Difficult-to-treat Fungal Infections: The Eye

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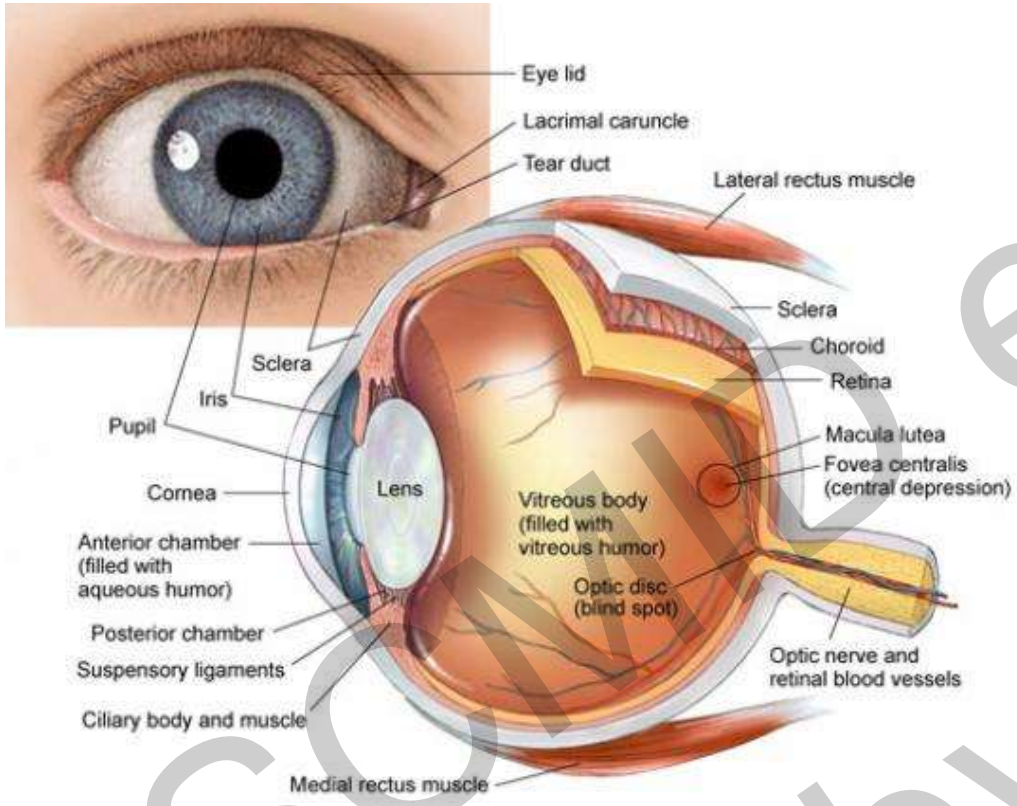
Fungal Infections of the Eye

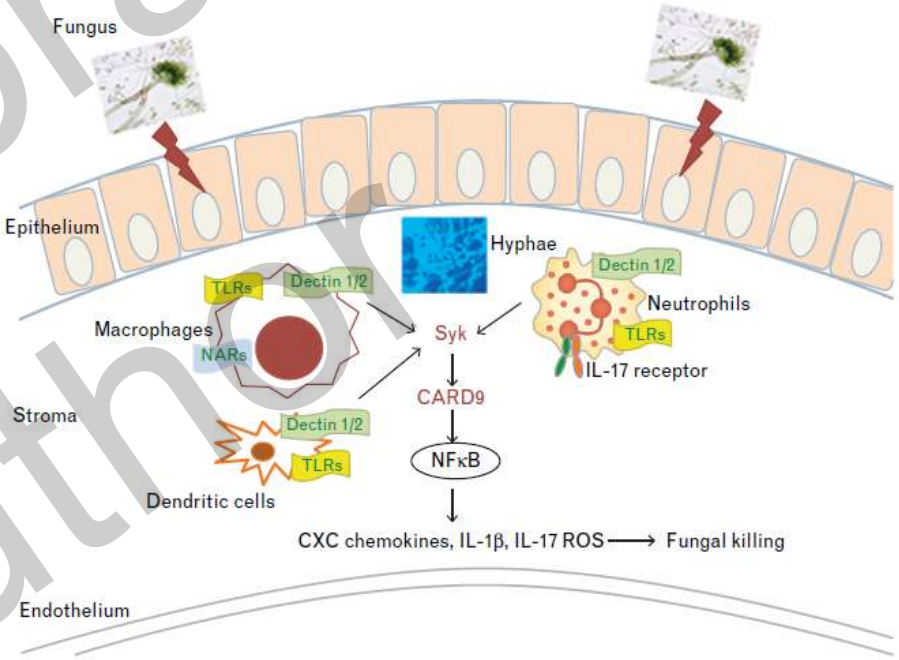


Internal Anatomy of The Eye

- most common:
  - cornea and retina/vitreous
  - rare or very rare:
    - lacrimal apparatus, conjunctiva, eyelids, orbital fungal infections
- increased incidence of ocular fungal infections over the past decades
  - increased clinical awareness
  - improved laboratory techniques
  - widespread use of corticosteroids, antibiotics, immunosuppressants, chemotherapeutic drugs

Mycotic keratitis (keratomycosis)

- important infection of the cornea
  - usually manifested by severe inflammation and the formation of a corneal ulcer
  - corneal ulceration is the second most common cause of blindness after cataract (worldwide)
    - mycotic keratitis constitutes 6 to 53% of all cases of corneal ulcers
    - strong geographical influence
    - major blinding eye disease in Asia



Gerg et al Curr Opin Ophthalmol 2016

Mycotic keratitis – Risk Factors

- **trauma**:
  - corneal injury with organic material
- **contact Lens**:
  - improper lens hygiene or chronic epithelial defects
  - bacterial infections associated fungal keratitis almost always due to *Candida* species
- **ocular surface disease:**
  - dry eye, chronic epithelial defects, neurotrophic keratitis, atopy
    - insufficient tear secretion, defective eyelid closure
    - 20% to 40% of fungal keratitis [1,2]
- **topical corticosteroid use:**
  - 7% to 21% of fungal keratitis (United States, developing countries) [1,2,3]

1. Ritterband DC, et al. Cornea. 2006;25
2. Tanure MA, et al. Cornea. 2000;19
3. Chowdhary A, Singh K. Cornea. 2005;24

Mycotic keratitis - Epidemiology

- more than 70 different fungal species reported to be pathogenic to human cornea
- wide geographic variation
- keratitis due to filamentous fungi:
  - usually after trauma with fungus-contaminated plant material in agricultural workers
    - e.g. South India: most common fungal pathogens *Fusarium* (37.2-47.1%) and *Aspergillus* (16.1- 30.7%) [1,2]
  - relatively infrequent in temperate climates
  - principal causes: species of *Fusarium*, *Aspergillus*, *Curvularia* and other phaeohyphomycetes, *Scedosporium apiospermum* and *Paecilomyces*
- keratitis due to yeast-like and related fungi:
  - almost always due to *Candida* species

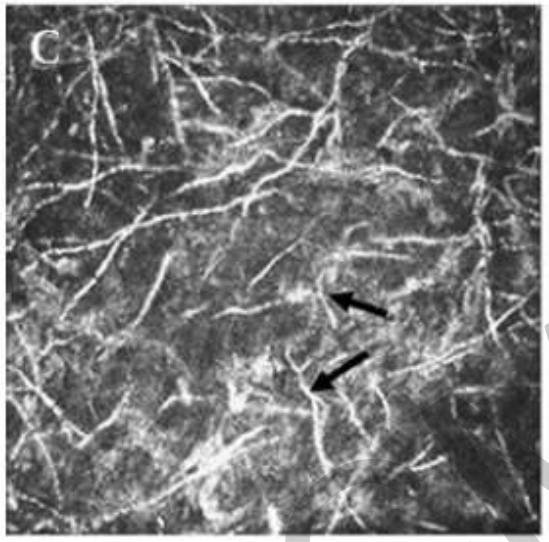
1. Srinivasan M, et al. Br J Ophthalmol. 1997;81.
2. Gopinathan U, et al. Cornea. 2002;21.

Mycotic keratitis - clinical presentation

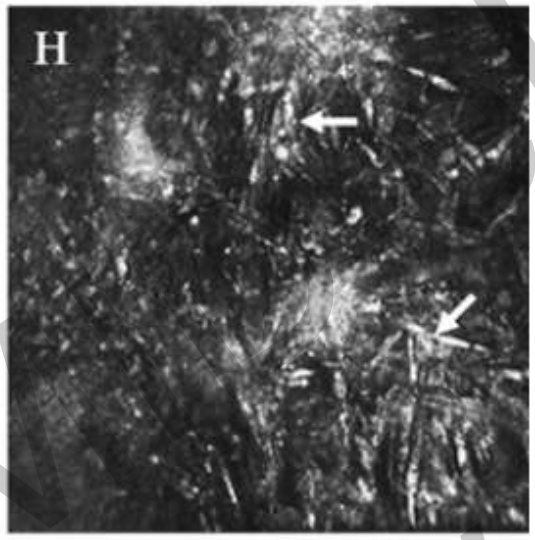
- typical **clinical presentation**:
  - elevated margins, multifocal granular grey-white ‘satellite’ stromal infiltrates
  - variations depending on the aetiological agent
  - yeast-like and related fungi usually resemble bacterial keratitis
- **symptoms** similar to any corneal infection:
  - blurred vision, redness, tearing, photophobia, pain, foreign body sensation
  - ~60% hypopyon
  - possibly more prolonged in duration (5–10 days) and rather indolent
- protraced course of fungal infections
  - delay of diagnosis and treatment
  - untreated or treatment-resistance:
    risk of corneal perforation and endophthalmitis

Mycotic keratitis – Diagnostics *in vivo*

confocal microscopy



(C) fungal hyphae

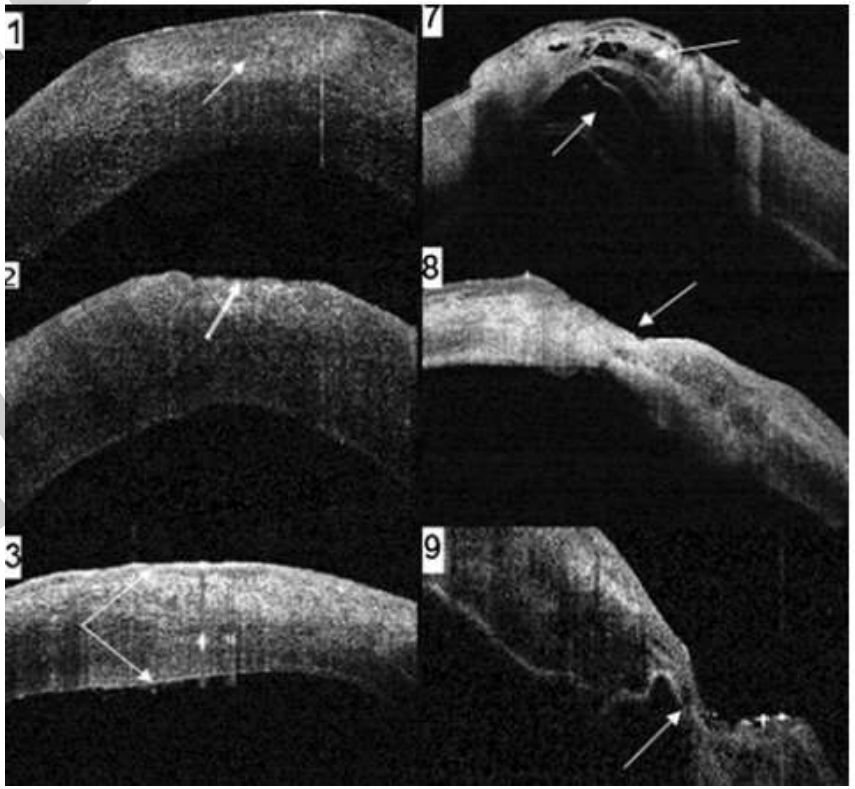


(H) cultured bacteria

Hau SC, et al. Br J Ophthalmol 2010.

-direct examination of the organism, inflammation, and corneal stromal cells
-to follow success or failure of therapy

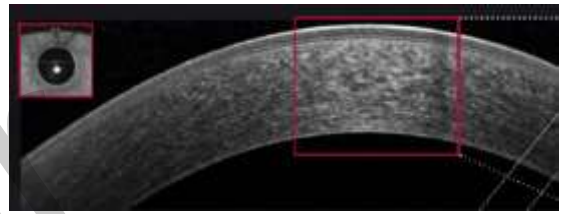
anterior segment optical coherence tomography



Soliman W, et al. Graefes Arch Clin Exp Ophthalmol 2012.

Mycotic keratitis - Diagnostics

- In vitro diagnosis using conventional microbiological methods:
  - Material collected using a corneal spatula or blade:
    - Scraping of base and edges of the ulcerated part of the cornea inoculated on culture plates



- In vitro diagnosis using molecular tools:
  - PCR requires only a small quantity of sample (ideal for corneal scrape material)
    - targets fungal ribosomal DNA regions
    - high sensitivity , rapid diagnosis, accurate species identification
    - increased risk of contamination, no sensitivity testing
  - good agreement between results obtained using conventional tests and using PCR [1]

1. Embong Z, et al. BMC Ophthalmol 2008

Mycotic keratitis – Topical Treatment

- **Topical** natamycin (5%), econazole (1%), amphotericin B (0.15–0.5%), flucytosine (1%), clotrimazole (1%), miconazole (1%), ketoconazole (1–2%), itraconazole (1%), fluconazole (0,2%), voriconazole (1–2%) and caspofungin (0.5%)
- limited access - special order
- preparation of eye drops by a compounding pharmacy:
  - diluted intravenous antifungal agents
  - requiring storage at 2-8°, usable 7 days
  - concentration to provide enough medication to eradicate the organism and at the same time is tolerated by the eye
- can cause toxicity (punctate keratitis, corneal epithelial erosions)

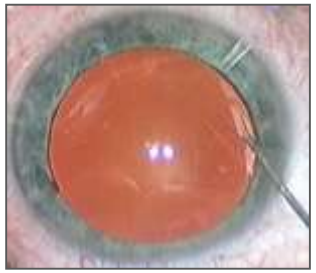
Mycotic keratitis – Topical Treatment

- in general poor penetration into the corneal stroma
  - periodic epithelial debridement recommended to achieve higher corneal stromal concentration
  - initially hourly application, dosage gradually reduced over several weeks
- **Natamycin** (5%) long-time first-line therapy for filamentous fungal keratitis
  - primary treatment failure in 31.3% of cases (115 patients [1])
- resistances against older azoles (Clotrimazol, Miconazol, Ketoconazol oder Itraconazol)
- **Fluconazol**: first choice against *Candida albicans*
- **Voriconazol**: broad antifugal spectrum (all *Candida* species, *Cryptococcus spp., Aspergillus, etc)*
- **Posaconazol**: broad antifugal spectrum including Aspergillen, *Candida sp., Fusarium sp., Zygomyzeten*; case reports of success in refractory cases
- concomitant use of corticosteroids to reduce destructive effects of immune defense
  - no negative effect of topical corticosteroids after initiation of antifungal therapy [2]

1. Lalitha P, et al. Ophthalmology 2006; 113.
2. Schreiber W etal (2003) *InvestOphthalmol Vis Sci 44*

Mycotic keratitis – treatment

- **intrastromal/ subconjunctival** injection of voriconazole and amphotericin B
  - not recommended, severe pain, tissue necrosis possible
- **intracameral** (anterior chamber)
  - voriconazole: no side effects of 10 µg/0,1 ml, rinsing with 3 µg/ml [1]
  - amphotericin B: good tolerance of repeated injections (7,5 µg) [2]
- **intravitreal** (vitreous)
  - voriconazole (100 µg/0,1 ml) or amphotericin B (7,5 µg)
- **systemic** antifungal treatment:
  - for deeper and larger lesions



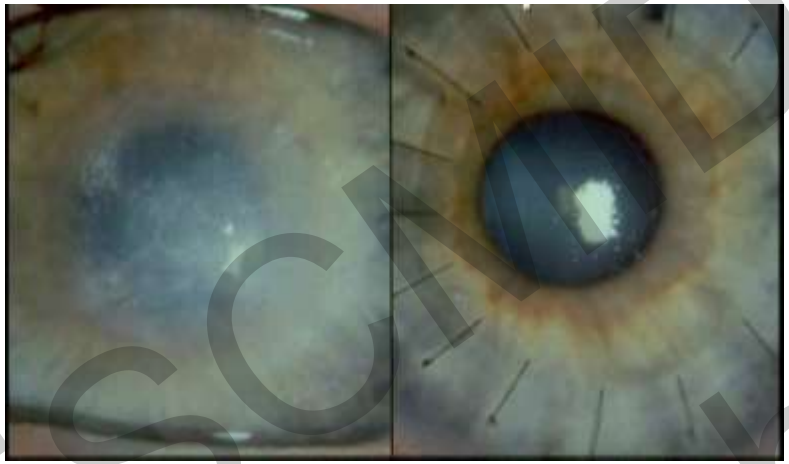
1. Reis A etal (2000) Br J Ophthalmol 84:932
2. Chapman F, etal (1998) *Br J Ophthalmol 82*

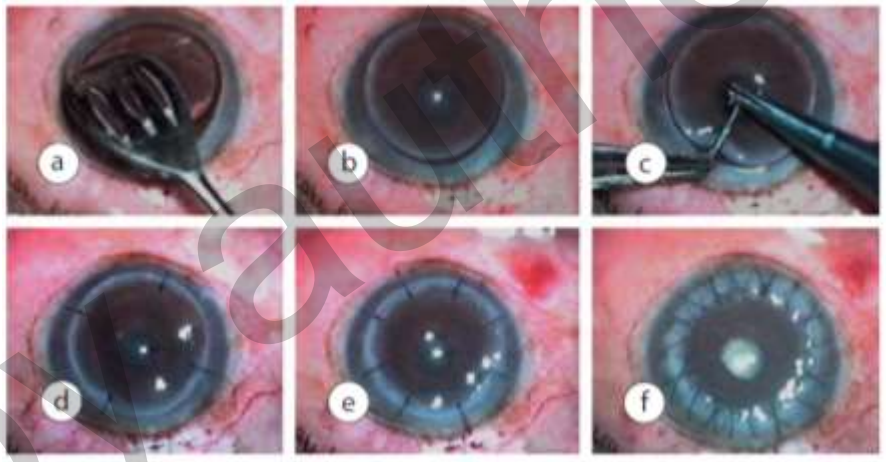
Mycotic keratitis – Treatment *Evidence*

- FlorCruz NV, Evans JR, Review Cochrane Database, Medical interventions for fungal keratitis (2015):
  - voriconazole, econazole, itraconazole, miconazole, natamycin, amphotericin B, chlorhexidine gluconate and silver sulphadiazine
    - Administered topically, intravenously, orally
  - in general low quality of evidence
  - exception comparison of natamycin and voriconazole: high quality of evidence from three trials that natamycin achived better outcomes than voriconazole (lower risk of corneal perforation) – attributable to improved results in *Fusarium* cases

Mycotic keratitis – Surgical Treatment

- Keratoplasty (corneal transplant)
  - for acute management of corneal perforation
    - unfavorable outcome in emergency setting
  - for visual rehabilitation following corneal scarring





Kanski Klinische Ophthalmologie 5. Auflage

Endophthalmitis

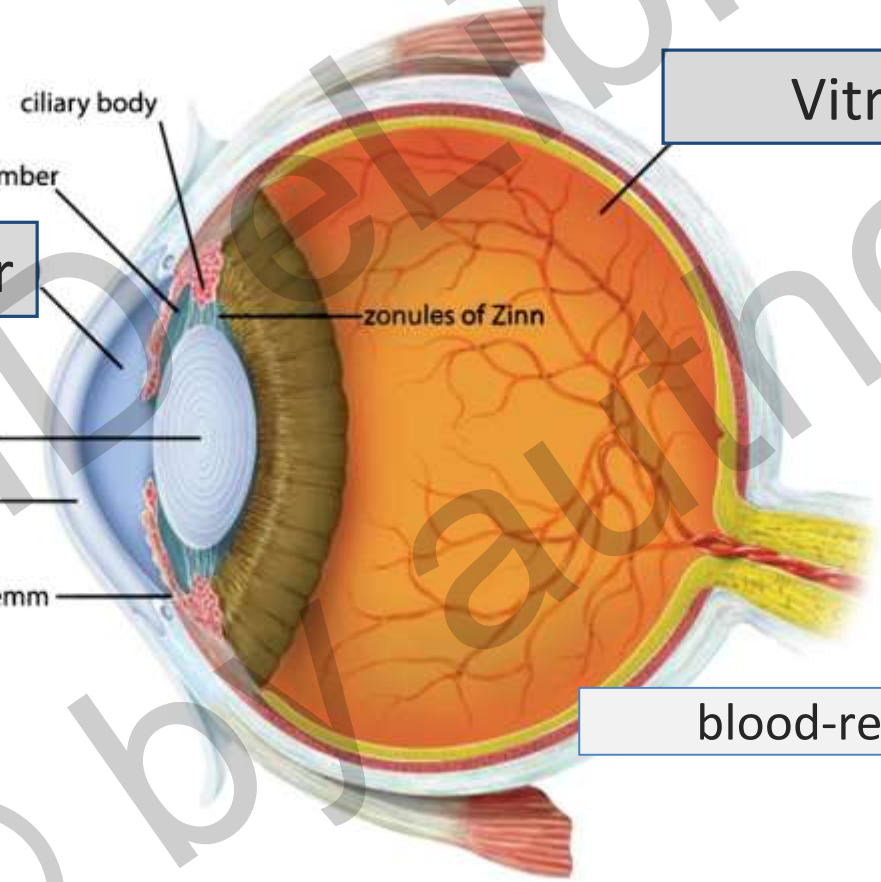
- infection of the vitreous and/or aqueous by bacteria and fungi

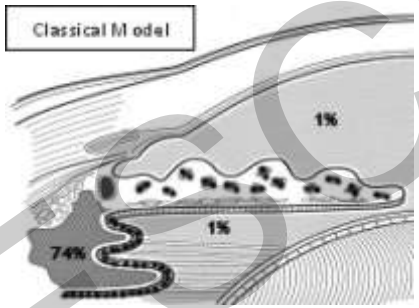
Vitreous

Anterior chamber

blood-aquous barrier

blood-retina-barrier





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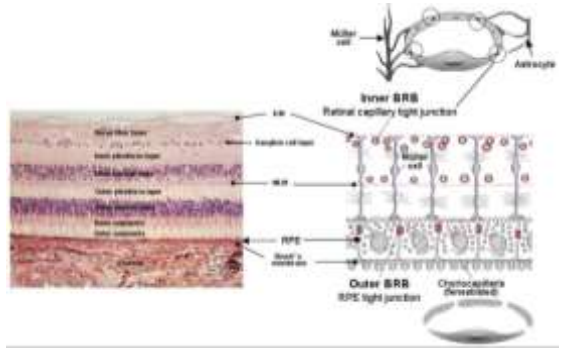

from: www.mdpi.com

Endophthalmitis

- infection of the vitreous and/or aqueous by bacteria and fungi
- severe eye infection – medical emergency
- permanent loss of useful vision possible
  - within hours or days of symptom onset
- rare disease, incidence varies by caegory:
  - after cataract surgery <0,1%
  - after penetrating eye trauma 1-18%

Endophthalmitis

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Bacterial and Fungal Endophthalmitis

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TABLE 1 Major categories of endophthalmitis

Category	Risk factor	Relative frequency (% of all endophthalmitis cases)	Major pathogens
Acute postcataract	Cataract surgery	40–80	Coagulase-negative staphylococci (70% of cases), *Staphylococcus aureus* (10%), streptococci (9%)
Postinjection	Intravitreal injection	0–50	Coagulase-negative staphylococci, streptococci
Posttraumatic	Penetrating eye trauma	2–15	Coagulase-negative staphylococci, *Bacillus*, streptococci, Gram-negative bacilli, fungi
Bleb related	Filtering bleb (for glaucoma)	0–5	*Streptococcus pneumoniae* and other streptococci, enterococci, *Haemophilus influenzae*
Keratitis related	Corneal infection	0–10	Fungi (*Aspergillus*, *Fusarium*) in 50%, *S. aureus*, streptococci, *Pseudomonas*
Endogenous	Bacteremia or fungemia	0–20	*Klebsiella pneumoniae* (especially in East Asian nations), *Candida*, streptococci, *S. aureus*, *Escherichia coli*

Exogenous Endophthalmitis

- Postoperative:
  - fungal endophthalmitis rare except in tropical regions (e.g. India 10-20% [1])
  - postkeratoplasty: 31% fungi (mostly *Candida*) (UK [2])
- Postinjection:
  - use of intravitreal injections (e.g. anti-VEGF) rapidly increased since 2004
  - risk of endophthalmitis ~0.05% per injection [3]; microbiology similar to postcataract
- Keratitis-related:
  - ~0.5% of keratitis progressed to endophthalmitis, fungal keratitis as a risk factor [4]
  - 53% due to molds (*Fusarium* and *Aspergillus*) [5]
- Post traumatic:
  - often mixed infctions (42% [6])
  - fungal in 10-15% [7], late onset (weeks to months after trauma)

1. Sharma S, et al. 2015. J Cataract Refract Surg 41.
2. Chen JY, et al, Ophthalmology 122:25–30.
3. Fileta JB, et al. 2014. Ophthalmic Surg Lasers 45.
4. Henry CR, et al. 2012. Ophthalmology 119.
5. Shen YC, et al. 2010. Am J Ophthalmol 149.
6. Boldt, H. C., et al. Ophthalmology 96, 1989
7. Meredith T.A Retina. Mosby Year Book Inc 3, St. Louis 2001

Exogenous Endophthalmitis

Exogenous fungal endophthalmitis

- any saprophytic fungi found in natural habitats may cause exogenous infection of the eye
  - mainly *Candida* species especially in the postsurgical group
  - *Fusarium* species especially in posttraumatic and postkeratitis patients
  - *Paecilomyces, Aspergillus, Acremonium, Exophiala, Pseudallescheria, Scytalidium, Sporothrix,* and *Penicillium species*
  - fungal pathogens in posttraumatic endophthalmitis are numerous and similar to those causing fungal keratitis
    - *Exophiala jeanselmei, P. boydii, A. niger, Scytalidium dimidiatum, Helminthosporium spp., S. schenckii,* and *Penicillium chrysogenum*

Endogenous Endophthalmitis

- metastatic spread of infection from a distant site
  - usually immunocompromised patients
    - predisposing factors: chronic indwelling catheters, intravenous hyperalimantation, malignancy, diabetes mellitus, hemodyalisis, organ transplant, neutropenia, IVDU, AIDS, pulmonary disease, hepatic insufficiency, postpartum
  - but can occur also in apparently healthy people
    - late onset of infection
    - high misdiagnosing rate [1]
    - specific nidus of infection not always found
- bilateral infection ~ 60% [2]

1. Greenwald, M. J., et al. Surv Ophthalmol 31, 1986.
2. 2. Schiedler V, et al. Am J Ophthalmol. 2004;137.

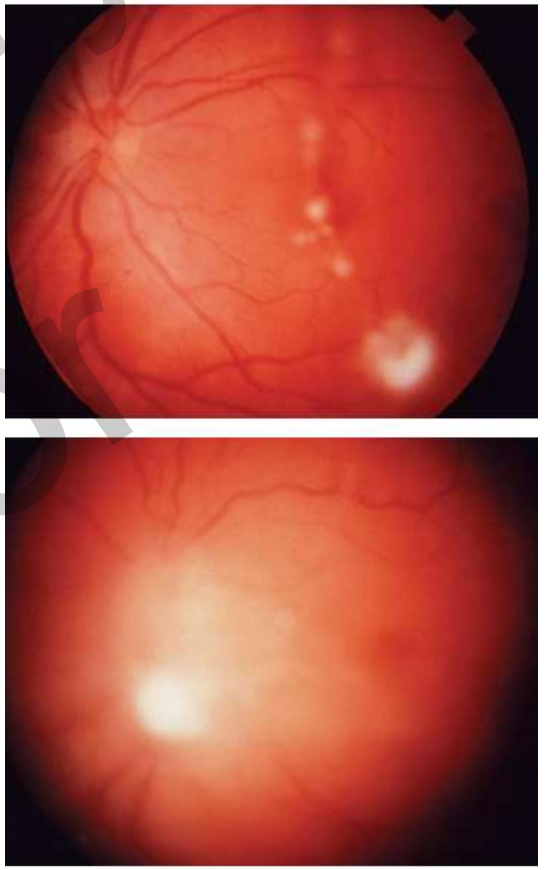
Endogenous Fungal Endophthalmitis

- fungi account for >50% of endogenous endophthalmitis [1,2]
  - *Candida* 34-36%, slower progression, overall better prognosis
  - *Aspergillus* ~10%
  - *Candida (C. albicans, C. tropicalis, C. parapsilosis), Aspergillus (A. fumigatus, A. flavus), Pseudallescheria boydii, Cryptococcus neoformans, Histoplasma capsulatum, Fusarium, Penicillium, Blastomyces, Coccidioides, Sporothrix*
- coincident systemic infection in 80% of patients with EFE [3]
- fungemic patients (positive blood culture):
  - clinically diagnosed EFE in 2.4-9% [4,5]
  - ocular candidiasis incidence <2% [6]
    - decreasing incidence
    - maybe related to earlier identification and treatment of candidemia

1. Binder MI, et al. Medicine. 2003;82.
2. Schiedler V, et al. Am J Ophthalmol. 2004;137.
3. McDonnell PJ, et al. Ophthalmology. 1985;92.
4. Tanaka M, et al. Retina. 2001;21.
5. Donahue SP, et al. Ophthalmology. 1994;101.
6. Feman SS, et al. Trans Am Ophthal Soc 2002;100.

Endogenous *Candida* endophthalmitis

- haematogenous seeding of choroid and retina
- may be clinically silent
  - until significant vitritis
  - until late in the infection
  - if candidemic patients too ill to relay visual symptoms
- patients with candidemia: [1, 2]
  - chorioretinitis in 8-11%
  - endophthalmitis in 0-1.6%
  - risk factors for ocular involvement:
    C. albicans species, inability to articulate visual symptoms
- funduscopic examinations in patients with candidemia
  - if unremarkable: subsequent retinal examination after 2 weeks [1]
- outpatients (e.g. after gastrointestinal procedures)
- candidemia transient, negative blood cultures

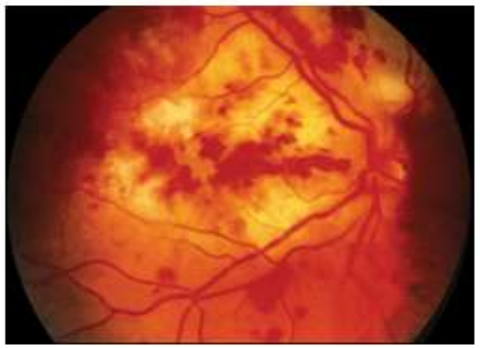


Initial manifestation focal chorioretinitis, subsequent spread into the vitreous cavity

1. C P Shah, et al *Br J Ophthalmol 2008:92*
2. Oude Lashof AM, et al 2011. Clin Infect Dis 53:262.

Endogenous mold endophthalmitis

- rare, seen primarily in immunocompromised patients
  - hematologic malignancies, transplant recipients, IVDU
- *Aspergillus* and *Fusarium* major pathogens
  - *Aspergillus flavus, A. fumigatus, A. niger, A. terreus, A. glaucus, and A. nidulans; Fusarium, Penicillium, Pseudallescheria, Cryptococcus species, dimorphic fungi Histoplasma capsulatum, Blastomyces dermatitis, Sporothrix schenckii, Coccidioides immitis*
  - tends to present more acutely than *Candida* and to progress more rapidly
  - tendency for causing macular scaring, low visual prognosis



Endophthalmitis – Clinical Features

- most common symptom: decreased vision
- eye pain or discomfort, red eye: not universal complaints
- onset:
  - bacterial: usually acute (within days)
  - fungal: typically subacute, symptoms worsening over days or weeks
  - depending on the pathogen

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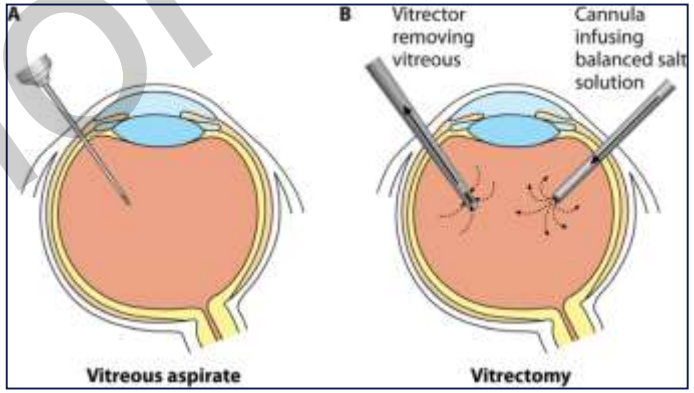
Endophthalmitis - Diagnosis

- endophthalmitis is a clinical diagnosis
  - supported by culture of the vitreous and/or aqueous
  - supported also by blood cultures in endogenous endophthalmitis
  - conjunctival or corneal cultures useless
- negative cultures do not exclude the diagnosis
  - ~20-30% of cases culture negativ
  - cultures are positive in [1]
    - 90% of vitrectomy specimens
    - 50-70% of vitreous aspirates
    - 40% of aquous aspirates

1. Durand Clinical Microbiology Reviews 2017

Endophthalmitis - Diagnosis

- sampling and culture techniques
  - aqueous is liquid, ~0.3ml, continuously regenerated (turnover of 100min)
    - needle aspiration: ~0.1ml
  - vitreous is a gel, ~4ml
    - needle aspiration: difficult to aspirate a gel, ~0.2-0.3ml
    - vitrectomy: surgical removal, operating room (PBA/GA)
- molecular diagnostic techniques
  - several types of PCR testing
    - studies mostly focused on bacterial pathogens
    - fungi detected by targeting the common ribosomal 18S/28S DNA sequence
  - in general: PCR and conventional culture methods complementary



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Treatment of Endogenous fungal endophthalmitis

- highly variable penetration of systemically administered antifungal agents
  - breakdown of barriers in inflamed eyes: higher concentrations in infected eyes
- Amphotericin B:
  - *systemic* administation:
    - relatively poor penetration into the vitreous (lipisomal AmB > AmB-d)
    - failures are common, toxicity of drug [1]
  - *intravitreal* application:
    - dose range from 5 to 10µg AmB-d without retinal toxicity [2,3]
    - adjunctive therapy (*Candida* species and *Aspergillus*)
- Flucytosine:
  - achieves high levels in all intraocular compartments [4]

1. Schmid S, et al Infection 1991; 19..
2. Weishaar PD, et al. Ophthalmology 1998; 105.
3. Essman TF,, et al. Ophthalmic Surg Lasers 1997; 28.
4. Walsh A, et al. Invest Ophthalmol Vis Sci 1978; 17.

Treatment of Endogenous fungal endophthalmitis

- Fluconazole:
  - levels in vitreous 70% of plasma levels [1]
  - few studies about intravitreal use
    - usually sole agents in chorioretinitis, in more advanced disease combined with e.g. intravitreal AmB +/- vitrectomy
- Voriconazole:
  - in humans: levels in vitreous 38% of plasma levels (non-inflamed eyes) [2]
  - *intravitreal* injection:
    - no toxic effects <25 µg/ml
    - advantage of voriconazole against fluconazole:
      - activity against *Aspergillus* species and fluoconazole resistant *Candida* species *(glabrata, krusei)*

1. Tod M, et al. Clin Microbiol Infect 1997; 3.
2. Hariprasad SM, et al. Arch Ophthalmol 2004; 122.

Treatment of Endogenous fungal endophthalmitis

- newer antifungal agents like posaconazole, echinocandins, micafungin, caspofungin, anidulafungin
  - poor ocular penetration [1]
  - in general not recommended for use in endophthalmitis [2]
  - posaconazole:
    - case reports about success in Fusarium keratitis and endophthalmitis
    - maybe alternative option in cases of intolerance to other antifungal agents
  - echinocandines:
    - successful case reports as well as treatment failures about caspofungin in *Candida* endophthalmitis, may act synergistically with voriconazole against Aspergillus [3]

1. Groll AH, et al. Antimicrob Agents Chemother 2001; 45.
2. James Riddell et al. Clinical Infectious Diseases 2011
3. Marr KA, et al. Clin Infect Dis 2004;39.

Ocular efficacy: Laboratory models

- Marangon FB et al: In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. Am J Ophthalmol 2004; 137:820-5

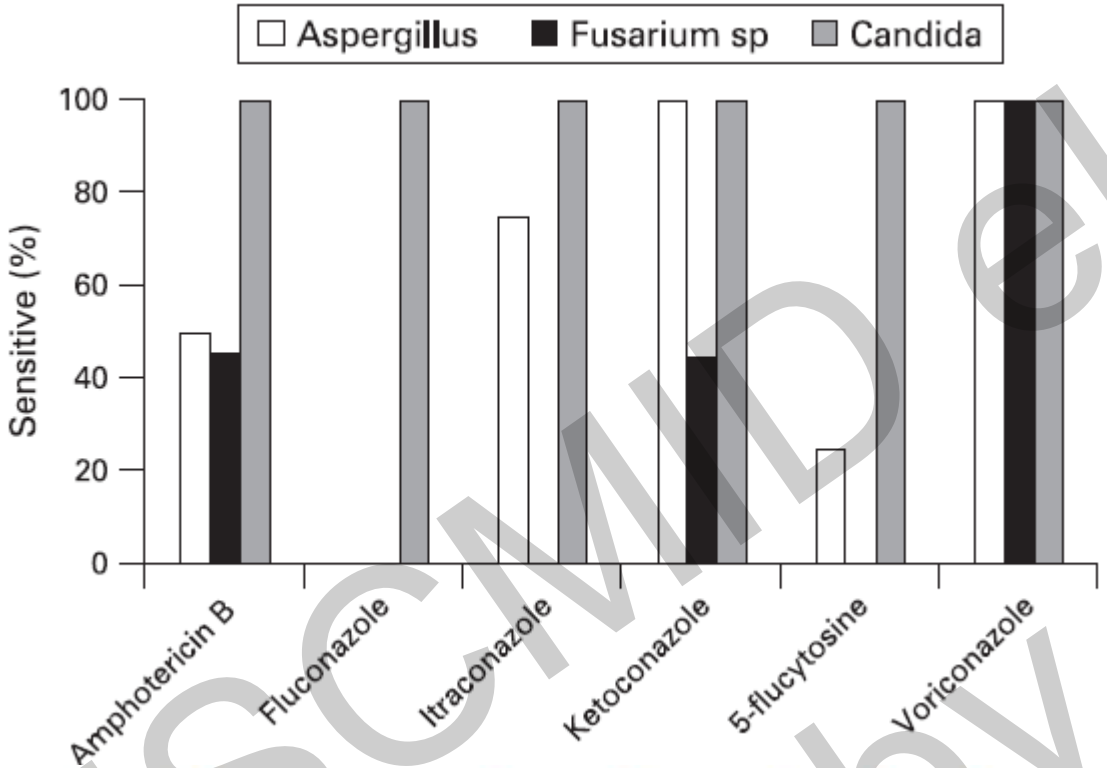

Figure 1 General susceptibilities of fungi isolates (*Aspergillus* species, n = 4; *Fusarium* species, n = 9; *Candida* species, n = 20) to amphotericin B, fluconazole, ketoconazole, 5-flucytosine, itraconazole and voriconazole. Reprinted from Marangon FB *et al*. In vitro

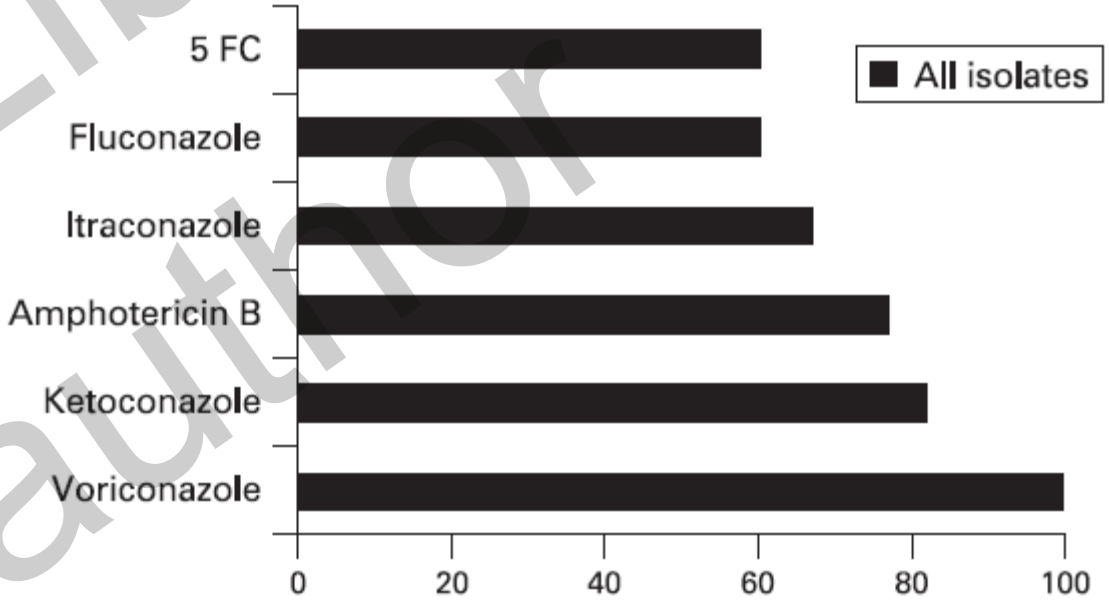

Figure 2 General in vitro susceptibility profiles of all isolates for each antifungal drug using a commercially available microdilution antifungal susceptibility test (Sensititre YeastOne, TREK Diagnostics, Cleveland,

ISDA Guidelines 2016: *Candida* endophthalmitis

General Approach

- 82. **All patients with candidemia should have a dilated retinal examination**, preferably performed by an ophthalmologist, **within the first week of therapy** in nonneutropenic patients **to establish if endophthalmitis is present**. For neutropenic patients, it is recommended to delay the examination until neutrophil recovery.
- 83. The extent of ocular infection (chorioretinitis with or without macular involvement and with or without vitritis) should be determined by an ophthalmologist .
- 84. Decisions regarding antifungal treatment and surgical intervention should be made jointly by an ophthalmologist and an infectious diseases physician .

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America.Pappas PG et al. Clin Infect Dis. 2016

ISDA Guidelines 2016: *Candida* endophthalmitis

Treatment for Candida ***Chorioretinitis Without Vitritis***

- 85. For **fluconazole-/voriconazole-susceptible** isolates, **fluconazole**, loading dose, 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) daily **OR voriconazole**, loading dose 400 mg (6 mg/kg) intravenous twice daily for 2 doses, then 300 mg (4 mg/kg) intravenous or oral twice daily is recommended.
- 86. For **fluconazole-/voriconazole-resistant** isolates, **liposomal AmB**, 3–5 mg/kg intravenous daily, **with or without oral flucytosine**, 25 mg/kg 4 times daily is recommended.
- 87. With **macular involvement**, antifungal agents as noted above **PLUS intravitreal injection** of either **AmB deoxycholate**, 5–10 µg/0.1 mL sterile water, **or voriconazole**, 100 µg/0.1 mL sterile water or normal saline.

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America.Pappas PG et al. Clin Infect Dis. 2016

ISDA Guidelines 2016: *Candida* endophthalmitis

Treatment for Candida ***Chorioretinitis With Vitritis***

- 89. Antifungal therapy **as detailed above** for chorioretinitis without vitritis, **PLUS intravitreal injection** of either **amphotericin B deoxy**cholate, 5–10 µg/0.1 mL sterile water, or **voriconazole**, 100 µg/0.1 mL sterile water or normal saline is recommended.
- 90. **Vitrectomy should be considered** to decrease the burden of organisms and to allow the removal of fungal abscesses that are inaccessible to systemic antifungal agents.

- 88.+91. The **duration of treatment** should be **at least 4–6 weeks**, with the final duration dependent on resolution of the lesions as determined by repeated ophthalmological examinations.

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America.Pappas PG et al. Clin Infect Dis. 2016

ISDA Guidelines 2016: *Aspergillus* endophthalmitis

- Recommendation 51
  - We recommend that Aspergillus endophthalmitis be treated with **systemic oral or intravenous voriconazole plus intravitreal voriconazole or intravitreal AmB** deoxycholate (strong recommendation; weak-quality evidence).

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Thomas F. Patterson et al. Clin Infect Dis. 2016

Treatment of Fungal Endophthalmitis

- suspected fungal endophthalmitis
  - systemic agents: [1]
    - voriconazole: broad-spectrum antifungal
      - in cases of unclear etiology
    - fluconazol: if suspected *Candida albicans*
    - alternative: itraconazole, amphotericin B
  - intravitreal agents
    - recommended for sight-threatening macular involvement and vitritis
    - compounding pharmacy needed
    - voriconazole (100µg) or AmB-d (5-10µg)
      - voriconazole might be safer, AmB-d longer half-life after intravitreal injection

1. Leitlinie zur Prophylaxe und Therapie von Endophthalmitiden DGII 2005

Treatment of Fungal Endophthalmitis

- vitrectomy:
  - diagnostic and therapeutic purpose
    - sampling of vitreous for culture data to guide treatment
    - decreases the overall burden of organisms
      - recommended for severe and sight-threatening cases
  - usually combined with administration of intravitreal antifungal agents
  - intravitreal half-life time of antifungal agents shortened in vitrectomized eyes
- duration of therapy
  - dependent on response observed in repeated ophthalmologic examinations
  - IDSA guidelines: at least 4-6 weeks

Thank you! Questions?

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