Clinical Work-Up of Corneal Ulcers

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5.1 Introduction

Microbial keratitis is a potentially blinding disorder in the developing world. It is defined as a breach in continuity of the corneal epithelium with underlying stromal infiltration and associated tissue necrosis. In a study from south India, the reported incidence of corneal ulceration was 113 per 10,000 population [1]. When these estimates are extrapolated to all of India, 840,000 new cases of corneal ulceration are expected to develop annually and the projections approach 1.5–2 million for Africa and Asia [2]. In comparison, the incidence of corneal ulcerations in the developed world range from 11–27.6/100000 in the United States, 3.6–40.3/100000 in the United Kingdom, and 6.3/100000 in the developed city of Hong Kong [3].

This high number of cases of corneal ulceration in developing world is reflected in corneal blindness as well. Corneal ulceration is the most important cause of corneal blindness and ocular morbidity in Africa and Asia. It is very well recognized that early institution of appropriate treatment plays a crucial role in preventing or limiting vision loss from this condition. Towards that, the identification of causative microorganism becomes crucial.

However, the management of corneal ulcer in developing nations poses several challenges. These are: (a) poor health education in community and nonavailability of health care system forcing rural population to resort to using homemade and often harmful remedies; (b) easy access to over-the-counter drugs, including corticosteroids, without prescriptions; and (c) irrational empirical management even by

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ophthalmologists. All of these limitations result in an inordinate delay in the institution of appropriate treatment, which in turn results in loss of vision and at times loss of eye.

5.2 Aims of Clinical Evaluation

Whenever we approach a case of microbial keratitis the clinical evaluation must help us in: (1) assessing severity of the disease; (2) suggesting probable etiological agent; and (3) finding associated complications and predisposing or aggravating factors. A detailed history and thorough ocular examination helps achieving these goals.

5.3 History

A careful and detailed history must include: (1) symptoms with severity and duration; (2) mode of onset; (3) pace of evolution of symptoms, i.e., rapidly progressive versus slowly progressive; (4) prior and current medical treatment with frequency and duration; and (5) response to treatment.

If the patient is a contact lens user ascertain the type of lens, age of the lens, pattern of lens worn including the history of overnight wear, and contact lens care regimen. Ascertain past history of any ocular disease and ocular surgery, and details of systemic illness and treatment. While eliciting history, carefully observe the patient. Some of the important observations include lesions around the eye, any proptosis or exophthalmos, blink rate and its completeness, and ocular deviation. Many of these conditions predispose for corneal infection and result in delayed healing or nonhealing.

5.4 Clinical Examination

Every patient of corneal ulcer must be subjected to a thorough and complete ocular examination including lid, lacrimal sac, tear film, conjunctiva, sclera, anterior chamber, and posterior segment. While evaluating corneal ulcer, make note of the following points:

ϴ	Location of ulcer:	• Central
		• Peripheral (within 3 mm of limbus)
		• Total
ϴ	Epithelial infiltrate:	• Defect size
		• Single/multiple
		• Size
		• Nature
		• Edge
		• Depth
		• Thinning
		• Perforation—size and site

ϴ	Vascularization:	• Type and qudrant
ϴ	Endothelium:	• Keratic precipitates
		• Exudates
		• Endothelial ring
ϴ	Surrounding cornea:	• Satellite lesions
		• Immune ring
ϴ	Limbal or scleral involvement	
ϴ	Make note of anterior chamber depth and reaction including the presence/absence of hypopyon	

5.5 Documentation and Diagrammatic Representation

It is important to document all these findings as a schematic diagram or using slit-lamp photograph. Making a diagrammatic representation of corneal lesions with appropriate color coding helps to follow the course of the disease systematically, improves observation skills, and is inexpensive compared to photographs while providing important clinical data. Ulcer severity is described in terms of the dimensions of the lesion. This involves recording the maximum length and width in two axes and denoting their orientation. The degree of corneal thinning is expressed as a percentage of the corneal thickness with indication of the location of the maximum thinning. Hypopyon is expressed as the maximum vertical height with any accompanying endothelial exudates or fibrin in the anterior chamber. Corneal edema is denoted by blue, scar and degeneration by black, infiltrates and keratic precipitates by orange, vessels by red lines and ghost vessels by dashed red lines, lens and vitreous by green, contact lenses by dashed black line, and sutures by solid black line [4]. It is a standard notation to represent a frontal view and a slit view of the cornea.

5.6 Interpretation of Clinical Evaluation Findings

Once clinical evaluation is complete, the following must be assessed:

(a) Severity of the microbial keratitis and associated complication
(b) Probable etiological agent
(c) Possible predisposing or risk factor

5.6.1 Assessment of Severity of Infectious Keratitis

The assessment of severity is important because a nonsevere case can be managed empirically on an outpatient basis with a close follow-up while severe cases must be managed as inpatient preferably by a cornea specialist with experience in infectious diseases and having access to microbiology setup (Table 5.1).

5.6.2 Identification of Probable Etiological Agent (Generating a Differential Diagnosis)

The second aim of clinical evaluation is to identify probable etiological agent. Table 5.2 will help in identifying probable etiological agent.

Table 5.1 Grades of severity of microbial keratitis

Features		Severity grade	
		Non-severe	Severe
Rate of progression		Slow	Rapid
Infiltrate			
ϴ	Area	<6 mm in diameter	>6 mm diameter
ϴ	Depth	Superficial 2/3	Inner 1/3
ϴ	Perforation	Unlikely	Imminent or present
ϴ	Scleral involvement	Absent	Present

Table 5.2 Possible etiologic agents for slowly progressive versus rapidly progressive microbial keratitis

Differential diagnosis of microbial keratitis	
Slowly progressive localized infiltrate	Rapidly progressive diffuse suppurative infiltrate
(A) Bacteria	
(a) Gram-positive	(a) Gram-positive
(i) *Staphylococcus epidermidis*	(i) *Staphylococcus aureus*
(ii) α-hemolytic streptococci other than *S. pneumoniae*	(ii) *Streptococcus pneumoniae*
(iii) Actinomycetales	(iii) ß-hemolytic streptococci
– *Actinomyces*	
– *Nocardia*	
– *Mycobacterium*	
(b) Gram-negative	(b) Gram-negative
(i) *Moraxella*	(i) *Pseudomonas*
(ii) *Serratia*	(ii) *Enterobacteriaceae*
	(c) Mixed infection
	(d) Drug toxicity
(B) Fungi	
(a) Filamentous fungi	
(i) *Fusarium*	
(ii) *Aspergillus*	
(iii) Dematiaceous Fungi	
(b) Yeast-like	
(i) *Candida*	
(C) Protozoa	
(a) *Acanthamoeba*	
(b) *Microsporidia*	

5.6.2.1 Distinctive Features of Specific Bacteria

Gram-positive cocci and bacilli produce a localized round or oval ulceration with grayish white stromal infiltrate having distinct borders and minimal surrounding corneal edema.

ϴ	*S. epidermidis*:	• Indolent course
ϴ	*S. aureus*:	• Marked suppuration
		• Deep stromal abscess
		• Endothelial plaque
		• Large hypopyon
ϴ	*S. pneumoniae* and other ß-hemolytic streptococci:	• Focal suppurative stromal infiltrate
		• Serpiginous leading edge
		• Cellular infiltration into the deep stroma
		• Radiating folds in Descemet's membrane
		• Retrocorneal fibrin deposition
ϴ	α-hemolytic streptococci other than *S. pneumoniae*:	• Indolent localized ulceration
ϴ	*Nocardia* and *Actinomyces*:	• Indolent ulcer
		• Superficial localized infiltrate
		• Ill-defined edges
		• Calcareous bodies at the edge (wreath pattern)
ϴ	Atypical *Mycobacteria*:	• History of metallic foreign body or surgery
		• Slow progression
		• Waxing and waning course
		• Lack of response to conventional antibiotics
		• Localized infiltrate with a paucity of suppuration

Gram-negative infections typically follow a rapid inflammatory destructive course.

ϴ	*Pseudomonas aeroginosa* and other enteric bacilli:	• Rapidly progressive ulcer
		• Severe conjunctival reaction
		• Dense stromal suppuration
		• Copious mucopurulent firmly adherent exudate
		• Ground glass appearance of surrounding cornea
ϴ	*Moraxella*:	• Indolent ulcer in a debilitated patient or compromised cornea
		• Superficial focal infiltrate with irregular margins
		• Mild to moderate anterior chamber reaction
ϴ	*Neisseria gonorrhoeae*:	• Rapidly paced keratitis in neonate or sexually active adult
		• Marked conjunctival hyperemia and chemosis
		• Thick copious purulent discharge
		• Dense suppurative stromal infiltrate
		• Preauricular lymphadenopathy

5.6.2.2 Distinctive Features of Fungi, Acanthamoeba, Microsporidia

Θ	Fungi:	• Slowly progressive keratitis
		• History of trauma with vegetable matter
		• Dry raised slough
		• Hyphate edges
		• Satellite lesions
		• Pigmented infiltrate
Θ	Acanthamoeba:	• Pain out of proportion to clinical signs
		• Slowly progressive course
		• History of exposure to contaminated water/contact lens
		• Epitheliopathy
		• Patchy stromal infiltrate which may be arranged in a ring shape
		• Radial keratoneuritis
Θ	Microsporidia:	• Pain, redness, Lacrimation, photophobia, foreign body sensation
		• Keratoconjunctivitis with multifocal, small, punctate, raised epithelial or subepithelial corneal lesions
		• History of exposure to contaminated water may be present
		• Stromal keratitis: Indolent, waxing and waning course, patchy deep stromal infiltrate, persists for months to years

5.6.3 Identify Predisposing or the Risk Factors

(a) Contact lens wear
(b) Traumatic corneal injury
(c) Protracted epithelial ulceration
(d) Corneal surgery
(e) Herpes simplex keratitis

5.7 How Clinical Features Are Pointers for Specific Microbiology Workup?

A good clinical examination and logical interpretation of its findings help a clinician in ordering specific microbiology tests. This is especially true for the diagnosis of rare forms of microbial keratitis (MK), viz., Acanthamoeba, atypical mycobacteria, and microsporidia.

For example, a patient with history of contact lens presenting without of proportion pain, exposure to tap or contaminated water associated with epitheliopathy or stromal keratitis should direct a clinician for suspecting Acanthamoeba. In developing nations where contact lens usage is less prevalent, clinical picture is different. In such nations trauma during agricultural activity and exposure to dirty contaminated water, soil, or mud are found to be common risk factors [5, 6]. The clinical picture is characterized by lack of disproportionate pain. However, a large majority of these

cases are treated as herpes simplex keratitis but without much response before the diagnosis of Acanthamoeba keratitis. One third or more of cases present with a typical ring infiltrate, radial keratopathy is associated in 2.7% of cases, and when present is pathognomic of Acanthamoeba keratitis (AK). In typical clinical setting presentation with pseudo dendritiform epitheliopathy or stromal keratitis that resembles HSV keratitis but does not resolve with antivirals or a dry, superficial, necrotic nonresolving keratitis with ring infiltrates and prior history of several weeks to months of treatment with antibiotics and antifungals that resembles fungal keratitis are clinical cues for possible underlying AK [6].

Atypical mycobacterium may present as late indolent corneal ulceration usually 3 weeks to 2 months post trauma, typically with a metallic foreign body. The corneal may have mid-stromal infiltrates with fluffy satellite infiltrates around the main lesion. When present a cracked windshield appearance of the corneal stroma is pathognomic [7].

Microsporidia may present as keratoconjunctivitis or as stromal keratitis. Keratoconjunctivitis may be a self-limiting condition presenting as diffuse superficial keratopathy with a typical stuck on appearance of coarse punctate epithelial lesions. They can be easily scraped off the cornea and appear as scattered rice grains under the 10% KOH-calcofluor white wet mount [8]. On the contrary microsporidial stromal keratitis has a very unusual chronic and indolent clinical course with episodes of waxing and waning. The lesions typically present as multifocal deep stromal infiltrates with or without endothelial plaques and may involve the full thickness of the corneal stroma with or without an overlying epithelial defect. Typically patients have a history of months to years and corneal scraping/biopsy provides a definitive diagnosis of underlying microsporidia keratitis. Treatment is surgical with penetrating keratoplasty which has good outcomes in such cases [9].

5.8 Why Clinical Examination Alone Is Not Reliable?

There are several clinical features that are characteristic of each particular variety of MK. For example, fungal keratitis is typically associated with a dry necrotic slough with feathery irregular margins. In a study based on clinical scoring patterns [10], trained ophthalmologists noted feathery irregular margins in 79% of fungal keratitis and 48% of bacterial keratitis. The probability of a particular type of MK is more when a set of typical clinical characteristics are present. Often this may not be the case due to variable time points of presentation, prior treatment with medications, or late presentation with complications such as perforation. Often ophthalmologists do not have access to microbiology or rely only on clinical features while managing MK. It is important to consider that there may be a significant overlap of clinical features among MK due to different etiologic agents and there are no reliable clinical features that assist in identifying causative organisms. Hence, it is recommended to send specimens for microbiology evaluation [10, 11].

5.9 Why Microbiological Evaluation of Microbial Keratitis Is Important?

Clinical diagnosis alone may not be sufficient to arrive at a probable etiologic cause of the infectious microorganisms. This could be due to overlapping clinical features of different types of corneal ulcerations and varied therapeutic interventions prior to presentation. A study reported lack of training and outlook as an important determinant rather than nonavailability of resources to investigate causes of microbial keratitis [11]. Clinical scoring to guide the treatment of microbial keratitis conducted simultaneously from two study locations recommended treating ophthalmologists to scrape corneal ulcers and subject to microbiological evaluation where available [10].

Microbiology laboratory techniques include corneal scraping and smear examination and inoculation into various media to allow growth of colonies for subsequent identification. We recommend instillation of preservative-free proparacaine 0.5% in the eye followed by using a sterile No.15 Bard-Parker blade on a handle to scrape the edges and base of an ulcer. Scraped material is subjected to 10% KOH-calcofluor white wet mount, Gram, and Giemsa staining on a sterile glass slide. The material is also inoculated into solid and liquid media in ensuring that the media is not cut or disturbed. Serial "C" streaks are made on the media plates to allow distribution of the sample adequately and enable distinct growth of colonies. Inoculum is gently touched to the center of non-nutrient agar without disturbing the media. Smear examinations provide a rapid diagnosis of causative organisms. Culture methods involve inoculation into appropriate media to allow the growth of relevant organisms for a period of 7 days before a negative report is generated [12].

Microbiological cultures are significant if: (a) growth of same organisms from two or more solid media, (b) microscopy consistent with confluent growth of same organism from one media, and (c) growth of same organism on repeated scraping [10]. Several media are used in the routine identification of causative organisms of ocular suppuration, these include: sheep blood agar, chocolate agar, Sabouraud's dextrose agar, potato dextrose agar, non-nutrient agar with *E. coli* overlay, thiolglycolate broth, brain heart infusion broth (Fig. 5.1). A study recommended that the detection rate of fungi and Acanthamoeba was higher in smears compared to bacteria [13]. They reported the sensitivity of gram stain to be 89.8% for fungi and 73.3% for Acanthamoeba compared to 56.6% to bacteria. The low sensitivity to bacteria was attributed to prior antibiotic usage and other patient-related factors [13]. Polymerase chain reaction (PCR) was a useful diagnostic technique to help detect organisms. PCR samples are collected during scraping and collected in sterile tubes containing 0.1 ml of balanced salt solution [14].

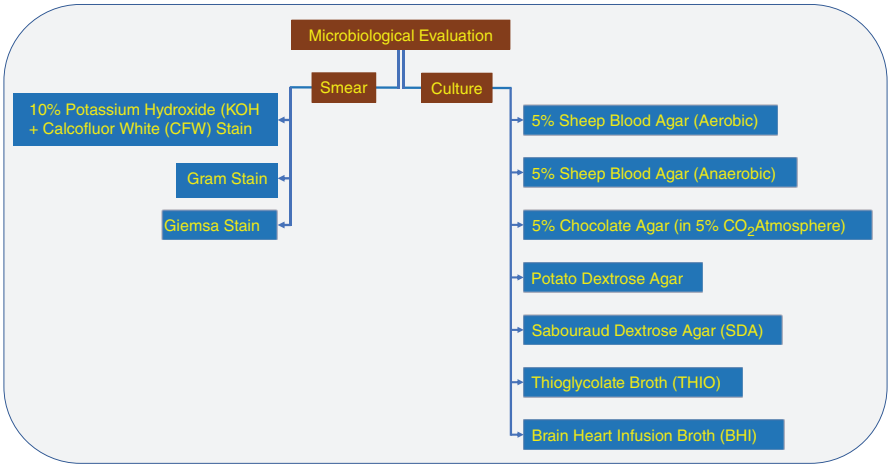

Fig. 5.1 Microbiological evaluation of microbial keratitis

5.10 Role of Confocal Microscopy for Evaluation of Microbial Keratitis

Confocal microscopy is a noninvasive diagnostic test for detection of fungal and acanthamoeba infection in the deeper corneal stroma [15]. The confocal has *x*- and *y*-axis resolution of 1.5 and 6.0 μm, and hence bacteria cannot be detected. However, fungi (3–8 μm) and Acanthamoeba cysts (12–15 μm) owing to their larger size can be detected by confocal microscopy. Both of these organisms have a chronic and indolent clinical course and require long-term treatment. Vaddavalli [16] et al. reported the sensitivity and specificity of confocal for detecting Acanthamoeba to be 88.3% and 91.1% and for fungus 89.2% and 92.7%. They recommend confocal microscopy under the following clinical scenarios:

(a) Deep corneal infiltrates that are not accessible to scraping and may require invasive procedures such as a corneal biopsy.
(b) Patients pretreated with anti-fungal or anti-Acanthamoeba medications are usually microbiologically negative; therefore, confocal may assist in arriving at an etiologic diagnosis.
(c) Post-LASIK interface keratitis and keratitis after radial or astigmatic keratectomy may have organisms embedded into the deeper corneal stroma and may be imaged with confocal microscopy.

Confocal microscopy has several limitations; besides the cost of the equipment, it is difficult to acquire images in a painful inflamed eye and is dependent on the operator skill and experience [17].

5.11 Conclusions

In conclusion, microbial keratitis presents as an ophthalmic emergency and unless managed appropriately may lead to loss of vison and eye. Typical history and characteristic clinical features assist the ophthalmologist in arriving at a probable etiologic diagnosis. It is equally important to confirm clinical findings with microbiology or confocal imaging where possible so as to target definitive treatment as per causative organisms.

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