**VILNIUS UNIVERSITY**
**MEDICAL FACULTY**

The Final thesis

# Contact Lens Related Microbial Keratitis. Literature review.

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## Summary

Microbial keratitis is frequently encountered condition in otherwise healthy individuals using contact lenses. The aim of this paper is to review the risk factors predisposing to this condition, most common causative agents and their pathologic mechanisms, diagnostic methods and treatment options.

## Key words:

Microbial keratitis, contact lenses, contact lens related microbial keratitis, infection, Acanthamoeba keratitis (AK), Pseudomonas aeruginosa keratitis, fungal keratitis (FK)

## Introduction

Contact lens related keratitis, also called microbial keratitis is infection of the anterior transparent layer of an eye, called cornea. Since the introduction of contact lenses, many people switched from wearing glasses to contact lenses. Nowadays, around 140 million people are contact lens users. Contact lens use, in turn, is one of the main risk factors for development of microbial keratitis. Various risk factors predispose to contact lens related microbial keratitis, out of which overnight contact lens wear and hygiene noncompliance, like prolonged use of storage cases, absence of hand hygiene, use of inappropriate cleaning solutions and improper disinfection of storage cases, are the leading ones. Microbial keratitis is a serious complication, which in some cases requires keratoplasty. Microbial keratitis is the result of either bacterial, fungal or protozoal infection. Among the causative agents are both Gram-positive and Gram-negative bacteria, with Pseudomonas aeruginosa being more prevalent than other Gram negative-bacteria as well as being responsible for majority contact-lens related microbial keratitis cases. Serratia marcescens, Acanthamoeba spp., Fusarium are potential microbes responsible for contact lens related microbial keratitis.

## Literature selection strategy

PubMed database was used during the literature selection. Literature selection was conducted using the following words: microbial keratitis, contact lens complications, contact lens related microbial keratitis, pseudomonas aeruginosa keratitis, Acanthamoeba keratitis. All article types were used with a time span of being not older than 5 years. All articles used are available as a free full text and were read in English language. Other than Pubmed website, “Ocular infection” by David Seal and Uwe Pleyer, was used.

## Clinical description of disease and clinical condition

Previously microbial keratitis has been largely associated with trauma as well as geographical location. Later on, contact lenses have become a major and the most significant risk factor in the development of microbial keratitis. Microbial keratitis causes infiltration of the corneal stroma and overlying epithelium. This condition generally presents with redness, discharge, photophobia, visual disturbance. Bacteria invade the cornea causing inflammation, subsequent ulceration and possibly neovascularization. In some cases, this can also lead to descemetocele, which is herniation of Descemet's membrane. Descemetocele occurrence is a big risk factor for perforation of the cornea. Microbial keratitis can be caused by a wide variety of microorganisms, which are gram- negative and positive cocci and rods, acid-fast bacteria, certain fungal microorganisms like Fusarium and Aspergillum, as well as Acanthamoeba species. The vast majority of keratitis is being caused by Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae and Pseudomonas aeruginosa. Pseudomonas aeruginosa accounts for most of the cases of microbial keratitis related to contact lens use.

### Bacterial keratitis

Bacterial keratitis is responsible for approximately 90% of keratitis cases. Among all the bacteria, Pseudomonas aeruginosa is implicated the most and it is highly associated with contact lens use.

Pseudomonas aeruginosa is a gram-negative rod, which is considered to be a human opportunistic pathogen. It is responsible for various infections in the human body, one of which is bacterial keratitis. Pseudomonas aeruginosa is the most common causative agent, which is associated with contact lens use. Both prolonged contact lens use as well as daily use of contact lenses is implicated as a risk factor for the development of keratitis. Surprisingly, the contamination route is thought to be from the eyes to the storage cases. It was estimated that only around 1.5% of storage cases were contaminated with Pseudomonas. Generally, Pseudomonas aeruginosa is found in the bathroom environment.

Serratia marcescens has been also mentioned as the causative agent of contact-lens related microbial keratitis. Serratia marcescens is a mobile, aerobic, Gram-negative rod belonging to Enterobacteriaceae family. The most significant risk factor for Serratia keratitis is contact lens use. As Pseudomonas, Serratia is found in damp places like bathrooms, for example. Soft contact lens use carries a high risk for Serratia keratitis.

Generally, patients with bacterial keratitis present with a central corneal ulcer. This is especially characteristic for Pseudomonas keratitis. The size of an ulcer is variable and can be up to 2mm and more. Patients with Pseudomonas keratitis have a ring infiltrate which consists of polymorphonuclear neutrophils (PMN). In severe cases, hypopyon may be present.  Patients usually present with pain, photophobia, injection, chemosis, conjunctival injection, corneal and stromal infiltrate, decreased visual acuity. Bluish green discharge is characteristic for Pseudomonas keratitis. Moreover, Pseudomonas keratitis has a short duration and progresses rapidly. It is prone to perforate quickly if left untreated for a couple of days.

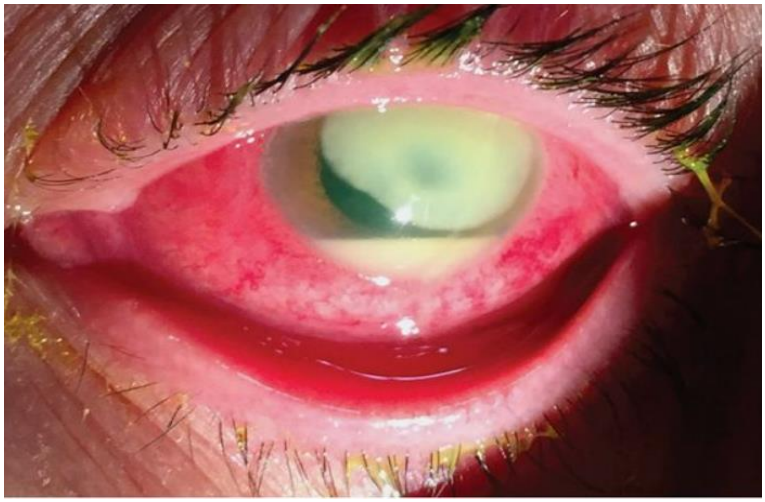


Figure 1. Pseudomonas aeruginosa keratitis. Corneal ulcer with hypopyon, conjunctival and ciliary injection

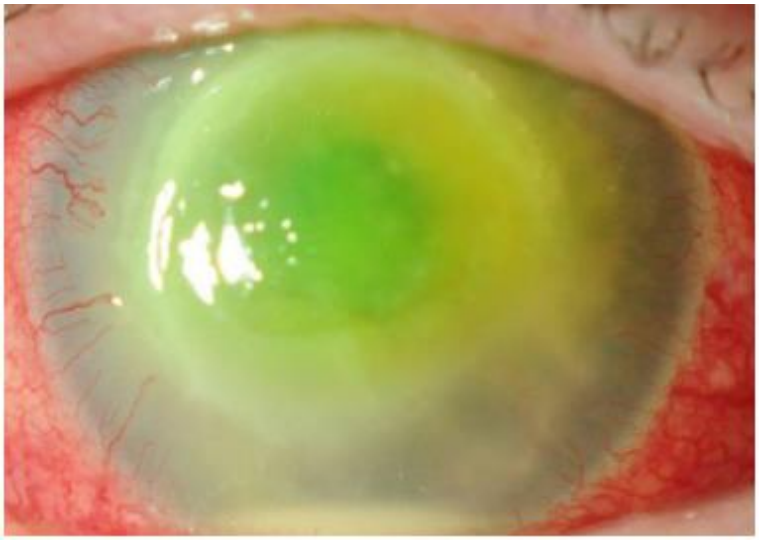


Figure 2. Pseudomonas aeruginosa keratitis. Ring-shaped infiltrate and hypopyon

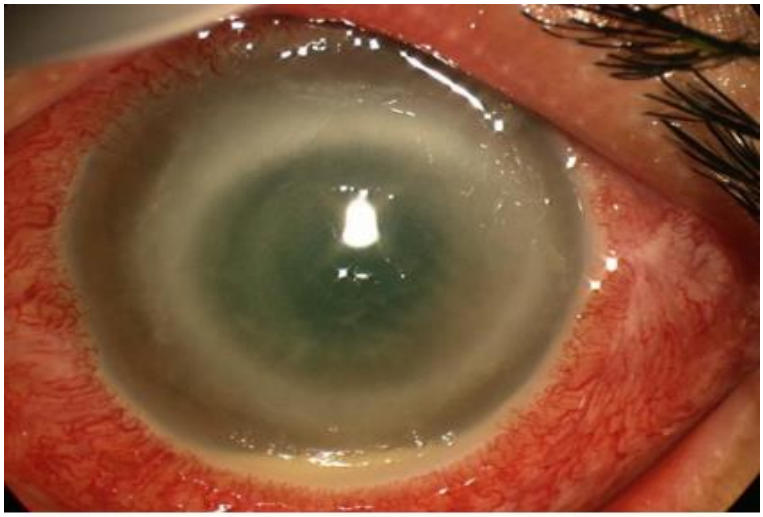


Figure 3. Serratia marcescens keratitis. Stromal infiltrates with corneal ring, conjunctival injection.

## Fungal keratitis

Fungal keratitis, also called keratomycosis, is infection of the cornea by fungal species, which can debilitate the vision severely. Fungal keratitis can be caused by various fungal species, which are yeast-like Candida, filamentous Aspergillus and Fusarium, Rhizopus, Curvularia, Cladosporium. However, the most common causative agents are Fusarium, Candida and Aspergillus species. Based on geographical location the causative agent may change. In general, the prevalence of fungal keratitis is higher in warmer climates. Keratitis due to filamentous fungi is more common in warm climate, whilst keratitis due to yeast-like fungi is more prevalent in temperate climates. Patient-related risk factors also play an essential role. Fusarium is most commonly associated with trauma and contact lens use, for example. Moreover, fungal keratitis is quite common in people engaging in agricultural activities. There is also a sexual preponderance towards males.

Fungal keratitis generally presents with a sudden onset ocular pain, blurry vision, discharge, photophobia, epiphora, redness. Signs vary depending on whether this is filamentous or yeast-like fungi. Filamentous fungi present as a stromal infiltrate with feathery margins, possible presence of satellite lesions and thick endothelial exudate. In contrast,fungal keratitis caused by Candida Albicans is a stromal keratitis similar to bacterial keratitis. It will present with overlying epithelial defect and conjunctival hyperemia.

Fungal keratitis is generally similar to bacterial keratitis,however, the lid edema is absent. Presence of lid edema suggests periocular injections or application of natural medications.

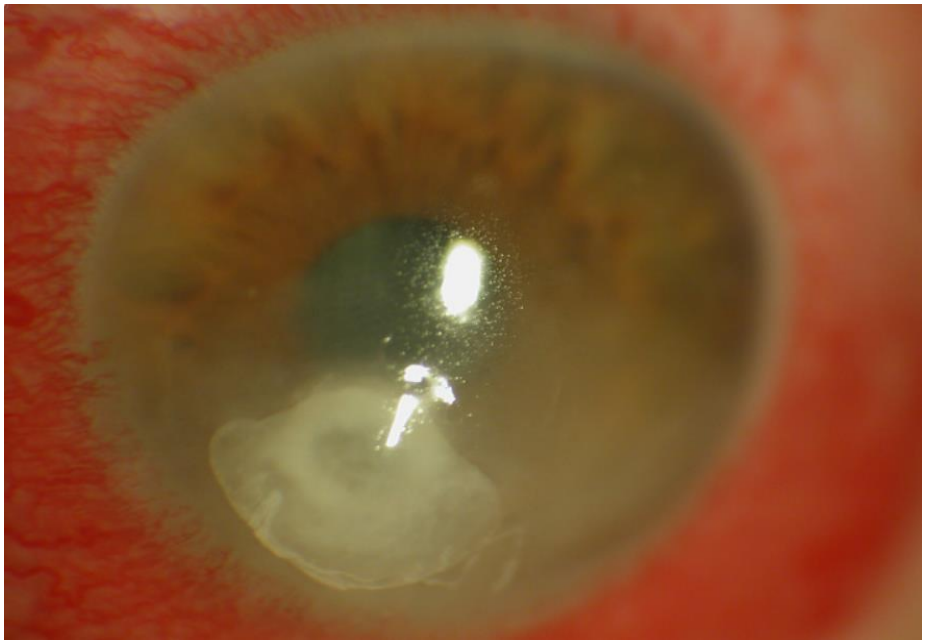


Figure 4. Candida keratitis

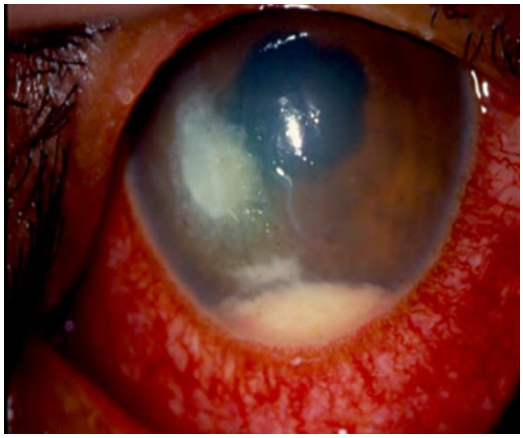


Figure 5. Fusarium solani keratitis

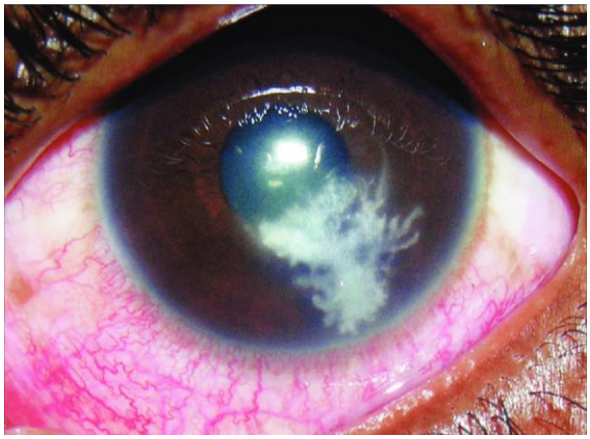


Figure 6. A typical fungal keratitis with hyphate margins

Table 1. Findings in filamentous and yeast-like fungus

| Filamentous fungi | Yeast-like fungi |
|---|---|
| • Stromal infiltrate with hyphate margins<br>• Dry elevated slough<br>• Satellite lesions<br>• Thick endothelial exudate | • Inferocentral location<br>• Overlying epithelial defect<br>• Slow progression<br>• Discrete infiltrate |

## Acanthamoeba keratitis

Acanthamoeba is a protozoa which is found in soil and various aquatic environments like ponds, tap water, hot tubs, pools and contact lens solutions. Acanthamoeba castellani and Acanthamoeba polyphaga account for most of the Acanthamoeba keratitis cases.
Acanthamoeba has two forms: a trophozoite and cyst form. The trophozoite form reproduces itself under favorable conditions. Under unfavorable conditions, including the presence of antimicrobials, the trophozoite form turns into a metabolically inactive cyst. The cyst form of Acanthamoeba is responsible for the failure of antimicrobial treatment as they are resistant to multiple antimicrobials, and this in turn can lead to recurrence of the disease.
The number of AK cases have risen in the past couple decades. It has also been estimated that Acanthamoeba keratitis approximately accounts for 5% of all microbial keratitis cases. However, despite its abundance in nature, the incidence of AK is not high. Contact lens use is the major risk factor for the development. Prolonged contact lens usage, inappropriate storage of lenses, rinsing the storage case with tap water, biofilm formation and swimming whilst wearing contact lenses are all implicated as risk factors for development of Acanthamoeba keratitis. However, keratitis caused by this type of species can also occur in hygiene-compliant contact lens wearers.
Symptoms of Acanthamoeba keratitis can be intermittent and severe at times. Acanthamoeba keratitis generally presents with severe pain, conjunctival injection, excessive lacrimation, sensation of the foreign body in the affected eye, as well as ptosis and photophobia. Subsequently infiltration of inflammatory cells occurs. The pathognomonic sign is formation of the ring infiltrate (Wessely immune ring). Moreover, patients present with characteristic “dirty epithelium”, epithelial erosions, microcysts, stromal as well as perineural infiltrate.

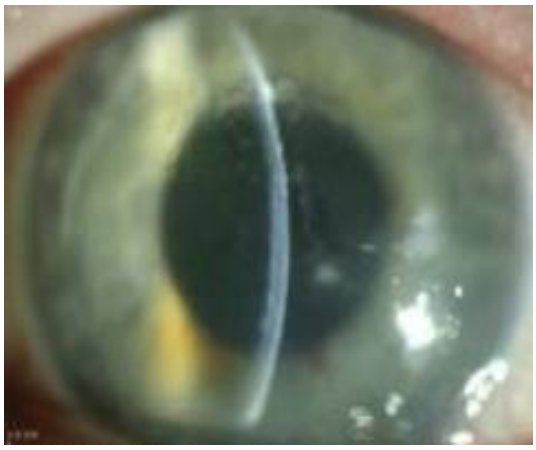


Figure 7. “Dirty epithelium”

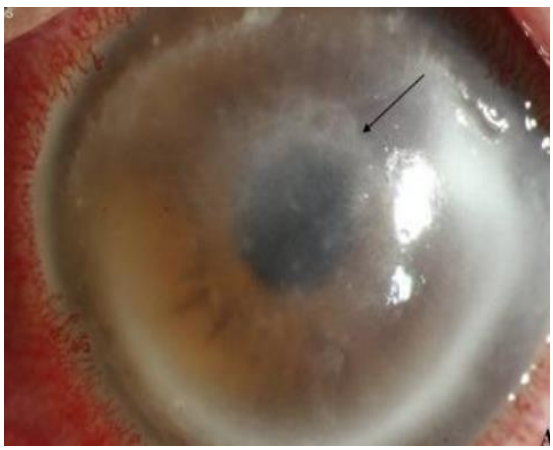


Figure 8. Stromal infiltrate and incomplete ring infiltrate

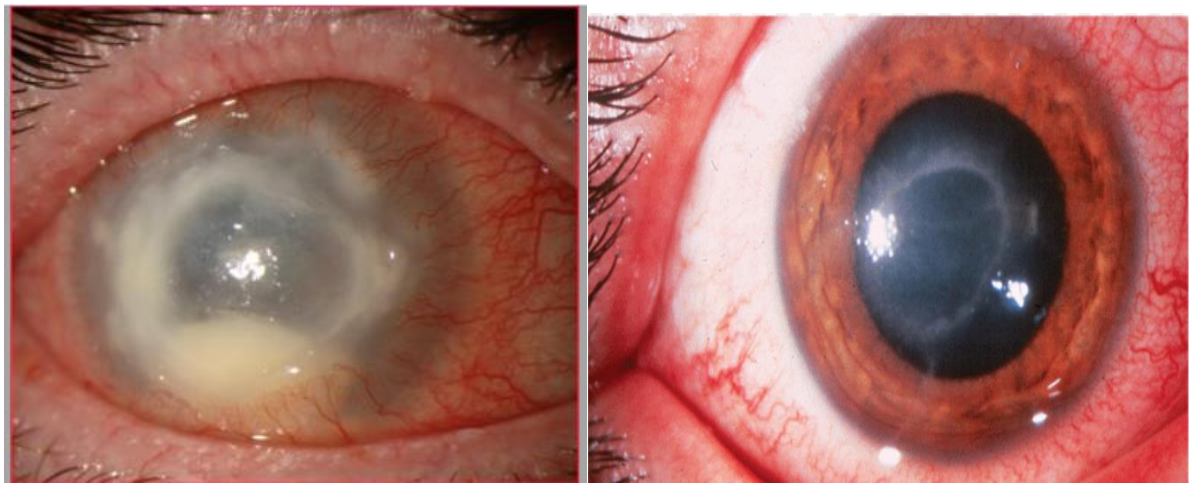


Figure 9 and Figure 10. Slit lamp photograph of the cornea showing ring infiltrate

Table 2. Acanthamoeba keratitis presentation

| Transmission | Symptoms | Signs |
|---|---|---|
| Exposure to Acanthamoeba via contact lenses | • Excruciating pain<br>• decreased vision<br>• epiphora<br>• discharge<br>• photophobia | • Dirty epithelium<br>• Ring-shaped infiltrates<br>• hypopyon<br>• satellite lesions<br>• conjunctival injection<br>• keratoneuritis |

Acanthamoeba keratitis is a vision-threatening disease and can result in corneal ulcer, abscess, reduced visual acuity, cataract,blindness and even enucleation.

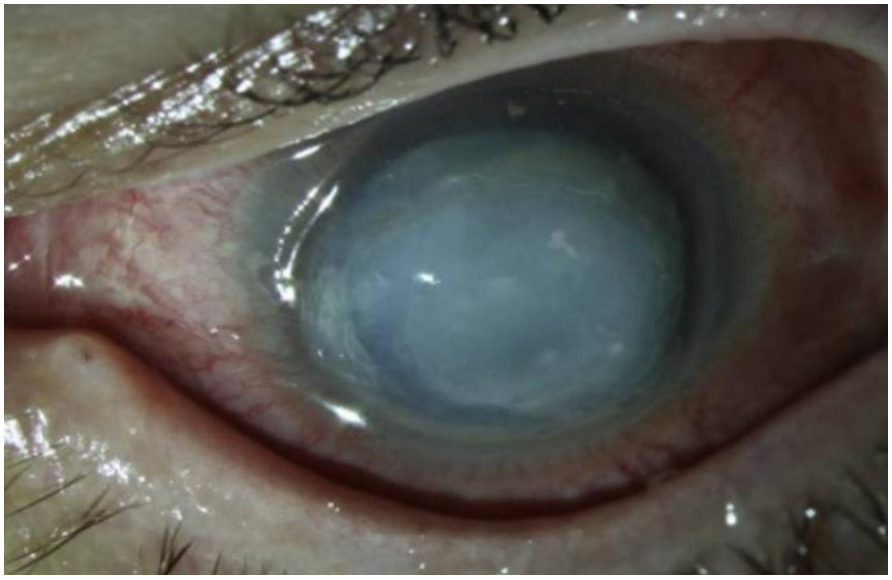


Figure 11. Corneal ulcer, persistent mydriasis, cataract in case of Acanthamoeba keratitis

## Disease mechanism and pathology

Virulence factors and host factors are the key points in the pathogenesis of microbial keratitis in general.

### Pathogenesis of Bacterial keratitis

First step in the pathogenesis of bacterial keratitis is adhesion of bacteria to the surface of the host cell, in this case cornea. Bacteria possess variable adhesions like fimbriae and pili to facilitate this process. Later on, bacteria invade the stroma with help of proteases and exotoxins, resulting in the cell lysis. Proteases and exotoxins are continuously being released and destroy the corneal stroma.

Pseudomonas aeruginosa has been divided into two categories based on the toxin it produces: ExoS and ExoU toxin. ExoU toxin has cytotoxic effects on cells and is more virulent. ExoS is associated with invasive infections as well as better visual acuity outcomes.

Other than toxins, Pseudomonas aeruginosa secretes proteases. The two most important ones are Protease IV and Pseudomonas aeruginosa small protease (PASP). Pseudomonas aeruginosa small protease is also a keratitis virulence factor.

Overstimulation of host immune system results in corneal damage. Macrophages and dendritic cells initiate immune response in the cornea. They activate toll-like receptors (TLR) as well as NOD-like receptors. This results in recognition of pathogen-associated molecular structures (PAMPs) by host. Subsequently, various cytokines like IL-1, IL-6 and IL-8 via NF-kB are released. Toll-like receptors 4 and 5 recognize the lipopolyssacharide and flagellin of P.aeruginosa and activate MyD88 gene which initiates inflammatory response. Continuous

recruitment of polymorphonuclear neutrophils is responsible for corneal scarring and decreased visual acuity.

Apart from inflammation cascade, there are certain compounds responsible for protection of ocular surface and maintenance of inflammation. The compound of tears, lactoferrin, defensins, phospoholipase A2, arachidonic acid metabolites fight off bacteria using various mechanisms resulting in recruitment of inflammatory cells.

## Pathogenesis of Fungal keratitis

A defect in the ocular epithelium results in invasion of stroma by the fungi. As the infection progresses, fungi spread circumferentially and form satellite lesions. Eventually, fungi can reach the Descemet's membrane and anterior chamber. This can result in corneal perforation and possible endophthalmitis. The infection can also spread to neighbouring structures like sclera, for example, and cause scleritis.

Cornea does not have any vascular supply. In addition to that, cornea possesses very limited defense mechanisms. Fungi, in turn, secrete various toxins and enzymes, including proteinases and matrix metalloproteinases. These make cornea susceptible to invasion by fungi.

In Fusarium induced keratitis, fungi invade the cornea and the mass at the pupillary area is formed. The mass obstructs normal drainage of aqueous humor resulting in glaucoma. Similar presentations have also been reported with Aspergillus keratitis.

The invasiveness of the fungus depends on the infectious load, as well as an underlying inflammatory response. Moreover, fungi possess an ability to change their shape, which enables them to survive in the presence of antifungal medications. For instance, Candida albicans undergoes morphogenic transformation from yeast form to invasive filamentous form.

## Pathogenesis of Acanthamoeba keratitis

Acanthamoeba adheres to the epithelial surface of the eye via mannose-binding protein and laminin-binding protein. The adhesion to the surface occurs in the trophozoite stage. Contact lenses, in turn, result in increased adhesion of Acanthamoeba to ocular surface. Adhesion and binding of trophozoite results in penetration of Bowman's membrane via phagocytosis and release of enzymes, followed by destruction of corneal epithelial lining, apoptosis and invasion of stroma. Acanthamoeba trophozoites release proteases, which are thought to be responsible for pain and radial keratoneuritis on slit lamp examination.

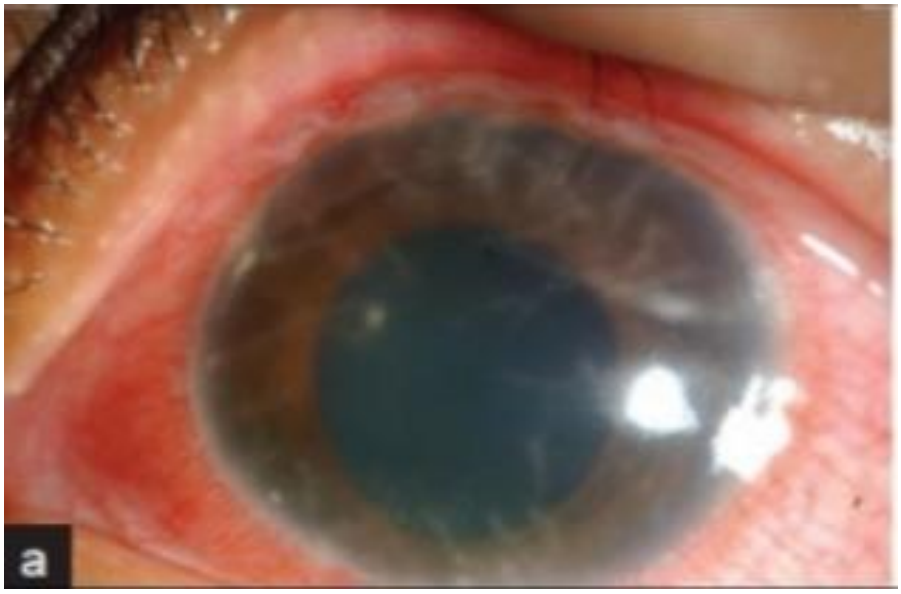



Figure 12. Slit lamp photograph of the cornea showing radial keratoneuritis

## Diagnosis

The diagnosis of microbial keratitis consists of three steps, which are history taking, careful clinical examination and laboratory investigations. History of contact lens use, recent travel or geographic predisposition should raise clinical suspicion. After clinical examination, laboratory investigations are performed. The basis for diagnosis is corneal scrapings and biopsy. In general, three corneal scrapings have to be taken, with the first on being disposed. The second scraping should be spread on a clear glass for microscopical examination. Whilst, the third scraping should be used for agar plates inoculation. The smear can be examined using the light microscopy, simple microscopy or culture. Various stains are being used depending on the causative agent. Gram and Giemsa staining are more or less universal. Lactophenol staining, for instance, is used for fungi. At the same time, silver can be used for both fungi, protozoa and parasites. Cultures, which can be possible utilized are the following: chocolate agar, blood agar, Sabouraud's agar, brain-heart infusion broth, thioglycolate infusion broth. If no organism has been identified on the culture or during microscopy, 2 corneal biopsies have to be performed. One of them is used for culture and PCR and the other one for electron microscopy and histology.

### Bacterial keratitis diagnosis

Presence of corneal ulcer, hypopyon, ring infiltrate, characteristic symptoms should prompt physician to obtain corneal scraping for Gram staining and culture. Moreover, contact lens storage cases should be sent for culture. As it was stated above, 3 scrapings are being taken,

with only 2 being used for microscopy and culture. In case of unsuccessful scraping, biopsy is taken for establishment of the diagnosis.

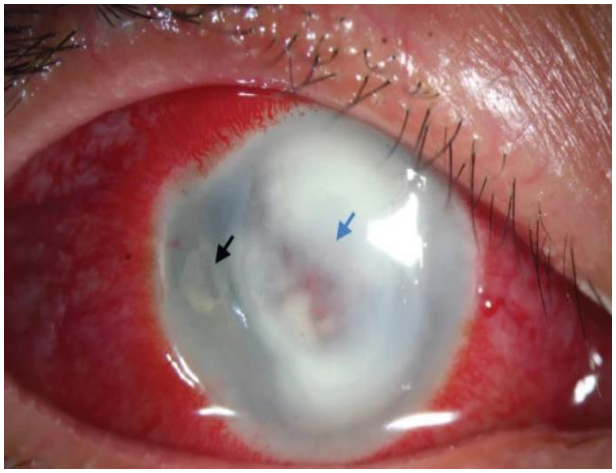


Figure 13. Central corneal infiltrate (blue arrow), satellite lesion (black arrow), conjunctival and ciliary injection

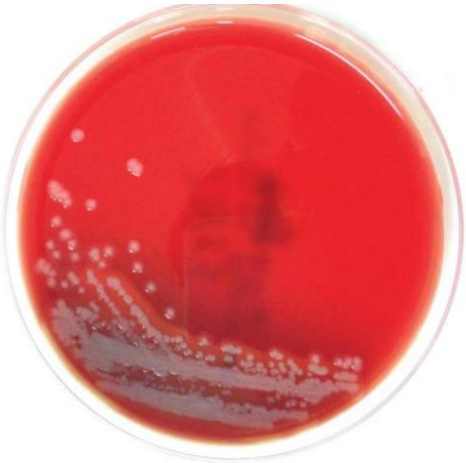


Figure 14. Culture growing Pseudomonas aeruginosa

## Fungal keratitis diagnosis

Prompt diagnosis of fungal keratitis is of utmost importance for successful treatment, as delay in diagnosis can lead to irreversible outcomes. It is important to pay attention at all the details, like failure to respond to antibacterial therapy and presence of satellite lesions. A thorough history has to be taken and documented. The physical examination is the next step in the process, during which all the peculiarities, like satellite lesions, hypopyon, anterior chamber reaction, vitreous reaction, lid edema, intraocular pressure should be documented. It is also essential to evert the lid in order to exclude a foreign body.

The diagnosis of fungal keratitis consists of the several steps. First of all, tissue samples are being taken and sent to laboratory investigation. Samples are being investigated by microscopy using Giemsa or silver stain. Fungi have predisposition to penetrate into the

deeper layers of the cornea and corneal swabs are not enough to establish the diagnosis. Therefore, corneal scrapings have to be performed and sometimes even corneal biopsy might be needed. The samples should be sent to culture and polymerase chain reaction (PCR). Generally, it takes up to 35 days for fungal cultures to grow. Different types of agars, like Sabouraud, blood, chocolate are being used. However, culture method has been reported as not a sensitive one, because of a small amount of corneal scrapings. The stains being used for cultures depend on the causative agents of fungal keratitis.

Potassium hydroxide (KOH) is being used for yeast-like fungi and Giemsa and Gram stains for filamentous fungi.

PCR is established to be more sensitive and fast method for diagnosis establishment. Moreover, it can be performed using small amount of sample or fluids like aqueous humor or tears. The results of PCR testing are available in up to 8 hours. The major disadvantage of PCR is possible identification of non-pathogenic bacteria. In addition to that, PCR requires special equipment and is not readily available in all hospitals.

In vivo confocal microscopy is widely used as it is not invasive and does not result in complications. It allows to visualize the morphology and microstructure of the ocular surface. Anterior segment optical coherence tomography is another non-invasive investigation method. It enables to visualize necrotic cystic spaces like in the cases of Aspergillus keratitis. Both in vivo confocal microscopy and anterior segment optical coherence tomography can be used in the follow-up of the treatment of keratitis.

Ophthalmic ultrasonography is used for diagnosis of keratitis-induced complication, endopthalmitis.

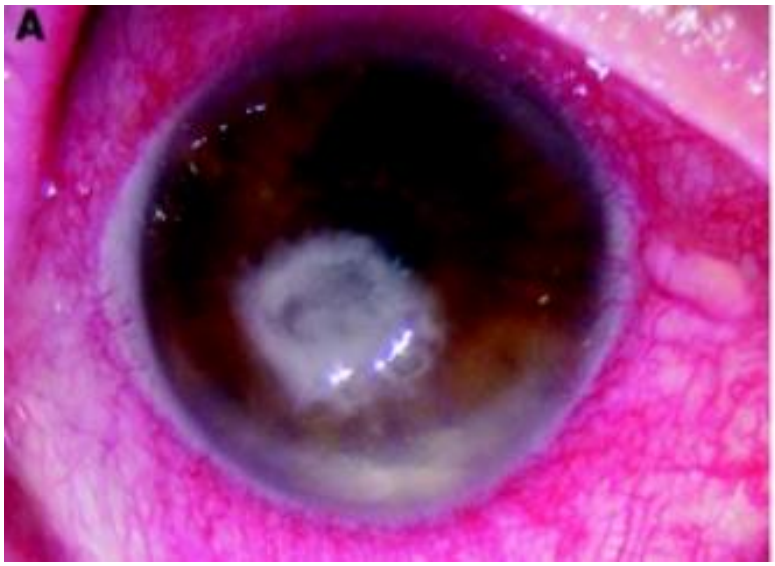



Figure 15. Slit-lamp examination of Fusarium solani induced fungal keratitis.

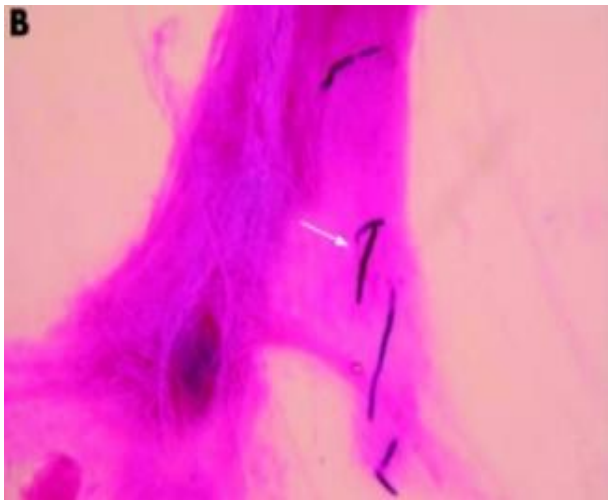
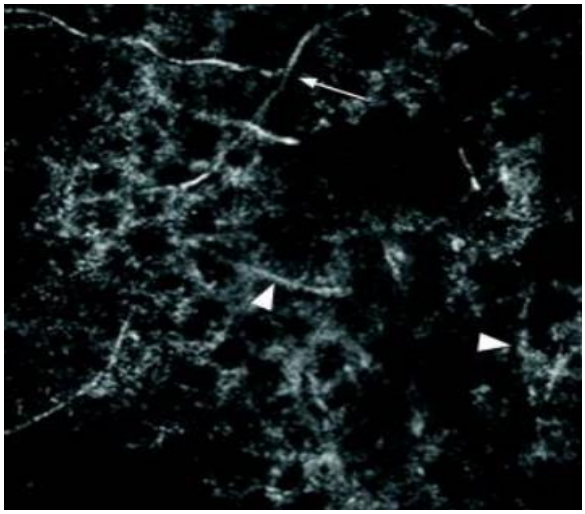



Figure 16. Microscopic examination of Fusarium solani



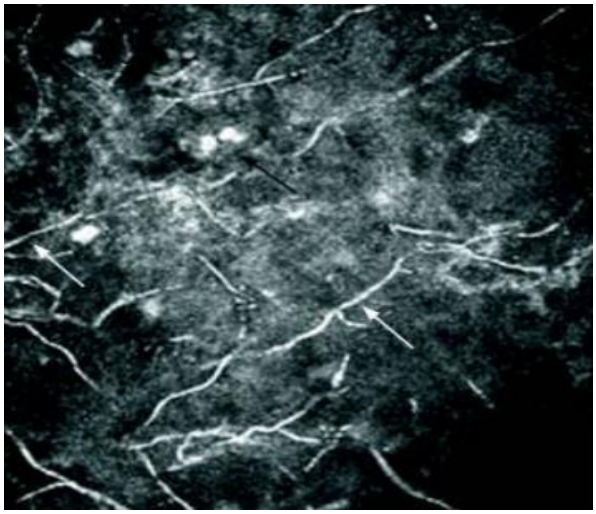


Figure 17 and Figure 18. In vivo confocal microscopy of Fusarium solani-infected patient. White arrows point to Fusarium hyphae, whilst arrowheads are consistent with corneal nerves. Black arrows indicate round inflammatory cells.

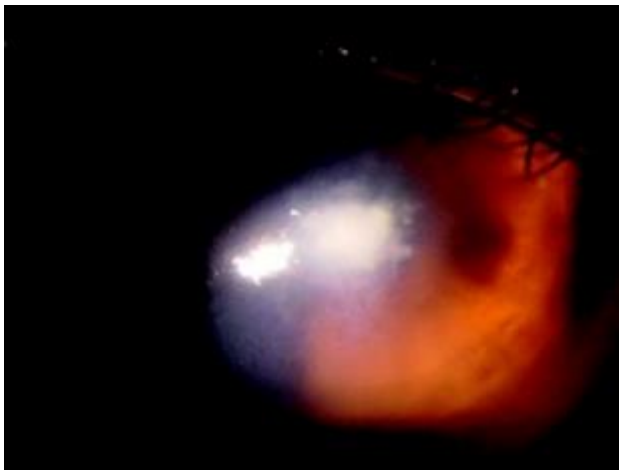


Figure 19. Slit-lamp examination of Candida albicans induced fungal keratitis

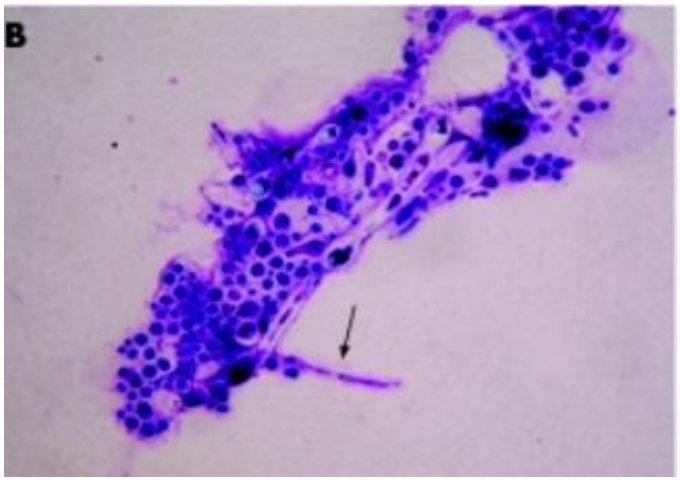
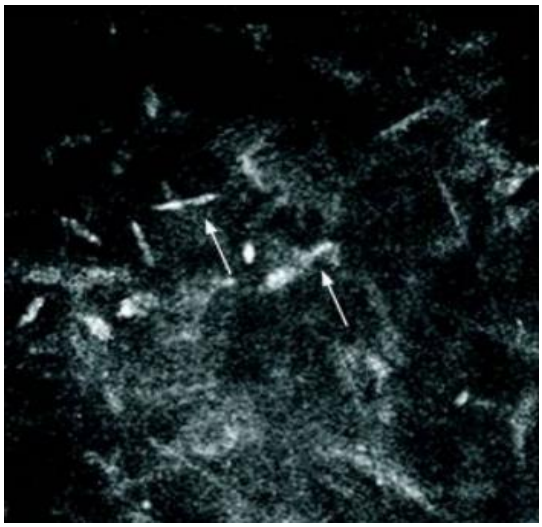



Figure 20. Microscopic examination of Candida Albicans induced fungal keratitis. Arrow shows Candida albicans pseudofilaments.



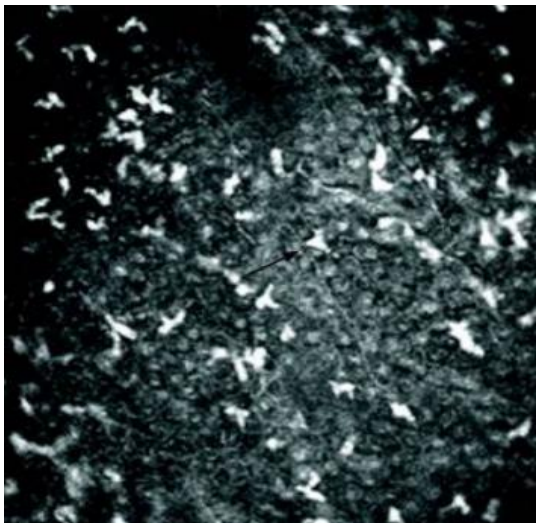


Figure 21 and Figure 22. In vivo confocal microscopy of C.albicans- infected patient. White arrows represent pseudofilaments. Black arrows resemble dendritiform inflammatory cells.

## Acanthamoeba keratitis diagnosis

Diagnosis of Acanthamoeba keratitis is complicated and often delayed. One of the possible reasons for that is patients presenting to the doctor's office late, because they are used to their eyes being irritated. A thorough history should be taken, including the inquiries about contact lens use, cleaning solutions, storage cases, use of tap water instead of cleaning solutions, recent exposure to water sources. A careful physical examination should be performed with an attention to all details, signs and symptoms. At the beginning patients may present with non-specific symptoms. However, later in the course of the disease they may develop anterior stromal infiltrates, ring-shaped infiltrates, radial keratoneuritis, synechiae and glaucoma. In advanced stages, corneal perforation can occur.

Various methods are used for diagnosis of Acanthamoeba keratitis. These include, histopathological examination, culture, PCR and in vivo confocal microscopy. If keratitis is suspected, corneal scrapings should be taken and sent for pathological examination. In the absence of corneal scrapings or biopsy no definitive diagnosis can be made. Acanthamoeba penetrates the cornea, therefore superficial swabs and other materials are not suitable. However, contact lens containers of healthy individuals can be positive for Acanthamoeba keratitis. Conversely, absence of Acanthamoeba indicates that patient has no keratitis. Only in case patient has changed his storage container recently.

The gold standard for diagnosis is culture method. The materials like corneal scrapings or biopsy are inoculated at 30 degrees on a non-nutrient or E.coli plated agar. Cultures are observed daily for the presence of Acanthamoeba and should be monitored for up to 1 week to exclude any false-negative diagnosis. After 1 week, cysts start to grow and can be assigned to a particular morphological Acanthamoeba group based on their appearance. Most of the Acanthamoeba keratitis are related to strains from group 2 and group 3 Acanthamoeba species.

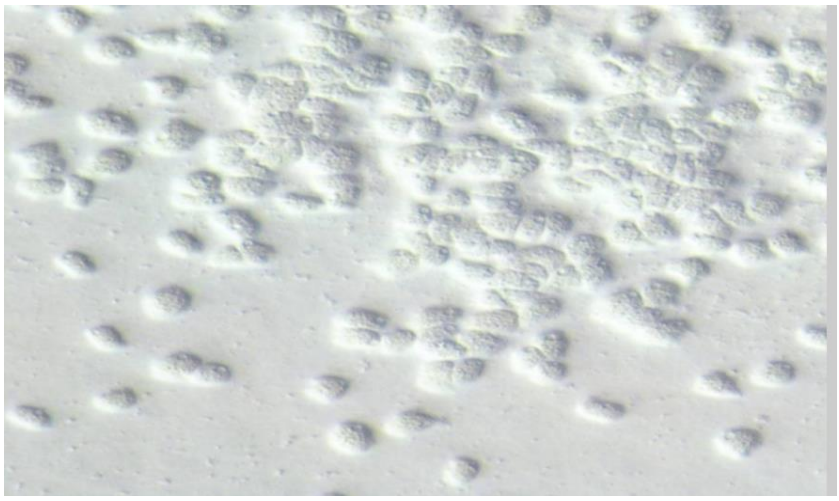


Figure 23. Acanthamoeba keratitis identified in culture

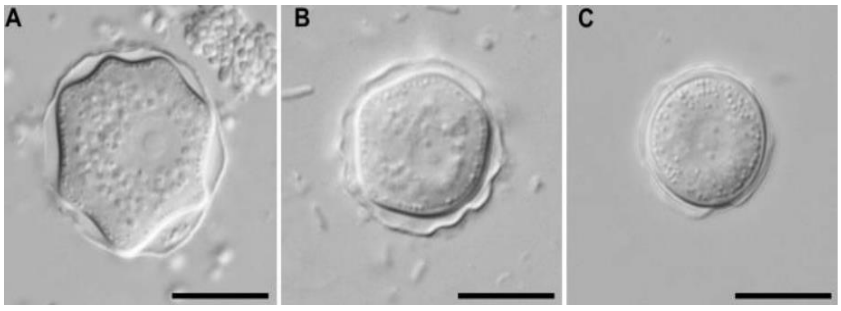



Figure 24. Acanthamoeba cysts. A contributes to morphological group 1 or so called “star shaped”, B and C to 2$^{nd}$ and 3$^{rd}$ morphological groups, polygonal and round-shaped cysts, respectively

Staining is generally used for visualization of the cysts. Different types of staining like Giemsa, silver, hematoxylin and eosin, lactophenol-cotton blue. Giemsa and lactophenol-cotton blue are considered to be the fastest.

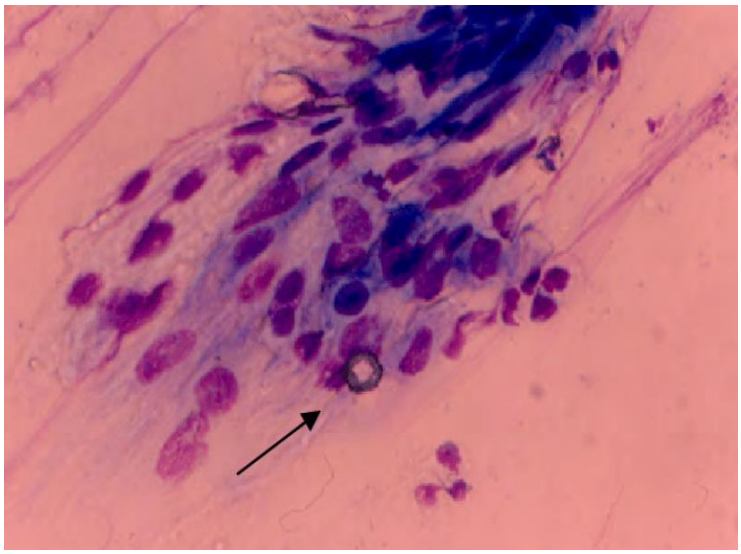


Figure 25. Acanthamoeba cyst on Giemsa staining

Each diagnostic investigation has its own advantages and disadvantages. For instance, PCR of corneal scrapings has a high sensitivity and can give result in up to 1 hour. However, the rates of false-positive results are quite high. The 18S rRNA gene is the most commonly used region to detect Acanthamoeba DNA. Genotyping is also performed along with PCR and the most widely identified is T4, however, T3 and T11 can be responsible for Acanthamoeba keratitis too.

In vivo confocal microscopy also has high sensitivity, but using this method only Acanthamoeba cysts can be diagnosed. Culture method, for example, has variable sensitivity and its biggest disadvantage is that it takes substantial time to confirm the diagnosis. Histopathologic examination of corneal scrapings is also one of investigation methods, however, its sensitivity reaches up to 65%.

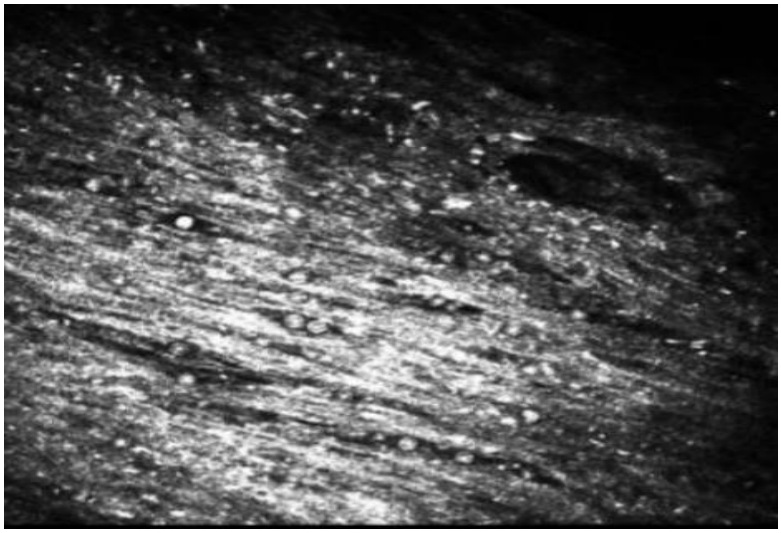


Figure 26. Confocal microscopy of the cornea showing multiple Acanthamoeba cyst

## Treatment methods

Treatment of microbial keratitis is based on medications depending on the causative agents. The surgical treatment is reserved for severe and treatment resistant cases, Keratoplasty is the surgery of choice, during which damaged cornea is removed and replaced with healthy donor tissue. Enucleation is a last resort option when all possible treatment options have already failed.

### Bacterial keratitis treatment

Pseudomonas aeruginosa is a global health burden due to its virulence, high pathogenicity and evolving antimicrobial resistance. Early diagnosis and immediate treatment are the key to successful healing. Pseudomonas form biofilms which result in resistance to antimicrobial drugs. It has been established, that around 13% of infections caused by Pseudomonas aeruginosa are multi-drug resistant, and this, in turn, results in severe and irreversible outcomes. The antimicrobial drugs effective against Pseudomonas are the following: fluoroquinolones, carbapenems and aminoglycosides. However, exposure of the bacteria to subinhibitory concentration of antimicrobial drugs can lead to more intense production of biofilms, instead of complete eradication of bacteria. The known intrinsic resistance mechanisms of Pseudomonas aeruginosa are presence of efflux pumps and low permeability of membrane. Inappropriate use of antibiotics contributes to resistance to antimicrobial drugs. Treatment of Pseudomonas keratitis is mainly conservative. As it was stated above, a number of antibiotics are considered to be effective against this bacteria. The treatment approach can be either monotherapy or combination therapy. The choice of antibiotic depends on the resistance rates in geographical location, strain of Pseudomonas, severity of the disease. For

example, tobramycin which is an aminoglycoside, has shown to be ineffective against invasive strains of Pseudomonas aeruginosa. The resistance of some strains of Pseudomonas to fluoroquinolones has to be taken into account. Pseudomonas keratitis is generally treated empirically with a frequent application of antibiotic drops. One of the possible treatment regimens is fluroquinolones like levofloxacin 0.5% or ofloxacin 0.3%. Initially the drops are introduced every 15 minutes for an hour. Later on, every hour for the next 24 hours and subsequently every other hour for upcoming 72 hours. At the end, every 4 hours for the whole week.

Apart from using corticosteroids, some doctors prescribe corticosteroids in combination with antibiotic drugs, which is a huge mistake in the treatment. Corticosteroids are contraindicated during initial treatment stages, because they inhibit bactericidal activity of antibiotics and result in the cell lysis. Topical corticosteroids can be used only when the bacterial infection has resolved. Despite that, the recurrence rates of infection are high. High dosage of antibiotics has to be prescribed if corticosteroids are used in addition to antimicrobials. Pseudomonas aeruginosa causes central corneal scarring which deteriorates patient's vision quality. The corneal graft surgery or so called "keratoplasty" is not encouraged in patients infected with Pseudomonas.

In some cases Pseudomonas can cause endophthalmitis, which is a complication of microbial keratitis resulting in enucleation and evisceration.

## Fungal keratitis treatment

The mainstay of treatment for the fungal keratitis are antifungal medications in the form of drops. In case of resistant keratitis, systemic antifungal drugs can be used. If the aforementioned treatment fails, keratoplasty is usually performed.

Fungal keratitis requires extensive and aggressive treatment. The medications themselves have a poor ability to reach the cornea. The drugs used are polyene antifungal drops like natamycin 5%. Before introduction of natamycin, amphotericin B was widely used. Nowadays it is still used and in combination with natamycin produces good outcomes. Voriconazole is available in the form of an oral pill, topical therapy and can even be injected into the cornea. Other antifungal medications, like different types of azoles and echinocandins are also being used. However, echinocandins are not effective against Fusarium keratitis. Oral Posaconazole is effective against resistant Fusarium keratitis.

The drug of first choice in case of fungal keratitis caused by filamentous fungi is natamycin 5%. Amphotericin B is suitable for yeast-like fungi. Subconjunctival injections are not

generally used because they painful and, in some cases, can lead to tissue necrosis. Subconjunctival injections are rarely used and reserved for patients with severe form of keratitis. Intravenous amphotericin B and oral fluconazole or itraconazole can be used as a systemic treatment.

Follow up of the patient has to be performed on a daily bases. Fungal keratitis has a prolonged course and the follow up of the patient might be longer. The treatment itself lasts for several weeks and can continue up to several months. Intraocular pressure should be monitored throughout the whole disease process. The ongoing epithelialization is not an indicator of a healing ulcer. In some cases, it may hinder the ongoing infection and lead to worse outcomes. Confocal microscopy is recommended to assess the ulcer during each follow-up.

Fungal keratitis is a complicated infection and conservative treatment may fail. Periodic surgical debridement can be performed every 24 to 48 hours to remove necrotic tissue. However, the main purpose of surgical debridement is enhancement of drugs' penetration into the cornea. Conjunctival flap is being performed to stop the progression of infection. If unsuccessful, lamellar or penetrating keratoplasty is performed. Moreover, scarring and opacification are possible in healed ulcer, and lamellar or penetrating keratoplasty can be performed for restoration of the vision. In case of perforation of the cornea, therapeutic keratoplasty is done. After the surgery, cornea has to be sent for evaluation by a pathologist. There are also cases of fungal keratitis, complicated by endophthalmitis, and they require intravitreal injections of antifungal agents and pars plana vitrectomy sometimes. Enucleation is the last resort therapy for patients who become blind.

After keratoplasty is performed, the patient has to be in a follow up for at least 2 weeks. The antifungal treatment has to be continued and systemic medications can be added as well. In pathological examination reveals pathogens, the treatment has to be extended,

The prognosis of fungal keratitis depends on various factors, like the degree of the penetration and infection, causative agent, time of diagnosis, response to treatment. Some patients respond to antifungal medications well and do not require any surgical intervention. On the other hand, there are patients who do not respond to therapy and they make up almost 30% of all cases. These patients need therapeutic keratoplasty to be performed. Patients developing a rare complication of fungal keratitis, endophthalmitis, have a poor prognosis. Even after successful treatment the vision of the patient is debilitated and lamellar or penetrating keratoplasty have to be performed in order to restore the vision. In complicated

and treatment-resistant cases, there is no other choice left, other than to perform either enucleation or evisceration.

Table 3. Treatment of fungal keratitis induced by filamentous and yeast-like fungi

| Filamentous fungi | Yeast-like fungi |
|---|---|
| Topical natamycin 5% | • Topical voriconazole 1%<br>• Amphotericin B 15% |

## Acanthamoeba keratitis treatment

There is no single treatment for Acanthamoeba keratitis. Treatment regimen consists from the combination of antibiotic, antiparasitic, antifungal and antiviral drugs. Combination of diamidine, biguanides, antibiotics and antifungal drugs are being used. Currently biguanides( polyhexamethylenebiguanide and chlorhexidine) and diamidine (hexamidine 0.1% and propamidine isethionate 0.1%) are considered to be the most effective drug regimen against Acanthamoeba keratitis. Drops should be introduced hourly during the day and night for the first 48 hours. After that, the dose can be diminished to every 1 hour during the day. Later on, the dose may be tapered to every 2 hours over the next 3 to 4 weeks. The subsequent treatment must be tailored according to individual case. In average, the treatment of acanthamoeba keratitis lasts for 6 months. In case of treatment resistant cases, azoles are added to biguanides and diamidines. The antifungal of choice is voriconazole in the form of drops (1%).

In cases of complicated course of infection, like corneal perforation, surgical interventions must be performed. Keratoplasty, also called corneal graft surgery, is the surgery of choice. Epithelial debridement and keratoplasty are reserved for the patients with extensive damage to the cornea or failed antimicrobial treatment. However, if active infection persists even after keratoplasty, antimicrobial treatment must be resumed, otherwise cysts may cause recurrence of infection.

Prompt diagnosis, intensive treatment and patient compliance are essential for successful therapy. The therapy usually lasts for extended periods of time. The reason for that is the cyst form of Acanthamoeba. Although trophozoites are susceptible to various drug regimens, cysts are highly resistant and they do not get destroyed during the treatment. Therefore, extensive treatment is required, otherwise the risk of infection recurrence is quite high. Patients should be under constant monitoring. The dose tapering should be done slowly and in a controlled manner. Surgical patients must be monitored as well. Post-surgical

complications include recurrent Acanthamoeba keratitis, glaucoma, cataract, wound leak, anterior synechiae and many others.

Prognosis for Acanthamoeba keratitis is substantially worse than for other types of microbial keratitis. Therefore, prevention and prompt diagnosis with extensive treatment are of utmost importance for preservation of the patient's vision.

## Conclusion

Contact lens related microbial keratitis is a serious condition, which can be caused by bacteria, fungi or parasites. Bacterial etiology accounts for most of contact lens related microbial keratitis causes, following Acanthamoeba keratitis. Overnight contact lens use and inappropriate storage of contact lenses are the major risk factors predisposing to keratitis. Clinical manifestations in all types of keratitis are more or less the same, with some characteristic pathognomonic signs for each one. Prompt diagnosis is a key for successful resolution of keratitis. Treatment with appropriate medications depending on the etiology is the first treatment option. Complicated cases can require keratoplasty, and in some cases even enucleation.

## Suggestions

Patients must be educated about the proper storage of contact lenses, hygiene rules and risks of prolonged contact lens wear. Patients should refer to doctors promptly. Diagnosis and therapy should be initiated as fast as possible to treat the condition. Usage of glasses should be encouraged. Patients can be advised to undergo refractive surgery as not to wear contact lenses.

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