ABSTRACT
Corneal disease is the second most important cause for the blindness. Among them Fungal Keratitis is very difficult to treat. Fungal Keratitis is a general term which has meaning that any inflammation of the cornea. Fungi can infect (and therefore inflame) the cornea. Aspergillus and Fusarium are the most common species that can lead to the fungal keratitis. Different types of corneal diseases are discussed in this review such Keratitis, Keratoconjunctivitis, Kerato-uveitis. Certain conditions like trauma to the eye and therapy with antibiotics and corticosteroids renders the eye susceptible to infection with various fungi especially in tropical parts of world. A good knowledge about the structure of eye is necessary for the research. Therefore, a brief on anatomy of eye and pathophysiology of fungal keratitis have been included. This article throws light on the common risk factors for the development of fungal keratitis and various symptoms of fungal keratitis. Also, methods for the diagnosis of fungal keratitis have been discussed. An attempt has been made to give details on the treatment for the fungal keratitis.

Keywords: Fungal keratitis, Cornea, Aspergillus, Antifungal agents.

INTRODUCTION
Human eye provides a window to the world. It helps them sense the color, shape, and state of physical objects. The cornea provides a physical barrier, and protects the inside of eye from germs, dust and other harmful matter. Fungal keratitis is a fungal infection caused by the
fungus Aspergillus in the corneal layers, is one of the major causes of blindness if not diagnosed and treated at the earliest stages. Fungi cannot penetrate an intact epithelium (the upper layer of Cornea) but can penetrate an injury or a previous epithelial defect and thereby enter the cornea. Once into the corneal layers, they are able to proliferate. To avoid permanent damage, it is important to diagnose and treat corneal infections at the earliest possible opportunity. [1]

Infection of the eye leads to conjunctivitis, keratitis, endophthalmitis and other infections which are responsible for incidence of morbidity and blindness. Suppurative keratitis can cause corneal opacity and perforation, which leads to severe visual loss and is the second most common cause for blindness in developing countries. The etiological cause for suppurative keratitis may vary at different geographical locations. [1]

ANATOMY OF THE EYE [2-6]
The human eye is the organ that gives us the sense of sight, allowing us to learn about the visual structure of our surrounding world than any of the other five senses. The eye allows us to see and interpret the shapes, colors, and dimensions of objects in the world by processing the light ray they reflect. The eye changes light rays into electrical signals then sends them to the brain, which interprets these electrical signals as visual images.

Fig. 1 Human eye

The eye is set in a protective cone-shaped cavity in the skull called the orbit and is one inch in diameter. The orbit is surrounded by layers of soft, fatty tissue, which protect the eye and enable it to turn easily. Six muscles regulate the motion of the eye. Among the more important parts of the human eye are the iris, cornea, lens, retina, conjunctiva, the macula, and the optic nerve.
**Cornea** \(^{2,3}\)

The cornea is the front window of the eye. The cornea is as smooth and clear as glass but strong and durable as plastic; it helps the eye in two ways:

1. The cornea provides a physical barrier that shields the inside of the eye from germs, dust, and other harmful matter.
2. It acts as the eye’s outermost lens. When light strikes the cornea, it bends or reflects the incoming light onto the crystalline lens. The lens then focuses the light onto the retina. Although the cornea is much thinner than the lens, the cornea provides about 65 percent of the eye’s refractive power.

**Importance of Cornea** \(^{4}\)

As the eye’s outermost tissue, the cornea functions like a window that controls the entry of light into the eye. The cornea filters out some of the most damaging ultraviolet (UV) wavelengths in sunlight. Without this protection, the lens and the retina would be highly susceptible to injury from UV radiation.

**Structure of the Cornea:**

![Fig. 2 Structure of the Cornea](image)

**Ep – Epithelium; S – Stroma; En – Endothelium**

Although the cornea is clear and seems to lack substance, it is actually a highly organized group of cells and protein. The cornea receives its nourishment from the tears and aqueous humor that fills the chamber behind it. Unlike most tissues in the body, the cornea contains no blood vessels to nourish and protect it against infection, which would disturb proper light refraction. The tissue is arranged in three main layers.

**Epithelium**

This is the outermost layer in the cornea, which comprises about 10 percent of the tissue’s thickness. The epithelium provides the following functions:
1. Block the passage of foreign material such as dust or water into the eye and other layers of the cornea.
2. Provide a smooth surface that absorbs oxygen and other needed cell nutrients that are contained in tears.

**Stroma**
The Stroma is located behind the epithelium and comprises about 90 percent of cornea. It consists primarily of water, layered protein fibers that give the cornea its strength, elasticity, and form, and cells that nourish it. The unique shape, arrangement, and spacing of the protein fibers are essential in producing the cornea’s light conducting transparency.

**Endothelium**
This single layer of cells is located between the stroma and the aqueous humor. Because the stroma tends to absorb water, the endothelium’s primary task is to pump excess water out of the stroma. Without this pumping action, the stroma would swell with water, become hazy, and ultimately opaque.

**CORNEAL DISEASES**
The cornea copes very well with minor injuries or abrasions. If dirt scratches the highly sensitive cornea, epithelial cells slide over quickly and patch the injury before an infection can occur. But if the scratch penetrates the cornea more deeply, the healing process will take longer, resulting in greater opportunity for invasion. Some of the most serious problems that affect the cornea are:
1. Microbial infections (Keratitis)
2. Conjunctivitis (Pink eye)
3. Ocular Herpes (Viral infection)
4. Corneal Dystrophies
   a. Keratoconus
   b. Map-Dot-Fingerprint Dystrophy
   c. Fuch’s Dystrophy
   d. Lattice Dystrophy

**FUNGAL KERATITIS**[^7.8]
Leber was first described fungal Keratitis in 1879. Keratitis is not a common cause of corneal infection, but it represents one of the major causes of infectious Keratitis in tropical areas of
The world. Aspergillus is a fungus which leads to fungal Keratitis and is common cause of Keratitis. Following are some images which gives idea about fungal Keratitis.

Fig. 3 Fungal ulcer

Fig. 4 Fungal corneal ulcer

Fig. 5 Fungal Keratitis

Fig. 6 Fungal infection

Fungal Keratitis is a general term which has meaning that any inflammation of the cornea. Fungi can infect (and therefore inflame) the cornea. The term fungal Keratitis refers to a corneal infection caused by fungi (either single cell or multi-cellular fungi). One another type of fungus that can infect the cornea is Fusarium. When Fusarium infects the cornea, the eye disease is referred to as Fusarium Keratitis. It is most often results from an injury, such as a scratch on the front of the surface of the eye, caused by plant matter.
As an example, while hiking or gardening the eye is scratched by a twig or leaf or the eye is rubbed by hands carrying fungal organisms to the eye. Florists, landscapers, gardeners, outdoor enthusiasts having high incidence of fungal Keratitis.

Fungal Keratitis remains a diagnostic and therapeutic challenge to the ophthalmologist. The incidence of fungal Keratitis has increased over the past 30 years. This increased occurrence of fungal keratitis is a result of the frequent use of topical corticosteroids and antibacterial agents in treating patients with Keratitis.

DIFFERENT TYPES OF KERATITIS\(^1\)

There are total 70 different fungi that causing fungal Keratitis. Two medically important groups responsible for corneal infection are yeast and filamentous fungi. Yeast produces characteristic creamy, opaque, pasty colonies on the surface of culture media. Candida is the most representative pathogen in this group, primarily affecting those corneas already compromised by topical steroids, surface pathology, or both.

- If Keratitis only involves the surface (epithelial) layer of the cornea, then it is called as Superficial Keratitis.
- If it affects the deeper layer of the cornea (corneal stroma), it is called Stromal Keratitis or Interstitial Keratitis.
- Keratoconjunctivitis is the inflammation of the cornea and conjunctiva.
- Kerato-uveitis is inflammation of the cornea and uveal tract, which consists of iris, ciliary body, and choroid.

Keratitis may be acute or chronic. It may occur only once or twice in an eye or be recurrent. It may be limited in its effects on the eye or be progressive in its damage.

CAUSES OF KERATITIS\(^{11}\)

The various causes of Keratitis may result in different clinical presentations, defining the location, severity, and frequency of the condition. Other helpful facts in establishing the cause of Keratitis can include demographic information such as age, sex, and geographic location of the patient. A medical history is often useful as well in finding the cause of Keratitis. Infection is the most frequent cause of Keratitis. Bacteria, viruses, fungi, and parasitic organisms may all infect the cornea, causing infectious or microbial Keratitis. Common risk factors for the development of fungal Keratitis include the following:\(^8\)\(^{-11}\)

- Trauma (eg, contact lenses, foreign body); in a study of fungal keratitis from south Florida, trauma with vegetable matter was the major risk factor in 44% of patients.
Use of Topical corticosteroids
Corneal surgery such as penetrating keratoplasty, clear cornea (sutureless) cataract surgery, photorefractive keratectomy, or laser in situ keratomileusis (LASIK)
Chronic Keratitis due to herpes simplex, herpes zoster, or vernal Keratoconjunctivitis
Young males
No significant ocular disease
Allergies to airborne or bacterial toxins in tears
Chemical injury
Contact lens over wear
Agricultural occupations
Systemic illness
Previous eye surgery
Atopic disease
Diabetes
Topical medication

Risk factors for Candida keratitis are as follows:
Older patients
Preexisting ocular disease
Exposure keratoplasty
Chronic keratitis
Long-term steroid use
Immunosuppressive disease

PATHOPHYSIOLOGY [8-10]
Many fungal organisms associated with ocular infections are saprophytic organisms and have been reported as causes of infection only in the ophthalmic literature. Fungal isolates have been classified into the following groups: Moniliaceae (non pigmented filamentary fungi, including Fusarium and Aspergillus species), Dematiaceae (pigmented filamentary fungi, including Curvularia and Lasiodiplodia species), and yeasts (including Candida species). Fungi gain access into the corneal stroma through a defect in the epithelium, then multiply and cause tissue necrosis and an inflammatory reaction. The epithelial defect usually results from trauma (foreign material, prior corneal surgery). The organism can penetrate an intact membrane and gain access into the anterior chamber or the posterior segment.
Fungal Keratitis has been described to occur secondary to fungal endophthalmitis. Another possibility is entry through corneo-scleral trabeculae into the many channels in the cornea that exist as a network. Organisms that infect preexisting epithelial defects belong to the normal microflora of the conjunctiva and adnexa. The most common pathogen that invades a preexisting epithelial defect is Candida. Filamentous fungi are the principal causes of posttraumatic infection. The intrinsic virulence of fungi depends on the fungal substances produced and the host response generated.

Filamentoentous fungi proliferate within the corneal stroma without release of chemotactic substances, thereby delaying the host immune/inflammatory response. In contrast, Candida albicans produces phospholipase A and lysophospholipase on the surface of blastospores, facilitating the entrance to the tissue. Fusarium solani, which is a virulent fungus, is able spread within the corneal stroma and penetrate the Descemet membrane.

**SYMPTOMS:** [8-11]

The symptoms of fungal keratitis include:

- Eye pain and redness
- Tearing
- Blurred vision
- Sensitivity to light
- Excessive tearing or discharge

If the patient experiences any of these symptoms, then suddenly remove the contact lenses. Fungal keratitis is very rare condition, but if left untreated, it can become serious and results in vision loss or blindness.

**DIAGNOSIS OF FUNGAL KERATITIS** [12-14]

To prevent complications like loss of vision, rapid initiation of appropriate treatment is needed. The aim of treatment is to quickly eradicate the infecting organisms and also to control inflammation and tissue damage so as to preserve the transparency of the cornea. An early diagnosis of an infective microorganism leading to effective treatment may improve the outcome of keratitis. Accurate and rapid identification of the infectious agent involved remains a challenge for the ophthalmologist. The diagnosis of infectious keratitis can be made through a detailed clinical search for specific signs which suggest an etiology, examination of corneal smear and culture, histopathological examination of the cornea.
More recently new molecular techniques are used for the diagnosis of keratitis such as polymerase chain reaction (PCR) and in vivo confocal microscopy (IVCM). [15-18]

**Traditional Diagnostic Methods**

The slit lamp is tool in clinical ophthalmology. This lamp is useful with 40 times magnification in the diagnosis of microbial keratitis. Corneal cultures are considered as gold standard tool in the diagnosis.

The most common signs on slit lamp examination are nonspecific and include the following:

- **Conjunctival injection**
- **Marginal ulcer, fungus positive**
- **Epithelial Defect**
- **Suppuration**

**Polymerase Chain Reaction** [19]

Purpose of PCR is to assess the utility of infection and compare its sensitivity and also specificity with the conventional microbiologic techniques used in the laboratory.

PCR have been shown to detect small amounts of microbial DNA and improved the diagnostic approach to infectious keratitis. Also it has been useful in the diagnosis of viral, fungal and amoebic keratitis.

This technique is expensive, not available in all laboratories and for all microorganisms. [20, 21] Studies showed that the PCR is more sensitive than the currently used conventional techniques.
- **In vivo Confocal Microscopy (IVCM)**[^22]
  
The main limiting factor in observing a structure with light microscopy is that the light reflected on adjacent structures the image is observed thus by reducing resolution and contrast. For this reason ophthalmic instruments such as the slit lamp cannot provide details of the corneal structures at the cellular level. Diagnosis of infectious keratitis is represents one of the most important clinical use of IVMC.

**TREATMENT OF FUNGAL KERATITIS**[^11,^23]

When the microscopic examinations of the corneal scrapes or corneal biopsies yields definite results that are consistent with the clinical picture then treatment should be immediately initiated.[^18] Early diagnosis and proper treatment is crucial to recovery from fungal keratitis. Treatment include following:

- Topical medication
- Oral antifungal medication
- Debridement of the corneal epithelium (surface of the cornea)
- Surgical intervention, including corneal transplant

The treatment depends on the cause of the keratitis. Infectious keratitis generally requires antibacterial, antifungal, or antiviral therapy to treat the infection. Most of the available agents only inhibit the growth of fungus necessitating the host defense mechanisms to eradicate the infection.

This treatment can involve prescription eye drops, pills, or even intravenous therapy. Any corneal or conjunctival foreign body should be removed. Wetting drops may be used if disturbance of the tears is suspected to be the cause of the keratitis. Steroid drops may often be prescribed to reduce inflammation and limit scarring.

The antifungal agents available today to treat the fungal keratitis are belongs to the following class:

1) Polyenes
2) Azoles includes newer azoles
3) Pyrimidines
4) Other derivatives

**a) Polyenes**[^24-26]

Polyenes binds to the ergosterol of the fungal cell membrane, creating pores thus disrupt the homeostatic mechanisms leading to cell death. **Nystatin** was the first polyenes antifungal to
be identified. It has been recommended for topical use. Amongst Polyenes, Natamycin is the first drug of choice for filamentous infection since is easily available. It is marketed as a 5% suspension for topical use and has broad spectrum of activity. A 5% suspension in the eye is well tolerated. However, this drug may be ineffective in cases with deep stromal abscess because of poor corneal penetration.

**Amphotericin-B**

Has widely been used as a topical and systemic drug for ocular infections. Preparation of a 0.5% suspension of Amphotericin B, reconstituted from the 50mg vial powder is universally adopted for topical use as the first line drug both for Candida keratitis as well as for keratitis due to other mycelial fungi. After topical application, this drug can penetrate deep into the corneal stroma and 0.15% suspension is well tolerated, when instilled every 15 to 30 minutes. However, intravenous administration, with the recommended dosage, may cause poor corneal bioavailability. The drug shows nephrotoxicity after systemic administration. It is used for the following purposes:

- Aspergillosis
- Candidosis
- Blastomycosis
- Cryptococcosis
- Fusariosis
- Histoplasmosis
- Sporotrichosis
- certain forms of mucormycosis

**Pharmakokinetics**

- no mucosal or cutaneous absorption
- minimal absorption from GI tract
- extensively bound to plasma proteins
- enters serious cavities to plasma lipoproteins
- crosses placental barrier
- plasma half 24 hrs
- renal excretion very slow
Adverse effects

- chills, fever, and vomiting
- anaphylaxis, flushing, and muscle and joint pains
- deterioration of renal function must be anticipated
- progressive norm chromic anemia is indicative of bone marrow depression

Drug Interactions

- administration with other nephrotoxic drugs should be avoided
- with corticosteroids it leads to hypokalemia

b) Azoles \(^{24-26}\)

These are the derivatives of imidazole ring with substitution mainly in position 2. The imidazoles and the structures related N-substituted triazoles are considered together because they share the same antifungal spectrum and similar mechanism of action. However, systemic triazoles have a longer half life than imidazoles. The imidazoles include Clotrimazole, Miconazole and Ketoconazole. The triazoles include Fluconazole and Itraconazole.

Ketoconazole

It is an azole derivative with fungiststic activity. It inhibits the synthesis of ergosterol, causing cellular components to leak, resulting in fungal cell death. Often is used systemically in the treatment of deep fungal infections.

Fluconazole

It is alternative drug to ketoconazole in the treatment of deep fungal keratitis caused by a variety of fungi. Synthetic oral antifungal (broad-spectrum bistriazole) that selectively inhibits fungal cytochrome P-450 and sterol C-14 alpha-demethylation, which prevents conversion of lanosterol to ergosterol, thereby disturbing cellular membranes.

Voriconazole

Voriconazole is the drug of choice for Aspergillus fumigates, Aspergillus flavus, Fusarium species, Blastomyces dermatitidis, Coccidioides immitis, Curvularia species, Candida albicans, and Cryptococcus neoformans. The mode of action is the inhibition of fungal cytochrome P-450, preventing fungal ergosterol biosynthesis, thus damaging the fungal cell wall. A 1% solution is used for local instillation, every hour during the day and every 2 hours during night.
**Itraconazole**
It is a newer triazole which has larger spectrum of activity than fluconazole against filamentous fungi. However, its only drawback is that it is quite hydrophobic, and being 90% protein-bound in the serum, does not penetrate the tissue as well as fluconazole does.

**Miconazole**\(^{[27, 28]}\)
It has a broad spectrum of activity, including against Aspergillus, Candida, and Scedosporium species. Systemic miconazole, however, is associated with significant toxicity and has resulted in undetectable concentrations in the cornea. Topical application of extemporaneously prepared 1% miconazole eye drops achieved high concentrations in the ocular tissues. The eye drops are generally well tolerated and are used as second-line therapy in fungal keratitis that is unresponsive to natamycin.

**Econazole**\(^{[27, 29]}\)
Econazole has a broad spectrum of activity against filamentous fungi, and is effective against Fusarium keratitis. Topical application of 2% econazole appears to be as effective as 5% natamycin in fungal keratitis, but has been associated with ocular irritation.

**Voriconazole**\(^{[27, 30]}\)
Voriconazole, a more recent azole antifungal, is available commercially for systemic administration in the form of oral and IV formulations. It has an excellent broad spectrum of antifungal activity and is active against species that are known to be resistant to the other antifungal agents commonly used in fungal keratitis. Voriconazole is increasingly being used, orally in particular, against fungal keratitis. Oral voriconazole is highly bioavailable (96%) and has demonstrated good penetration into the different parts of the eye, with sufficient concentrations achieved to cover a wide range of keratitis-causative fungi. However, oral voriconazole can be associated with side effects as well as significant drug interactions. Topical Voriconazole eye drops, manufactured extemporaneously and used in an off-label manner, have also been prescribed for the treatment of keratitis.

**b) Pyrimidines**

**Flucytosine 1% (Ancobon)**
Flucytosine a synthetic Pyrimidines analogue is available in the form of 1% suspension for topical use. It can be given orally (150 mg/kg) as well. It has synergistic effect with Amphotericin-B. Its topical form is nontoxic to the eye. If it is given systemically it may
cause bone marrow depression and gastrointestinal upset. The main drawback of this drug is limited spectrum of the activity against filamentous fungi and rapid development of resistance by Candida species.\textsuperscript{[11, 24, 25]}

It gets converted to fluorouracil after penetrating fungal cells. Inhibits RNA and protein synthesis. Active against Candida and Cryptococcus and used in combination with Amphotericin B. High incidence of acquired resistance has occurred; therefore, combined treatment with other agents is recommended. In the treatment of fungal keratitis, polyenes and imidazoles have mostly replaced Flucytosine.\textsuperscript{[24, 25, 26]}

**MARKETED FORMULATIONS:**\textsuperscript{[31]}

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Drug</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Natamycin</td>
<td>Natacyn</td>
</tr>
<tr>
<td>2</td>
<td>Voriconazole</td>
<td>Vfend</td>
</tr>
<tr>
<td>3</td>
<td>Amphotericin</td>
<td>Fungizone cream</td>
</tr>
<tr>
<td>4</td>
<td>Econazole</td>
<td>Pevaryl</td>
</tr>
<tr>
<td>5</td>
<td>Fluconazole</td>
<td>Diflucan</td>
</tr>
<tr>
<td>6</td>
<td>Itraconazole</td>
<td>Sporanox</td>
</tr>
<tr>
<td>7</td>
<td>Ketoconazole</td>
<td>Nizoral</td>
</tr>
<tr>
<td>8</td>
<td>Vancomycin</td>
<td>Vanocin</td>
</tr>
<tr>
<td>9</td>
<td>Miconazole</td>
<td>Daktarin</td>
</tr>
<tr>
<td>10</td>
<td>Moxifloxacin</td>
<td>Avelox</td>
</tr>
<tr>
<td>11</td>
<td>Clotrimazole</td>
<td>Fungoid solution</td>
</tr>
<tr>
<td>12</td>
<td>Chloramphenicol</td>
<td>Chloromycetin sodium succinate</td>
</tr>
<tr>
<td>13</td>
<td>Ofloxacin</td>
<td>Floxin</td>
</tr>
<tr>
<td>14</td>
<td>Propamidine</td>
<td>Brolene</td>
</tr>
<tr>
<td>15</td>
<td>Cefazoline</td>
<td>Kefzole</td>
</tr>
<tr>
<td>16</td>
<td>Amikacin</td>
<td>Amikin</td>
</tr>
<tr>
<td>17</td>
<td>Kanamycin</td>
<td>Kantrex</td>
</tr>
<tr>
<td>18</td>
<td>Terbinafine</td>
<td>Lamisil</td>
</tr>
<tr>
<td>19</td>
<td>Tobramycin</td>
<td>Nebcin</td>
</tr>
<tr>
<td>20</td>
<td>Oxiconazole</td>
<td>Oxistate</td>
</tr>
</tbody>
</table>
REFERENCES
12. Contribution of In Vivo Confocal Microscopy to the Diagnosis and Management of Infectious Keratitis. ANTOINE LABBÉ, MD,1,2 CYRINE KHAMMARI, MD,1 BÉNÉDICTE DUPAS, MS,1 ERIC GABISON, MD, PHD,2,3 EMMANUELLE BRASNU, MD,1,2MARC LABELTOULLE, MD, PHD,4 CHRISTOPHE BAUDOUIN, MD, PHD1, 2 .THE OCULAR SURFACE / JANUARY 2009, VOL. 7, NO. 1 / www.theocularsurface.com.
17. Pachigolla G, Blomquist PH, Cavanagh HD. A 5-year review of 12 cases of microbial keratitis at a major urban county hospital. Eye Contact Lens, 2007; 33:207.
31. https://www.medify.com/treatments/natamycin