



# An Update on Fungal Keratitis

Course 35: Infectious keratitis.



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- ▶ Patients do not come classified
- ▶ Overlap in the clinical picture
- ▶ Poly microbial infection
- ▶ Know the limits of the clinical judgment.
- ▶ Know the limits of the lab tests.

## Clinical Picture

- ▶ Raised surface
- ▶ Hyphate margin
- ▶ Immune ring
- ▶ Endothelial plaque
- ▶ Satellite lesions
- ▶ Clotted hypopion



## Case 1

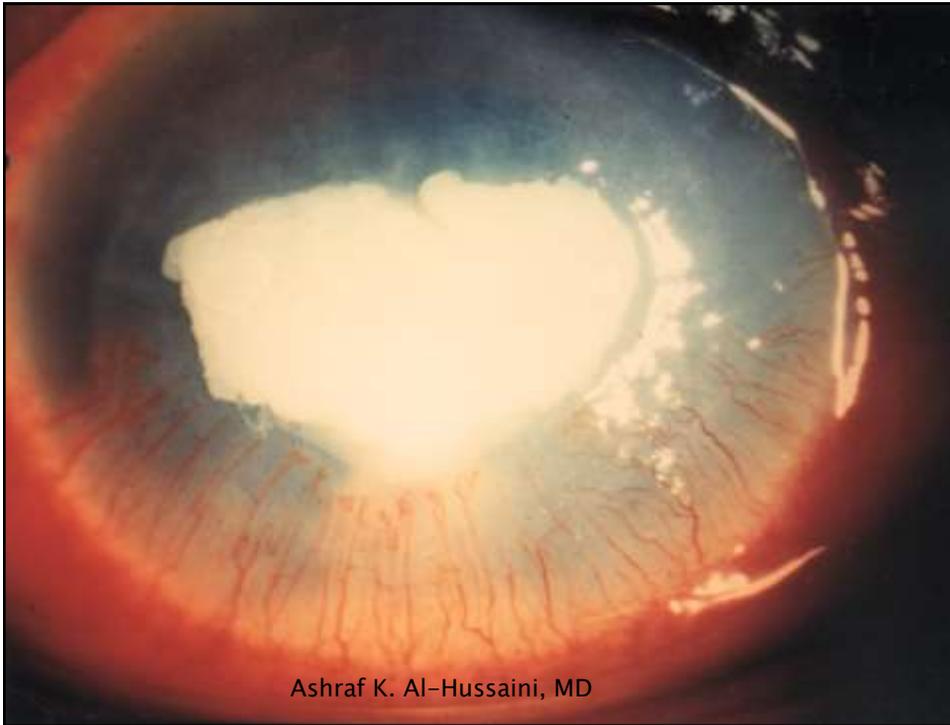


Front view



Slit view



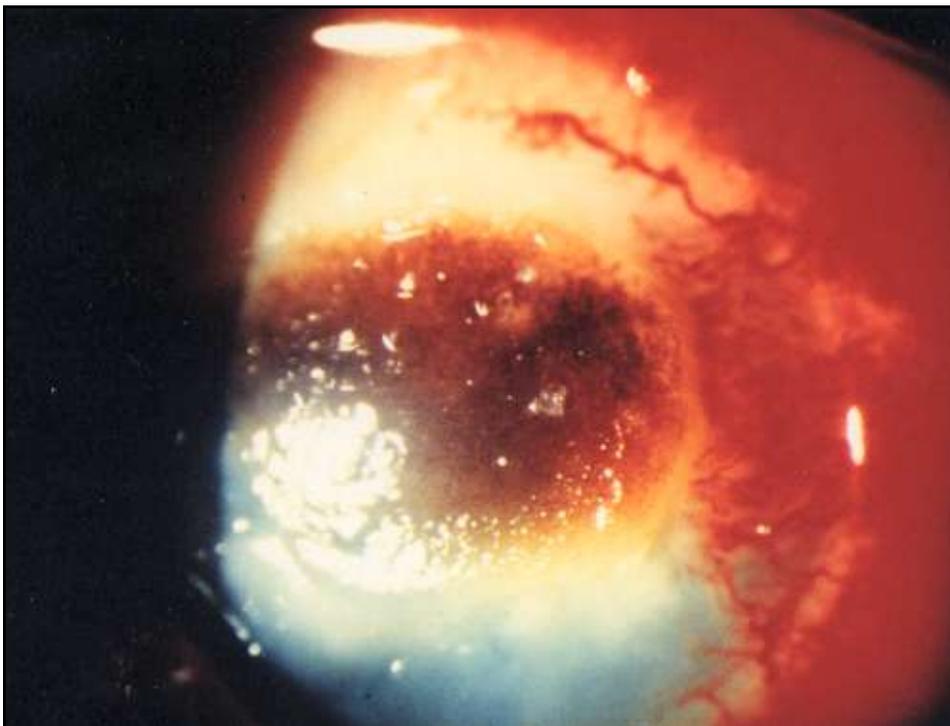
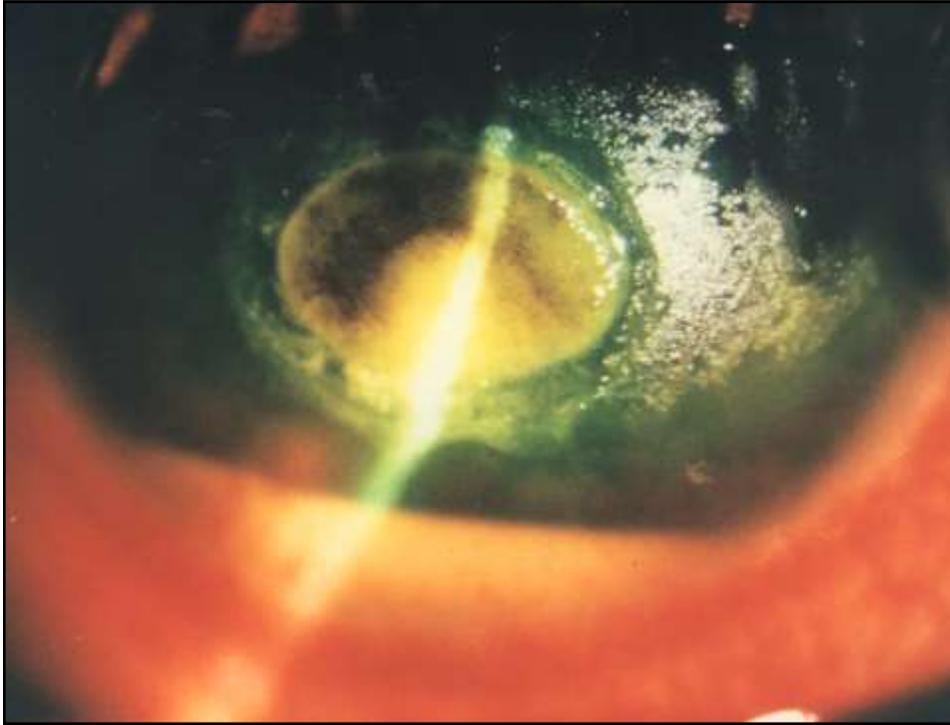


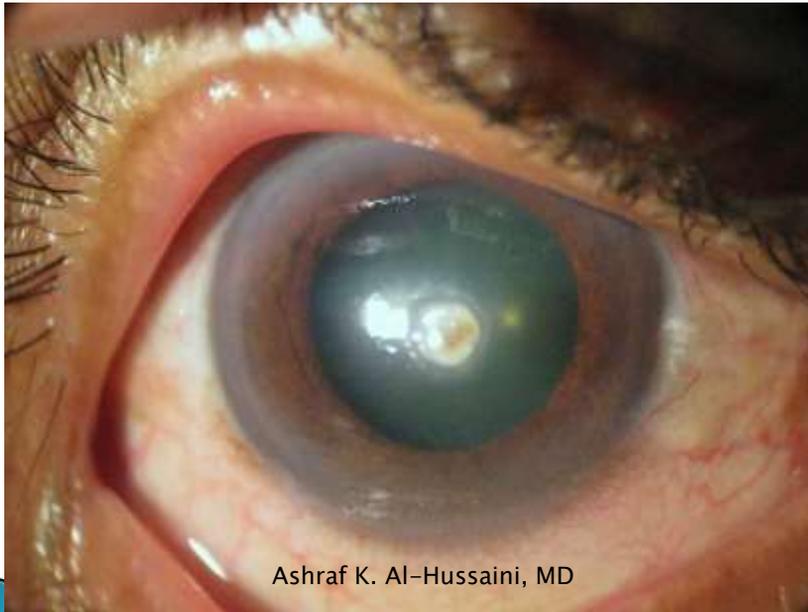
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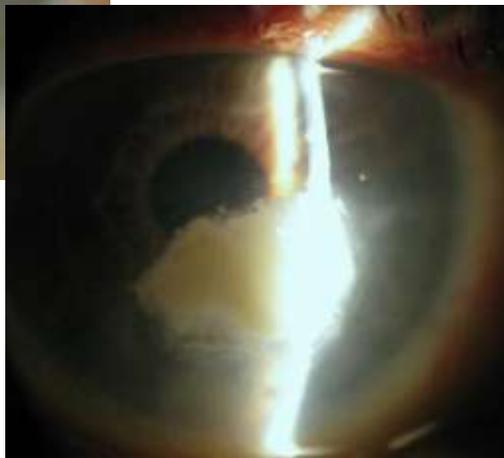
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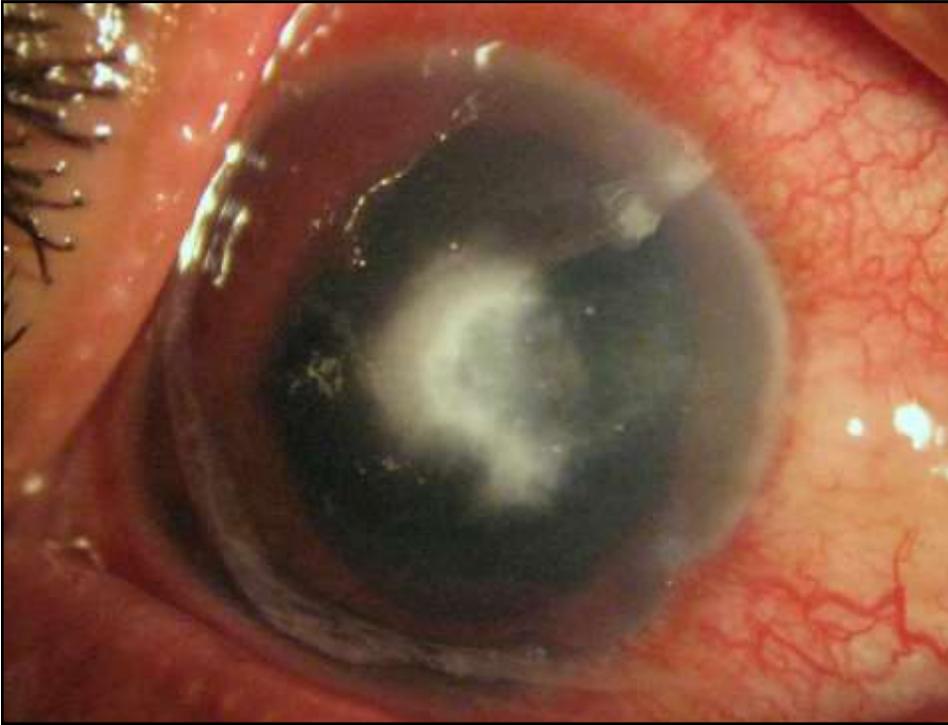






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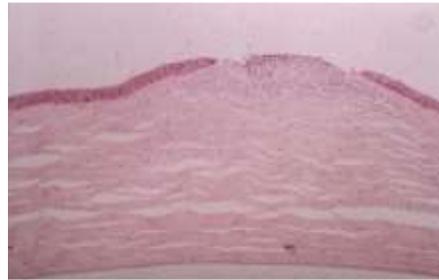
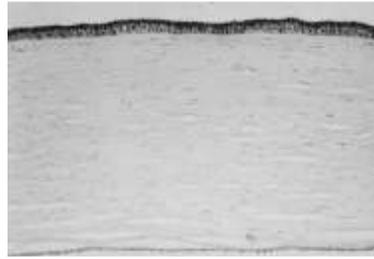


## Laboratory diagnosis



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## Histopathology



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## Obtaining specimens



- ▶ A flame-sterilized platinum spatula (Kimura or Lidner)  
Lids, conj, ulcer.
- ▶ Sterile metal scrapers
- ▶ **Disposable blades no. 15**
- ▶ Corneal biopsy



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## Kit for the lab workout



## Direct smear



- ▶ Advantages:
  - Immediate
  - Sure
  - No false positive
- ▶ Disadvantages:
  - Low yield (30–80%)
  - No identification

# Direct Smears



- ▶ Ink KOH
- ▶ Gram
- ▶ Giemsa
- ▶ PAS
- ▶ GMS

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## Example 1



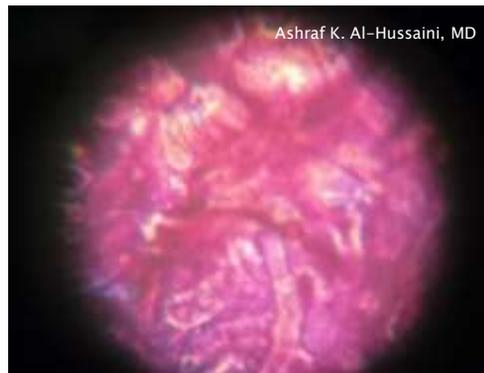
## Example 2



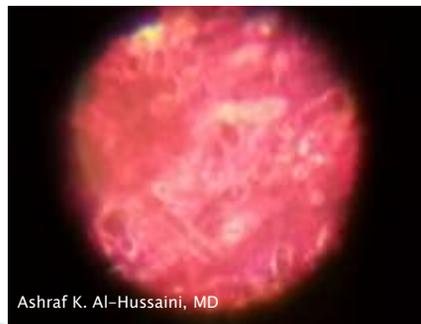
## Example 3



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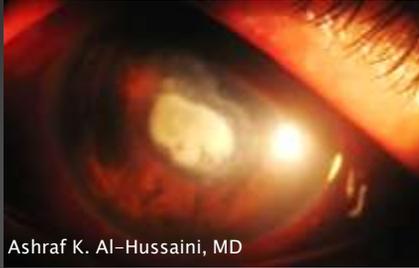


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# Case 3



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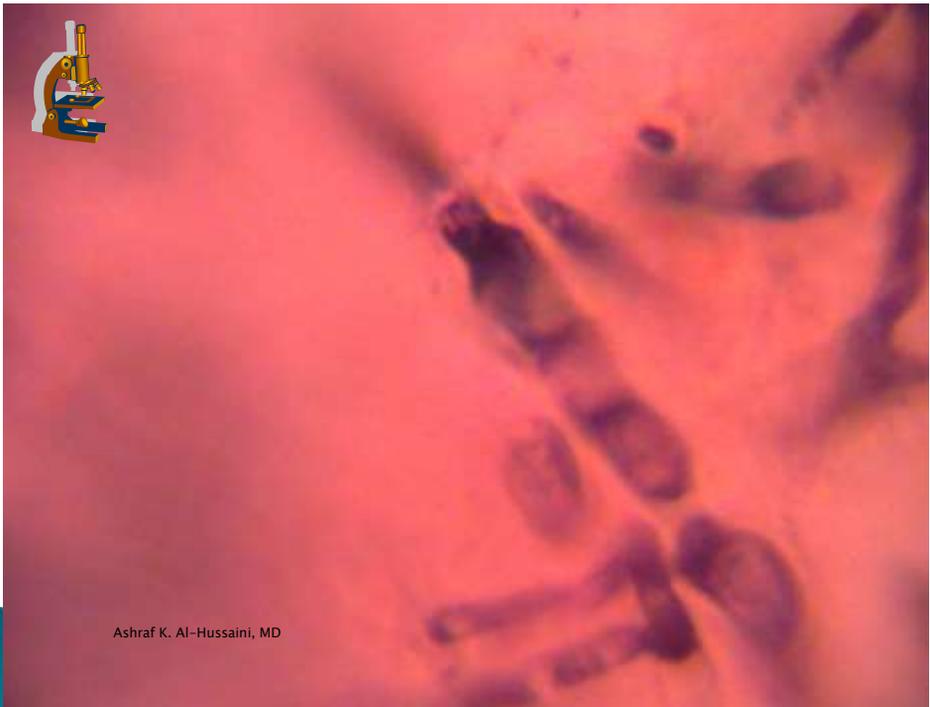
# Case 4



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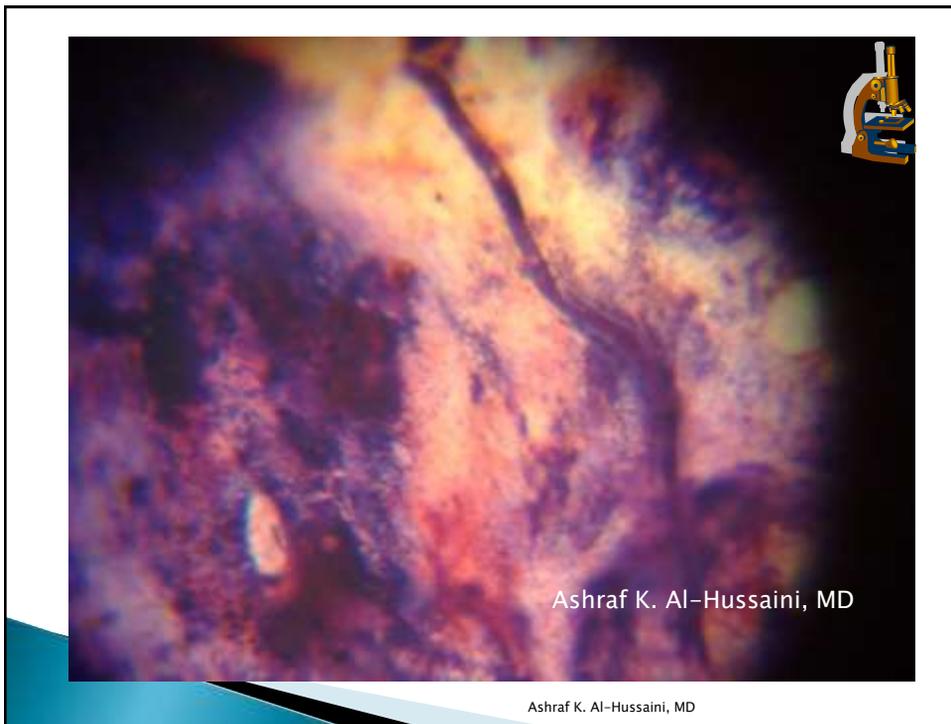
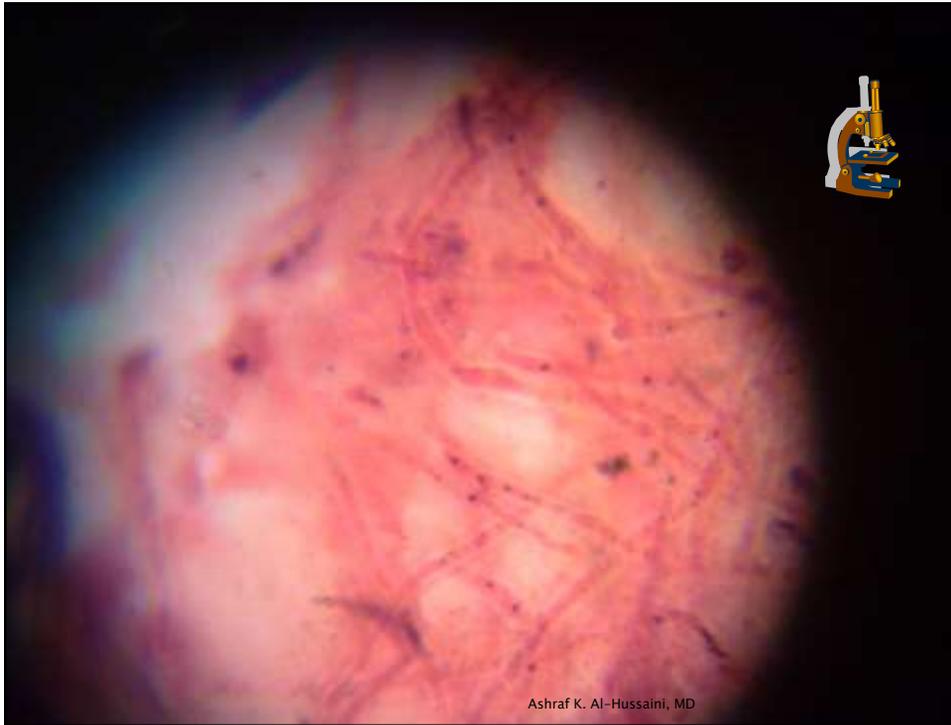
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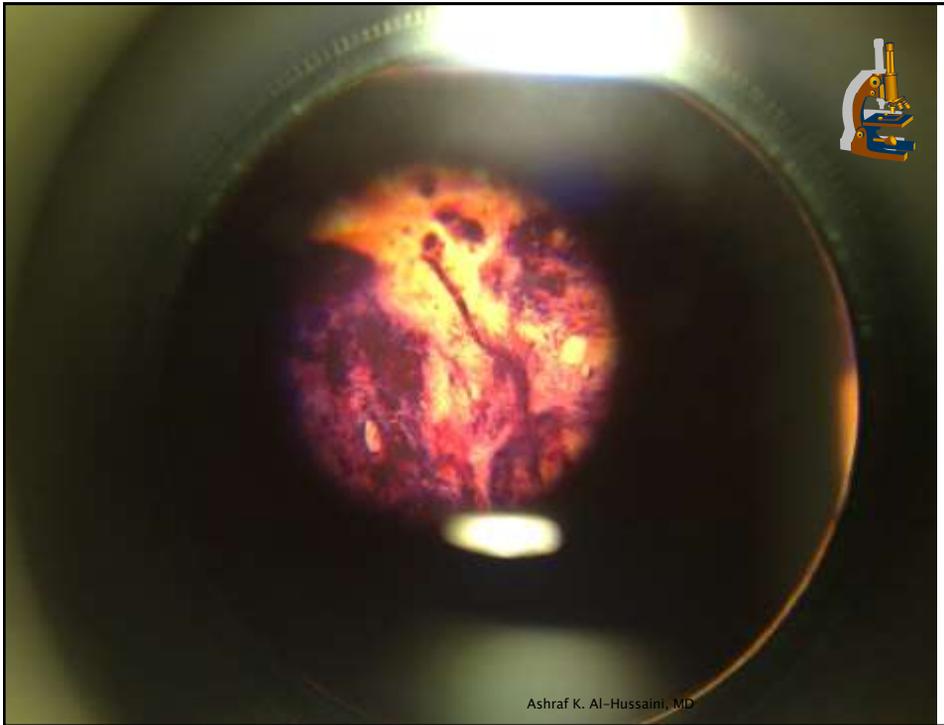
The top section of the slide features two ophthalmological images. On the left is a fundus photograph showing a dark, pigmented lesion in the retina. On the right is a fluorescein angiogram showing a network of retinal vessels with some leakage of dye. The name 'Ashraf K. Al-Hussaini, MD' is printed below each image.

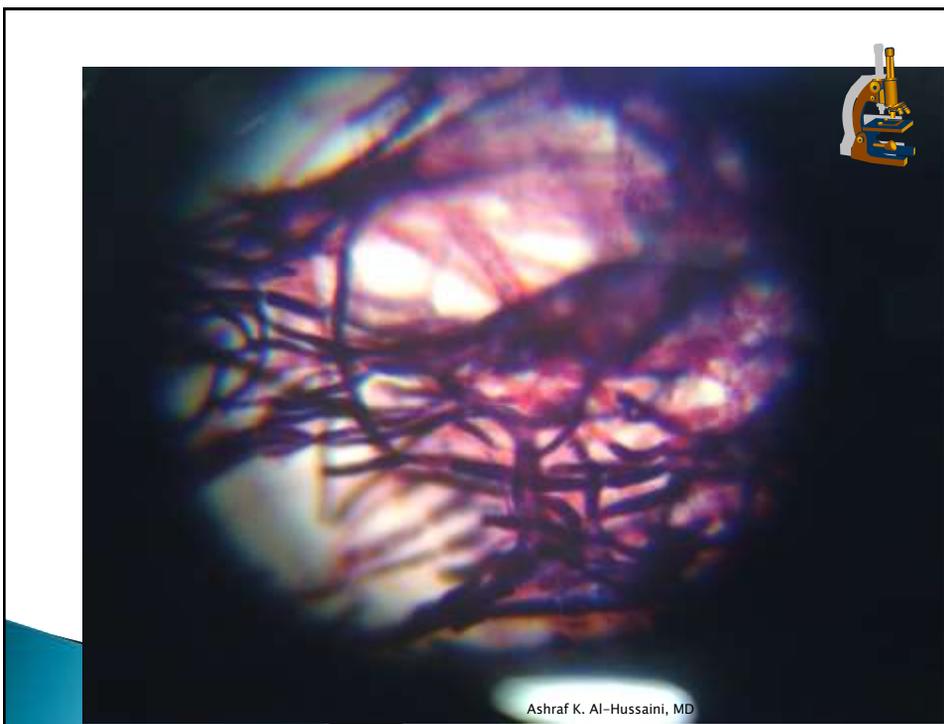
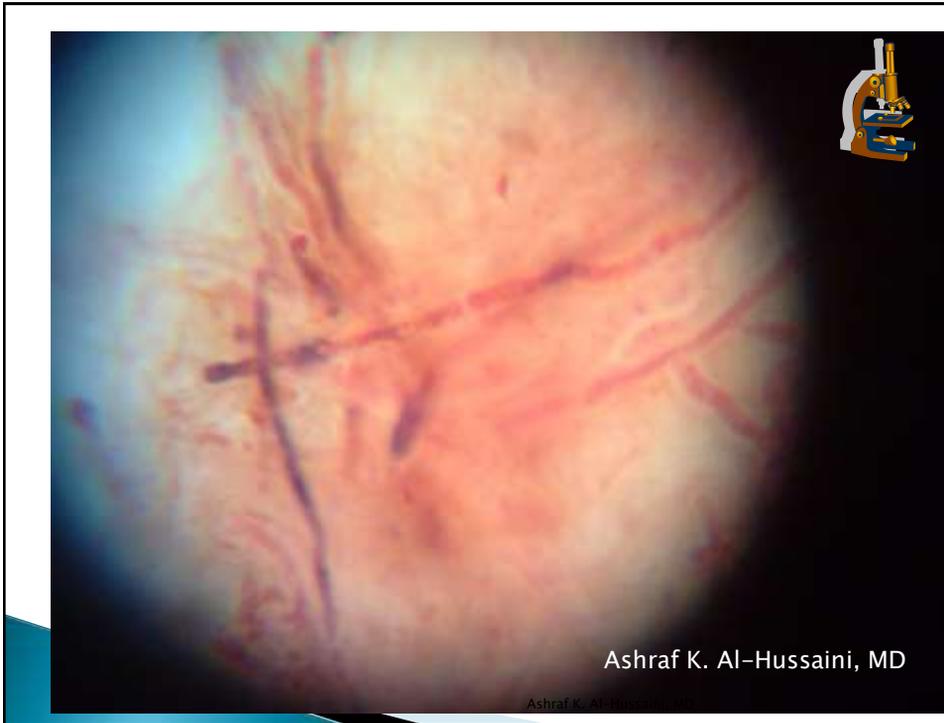


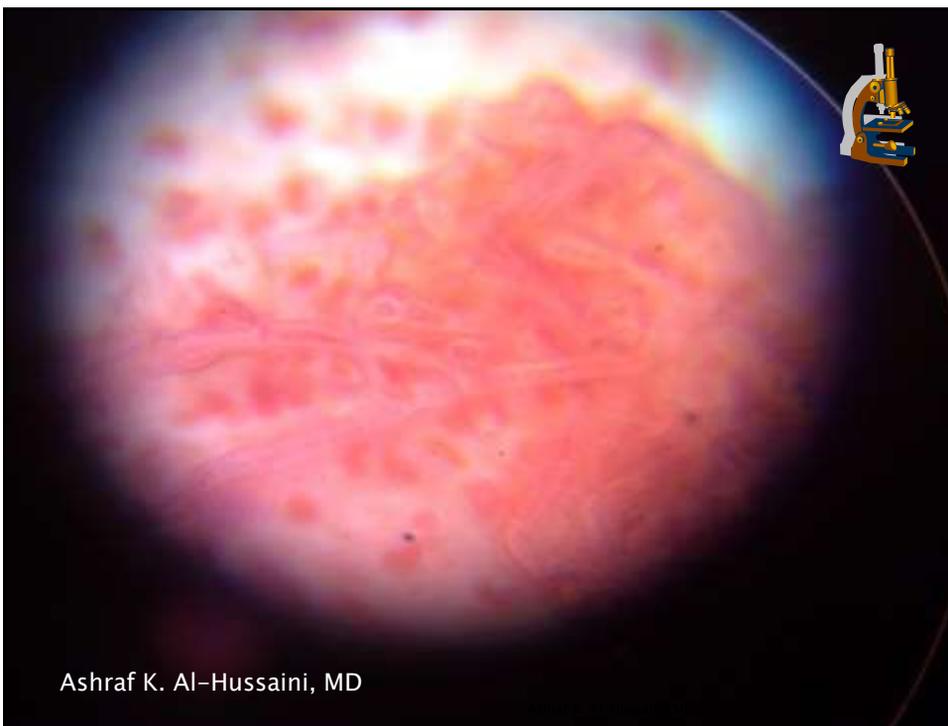
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The bottom section of the slide contains a large microscopic image of a tissue section stained with hematoxylin and eosin (H&E). The image shows elongated, spindle-shaped cells with dark purple nuclei and pink cytoplasm/extracellular matrix. A small icon of a microscope is located in the top-left corner of the image area. The name 'Ashraf K. Al-Hussaini, MD' is printed at the bottom left of the image.









## Gram stain



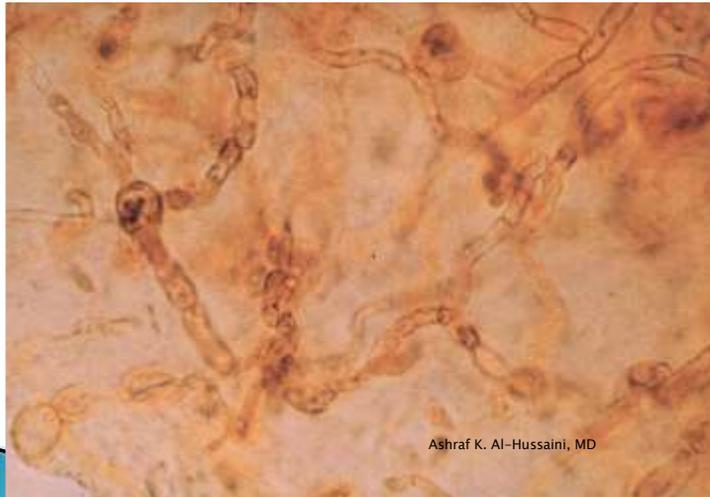
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## Ink KOH



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## Ink KOH (Darkly pigmented septate organism)



## Culture techniques



- ▶ Blood agar
- ▶ Chocolate agar
- ▶ Sabouraud's agar
- ▶ Thioglycolate broth
- ▶ Brain–heart infusion broth

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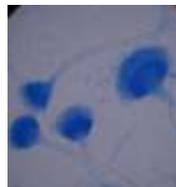
# Culture techniques



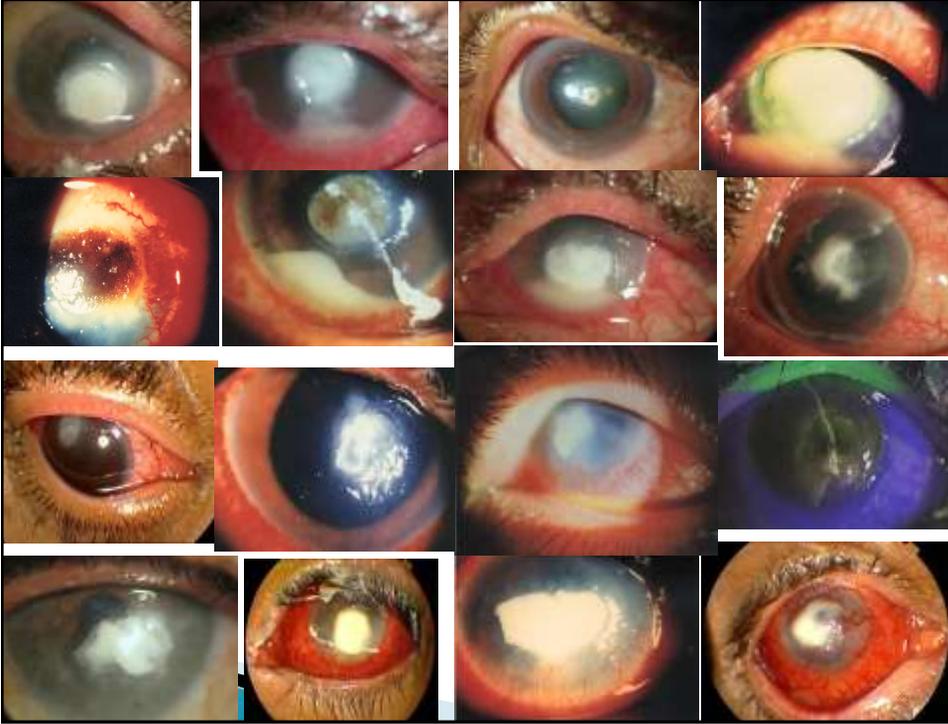
- ▶ Identificaion
  - Morphology
  - Growth characteristics
  - Biochemical reactions
- ▶ Culture sensitivity testing
- ▶ Slow
- ▶ Subject to a false positive result (contamination)

Advantages

Disadvantages



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Increasing incidence &/  
awareness?

## Epidemiology

- ▶ > 50 % of the cases worldwide (D. Tan 2012, AAO).
- ▶ India – Egypt – Sri Lanka – Japan – Singapore – China – USA– Europe – South America – Ghana

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## Fungal infections of the cornea is Assiut

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3. Al-Hussaini AK, Daef EAE, El-Shanawany AR et al: Etiology of microbial keratitis. Bull Ophthalmol Soc Egypt 1994; 87: 647-651.

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## Experimental Studies

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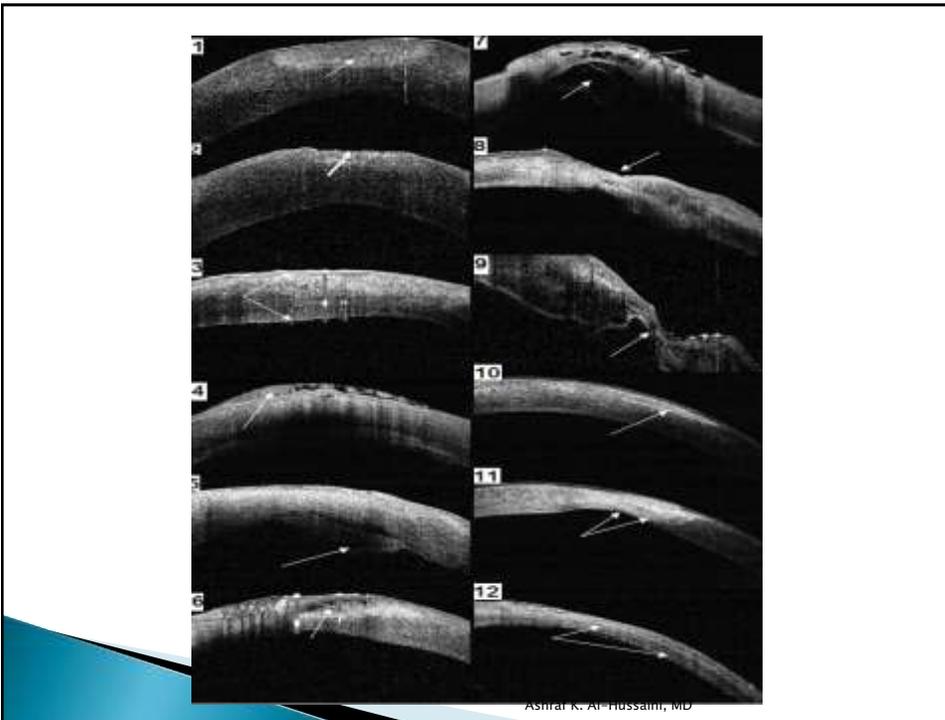
## Clinical & Experimental

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9. Ashraf K. Al-Hussaini, Ahmed M. Moharram, Mohamed I. Abdel-Kader, Saeed M. AlGhalibi. *Extracellular enzymes and toxins produced by fungi isolated from human corneal infections*. Presented at the 34th Annual Meeting of the Ocular Microbiology and Immunology Group, Dallas, Texas USA, 2000. Published in The Egyptian Journal of Cataract and Refractive Surgery vol 6 No.1 2000 5-14
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## Fungal Keratitis

- ▶ Predisposing factors
  - *Agricultural trauma*
  - *Corticosteroid use*
  - Antibiotic use
  - Dry eye
  - Immune compromise
  - Eye surgery
  - *Herpetic eye disease*
  - *Contact lens wear*

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## Contact lens wear

- ▶ Re Nu epidemic (2006)
- ▶ Contaminated solutions.
- ▶ Sharing cosmetic lenses (beauty saloons)
- ▶ Disposable lenses
- ▶ Overnight wear

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## Fungal keratitis (epidemiology)

- ▶ Filamentary fungal keratitis:
  - Working men
  - Contact lens users
- ▶ Candida fungal keratitis:
  - Diabetics
  - Immune compromised patients

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## Fungal keratitis

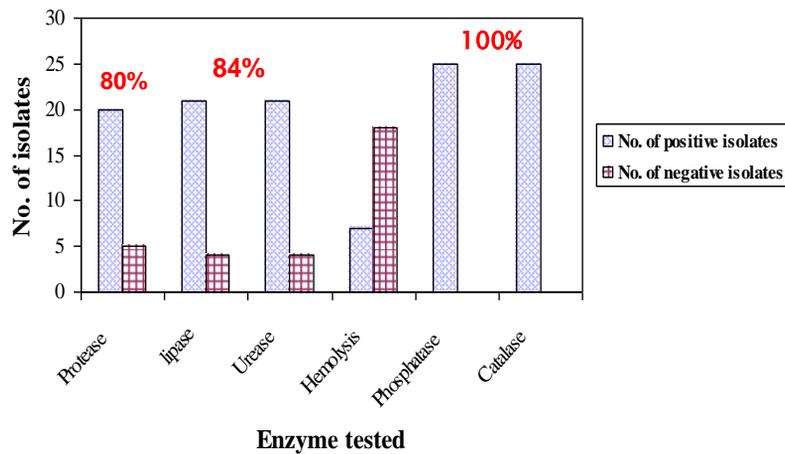
- ▶ Causative organisms > 70 species:
  - *Aspergillus*
  - *Fusarium*
  - *Curvularia*
  - *Alternaria*
  - *Drechslera*
  - *Candida*
  - Others

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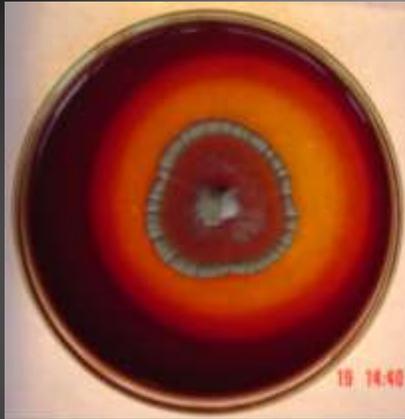
## Why are fungi toxic to the conea?

- ▶ Extracellular Enzymes
- ▶ Mycotoxins

**Figure (24):** Extracellular enzymes produced by 25 fungal isolates.



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Figure(31): Haemolytic activity of *Aspergillus flavus* ( $\beta$ -haemolysis).



Figure(32): Haemolytic activity of *Aspergillus terreus* ( $\gamma$ -haemolysis).

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**Table(3): Mycotoxins produced by fungi isolated from keratitis cases (10 types).**

Fungi tested	AUMC o.N	Mycotoxin detected	Toxin Level
<i>Aspergillus flavus</i>	3939	-	-
<i>A. flavus</i>	3940	-	-
<i>A. flavus</i>	3941	Aflatoxin B1	L
<i>A. flavus</i>	3942	-	-
<i>A. flavus</i>	3943	Aflatoxin B1	H
<i>A. flavus</i>	3944	Aflatoxin B1,G1	M
<i>A. flavus</i>	3945	Aflatoxin B1	H
<i>A. flavus</i>	3946	Aflatoxin B1	L
<i>A. fumigatus</i>	3947	Sterigmatocystin	M
<i>A. niger</i>	3950	-	-
<i>A. terreus</i>	3951	-	-
<i>A. terreus</i>	3886	Aflatoxin B1,B2,G1,G2	M

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Fungi tested	AUMC No.	Mycotoxin detected	Toxin Level
<i>A. terreus</i>	3952	Fumagillin	L
<i>Cladosporium cladosporioides</i>	3955	-	-
<i>C. cladosporioides</i>	3956	-	-
<i>Cochliobolus spicifer</i>	3957	-	-
<i>Candida</i> sp.	3958	-	-
<i>Candida</i> sp.	3959	-	-
<i>Fusarium oxysporum</i>	3961	Diacetoxyscirpenol	M
<i>F. Solani</i>	3962	Zearalenone Diacetoxyscirpenol	H M
<i>F. verticellioides</i>	3963	T-2	L
<i>P. chrysogenum</i>	3965	Sterigmatocystin	H
<i>Stemphylium botryosum</i>	3966	-	-
Sterile mycelia	3954	-	-
<i>Trichoderma hamatum</i>	3967	Trichodermin	L

L= Low (less than 100 mg/50 ml medium)  
M= Moderate ( from 100 – 500 mg/50 ml medium)  
H = High ( more than 500 mg / 50 ml medium)

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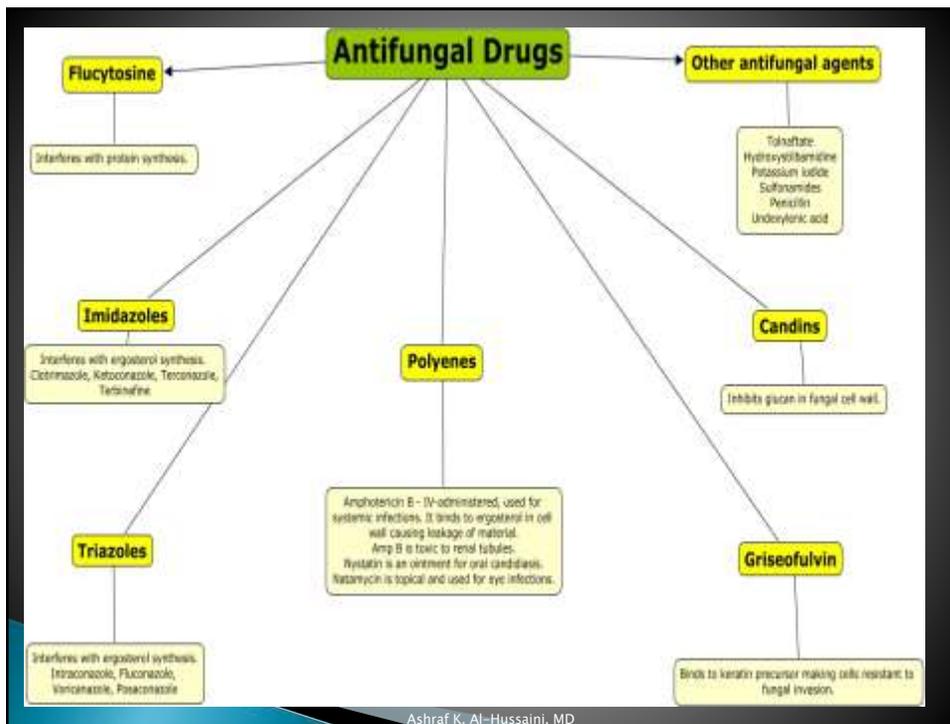
## Treatment goals

- ▶ Sterilize the cornea
- ▶ Stop the spread of infection to the inside of the eye
- ▶ Avoid antifungal toxicity
- ▶ Maintain or recover the structural integrity of the cornea
- ▶ Recover its transparency

# Treatment options

- ▶ Medical treatment
  - Topical antifungal treatment
  - Systemic antifungal treatment
  - *Intrastromal injection*
- ▶ Surgical treatment :
  - Scraping
  - Conj. Flap
  - Amniotic membrane transplantation
  - *Therapeutic keratoplasty*

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## Topical Antifungal Treatment



- ▶ *Natamycin suspension (5%)*
- ▶ Ketoconazole suspension 1–5%
- ▶ Econazole 1%
- ▶ Clotrimazole 1%
- ▶ Miconazole nitrate 1%
- ▶ Fluconazole 1–5 %
- ▶ Itraconazole 1.0 %
- ▶ Amphotericin B 0.15 %
- ▶ Voriconazole : 1.0 %



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2022 Feb 1;140(2):179-184.

doi: [10.1001/jamaophthalmol.2021.5765](https://doi.org/10.1001/jamaophthalmol.2021.5765).

Patterns of Antifungal Resistance in Adult Patients With Fungal Keratitis in South India  
A Post Hoc Analysis of 3 Randomized Clinical Trials

[N Venkatesh Prajna](#), et al PMID: 35024776

•PMCID: [PMC8759027](#)

•DOI: [10.1001/jamaophthalmol.2021.5765](https://doi.org/10.1001/jamaophthalmol.2021.5765)

- ▶ This post analysis suggests that susceptibility to both natamycin and voriconazole may be decreasing over the last decade in South India.

## Problems with antifungal medications

- ▶ Limited armamentarium
- ▶ Poor penetration
- ▶ Every hour
- ▶ Toxicity
- ▶ Repeated debridement
- ▶ ?? Intrastromal injection



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## Natamycin 5% topical treatment



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## Voriconazole (Vfend)

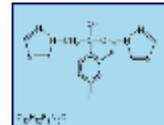


- ▶ Voriconazole
  - Topical 1%
  - Oral 200 mg/day BD
  - Intrastromal



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## Fluconazole (Diflucan)



- ▶ Water soluble having wider range of activity than Ketoconazole
- ▶ Good activity against *C. albicans* and *Cryptococcus neoformans*
- ▶ *Ineffective against filamentary fungi*

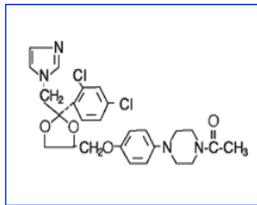


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## Ketoconazole (Nizoral)



- ▶ 1–5 % topical suspension :
- ▶ every 1 hour
- ▶ Oral 200 mg bid



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## Itraconazole (Spranox–Itracon)



- ▶ Topical 1%
- ▶ Oral 100 mg BID
- ▶ Orally active triazole
- ▶ *Broader spectrun than KTZ and FCZ* – includes moulds like aspergillus
- ▶ Fungistatic action but very effective in immunocompromizrd patients
- ▶ Steroid hormone synthesis inhibition is *absent and no serious hepatotoxicity*

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## Amphotericin B (Fungizone)



- ▶ Amphotericin B
  - Topical 0.15%
  - Subconj
  - Intrastromal
  - (freshly prepared)
  - Dark bottles
  - Refrigerated (2–8 Degrees).
  - Highly toxic

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## Surgical management



- ▶ Repeated scraping
- ▶ AMT
- ▶ PKP
- ▶ DALK
- ▶ ??? CXL

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## Challenges

- ▶ Delayed presentation
- ▶ Limited armamentarium
- ▶ Prolonged treatment time
- ▶ Exhausting hourly regimen
- ▶ Lack of efficacy
- ▶ Limited number of RCTs
- ▶ High expenses

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## Mucormycosis



- ▶ Fungal infection of the orbit
- ▶ Diabetics
- ▶ Corticosteroid users
- ▶ Following ocular or sinus surgery
- ▶ **Covid 19**
- ▶ Slowly progressive proptosis
- ▶ Skin gangrene Rapidly fatal
- ▶ Rx:
  - Surgical debridement
  - + IV Amphotericin B

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Thank you !

