therapy is tapered more slowly to ensure complete eradication of cyst, lasting 3−6 months, even up to a year or more in resistant cases.

Systemic drugs found to be useful in *Acanthamoeba* keratitis are Voriconazole and Miltefosine. Oral Voriconazole in a dose of 200 mg twice daily for 4–6 weeks can be started. Miltefosine is an alkyl phosphocholine that has demonstrated efficacy in other protozoal infections such as visceral leishmaniasis, *Trichomonas*

vaginalis and *Entamoeba histolytica*. Oral Miltefosine in the dose of 50 mg three times for 4–6 weeks has shown to be efficacious. Gastrointestinal symptoms after prolonged treatment have been of concern in some patients. However, the dosing frequency can be reduced to 50 mg once or twice daily in such cases

Mechanical debridement of the ulcer helps to remove organism and also to improve drug penetration. Patients requiring therapeutic corneal transplantation should be evaluated carefully to identify the healthy margins free from infection in host cornea. However, recurrence of infection in the graft has been commonly reported by various authors [30, 32].

7.9 Pythium Keratitis

Microbial keratitis caused by *Pythium insidiosum* has garnered much interest over the last decade. It is an oomycete that causes a devastating infection of the cornea and can cause severe visual loss owing to its aggressive course refractory to standard treatment. Incidence is found to be more in tropical and subtropical climates. Clinical, microbiological, histopathological and confocal microscopy features of *Pythium insidiosum* closely resembles that of fungus, increasing the difficulty in diagnosis and resulting in an under diagnosis of *Pythium* keratitis (Fig. 7.14). Major reports have identified it to be refractory to both medical and surgical treatment

7.9.1 Diagnostic Differentiators

Morphological features on clinical presentation comprise mainly of cotton wool or dot-like infiltrates in early stage which later progress to larger size ulcer with hyphate edges extending into surrounding cornea resembling that of filamentous fungi [33]. Additionally, tentacle-like lesions and peripheral furrowing may be seen. Pythium

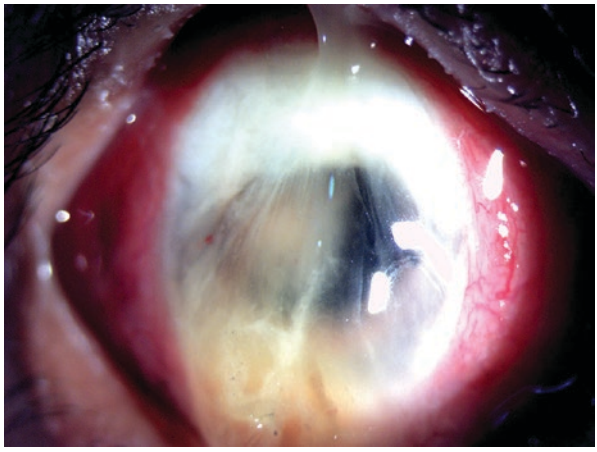

Fig. 7.14 Rapidly sloughing corneal ulcer due to *Pythium Insidiosum*

keratitis has an aggressive course that can lead to descemetocele formation, perforation and sloughing within a week (Fig 7.14). At times the lesions mimic the radial keratoneuritis of *Acanthamoeba* keratitis misleading the diagnosis and management.

7.9.2 Diagnosis

Electron microscopy of Pythium filaments on cursory look mimic filaments of hyphate fungi, however, important differentiating feature being a sparse or complete absence of septae in filaments. They are broad ribbon shaped with right angle branching. The growth on SDA/blood agar is characterised by flat, colourless or light brown glabrous colonies. Identification is best confirmed by demonstrating zoospore formation or PCR DNA sequencing [33, 34].

7.9.3 Treatment

Various treatment options have been suggested for treatment of *Pythium* keratitis. In vitro sensitivity of antibiotics such as azithromycin, minocycline and tigecycline have been tested and found to be effective. Topical azithromycin 1% and linezolid 0.2% eyedrop every hour along with oral azithromycin 500 mg once per day or linezolid 1200 mg/day has been found to be effective [33]. Treatment needs to be continued for 2–4 weeks. Additionally, Tetracycline ointment four times a day, Chloramphenicol eye drops hourly and Caspofungin 200 mg twice a day has been shown to be effective. However, despite the initiation of medical treatment the aggressive course of pathogen warrants surgical intervention in majority of cases. Therapeutic keratoplasty is the treatment of choice in such cases. Recurrence of disease in grafted tissue remains an important impedance to visual and structural improvement.

7.10 Surgical Management

Occasionally, adjuvant surgical therapy is indicated in the treatment of microbial keratitis composed of therapeutic contact lenses, collagenase inhibitors, tarsorrhaphy, conjunctival flap [35], cyanoacrylate glue [36] and lamellar or penetrating keratoplasty [37].

Impaired healing manifesting as persistent epithelial defect that fails to respond to conventional therapy of lubricating eye drops, necessitates the use of soft bandage contact lens, amniotic membrane transplantation and temporary tarsorrhaphy. Gundersen conjunctival flap can be advanced over the defect for surface healing and control of inflammation. Nevertheless, such eyes may need a penetrating keratoplasty at a later date.

Small perforations less than the size of 3 mm are amenable for closure by cyanoacrylate glue. Larger perforations more than 3 mm in size will require penetrating keratoplasty [38]. The size of the graft in such cases should be compatible with size of the defect by oversising of 0.25–0.5 mm.

Corneal transplantation done for HSV keratitis are likely to have stronger post-operative inflammation causing a risk of graft rejection in addition to recurrence of infection in the graft. Post-operative treatment regimen in such cases should include topical and systemic antivirals and corticosteroids in tapering doses for a period of 6 months. Patients with deep stromal opacity may be benefitted from DALK which has the advantage of a low rejection rate.

7.11 Corneal Emergencies Associated with Microbial Keratitis and Their Management (Table 7.1)

7.11.1 Penetrating Trauma with/Without Foreign Body

In microbial keratitis associated with penetrating trauma primary management is directed towards repair of the corneal tear followed by treatment of keratitis as described above. Foreign body if present must be removed during primary repair. Special attention should be given to clinical signs indicative of endophthalmitis. Cautious use of steroids must be exercised.

7.11.2 Descemetocele and Corneal Melt or Perforation

Severe ulceration may lead to descemetocele formation which may progress to perforation or sloughing particularly in *Pseudomonas, Pythium* and necrotising stromal mycotic keratitis. This can further be complicated with the onset of endophthalmitis or expulsion of the contents of eyeball leading to an irreversible visual and structural damage. Depending on the extent of involvement treatment can be initiated by following procedures:

- Tissue adhesives—cyanoacrylate glue, fibrin glue [39]
- Conjunctival flaps—Gundersen or Cies's racquet conjunctival flap [35, 40]
- Amniotic membrane transplantation—especially for central lesions [41]
- Tenon's patch graft
- Keratoplasty—lamellar or penetrating keratoplasty
- Superficial keratectomy and/or tectonic epikeratoplasty

7.11.3 Scleritis

Peripheral corneal and perilimbal infections can be complicated with scleritis. Various predisposing factors include trauma, systemic infection with or without immunocompromised state, use of corticosteroids and immunomodulators, or previous ocular surgery [42, 43]. If not addressed timely and adequately infectious scleritis follows a more rapid and aggressive course, requiring evisceration to address the disease course [44]. Hence, infectious keratitis associated with scleritis

usually evolves into a poorer visual and anatomical outcome in comparison to that without scleritis.

The management often presents a greater challenge due to lack of consensus on therapeutic intervention. Early microbiological analysis, institution of specific antimicrobial therapy and complete cessation of all forms of corticosteroids combined with surgical debridement if needed, especially in deeper scleral involvement remain standard treatment approaches in cases of keratitis associated with infectious scleritis especially fungal. Simultaneously the underlying predisposing factor must be addressed while the infection is being managed.

7.11.4 Endophthalmitis

Microbial keratitis associated endophthalmitis carries a dismal prognosis and requires extensive surgical management. A major challenge in such a condition is the inability to visualise posterior segments to carry out complex vitreoretinal procedures, due to corneal opacification. Often surgeons' resort to using combined penetrating keratoplasty and pars plana vitrectomy and lensectomy assisted by temporary keratoprosthesis. Long-term silicone oil tamponade is required and the procedure remains globe salvaging more often than vision restoring.

7.12 Conclusion

Microbial keratitis is a frequent cause of corneal emergency requiring well-timed appropriate intervention to salvage visual and structural integrity. Last two decades have witnessed a sea change in the treatment of corneal ulcers with excellent visual and structural outcomes. Nevertheless, diagnosing and treating corneal ulcers should not be regarded as a simple task. Optimal treatment aims at maximising the chances of complete recovery by identifying the exact aetiology and then instituting a tailored treatment.

Key Points

- Microbial keratitis is a frequent cause of corneal emergency. Appropriate and timely intervention can salvage visual and structural integrity.
- The incidence of microbial keratitis varies according to geographical location, climatic conditions and socio-economic status.
- Meticulous history, clinical examination, microbiological evaluation and knowledge of pre-disposing factors, are crucial in management.
- Knowledge about morphological patterns is an important diagnostic differentiator in arriving at a provisional diagnosis of probable pathogen.
- Bacterial keratitis is the most common form of microbial keratitis accounting for more than 90% of cases, while fungal keratitis contributes maximally to the burden of corneal perforations.

- HSV keratitis is by far the most under diagnosed and an equally challenging entity, both from diagnostic and therapeutic perspectives.
- *Acanthamoeba keratitis* is commonly associated with contact lens wear and is particularly difficult to treat. It may mimic HSV keratitis and demands a high degree of suspicion for timely diagnosis.
- *Pythium insidiosum* keratitis is usually associated with poor response to medical treatment. Therapeutic keratoplasty is indicated early, however, recurrence of infection in graft is not uncommon.
- Descemetocele, corneal perforation, sloughing, toxic epitheliopathy, neurotrophic ulcer, corneal abscess and corneal fistula are commonly encountered corneal emergencies associated with microbial keratitis.

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