Difficult-to-treat Fungal Infections: The Eye

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Fungal Infections 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]

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

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


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

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]

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°C, 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 antifungal spectrum (all *Candida* species, *Cryptococcus* spp., *Aspergillus*, etc)
• **Posaconazol**: broad antifungal 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]

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


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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 achieved 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
Endophthalmitis

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

Aus: Freddol ExpEyeRes 2010

blood-aqueous barrier

blood-retina-barrier

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 category:
  - after cataract surgery <0.1%
  - after penetrating eye trauma 1-18%
# Endophthalmitis

## Bacterial and Fungal Endophthalmitis

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### TABLE 1 Major categories of endophthalmitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factor</th>
<th>Relative frequency (% of all endophthalmitis cases)</th>
<th>Major pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute postcataract</td>
<td>Cataract surgery</td>
<td>40–80</td>
<td>Coagulase-negative staphylococci (70% of cases), <em>Staphylococcus aureus</em> (10%), streptococci (9%)</td>
</tr>
<tr>
<td>Postinjection</td>
<td>Intravitreal injection</td>
<td>0–50</td>
<td>Coagulase-negative staphylococci, streptococci</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td>Penetrating eye trauma</td>
<td>2–15</td>
<td>Coagulase-negative staphylococci, <em>Bacillus</em>, streptococci, Gram-negative bacilli, fungi</td>
</tr>
<tr>
<td>Bleb related</td>
<td>Filtering bleb (for glaucoma)</td>
<td>0–5</td>
<td><em>Streptococcus pneumoniae</em> and other streptococci, enterococci, <em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Keratitis related</td>
<td>Corneal infection</td>
<td>0–10</td>
<td>Fungi (<em>Aspergillus, Fusarium</em>) in 50%, <em>S. aureus</em>, streptococci, <em>Pseudomonas</em></td>
</tr>
<tr>
<td>Endogenous</td>
<td>Bacteremia or fungemia</td>
<td>0–20</td>
<td><em>Klebsiella pneumoniae</em> (especially in East Asian nations), <em>Candida</em>, streptococci, <em>S. aureus</em>, <em>Escherichia coli</em></td>
</tr>
</tbody>
</table>
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 infections (42% [6])
  - fungal in 10-15% [7], late onset (weeks to months after trauma)

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 hyperalimentation, malignancy, diabetes mellitus, hemodyalisis, organ transplant, neutropenia, IVDU, AIDS, pulmonay 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]

Endogenous Fungal Endophthalmitis

- fungi account for >50% of endogenous endophthalmitis [1,2]
  - *Candida* 34-36%, slower progression, overall better prognosis
  - *Aspergillus* ~10%

- 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

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

- fundusscopic 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

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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
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 negative
  • cultures are positive in [1]
    • 90% of vitrectomy specimens
    • 50-70% of vitreous aspirates
    • 40% of aqueous aspirates

1. Durand Clinical Microbiology Reviews 2017

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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
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 administration:
    - relatively poor penetration into the vitreous (liposomal 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 \(^{[4]}\)

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 fluconazole resistant Candida species (glabrata, krusei)

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 \[3\]

2. James Riddell et al. Clinical Infectious Diseases 2011
Ocular efficacy: Laboratory models


**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.
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.

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 deoxycholate, 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.

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).

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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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