

Microbial Keratitis—A Review of Epidemiology, Pathogenesis, Ocular Manifestations, and Management

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Abstract

Purpose: To review updated knowledge on the epidemiology, pathogenesis, clinical features, and treatment of microbial keratitis (MK). **Source of Data:** International and local journals containing current literature on MK were sourced through the Internet. **Study Selection:** Findings consistent with our objectives were compiled and reviewed. **Data Extraction:** Data were extracted using endnotes. **Results:** MK is a sight-threatening ocular infection caused by bacteria, fungi, and protist pathogens. The pathogenesis comprises molecular mechanisms describing microbial activities which involve virulence and host factors responsible for ocular tissue damage and progression in keratitis. Clinical features include redness, pain, tearing, blurred vision, and inflammation, but symptoms vary depending on the causative agent. The primary treatment goal is the elimination of causative organism in addition to neutralization of virulence factors and healing of damaged host tissue. A timely review of our current understanding of MK with the recent advances in its treatment will ensure improved management outcomes. **Conclusion:** Optimal outcome from management of MK will require an updated knowledge of its pathogenesis, clinical features, and treatment protocols, especially in sub-Saharan Africa where its prevalence is on the increase.

Keywords: Epidemiology, management, microbial keratitis, ocular manifestations, pathogenesis

INTRODUCTION

Microbial keratitis (MK) is a spectrum of ocular infectious diseases, affecting the cornea and pathogenically resulting from bacterial, fungal, and protozoal etiologic organisms which can potentially cause ocular morbidity and disability.^[1] The severity of the corneal infection is dependent on three factors: the degree of pathogenicity of the etiologic organism, the underlying condition of the cornea, and the immunological state of the individual.^[2] The defense mechanisms which limit infection include blinking, presence of tight junctions present in the corneal epithelial cells, and presence of chemicals which control bacterial growth (lactoferrin, lysozyme, antimicrobial peptides, antibodies, and bacteriocins).^[3]

A breach in these anatomical barriers, mainly from ocular injuries and epithelial defects, reduces the effectiveness of host defenses against pathogens, resulting in ocular infection, inflammation, and eventual visual loss.^[4,5] The most common predisposing factors include trauma, systemic diseases such as diabetes mellitus and/or extended use of topical corticosteroids, the use of contact lenses (overnight or

extended wearing of lenses), ocular surgery (corneal surgery), inadequate disinfecting solutions, and chronic ocular surface disease.^[6]

EPIDEMIOLOGY

The prevalence of MK has been found to vary according to type, geographical location, and causative factors. An estimate of 1.5 to 2 million cases of corneal ulcers occur annually in the developing countries.^[7] In the United States, the incidence of MK varies from 11/100,000 persons/year to 799/100,000 persons/year in developing countries; thus, MK is a significant public health problem. The geographical influence of MK economically has been associated with wearing contact lens. In developed countries, the picture portends more of bacterial ulcers with reduced risk of

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agriculturally related trauma from organic matter which is mainly responsible for fungal infections found more in developing countries. Bacterial keratitis is the most common form of MK in temperate climates such as USA accounting for 89% to 96% of cases of MK.^[8,9]

The highest reported cases of bacterial keratitis have been in Australia, Singapore, Netherlands, and Western Europe in addition to USA.^[10] However, in sub-Saharan Africa (Ghana), filamentous fungi accounted for 42% of cases of MK.^[11]

There is a 20 times higher risk of developing blindness in children from MK in developing countries compared with developed countries, with an average of 42% of reported cases of infectious keratitis in children resulting from ocular trauma.^[12]

In Nigeria, there have been variations in the pattern of MK. Ashaye and Oluleye,^[13] in Ibadan, found that 26.7% of causes of corneal opacity resulted from MK. Oladigbolu *et al.*^[14] in Kaduna, Northern Nigeria, reported the most common organisms as *Staphylococcus aureus* 19.0%, fungal hyphae 15.8%, and *Streptococcus pneumoniae* 4.8%. Saka *et al.*^[15] in Ilorin, Nigeria found the predisposing factors as trauma in 30 (55.6%) cases, self-medication with topical steroids in 12 (22.2%), and the use of traditional eye medication in 12 (22.2%). Nwosu and Onyekwe^[16] in Onitsha, Nigeria found that farmers, pensioners, and housewives presented late to hospital compared literate patients, traders, and artisans. Major predisposing factors were trauma, traditional eye medications, and self-medication with corticosteroids. Corneal infections following vegetative matter trauma show a varied etiological profile; however, bacterial and polymicrobial infections were more prevalent. Empirical antifungal therapy, as commonly practiced, must be avoided in cases with vegetative matter injury.^[17]

Ezegwui^[18] in Enugu, Nigeria emphasized on early intervention, recommending a cost-effective approach using prophylactic antibiotic treatment with 1% chloramphenicol ointment administered by trained village health worker as a public health intervention strategy for Africa to prevent binding complications.

Classification

This is classified according to the causative organism into

- (1) Bacterial
- (2) Fungal
- (3) Protist

The most common causative bacterial pathogens include *S. aureus*, *Pseudomonas aeruginosa*, *S. pneumoniae*, and *Serratia* species.

The most common causative fungal agents implicated include both filamentous as well as yeast, including *Fusarium*, *Aspergillus*, phaeohyphomycetes, *Curvularia*, *Paecilomyces*, *Scedosporium*, and *Candida* species.

The third class of pathogens include the protists, *Acanthamoeba* spp.^[15]

PATHOGENESIS

The key predisposing factors underlying ocular susceptibility to corneal pathogens include epithelial defects and injuries.

There are two molecular mechanisms underlying the pathogenesis of MK: virulence factors and host factors. These factors encourage progression of keratitis and damage of ocular tissue.

Pathogenesis of bacterial keratitis

Adhesion

Adhesions on bacterial surfaces, such as pili or fimbriae, recognize specific carbohydrates or proteins on the surface of host cell causing adherence. *P. aeruginosa*, *S. pneumoniae*, and *S. aureus* are most commonly isolated.

Bacterial invasion and cytotoxic effects

Following adherence to the epithelial surface, the pathogen invades into the corneal stroma. This invasion is facilitated by proteases and exotoxins, resulting in degradation of basement membrane and extracellular matrix, causing cell lysis.

Stromal necrosis and production of ring infiltrate

Bacterial exotoxins and proteases released during bacterial multiplication persist in the cornea, causing continual stromal destruction. Most exotoxins are heat-labile and have antigenic properties. The bacterial lipopolysaccharide, an endotoxin within the cell wall of Gram-negative bacteria, is released, resulting in the production of stromal rings. These rings consist of polymorphonuclear leukocytes within the corneal stroma, which are chemoattracted by the alternate complement pathway.^[19]

Pathogenesis of fungal keratitis

Adhesion

Adhesion of fungal pathogens *via* adhesions facilitates binding to fungal binding sites such as laminin, fibronectin, collagen, and so on.^[20]

Invasiveness and morphogenesis

In *Fusarium* keratitis, fungal pathogens invade the cornea, gaining access to the anterior chamber of the eye. It forms a lens-iris-fungal mass at the pupillary area, affecting the normal drainage of aqueous humor, thus leading to an increase in the intraocular pressure causing fungal malignant glaucoma^[21]; *Aspergillus*-induced malignant glaucoma has also been reported.

Fungal invasiveness is directly related to the fungal load and inversely proportional to the intensity of inflammatory response.^[22] Phenotypic switching or morphogenesis, an adaptative mechanism, permits fungi to survive in the

presence of antifungal drugs and resist antimicrobial therapy. In *Candida albicans* keratitis, proteases are associated with morphogenic transformation from yeast to invasive filamentous forms.

Pathogenesis of *Acanthamoeba* keratitis

Adhesion

It refers to amoeba binding to mannose receptors on the ocular surface through adhesion (mannose binding protein) expressed on the trophozoite membrane.^[23,24] In addition, mild trauma or corneal abrasion and the use of contact lenses upregulate mannose glycoproteins on the corneal epithelium, encouraging increased adherence.^[23]

Cytopathic effect

Trophozoite binding to corneal surface causes extensive desquamation of the corneal epithelium, leading to penetration of the underlying Bowman's membrane *via* direct cytolysis, phagocytosis, and apoptosis. *Acanthamoeba* phagocytose corneal epithelial cells *via* amoebastomes present on the surface of amoebae^[25] through membrane blebbing, formation of apoptotic bodies, DNA laddering, and nuclear chromatin condensation of host cell (markers for apoptosis).^[26,27]

Stromal invasion: this is facilitated by proteases secreted by *Acanthamoeba* trophozoites *via* their collagenolytic activity.

Neuritis: they chemotactically cluster around the corneal nerves, producing radial keratoneuritis.

Moreover, these trophozoites directly kill nerve cells *via* direct cytolysis and/or apoptosis.^[27] These cytopathic effects may account for the excruciating eye pain and infection *in vivo*.

Bacterial keratitis

Bacterial keratitis accounts for approximately 90% of all cases of MK^[28] with *P. aeruginosa* as the most common organism implicated worldwide.^[29] *Pseudomonas* is widely associated with the use of contact lenses.^[27] *Pseudomonas* is resistant to disinfectants and adheres to plastics. In developing countries, *S. pneumoniae*, *P. aeruginosa*, and/or *S. aureus* are most commonly implicated for MK.^[30]

S. aureus is a commensal organism that can readily gain access into the eye, if given the opportunity.^[31]

Risk factors for infection include trauma, ocular surgery, contact lens use, viral infection, or other eye illnesses. *S. aureus* tends to develop antibiotic resistance, making it difficult to treat. *Serratia marcescens* has been implicated in contact lens wearers.^[32]

Mycotic keratitis

Mycotic keratitis is a fungal infection of the cornea caused by either filamentous and/or yeast-like fungi, accounting for approximately 50% of MK cases, especially in tropical and subtropical countries.^[33]

Keratitis due to yeast-like fungi tends to be more common in temperate climates, whereas corneal ulcers caused by filamentous fungi appear to be more common in the tropics.^[11]

Keratitis caused by filamentous fungi is frequently seen in healthy young males engaged in agricultural or other outdoor activities following ocular trauma.^[34] Traumatizing agents of animal origin or vegetative matter, soil, or dust particle directly implant fungal conidia when the corneal epithelium is abraded. They do not penetrate the intact cornea.^[34] Significant risk factors include corticosteroid use, ocular surgery, ocular surface disease, and wearing contact lens. Conversely, significant risk factors for *C. albicans* and related fungi-associated keratitis include reduced tear secretion, lagophthalmos, or some systemic illness such as diabetes mellitus or immunosuppression.^[20] This form of keratomycosis may also supervene on a preexisting epithelial defect caused by herpes keratitis or abrasion due to contaminated contact lenses.

Prompt and adequate treatment is mandatory for all fungal infections of the cornea.

Acanthamoeba

Acanthamoeba keratitis is a rare but sight-threatening corneal infection, caused by an opportunistic protist pathogen belonging to the genus *Acanthamoeba*. They are ubiquitous, free-living protists dispersed in air, soil, freshwater, tap water, chlorinated swimming pools, sewage, hospital equipments, surgical instruments, showers, ventilation ducts, air-conditioning units, and so on.^[35] Phenotypic switching into a cyst form enables *Acanthamoeba* to withstand adverse environmental conditions. The *Acanthamoeba* trophozoite has an amoeboid shape that contains spike-like structures known as acanthopodia, and during this stage, amoebae feed and reproduce under favorable environmental conditions.^[36] However, under extreme situations such as lack of nutrients, hyperosmolarity, desiccation, extreme pH, temperatures, and the presence of antimicrobials; the trophozoite rounds up and confines itself within a double-walled resistant cyst form that has minimal metabolic activity. The cyst stage presents a major problem in the successful treatment of *Acanthamoeba* infections as they are resistant to various antimicrobial agents, often leading to recurrence of the disease upon discontinuation of therapy.^[37] Although exposure to *Acanthamoeba* spp. appears to be common due to its ubiquitous nature, the incidence of *Acanthamoeba* keratitis is less common. The main risk factors for *Acanthamoeba* keratitis are wearing contact lens for extended periods, corneal trauma, nonsterile contact lens rinsing, swimming while wearing contact lenses, and biofilm formation on contact lens.^[38] In noncontact lens users, it is usually associated with trauma and/or exposure to contaminated water, soil, and organic matter. It has also been reported after laser-assisted *in situ* keratomileusis and invasive or radial keratoplasty.^[39]

CLINICAL MANIFESTATIONS

Clinical features of bacterial keratitis

A bacterial corneal ulcer usually presents with chemosis and conjunctival injection, eyelid edema, decreased vision, pain, tearing, photophobia, and purulent discharge. It manifests a predominantly papillary conjunctival response, with limbal injection, a gray-white infiltrate corneal epithelial and stromal infiltrate which may appear necrotic, corneal edema, an anterior chamber reaction, and fibrin plates on the endothelium in severe cases with a fibrinoid aqueous or hypopyon.^[40]

The hypopyon is produced by the toxic effects of infection on vessels of iris and ciliary body, with consequent pouring of fibrin and polymorphonuclear leukocytes. It is usually a sterile hypopyon as Descemet's membrane is intact and frequently seen in ulcers caused by *S. pneumoniae* and *Pseudomonas* sp. in addition to viral and fungal ulcers.^[41]

Signs and symptoms of bacterial corneal ulcers vary depending on the virulence of the organism, the previous state of the cornea, the duration of the infection, host immune status, and prior use of antibiotics and steroids.^[42] Infections associated with contact lenses have an altered presentation, often multifocal with diffuse epithelial and stromal infiltrate. Corneal abrasions associated with wearing contact lens is a predisposing factor.^[43,44]

Clinical manifestations of filamentous keratitis

Include sudden onset of pain; reduced vision; photophobia; discharge; corneal opacity suggestive of an ulcer^[45]; firm, sometimes dry, elevated slough, hyphae lines involving the cornea beyond the ulcer edge; multifocal granular or feathery grey-white satellite stromal infiltrates; immune ring; Descemet's fold; and mild iritis.

These findings may vary depending on the etiological agent.

Severe, chronic filamentous keratitis somewhat resembles bacterial suppuration and may involve the entire cornea.

However, those due to yeast-like and related fungi may resemble bacterial keratitis with an overlying epithelial defect, discrete infiltrate, and slow progression.^[44]

Clinical features of *Acanthamoeba* keratitis

Include excruciating pain characterized by redness, epiphora, lacrimation, ptosis, conjunctival hyperemia, foreign body sensation, and photophobia.^[46] As the disease progresses, stromal involvement results in infiltration of inflammatory cells, displaying a characteristic ring infiltrate. This progresses to corneal ulceration, perforation, ring infiltrate, stromal abscess formation, loss of visual acuity, and eventually blindness and enucleation.

SUMMARY OF CLINICAL FEATURES

Laboratory diagnosis/investigations

Microbiological evaluation is mandatory to achieve a definitive diagnosis and to ensure specific treatment as there is no definite pathognomonic clinical feature for distinguishing corneal ulcers [refer to Table 1].^[47]

Lab investigations include Gram stain, KOH, culture on blood agar, Sabouraud's agar, chocolate agar, brain heart infusion agar, and so on.

Management

Initial empirical management with broad-spectrum topical antimicrobials is the protocol, as current microbiological investigations can take days or even weeks to identify a causative organism. However, this has been implicated in the emerging resistance in some countries to some of these commonly used antimicrobial agents. Improved therapies for MK are required for a more rapid and correct identification of the infectious agent and an effective treatment.

Treatment

Thus, treatment goals would include elimination of causative organisms,

Table 1: Summary of clinical features

Features of bacterial ulcer

- History of trauma to the cornea, contact lens wear
- Pain, redness, watering, decrease in vision
- Lid edema (marked in gonococcal ulcer), purulent discharge in gonococcal ulcer and bluish green discharge in pseudomonas corneal ulcer
- Round or oval in shape involving central or para central part of the cornea. Rest of the cornea is clear. Hypopyon may or may not be present
- In pneumococcal ulcer the advancing border will have active infiltrate with undermined edges and the trailing edge may show signs of healing. Most of the pneumococcal ulcers will show leveled hypopyon associated with dacryocystitis.
- Pseudomonas ulcer will have short duration, marked stromal edema adjacent to the ulcer with rapid progression. If untreated, will perforate within 2–3 days. Advanced ulcer may involve the sclera also
- Ulcers caused by *Moraxella* and *Nocardia* are slowly progressive in immunocompromised hosts

Features of fungal ulcer

- History of trauma with vegetable matter
- Suspect fungal ulcer if patient reports agriculture as main occupation
- Pain and redness are similar to bacterial ulcer. But lid edema is minimal even in severe cases unless patients have received native medicines or periocular injections.
- Early fungal ulcer may appear like a dendritic ulcer of herpes simplex virus. The feathery borders are pathognomonic clinical features. Satellite lesions, immune ring, and unlevelled hypopyon may aid in diagnosis
- The surface is raised with grayish white creamy infiltrates, which may or may not appear dry
- Ulcer due to pigmented fungi will appear as brown or dark; raised, dry, rough, leathery plaque on the surface of the cornea

neutralization of virulence factors to minimize the damage, repairing the damaged tissue.

Management guidelines for suppurative keratitis by WHO

History and examination^[47]: Use a standard form and classification of corneal ulceration.

Take a corneal smear: Prepare a KOH wet mount (or other fungal stain) and Gram stain.

- (1) Culture on
 - (a) Sheep blood agar
 - (b) Sabouraud's dextrose agar
 - (c) if possible, brain heart infusion.

Other culture media may also be indicated in selected cases.
- (2) Admit the patient for in-patient treatment
 - (a) If there is immediate threat to vision
 - (b) If the patient is a child
 - (c) To ensure hourly treatment as below
 - (d) To ensure follow-up as below
- (3) Treatment guidelines for suppurative keratitis^[47] [refer to Table 2]
 - (a) Guidelines treatment frequency, duration, and follow-up^[47] [refer to Table 3]: Empirical antibiotic therapy should be started promptly while awaiting laboratory results. The two treatment options commercially available are fluoroquinolone monotherapy or a combination therapy of fortified antibiotics (gentamicin or tobramycin 1.4% and cefazolin 5%). The frequency of drops depends upon the severity, but it is usual to start half-hourly drops all through 24 h for most patients. A loading dose of a drop every 5 min for the first 30 min is used in severe ulcers. The frequency is reduced based on the clinical response.^[48]
 - (b) Gentamicin and tobramycin are aminoglycosides used in fortified drops and are active against Gram-negative organisms, *staphylococci* and some *streptococci* but not against *pneumococci*. They are however epitheliotoxic. Fortification is achieved by adding 80 mg/2 ml of antibiotic injection to 5 ml of commercially available antibiotic eye drops (0.3%) to get a concentration of 1.35%. Cefazolin is the most commonly used cephalosporin in fortified drops, covering for nonpenicillinase-producing Gram-positive bacteria. It is constituted by adding 5 ml of water to cefazolin 250-mg injection. The drops are refrigerated and discarded after a week or if discoloration to yellow is noted.^[48]
- (c) Monotherapy with fourth generation fluoroquinolones such as 0.5% moxifloxacin and 0.3% gatifloxacin have been found to be effective as fortified drops.
- (4) Adjunctive therapy includes cycloplegics, analgesics, and antiglaucoma medication, if indicated.
- (5) Decision-making algorithm in the management of therapeutic failures in presumed bacterial keratitis^[47] [refer to Figure 1]
- (6) International council for ophthalmology (ICO) international clinical guidelines: bacterial keratitis (management recommendations)^[47] [refer to Table 4]
- (7) Role of topical steroids^[49]
 - (a) Topical steroids are not recommended in any case of fungal keratitis.
 - (b) The role of topical steroids in bacterial keratitis is controversial.
 - (c) If steroids are used, it should be with great caution and close observation.
- (8) Role of systemic antimicrobials^[50] Systemic antifungals are recommended in fungal ulcers, which are
 - (a) large and deep, or
 - (b) perforating, or
 - (c) have scleral involvement

Systemic antibiotics are recommended in bacterial ulcers if there is scleral involvement and may be used in perforated cases.
- (9) Role of surgery^[49]: Surgical procedures may include.

Table 2: WHO treatment guidelines for suppurative keratitis

Smear not possible	No organism seen on smear	Gram-positive bacteria seen	Gram-negative bacteria seen	Fungal hyphae seen
Cefazolin 5% and gentamicin 1.4% drops hourly Ciprofloxacin may be used instead of gentamycin. If hourly drops is not possible then a subconjunctival injection can be considered				Natamycin 5% drops hourly Or Amphotericin 0.15% drops hourly

Table 3: Treatment frequency, duration and follow up^[47]

No fungal hyphae seen on smear	Fungal hyphae seen on smear
Daily examination until the ulcer starts improving	Examination every 2 days until the ulcer starts improving
– Then gradually reduce the frequency of drops and follow-up over 2 weeks	Then continue drops at least 3 hourly for at least 2 weeks after healing of the ulcer

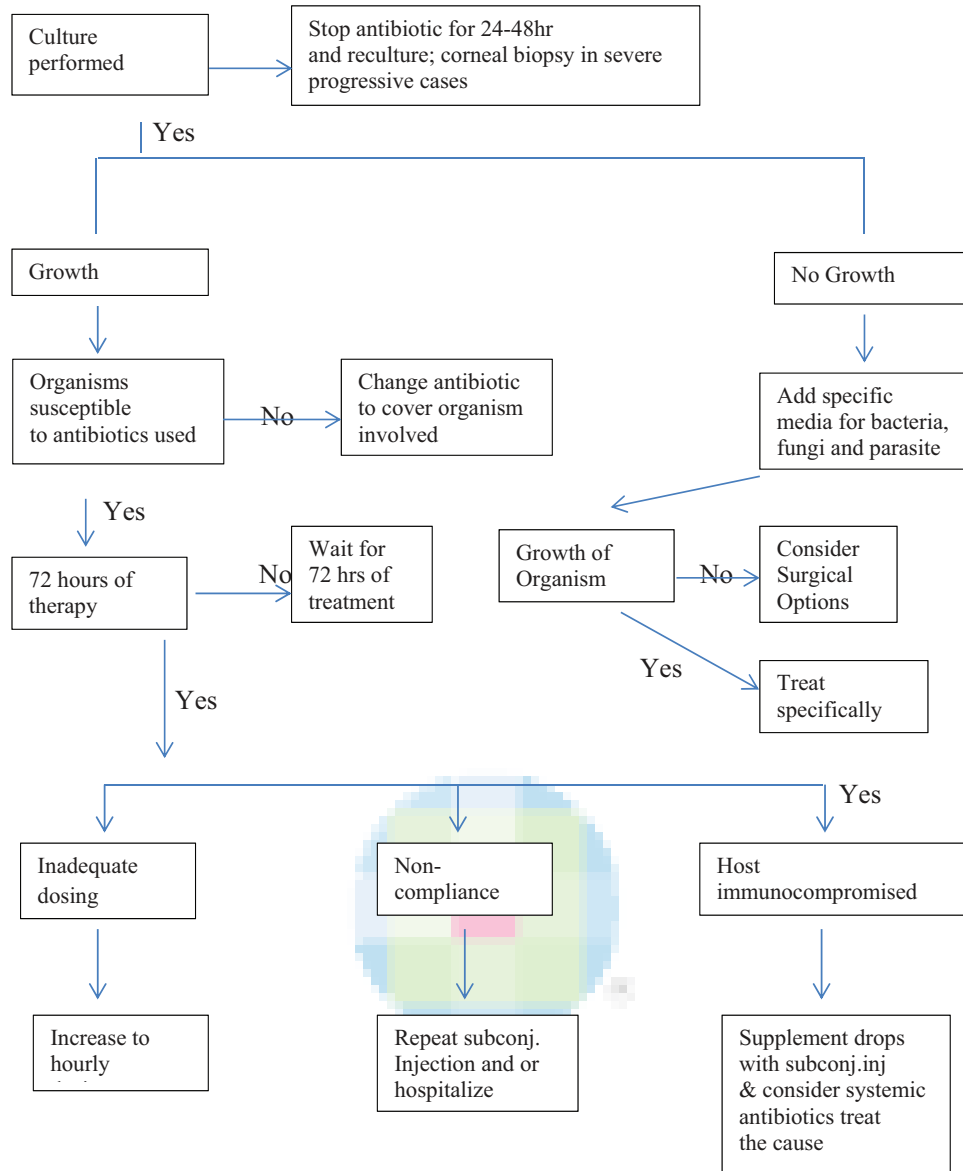


Figure 1: Decision-making algorithm in the management of therapeutic failures in presumed bacterial keratitis^[48]

- (10) Debridement/superficial keratectomy^[49]: Surgical removal of corneal epithelium without causing injury to the basement membrane.
- (a) Indication
- Epithelial herpes simplex virus keratitis
 - Recurrent corneal erosion
 - For diagnosing superficial infective keratitis
 - Enhances penetration of topical antibiotics
- (a) Techniques
- This procedure is performed under topical anesthesia on a slit lamp or operating microscope with sterile cotton-tipped applicator, weckel sponge, or surgical blade.
- (11) Superficial keratectomy^[49]: Surgical removal of corneal epithelium including Bowman's membrane and anterior stroma of the diseased cornea.
- (a) Indication
- Biopsy in nonhealing corneal ulcer
- Debulking of infective material
- (a) Technique
- This procedure is performed under aseptic condition with topical or subconjunctival anesthesia using 15# Bard-Parker blade.
- (12) Tarsorrhaphy^[49]
- (a) Lateral
- (b) Central
- (1) Indication
- Exposure keratitis (Bells palsy)
 - Neuroparalytic keratitis
 - Bell's palsy with nonhealing suppurative keratitis.
- (2) Technique
- This procedure is performed at a minor operating theater: local infiltration with 2% lidocaine at the lid margins. About 1 to 2 mm of intermarginal strip is shaved off

Table 4: ICO International Clinical Guidelines: bacterial keratitis (management recommendations)^[47]

Organism	Antibiotic	Topical concentration	Subconjunctival dose
No organism identified or multiple types of organisms	Cefazolin with tobramycin/gentamicin or fluoroquinolones	50, 9–14, 3 or 5 mg/ml	100 mg in 0.5 ml 20 mg in 0.5 ml
Gram-positive cocci	Cefazolin vancomycin* Bacitracin* Moxifloxacin or gatifloxacin	50, 15–50 mg/ml 10,000 IU3 or 5 mg/ml	100 mg in 0.5 ml 25 mg in 0.5 ml
Gram-negative rods	Tobramycin/gentamicin ceftazidime fluoroquinolones	9–14, 50, 3 or 5 mg/ml	20 mg in 0.5 ml 100 mg in 0.5 ml
Gram-negative cocci**	Ceftriaxone, ceftazidime, fluoroquinolones	50, 50, 3 or 5 mg/ml	100 mg in 0.5 ml 100 mg in 0.5 ml
Nontuberculous mycobacteria	Amikacin, clarithromycin***, fluoroquinolones	20–40, 3 or 5 mg/ml	20 mg in 0.5 ml
Nocardia	Amikacin trimethoprim/sulfa methoxazole: trimethoprim sulfamethoxazole	20–40, 16, 80 mg/ml	20 mg

Treatment of fungal keratitis is as outlined by WHO guidelines for management of Infectious keratitis at the primary, secondary, and tertiary levels of care. However, problems of unavailability of these drugs in developing countries and high cost are major impediments to adherence. *Correspondence to 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 empirically in treating bacterial keratitis. **Correspondence to Systemic therapy is necessary for suspected gonococcal infection. *** Dosage for oral systemic therapy in adults is 500 mg every 12 h. Topical therapy has had some success but the medication is irritating and clinical experience is limited.

deep up to dermis and apposed with 4 “0” silk suture and anchored with bolsters. The release of tarsorrhaphy depends upon the etiology of lagophthalmus and healing response of the ulcer.

(3) Tissue adhesive^[49]: This procedure is performed for the followings:

- (a) wounds with a small amount of tissue loss
 - (b) persistent aqueous leakage
 - (c) small lacerations
 - (d) puncture wounds
- The tissue bed must be dry and free of epithelial cells.

(4) Technique

- (a) A thin film of adhesive is applied using a small gauge disposable needle, a microcapillary applicator, or the broken wooden end of a sterile cotton applicator.
- (b) Following application, adhesives should be given several minutes to dry before any other manipulation.

(5) Conjunctival flaps^[49]: This is rarely performed for suppurative keratitis.

- (a) Indications
 - Nonhealing superficial ulcer
 - Peripheral corneal ulcers with descemetocoele or small perforation
- (a) Contraindication
 - Perforated central corneal ulcer
- (a) Advantages
 - Promotes healing, providing better nourishment to the underlying cornea
- (a) Disadvantages
 - Monitoring the progress of ulcer is difficult
 - Delays or impedes the penetration of topical antibiotics
 - Visual outcome will be poor due to scarring and vascularization

(a) Technique

This procedure is performed under local anesthesia as in cataract surgery. It is taken up under general anesthesia if the patient is non-cooperative or in the paediatric age group. Specific drugs should be continued postoperatively.

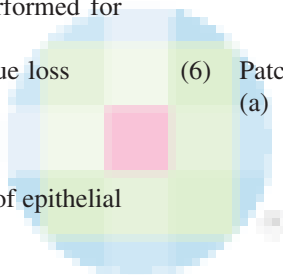
(6) Patch graft^[49]

(a) Indication

Descemetocoele
Small perforation
Patch graft is usually 5 or 6 mm in size. Recipient bed is cleared of debris and not trephined. Lamellar or full-thickness donor button could be anchored.
This procedure is performed in the operating room under surgical microscope.
Interrupted suture (12–16) is applied using 10/0 or 9/0 nylon. Appropriate antibiotics are continued postoperatively.

(7) Penetrating keratoplasty

- (1) Maintains the integrity of the globe for future optical grafts
- (2) Promotes healing of corneal ulcer by total removal of pathology
- (3) As a diagnostic technique to form a good source for histopathological and microbiological examination, 40% to 50% of these patients recover useful vision.
- (4) Carries better prognosis in bacterial corneal ulcers
 - (1) The indications for surgical intervention include
 - Nonhealing in spite of all medical therapy
 - Impending or actual perforation
 - (2) If the ulcer does not respond to treatment
 - Review with Gram stain, culture, and sensitivity results



If the organism is unknown, consider stopping all treatment for 48 h, take new smears, cultures, and, if required, a corneal biopsy. Use culture media for viral and uncommon pathogens (anaerobes, *Acanthamoeba*, mycobacteria).

Acanthamoeba keratitis

There is no single effective drug treatment against *Acanthamoeba* keratitis; thus, the current modality of treatment is topical application of a cocktail of drugs.^[50,51] This is mainly because of the degree of virulence of the infecting isolate which is different for each individual case and therefore makes it impossible to establish a correlation between *in vitro* and *in vivo* efficacies. Early diagnosis, and adequate and aggressive treatment with a high level of patient compliance are mandatory for best therapeutic outcomes. Successful management necessitates extended therapy with a combination of well tolerated drugs with minimal toxicity to host cells with minimal need for surgical interventions. This is because, though *Acanthamoeba* trophozoites are sensitive to most available drugs, the cysts are not destroyed and hence is the major reason for recurrence of infection upon cessation of treatment.

The most effective topical agents currently used against *Acanthamoeba* trophozoites and cysts are the biguanides [polyhexamethylene biguanide (PHMB) 0.02%–0.06% or chlorhexidine 0.02%–0.2%] in combination with diamidine (propamidine isethionate 0.1% or hexamidine 0.1%).^[50,51]

The former drugs are membrane-acting cationic biocides that interact with negatively charged surface proteins of *Acanthamoeba*, resulting in leakage of the cellular components.^[52] The latter however exert their amoebicidal effects *via* cationic surface-active properties inducing structural changes resulting in cell permeability and are effective DNA synthesis inhibitors.^[53] *In vitro* studies revealed that cationic agents have the best and most constant amoebicidal and cysticidal activity.^[50] If these drugs are applied early on in the development of infection, at high frequency along with neomycin and 0.15% dibromopropamidine, they show successful prognosis.^[54]

Early high-frequency application of these medications, along with neomycin and 0.15% dibromopropamidine, shows successful prognosis.^[55]

Hourly drops of PHMB and hexamidine day and night may be tapered off after 48 h to alleviate epithelial toxicity, to hourly drops during the day for the next 72 h. This therapy reduces viable trophozoites when they are more susceptible and prevent them from turning into fully mature cysts. This treatment is then reduced to 2-hourly application during the day for the next 3 to 4 weeks and then gradually tailored depending on the individual case. Treatment

regimen on average lasts over a period of 6 months, ranging from 0.5 to 29 months.^[54] Azoles are used as an adjuvant to biguanide and diamidine therapy in resistant *Acanthamoeba* keratitis cases.^[55] Therefore, topical and intrastromal voriconazole drops (1%) have been used successfully in three cases with resistant *Acanthamoeba* keratitis. Surgical management *via* epithelial debridement, corneal graft surgery (keratoplasty), and/or deep lamellar keratoplasty may be required in some cases where the corneas are permanently scarred or where the topical and oral treatments have failed.^[56,57]

CHALLENGES

Challenges in resource-constrained environment such as Nigeria include diagnostic and treatment challenges. Several laboratory agents are unaffordable and thus unavailable. Poor access to laboratory reagents.^[16,18]

Bacterial resistance is a big issue in Nigeria. This is due to the widespread misuse of antibiotics, thus leading to bacterial resistance. A huge number of specimens are culture negative, and in these cases, anaerobic etiology cannot be ruled out, though rare.

Late presentation is another major challenge giving rise to higher rate of ocular morbidity and mortality.

Late presentation is fueled by tendency to patronize traditional practitioners first due to low literacy level, ignorance, poverty, and problems of accessibility.

Contact lens use is not common in Nigeria, thus the low incidence of contact-lens-related keratitis

Indiscriminate self-medication with steroid preparation and use of traditional eye medication is another huge challenge. Traditional healers see a significant proportion of eye patients and thus should be censored and monitored, ensuring that they refer appropriately and promptly.

The Nigerian National Health Policy based on primary health care (PHC) has been established nationwide. However, most of these centers are ill equipped and run by staff who are hardly present at these facilities. The issue of lack of eye care services in these PHC centers is also a factor. Thus, these PHC providers cannot be reached. Patients then resort to traditional healers and drug sellers (patent medicine dealers or chemists). The actual PHC advisors then become influential members of the community, patients, peers, and nonmedical and non-skilled workers such as orderlies and porters. These lay persons are usually the first to be consulted by ill persons in the community. Patent medicine dealers dispense antibiotics and steroids unsupervised despite its prohibition by the law.

RECOMMENDATIONS

There is need for enforcement of legislative laws prohibiting the sale of antibiotics and steroids without doctor's prescription.^[16,18]

Steps must be taken to educate traditional healers on how to eliminate harmful aspects of practice. A manual for management could be given to them, thus making them aware of cases to promptly recognize and refer.

There should be a proper integration of primary eye care into PHC. These structures are not existence in Nigeria yet. PHC workers should be trained on basic eye care management and instructor manual providing guidelines given to them.

A structure should be put in place at the tertiary level to monitor and supervise the activities of these eye care providers.

The importance of prompt and accurate laboratory diagnosis for accurate microbial identification and drug sensitivity test must be emphasized and implemented.

Empirical broad-spectrum antibiotic therapy based on local epidemiological trends and presentation and close monitoring of disease progression should be instituted.

Prompt referral of cases of failed initial therapy to specialist must be the protocol.

Due to the practical limitations in developing countries for laboratory diagnosis and drug availability for treatment, early use of broad-spectrum topical antibiotics in addition to subconjunctival antibiotic injections is recommended.

Management of corneal abrasions or lacerations at the PHC level should start with a cheap intervention involving the use of ointment chloramphenicol.

Drug regulatory agencies should enforce drug availability, affordability, and ensure they are not adulterated.

Antifungal preparations which are usually scarce should be made available, but in the absence of this, anecdotal evidence has shown that vaginal antifungal cream works, though this has not been subjected to clinical trials and approval by local dangerous drug act. However, side effects of pains, redness, and general discomfort should be explained.

Common causative pathogens isolated in Nigeria include fungus (*Fusarium* and *Aspergillus*), herpes simplex, and bacterial pathogens including *S. aureus*, *S. pneumoniae*, and coliforms.

RECENT TRENDS

This is divided into diagnosis and treatment.

Diagnosis

In vivo confocal microscopy is emerging as a tool for rapid diagnoses in severe infectious keratitis with high sensitivity. In addition, it can be used to monitor treatment response, allowing guidance to clinicians for medical or surgical management.^[58]

Polymerase chain reaction is also a potent emerging tool in diagnosis. It has high sensitivity and specificity, readily

available within 24 h, thus faster than cultures and particularly useful in making diagnosis of *Acanthamoeba* and fungi.^[59]

Treatment

Corneal collagen crosslinking appears to be a promising adjunctive treatment in mild-to-moderate bacterial keratitis, especially in cases restricted to the anterior stroma. However, its efficacy in fungal and amoebic keratitis is not established.^[60]

Currently available topical antifungal agents are limited by poor bioavailability and limited ocular penetration, especially in deeper lesions. Intrastromal delivery of antifungal agents holds promise for circumventing some of the above limitations. To this end, voriconazole is the most commonly reported antifungal for intrastromal delivery.^[61]

There are three novel drug delivery devices, namely, iontophoresis, contact lenses, and collagen shields for recalcitrant MK especially bacterial. In iontophoresis, a small electrical charge drives charged drug molecules across a biological membrane toward an opposite charge. The technique has been used transcorneally and transclerally to deliver therapeutic drugs to the cornea, aqueous, and vitreous; for the cornea, an eye cup or hydrogel delivery vehicle is used.^[61]

The Steroids for Corneal Ulcers Trial (SCUT)^[42] attempted to definitively assess the effect of adjunctive topical corticosteroids on clinical outcomes in patients with bacterial keratitis. SCUT was a randomized, placebo-controlled, double-masked multicenter clinical trial comparing clinical outcomes of bacterial keratitis treated with topical moxifloxacin 0.5% and topical prednisolone phosphate 1% with those of moxifloxacin 0.5% and placebo. At 3 months, SCUT found no difference in best spectacle-corrected visual acuity or epithelial healing in the two groups. However, a subgroup analysis demonstrated benefit of corticosteroid treatment in patients with severe keratitis, that is, those with central corneal ulceration and worst visual acuity at enrollment.

Photorefractive surgery seems to be a very promising modality in treating early stage *Acanthamoeba* keratitis.^[62]

Autophagy inhibitors have anti-amoebic effects and if used with low concentrations of PHMB (0.00125%) has very low cytopathic effect on human corneal cells and a high cytopathic effect on *Acanthamoeba* cells.^[63]

CONCLUSION

MK is a disease of public health importance. This is particularly significant in developing countries where cost and limited access to health care are major concerns, especially in the younger population. Proper understanding of the pathogenesis of the disease entity, prompt identification of etiologic agent, and early and appropriate

diagnosis with optimal treatment are key to the prevention of visually disabling complications.

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