QUERATITIS FÚNGICA

Núria Artells de Jorge

Servei d'Oftalmologia

Secció còrnia i superfície ocular

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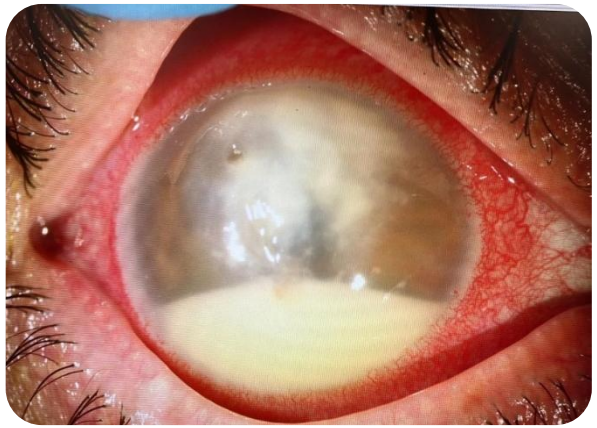
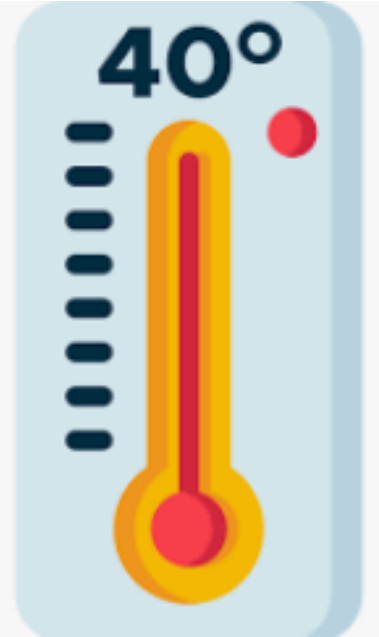
INTRODUCCIÓ



- La queratitis micòtica és una infecció **greu de la còrnia**
- Suposa un **repte diagnòstic i terapèutic**
- **Fongs : creixement lent → retard en el diagnòstic microbiològic.**
- **Increment** de la incidència→ abús de **lents de contacte i corticoides**
- Infeccions avançades → sovint la **queratoplàstia terapèutica** és la única alternativa terapèutica

EPIDEMIOLOGIA



- Distribució latitud i temperatura depenent.
  - Índia 45%
  - Florida 30%
  - Nova York- Londres 1-3%

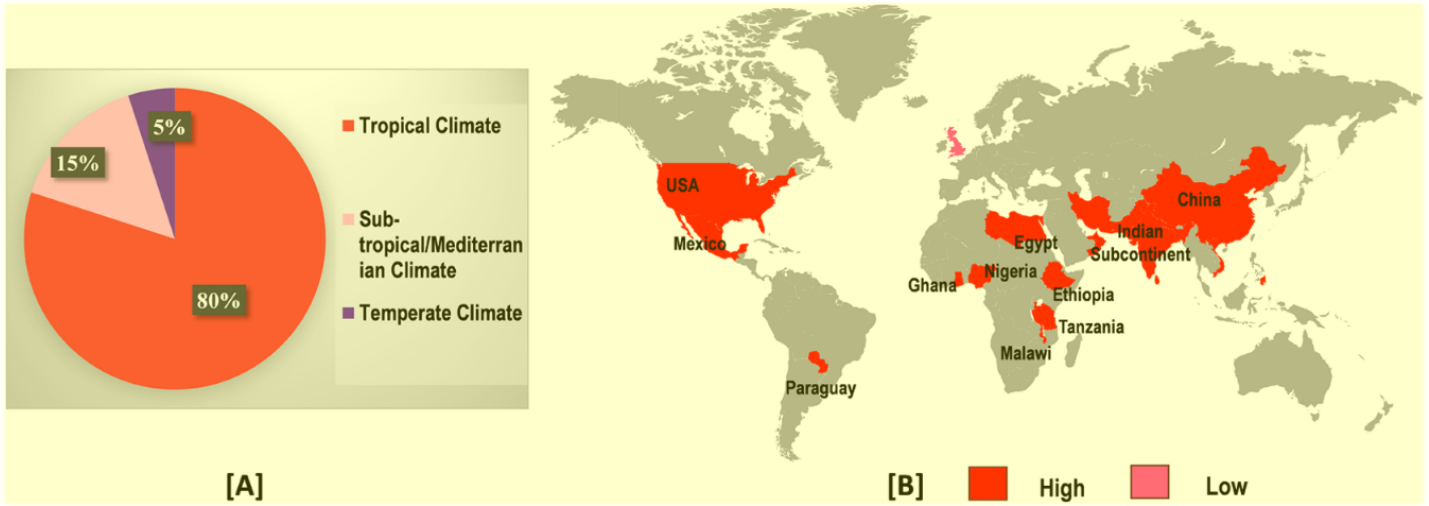


Figure 1. Approximate distribution of FK as per the [A] climatic zones and [B] its prevalence in different regions across the globe (This map is for illustration purposes only).

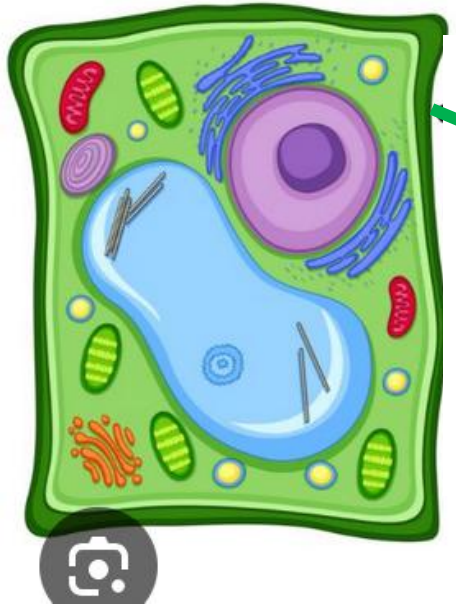
CARACTERÍSTIQUES FONGS

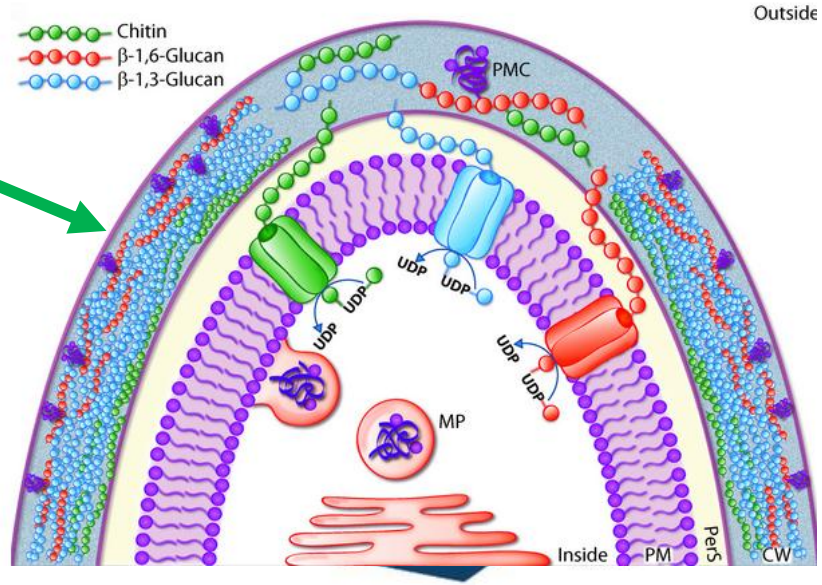
ORGANISMES UBICS

PARET DE **QUITINA I GLUCANO**

ERGOSTEROL MEMBRANA CEL·LULAR

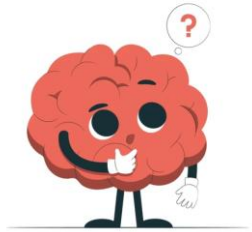
BIOFILM





FACTORS DE RISC

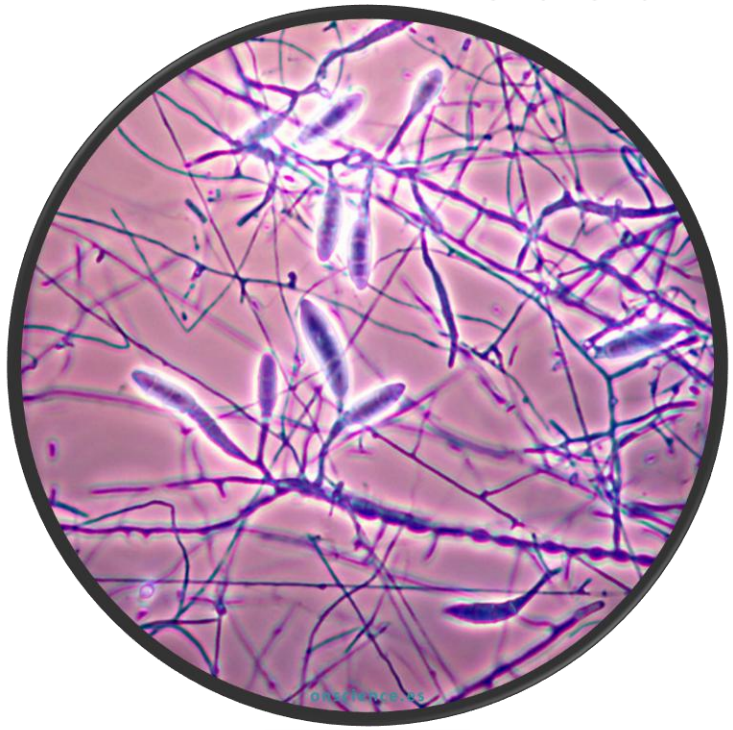
- **Traumatisme ambiental**: vegetal, mineral, pols, fang…
- **Malaltia crònica** de la superfície ocular (blefaritis, ull sec,…)
- **Queratoplàstia** prèvia
- Ús crònic de **corticoides** i antibacterians tòpics
- Portadors de **lents de contacte**



AGENTS CAUSALS

250.000 espècies → **100** causants de queratitis micòtica

FILAMENTOSOS



LLEVATS

FONGS FILAMENTOSOS

- ***Fusarium sp, Aspergillus sp,***
  Penicillinum sp, Paecilomyces sp

- Espores: molt resistents.
- Terra, plantes i fusta en descomposició 🌳
- Traumatisme ocular vegetal 🌱
- Portadors de lents de contacte

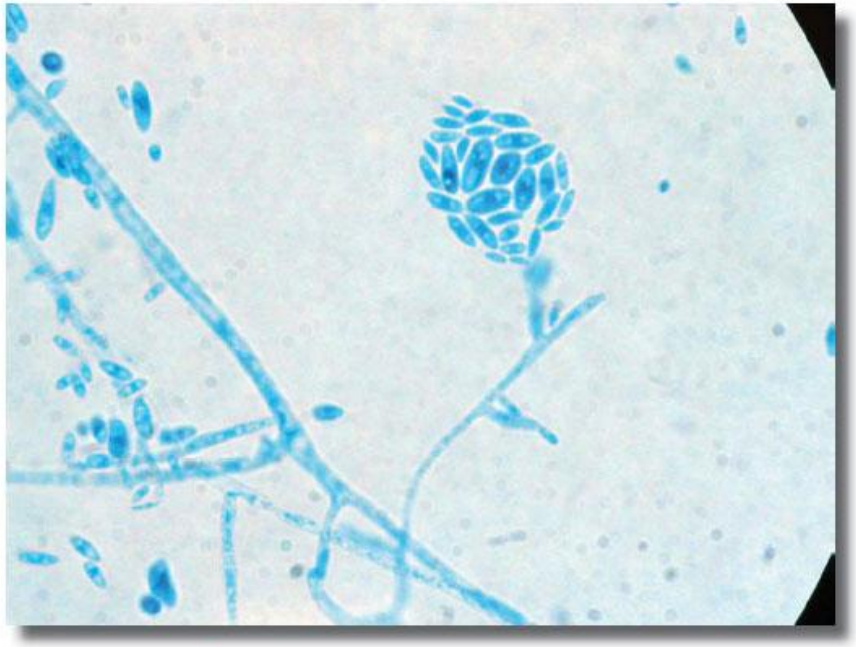
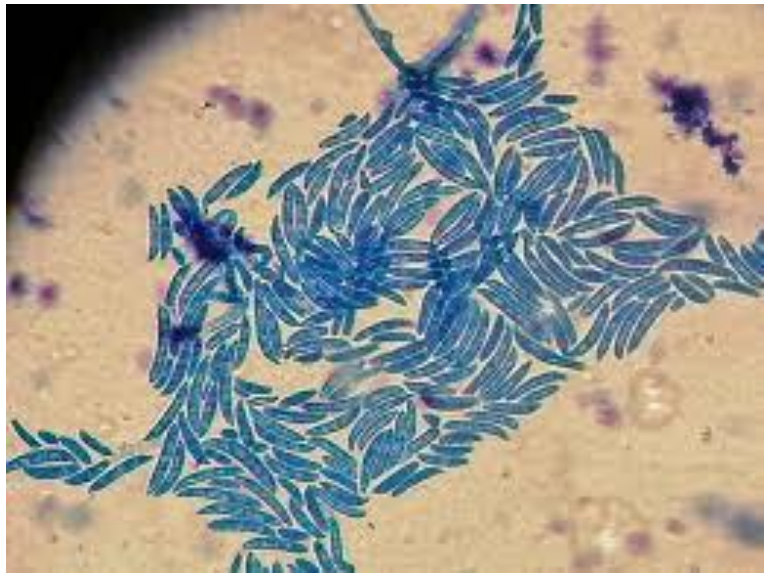
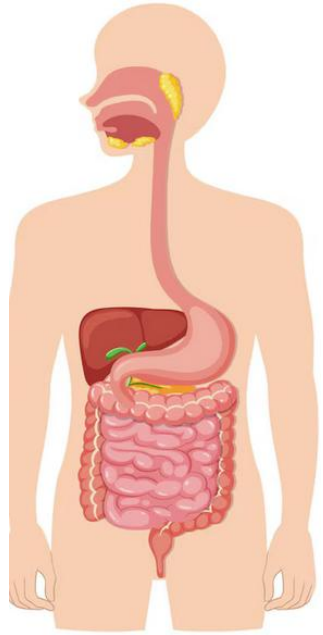


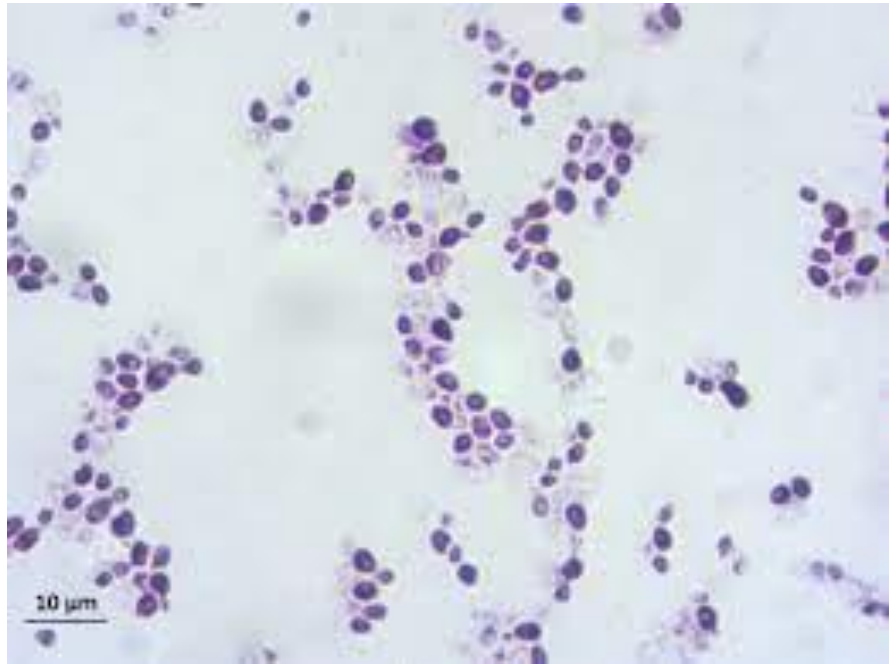
Figura 1. Hifas característices de *Fusarium*.



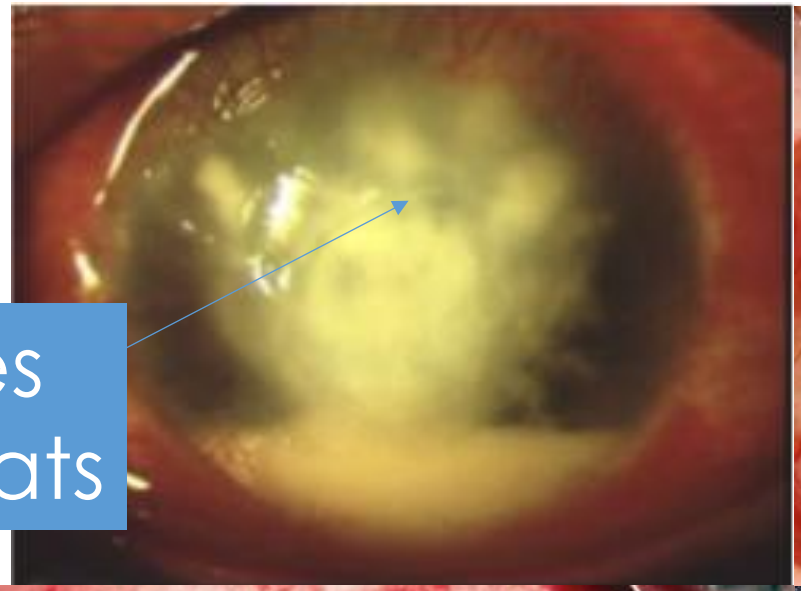
LLEVATS

- ***Candida albicans, parapsilosis, krusei, tropicalis***
- Pacients immunodeprimits (flora pròpia de l'hoste)
- Malaltia cornial crònica preexistent.
- Progressió lenta

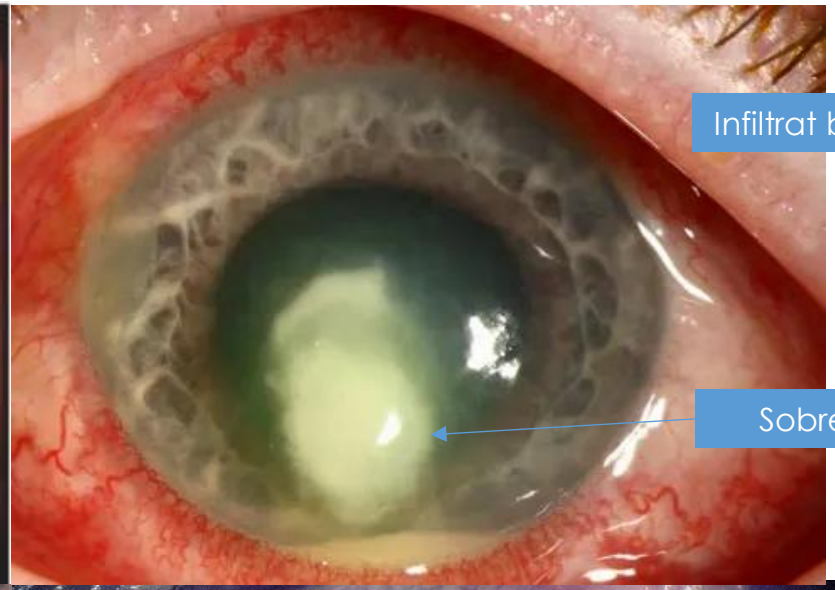




CLÍNICA

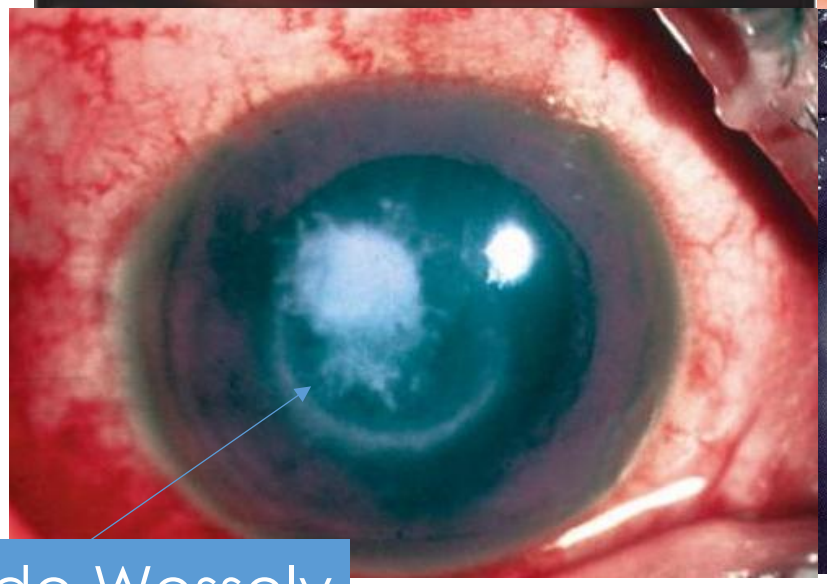


Marges fistonejats

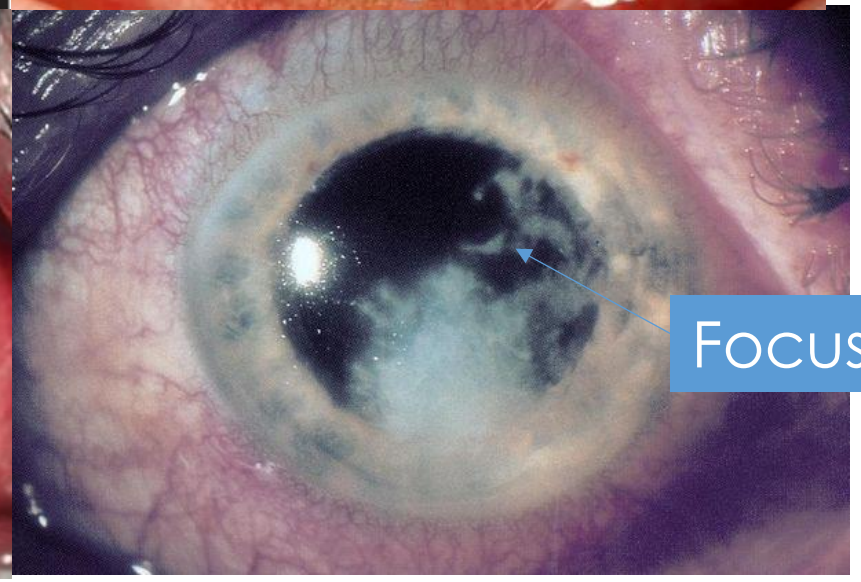


Infiltrat blanc-grogós

Sobreelvació



Anell immune de Wessely



Focus satèl·lit

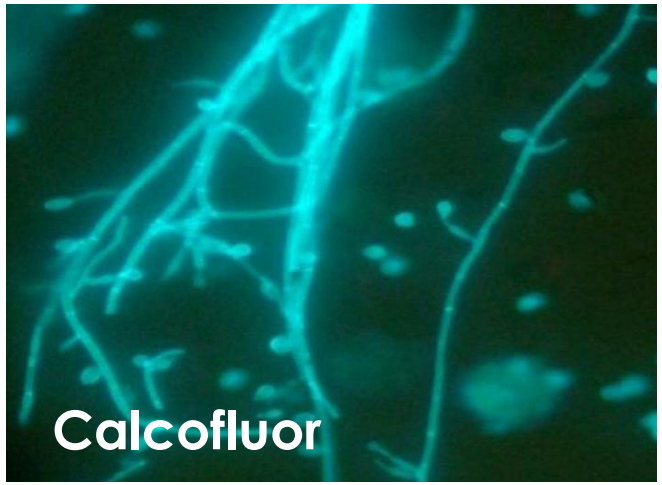
DIAGNÒSTIC

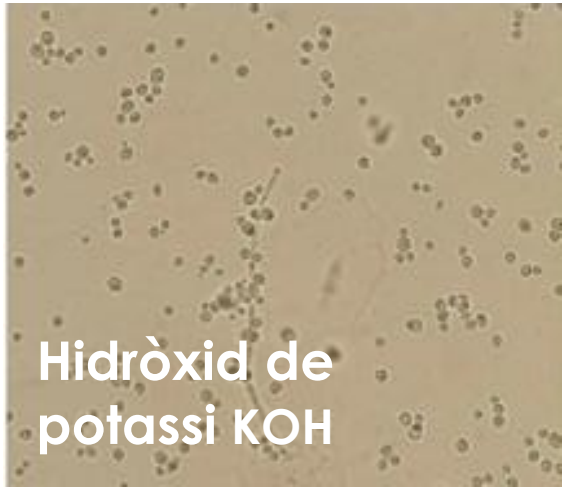
- **TINCIÓ → visualització directa, informació ràpida i fàcil de realitzar**
  - Giemsa, gram, blau algodón-lactofenol

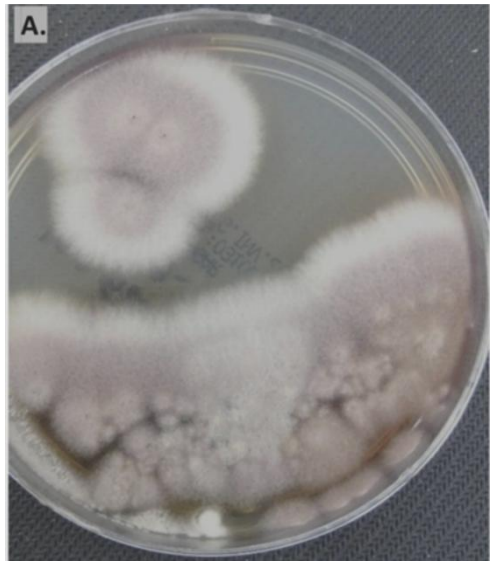
CULTIU → gold estàndard

Permet **identificar** microorganismes i **sensibilitat** antifúngics

Agar Sabouraud







CAS CLÍNIC 1

76 anys

Agost 2024

Queratitis greu per ***Fusarium Solani***

Tractament

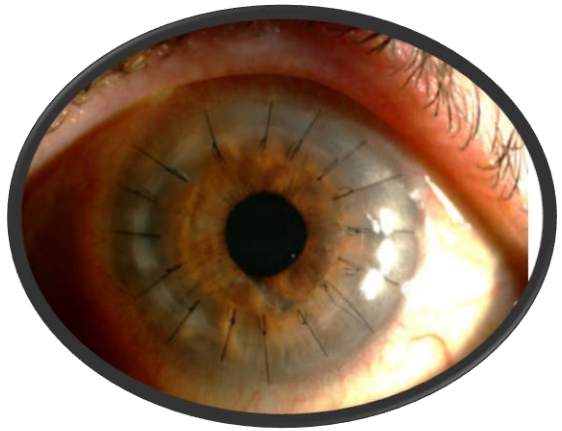
Voriconazol 200mg c/12h
Voriconazol 1% c/2h
Natamicina 5% c/3h
Clorhexidina 0,02% c/5h

13/9/24

Queratoplàstia de gran diàmetre + rentat de cámara anterior

23/10/24

2ª Queratoplàstia



CAS CLÍNIC 1

4/12/24

Nova recidiva

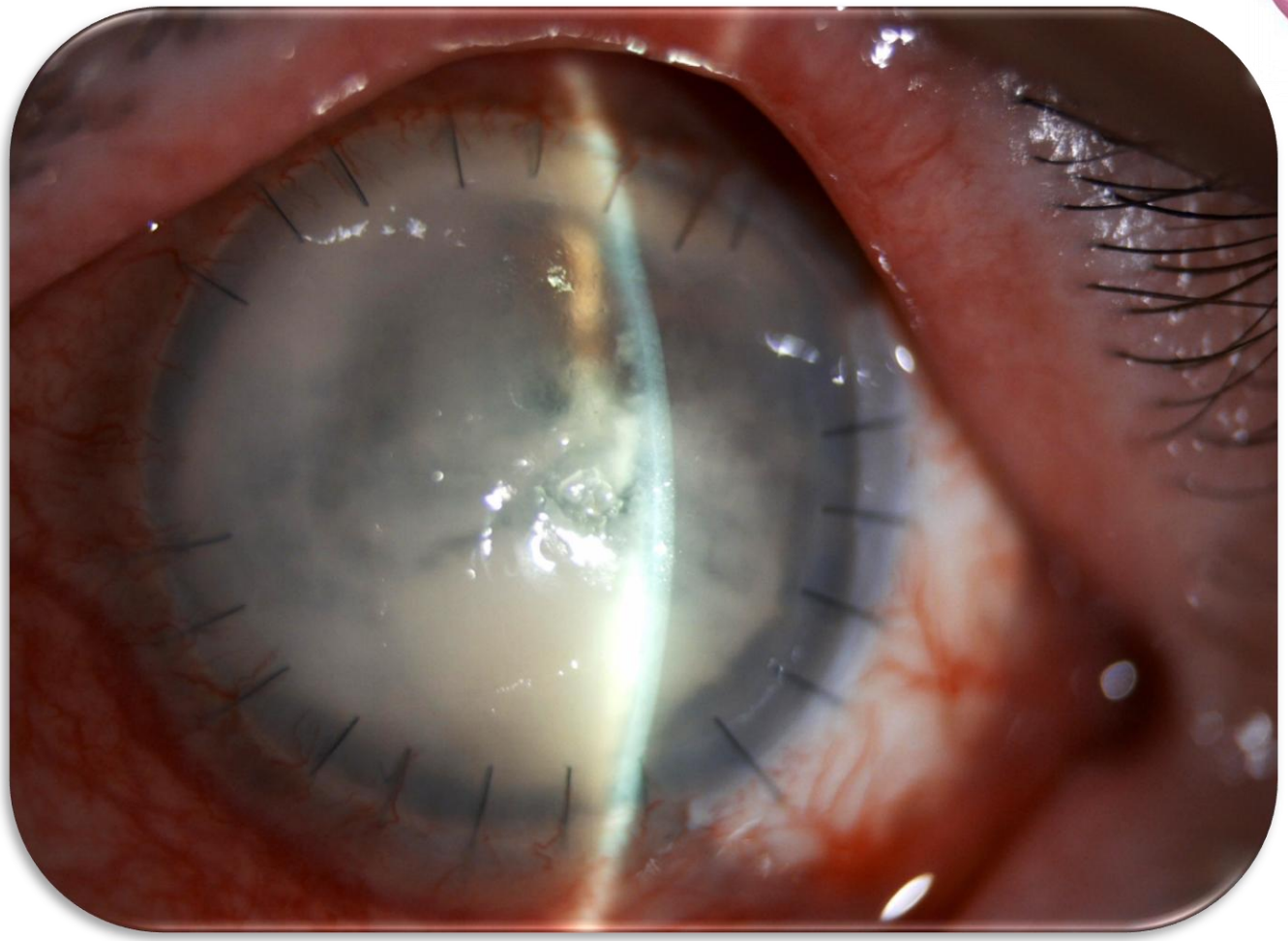
Rentat cámara anterior **Voriconazol**

11/12/24

Acut CEX

Oftalmologia Trueta

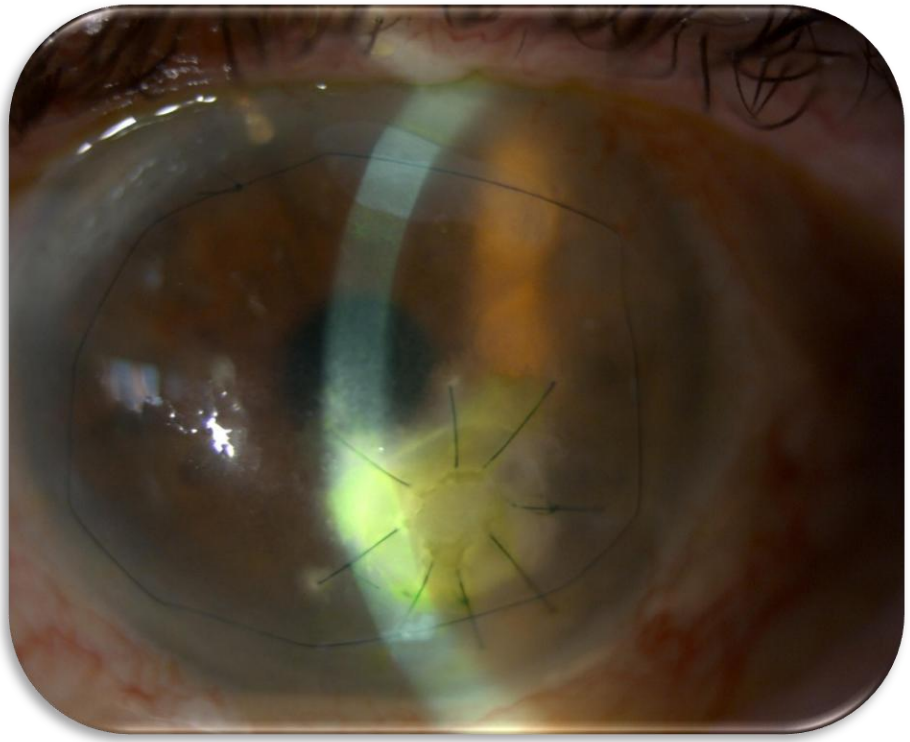
Recidiva *Fusarium Solani*

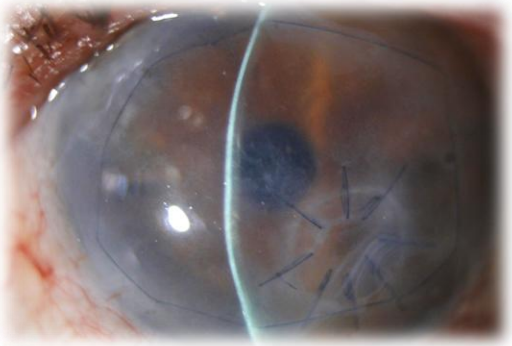


CAS CLÍNIC 2

Gener 2025
Perforació cornial per queratitis herpètica

85 anys





23/01/25
Intervenció per sellar perforació

4/03/25
Contaminació botó cornial donant ***Candida tropicalis***

Tractament
Voriconazol 1% c/2h
Amfotericina B 0,15% c/3h

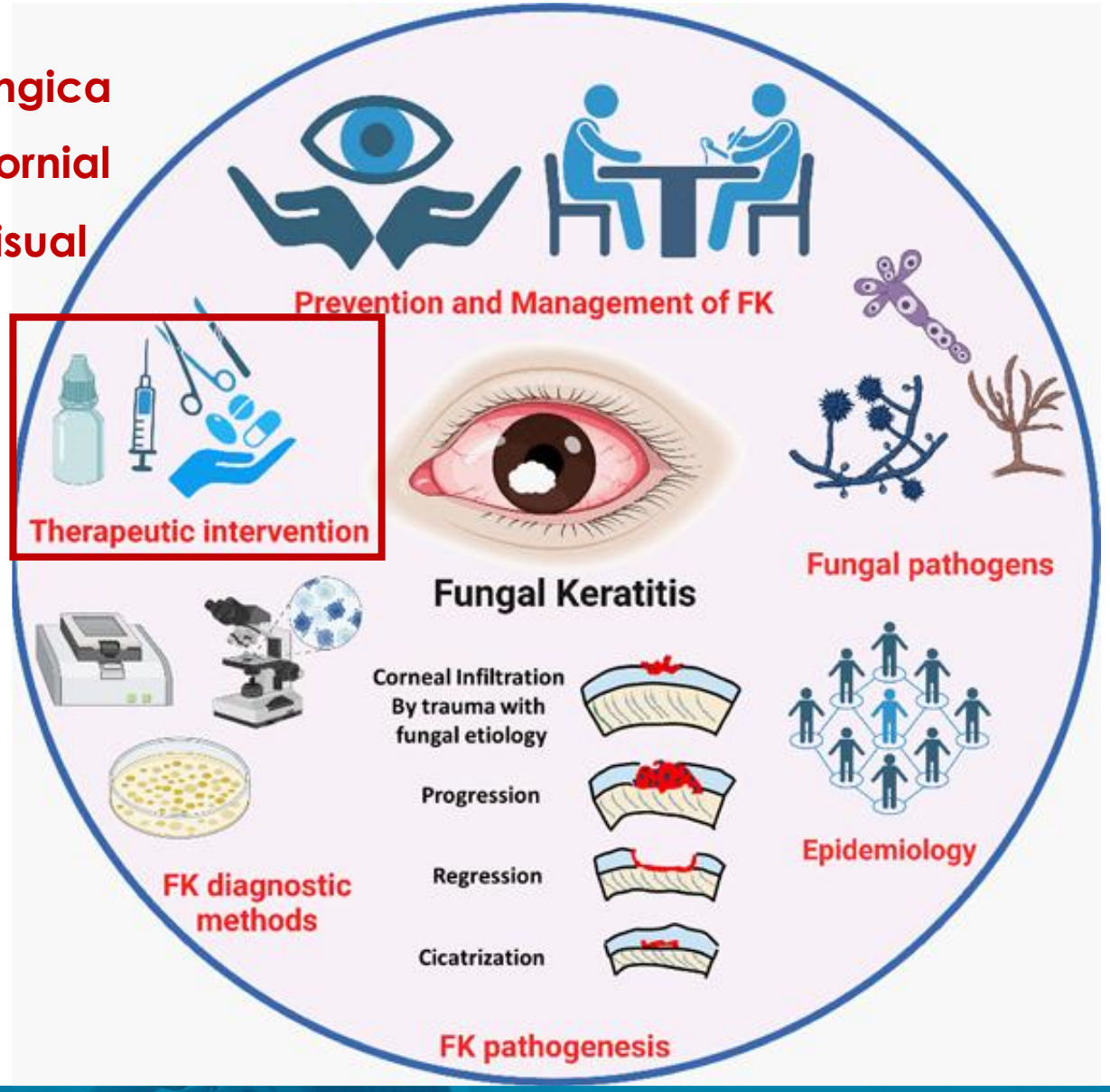
TRACTAMENT DE LA QUERATITIS FÚNGICA

QUERATITIS FÚNGICA

Erradicar infecció fúngica

Minimitzar el dany cornial

Preservar la funció visual



Tractament antifúngic d'elecció per QF ???

Via tòpica vs intraocular vs sistèmica ???

Disponibilitat actual a Espanya d'antifúngics ???

Paper de la formulació magistral oftàlmica ???

ACS Infectious Diseases

pubs.acs.org/journal/aidcbc

Review

Etiopathology, Epidemiology, Diagnosis, and Treatment of Fungal Keratitis

Published as part of ACS Infectious Diseases virtual special issue "Fungal Pathogens - Life Cycle, Infection, Host Immunity, and Drug Discovery".

Amol Chhatrapati Bisen, Sachin Nashik Sanap, Sristi Agrawal, Arpon Biswas, Anjali Mishra, Sarvesh Kumar Verma, Vaishali Singh, and Rabi Sankar Bhatta*

Cite This: ACS Infect. Dis. 2024, 10, 2356–2380 Read Online

microorganisms MDPI

Review

Recent Advances in Diagnosis and Treatment Approaches in Fungal Keratitis: A Narrative Review

Laura Andreea Ghenciu [1,2], Alexandra Corina Faur [3,*], Sorin Lucian Bolintineanu [3], Madalina Casiana Salavat [2] and Anca Laura Maghiari [3]

Clinical Ophthalmology Dovepress

open access to scientific and medical research

Open Access Full Text Article REVIEW

Fungal Keratitis: Diagnosis, Management, and Recent Advances

Ramy Awad[1], Alaa Atef Ghaith[2], Khaled Awad[1], Marina Mamdouh Saad[1], Ahmed Ak Elmassry[2]

[1]Department of Ophthalmology, Alexandria General Ophthalmology Hospital, Alexandria, Egypt; [2]Department of Ophthalmology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Adv Ther (2024) 41:3316–3327
https://doi.org/10.1007/s12325-024-02929-3

ORIGINAL RESEARCH

Treatment Strategies for Filamentous Fungi Keratitis

Julia Storr · Daniel Zapp · Nathalie Bleidißel · Christian S. Mayer · Mathias M. Maier ·

Invited Commentary

Challenges in the Management of Fungal Keratitis

Bennie H. Jeng, MD

Journal of Fungi MDPI

Review

Management of Filamentous Fungal Keratitis: A Pragmatic Approach

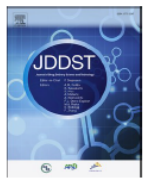
Jeremy J. Hoffman [1,2,*], Simon Arunga [1,3], Abeer H. A. Mohamed Ahmed [1], Victor H. Hu [1] and Matthew J. Burton [1,4]

Journal of Drug Delivery Science and Technology 75 (2022) 103721

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst



Review article

A recent update on therapeutic potential of vesicular system against fungal keratitis

Experimental Eye Research 202 (2021) 108372

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

The role of fungi in fungal keratitis

Bethany Mills [a], Naveen Radhakrishnan [b], Siva Ganesa Karthikeyan Rajapandian [c], Gunasekaran Rameshkumar [c], Prajna Lalitha [c], N. Venkatesh Prajna [b,*]

[a] Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, UK
[b] Department of Cornea and Refractive Surgery, Aravind Eye Hospital, Madurai, India
[c] Department of Ocular Microbiology, Aravind Eye Hospital, Madurai, India

QUERATITIS FÚNGICA

- Formes més difícils de queratitis infecciosa pel seu **difícil diagnòstic** i la **dificultat** de **disposar de preparacions antifúngiques tòpiques efectives**

- La **primera opció terapèutica són els antifúngics tòpics** que s'han **d'iniciar** de forma **precoç** i la **durada del tractament** pot superar les **6 setmanes** arribant a les **12 setmanes** en el cas de fongs filamentosos
- La **selecció del tractament** dependrà del fong implicat i la severitat de la infecció

NATAMICINA 5% suspensió oftàlmica
Primera línia de tractament QF principalment filamentoses (*Aspergillus* i *Fusarium spp*)

VORICONAZOL 1 % col·liri
Cobreix QF filamentoses i *Candida spp*

AMFOTERICINA B 0,15 % col·liri
Primera línia QF per *Candida spp*

QUERATITIS FÚNGICA

Principal limitació:

- **Arsenal terapèutic** de col·liris antifúngics molt **limitat**.

- **Sistemes d'administració** ocular amb importants **deficiències**:

  mala penetració, baixa disponibilitat del fàrmac a la còrnia, eficàcia limitada, toxicitat ocular...

MUTT 1

Sur India
328 pacients

Table 1. Inclusion and Exclusion Criteria for the Mycotic Ulcer Topical Treatment Trial I

Criteria
Inclusion, all must be met
Presence of a corneal ulcer at initial visit
Evidence of filamentous fungus on smear, potassium hydroxide wet mount, Giemsa staining, or Gram staining
Basic understanding of the study including commitment to return for follow-up visits
Willingness to be treated as an inpatient or to return every 3 d (±1 d) until reepithelialization and every 1 wk (±2 d) to receive fresh medication for 3 wk
Appropriate consent
Visual acuity between 6/12 (20/40) and 6/120 (20/400), inclusive
Exclusion, any exclude
Impending perforation
Evidence of bacteria on Gram staining at time of enrollment
Evidence of *Acanthamoeba* by staining
Evidence of herpetic keratitis by history or examination
Corneal scar not easily distinguishable from current ulcer
Age <16 y, before 16th birthday
Bilateral ulcers
Previous keratoplasty in affected eye
Pregnancy, by history or urine test, or breastfeeding, by history
Visual acuity <6/60 (<20/200) in fellow eye
Known allergy to study medications
No light perception in affected eye
Not willing to participate

CLINICAL TRIALS

JOURNAL CLUB

The Mycotic Ulcer Treatment Trial

A Randomized Trial Comparing Natamycin vs Voriconazole

N. Venkatesh Prajna, MD; Tiruvengada Krishnan, MD; Jeena Mascarenhas, MD; Revathi R
Lalitha Prajna, MD; Muthiah Srinivasan, MD; Anita Raghavan, MD; Catherine E. Oldenbu
Michael E. Zegans, MD; Stephen D. McLeod, MD; Travis C. Porco, PhD, MPH; Nisha R. Ac
Thomas M. Lietman, MD; for the Mycotic Ulcer Treatment Trial Group

Objective: To compare topical natamycin vs voriconazole in the treatment of filamentous fungal keratitis.

Methods: This phase 3, double-masked, multicenter trial was designed to randomize 368 patients to voriconazole (1%) or natamycin (5%), applied topically every hour while awake until reepithelialization, then 4 times daily for at least 3 weeks. Eligibility included smear-positive filamentous fungal ulcer and visual acuity of 20/40 to 20/400.

Main Outcome Measures: The primary outcome was best spectacle-corrected visual acuity at 3 months; secondary outcomes included corneal perforation and/or therapeutic penetrating keratoplasty.

Results: A total of 940 patients were screened and 323 were enrolled. Causative organisms included *Fusarium* (128 patients [40%]), *Aspergillus* (54 patients [17%]), and other filamentous fungi (141 patients [43%]). Natamycin-treated cases had significantly better 3-month best spectacle-corrected visual acuity than voriconazole-treated cases (regression coefficient=−0.18 logMAR; 95% CI, −0.30 to −0.05; $P=.006$). Natamycin-treated cases were less likely to have perforation or require therapeutic penetrating keratoplasty (odds ratio=0.42; 95% CI, 0.22 to 0.80; $P=.009$). *Fusarium* cases fared better with natamycin than with voriconazole (regression coefficient=−0.41 logMAR; 95% CI, −0.61 to −0.20; $P<.001$; odds ratio for perforation=0.06; 95% CI, 0.01 to 0.28; $P<.001$), while non-*Fusarium* cases fared similarly (regression coefficient=−0.02 logMAR; 95% CI, −0.17 to 0.13; $P=.81$; odds ratio for perforation=1.08; 95% CI, 0.48 to 2.43; $P=.86$).

Conclusions: Natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to improved results in *Fusarium* cases.

Application to Clinical Practice: Voriconazole should not be used as monotherapy in filamentous keratitis.

Trial Registration: clinicaltrials.gov Identifier: NCT00996736

JAMA Ophthalmol. 2013;131(4):422-429.
Published online December 10, 2012.
doi:10.1001/jamaophthalmol.2013.1497

"***Natamicina va resultar ser superior*** *a voriconazol en el tractament de les* ***úlceres fúngiques filamentoses superficials*** *en termes de curació de la úlcera, millora de la visió i seguretat del tractament".*

Research

JAMA Ophthalmology | Original Investigation | CLINICAL TRIAL

Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II)

A Randomized Clinical Trial

Key Points

Question Is oral voriconazole beneficial when added to topical antifungals in the treatment of fungal keratitis?

Findings In this randomized clinical trial of 240 patients in India and Nepal with severe filamentous fungal keratitis, oral voriconazole or placebo was administered in addition to topical antifungal eyedrops. Oral voriconazole did not decrease the rates of perforation or need for therapeutic penetrating keratoplasty, and patients receiving oral voriconazole experienced more adverse events.

Meaning This study shows no benefit to adding oral voriconazole to topical antifungal eyedrops in the treatment of severe filamentous fungal ulcers.

Research

JAMA Ophthalmology | Original Investigation | CLINICAL TRIAL

Adjunctive Oral Voriconazole Treatment of *Fusarium* Keratitis

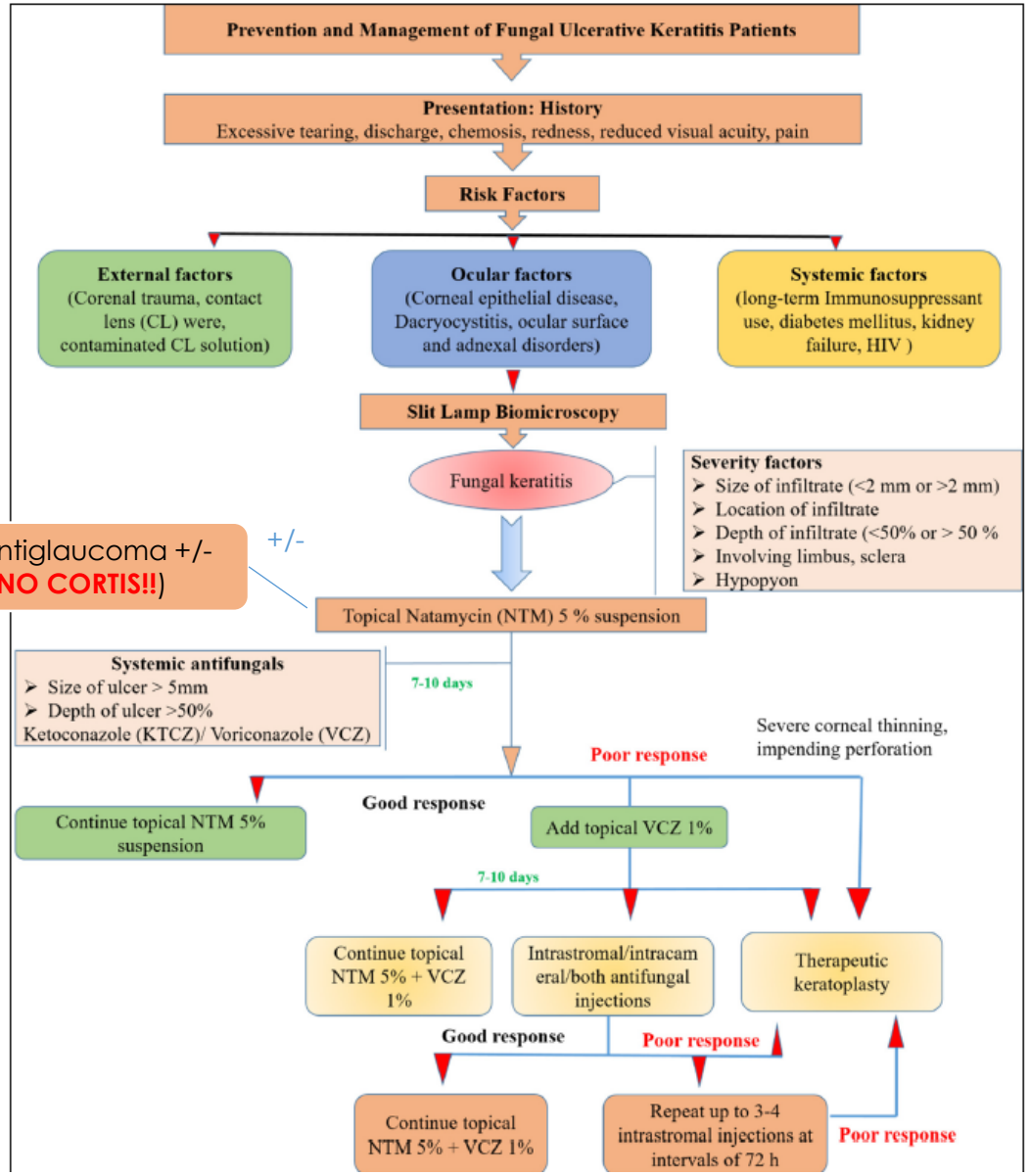
A Secondary Analysis From the Mycotic Ulcer Treatment Trial II

Key Points

Question Is adjunctive oral voriconazole beneficial in *Fusarium* keratitis?

Findings This prespecified subgroup analysis of a randomized clinical trial of 72 patients with culture-positive fungal ulcer and baseline visual acuity of 20/400 or worse evaluated the effect of adjuvant oral voriconazole vs placebo on *Fusarium* keratitis. The study found that *Fusarium* ulcers randomized to treatment with oral voriconazole in addition to topical natamycin and voriconazole had a decreased rate of corneal perforation, smaller scar size, and more rapid reepithelialization.

Meaning *Fusarium* keratitis may benefit from the addition of oral voriconazole to topical natamycin.



Ciclopègic +/- antiglaucoma +/- antiinflamatoris (**NO CORTIS!!**)

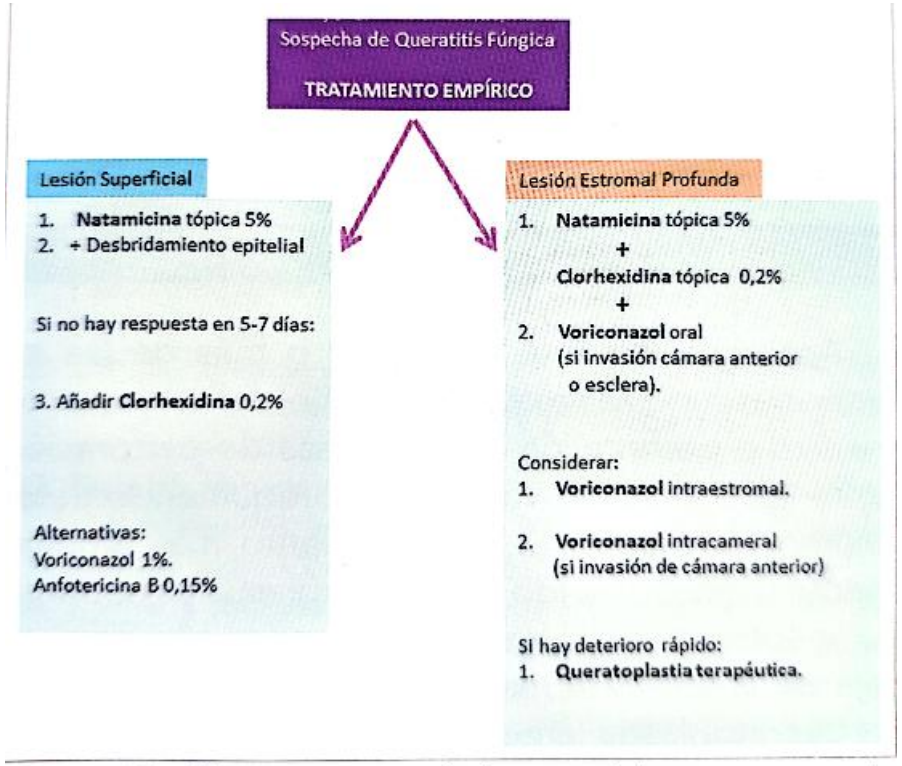


Figura 23. Algoritmo terapéutico empírico en espera de los resultados del cultivo o biopsia corneal ante una sospecha fundada de queratitis fúngica.

DISPONIBILITAT D'ANTIFÚNGICS

DISPONIBILITAT DE PRESENTACIONS OFTÀLMIQUES COMERCIALITZADES D'ANTIFÚNGICS

agencia española de medicamentos y productos sanitarios

Table 5. Commercially Available Topical Antifungal Formulations Used to Treat Corneal Mycotic Ulcers

Drug[a]	Proprietary name	Formulation type	Composition	Marketer
Natamycin	Natamet ED	Ophthalmic suspension	Natamycin (5% w/v), BAK (0.02% w/v), sterile aqueous buffered vehicle (q.s.)	Sun Pharmaceutical Industries Ltd.
	Nataforce ED	Ophthalmic suspension	Natamycin (5% w/v), BAK (0.02% w/v), sterile aqueous buffered vehicle (q.s.)	Mankind Pharma Ltd.
	Natacin ED	Ophthalmic suspension	Natamycin (5% w/v), BAK (0.02% w/v), sterile aqueous buffered vehicle (q.s.)	Entod Pharmaceuticals Ltd.
Amphotericin B[b]	--	Ophthalmic Solution	Amphotericin B (0.5% w/v)	VLS Pharmacy Inc. and Bayview Pharmacy
Fluconazole	Zocon ED	Ophthalmic Solution	Fluconazole (0.3% w/v), BAK (0.02% w/v), WFI (q.s.)	FDC Ltd.
	Esfung ED	Ophthalmic Solution	Fluconazole (0.3% w/v), BAK (0.02% w/v), sterile aqueous buffered vehicle (q.s.)	Essential Pharmaceuticals
	Otoflu ED	Ophthalmic Solution	Fluconazole (0.3% w/v), BAK (0.02% w/v), WFI (q.s.)	Sunways India Pvt Ltd.
Voriconazole	Vozole ED	Sterile lyophilized powder for ED	Voriconazole (30 mg), BAK (0.3 mg), WFI (for reconstitution to make 1% w/v)	Aurolab (Madurai, India)
Itraconazole	Itrapress ED	Ophthalmic suspension	Itraconazole (1% w/v), BAK (0.01% w/v), Sterile aqueous base (q.s.)	Synovia Life Sciences Pvt Ltd.
	Itral ED	Ophthalmic suspension	Itraconazole (1% w/v), BAK (0.02% w/v), Sterile aqueous base (q.s.)	Jawa Pharmaceuticals Pvt Ltd.
	Itral	Ophthalmic ointment	Itraconazole (1% w/v), Sterilized ointment base (q.s.)	Jawa Pharmaceuticals Pvt Ltd.
	Hescitra ED	Ophthalmic suspension	Itraconazole (1% w/v), BAK (0.02% w/v), Sterile aqueous base (q.s.)	Sun Eye Care Pharmaceuticals Pvt. Ltd.
Miconazole	Micozole Eye Caps (Aplicap)	Eye ointment	Miconazole nitrate (1% w/v), Sterilized ointment base (q.s.) packed as 10 × 10 soft gel blister	Jyoti Capsulations Pvt. Ltd.
Econazole	Aurozole ED	Ophthalmic Solution	Econazole (2% w/v), sterile aqueous buffered vehicle (q.s.)	Aurolab (Madurai, India)

[a]ED- Eye drop, BAK- Benzalkonium chloride, WFI- water for injection, q.s. – quantity sufficient. [b]This drug does not have any marketed products. Marketers are providing compounded ED upon request.

POLIENS

AZOLS

PIRIMIDINES

EQUINOCANDINES

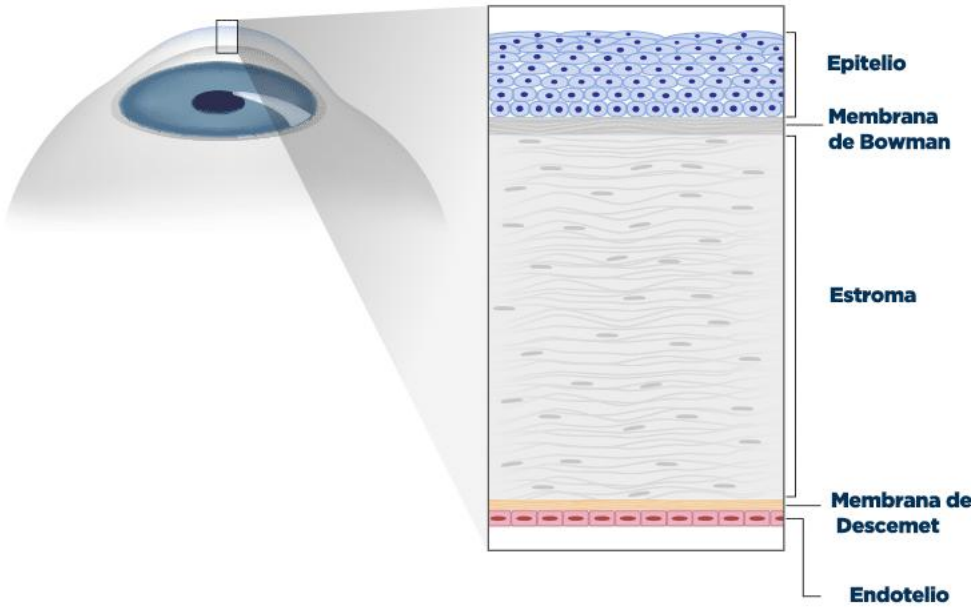
Table 3. Available Antifungal Agents with Their Limitations for the Treatment of FK[277–279]

Agent	Route of administration/Dose	Indication	Limitations
Polyenes			
Amphotericin B	Topical (1.5–5 mg/mL)	First line therapy for *Candida* species. Good to moderate activity against filamentous fungi.	Not commercially available.
		Deep keratitis with partial response to topical therapy	Side effects: cataract, transient iritis and corneal edema
Natamycin	Topical (50 mg/mL)	First choice for *Fusarium*, Good activity against *Aspergillus*, less effective against *Candida* species	Low corneal penetration
Imidazoles			
Econazole	Topical 2%	Effective against *Fusarium*, *Aspergillus*, and *Candida* species	Not commercially available for ophthalmic use
Miconazole	Topical (10 mg/mL)	Effective against *Candida*	Less effective than polyenes
		Adjuvant with topical therapy in patients with low compliance	
Ketoconazole	Topical 1–2%	Broad spectrum	Less effective systemic toxicity (gastric intolerance, hepatotoxicity)
	Oral 200–400 mg/day	As an adjuvant in deep keratitis	
Triazoles			
Fluconazole	Topical 0.3%	Effective against yeast, less effective against filamentous fungi	Filamentous fungi exhibit resistance liver enzyme monitoring
	SC 2 mg/mL		
	Oral 100–400 mg/day	Good intraocular penetration used as adjuvant with topical agents	
Itraconazole	Topical 1%	Effective against *Aspergillus*, *Candida*, less effective against *Fusarium*	Less effective than natamycin
	Oral 200–400 mg/day	As adjuvant with topical therapy in deep keratitis/ intraocular involvement by yeasts	Lower bioavailability, and penetration into ocular tissues than other azoles
Voriconazole	Topical 1–2%	Broad spectrum, FK resistant to polyenes/first-line triazoles.	Less effective than natamycin
	Oral 200 mg BID	Deep keratitis and intraocular involvement	Side effects- blurred vision change in color perception; liver enzyme monitoring during oral use
Posaconazole	Topical 100 mg/mL; 40 mg/mL	Broad spectrum, FK resistant to polyenes/first-line triazoles.	Limited information
	Oral 200 mg QID/ [illegible] BID		
Pyrimidines			
Flucytosine	Topical 10 mg/mL	Synergistic effect with topical Amphotericin B in FK due to yeasts	Narrow spectrum/low penetration into ocular tissues
Echinocandins			
Capsofungin	Topical 0.5%	Yeasts resistant to polyenes and first-line triazoles	Limited information
Micafungin	Topical 0.1%	Yeasts resistant to polyenes and first-line triazoles	Limited information
Allylamine			
Terbinafine	Topical 0.5%	Active against *Aspergillus*, *Fusarium*, *Scedosporium* and *Candida*.	Limited information
	Oral 250 mg/day		

FORMULACIÓ MAGISTRAL OFTÀLMICA ANTIFÚNGICA

"El repte de la formulació oftàlmica tòpica és eludir les barreres de l'ull sense causar dany permanent al teixit".

En general, la biodisponibilitat d'aquestes formulacions és inferior al 5%



Factors fisicoquímics dels fàrmacs

SOLUBILITAT:

Fàrmacs de **naturalesa lipídica** per penetrar a l'epiteli i endoteli però **hidrosolubles** per penetrar a l'estroma.

PES MOLECULAR:

Dificultat molècules hidrosolubles amb **PM > 500 D**

La majoria dels antifúngics utilitzats presenten un perfil de solubilitat en aigua baix i, per tant, una distribució deficient a traves de la barrera cornial.

FORMULACIÓ MAGISTRAL OFTÀLMICA ANTIFÚNGICA

Vehicles utilitzats a les formulacions

Fórmules senzilles amb baixa adaptació a la via oftàlmica
Sistemes de **baixa eficàcia** amb temps de permanència a la superfície ocular molt reduït

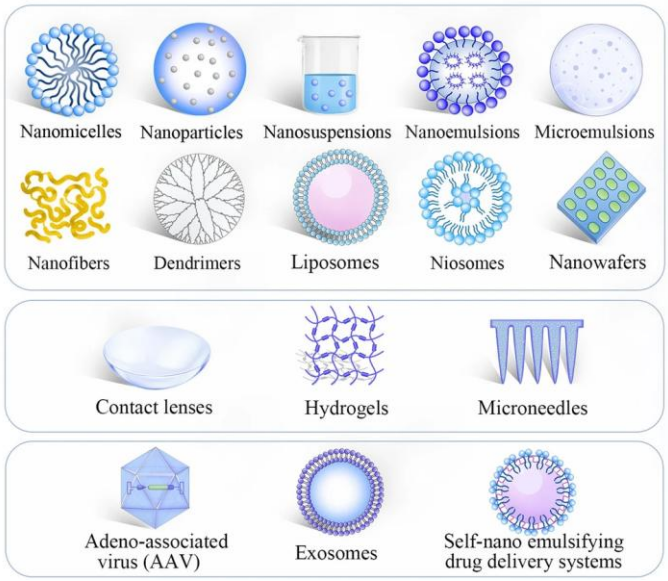
La dilució i el drenatge lacrimal eliminen ràpidament el fàrmac

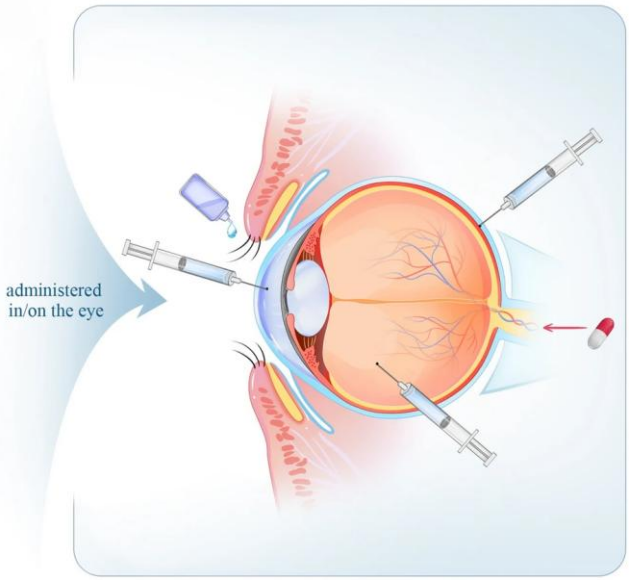
Intervals posològics molt curts, dificultant l'adherència

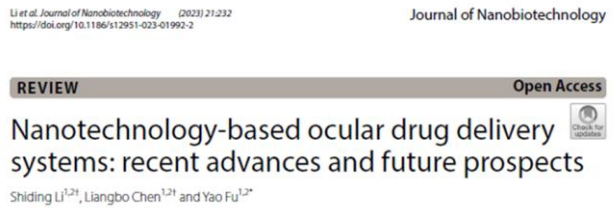
Necessitat de noves formulacions oculars:

Table 1
Advantages and disadvantages of different ocular formulations.

Drug delivery system	Advantages	Disadvantages
Hydrogels	Prolongs residence time and increases bioavailability	Depending on temperature, pH, ion trigger
Cyclodextrin Inclusion complex	Increases solubility, improves bioavailability, Increases permeability, and extends residence time	Limited to improve solubility in soluble drugs
Liposomes comfortable	Long-lasting, reducing the number of administration, controlled release, reducing the number of administration	Stability is poor, clear fast, conjunctival cell absorption problems
Nanoparticle	Small particle size, extended shelf-life, good stability, improved bioavailability, and reduced number of administration	Difficult to control the range of particle size distribution
Nano-suspension	Stability, prolonged contact time	Blurred vision poor patient compliance






Li et al. Journal of Nanobiotechnology (2023) 21:232
https://doi.org/10.1186/s12951-023-01992-2

Journal of Nanobiotechnology

REVIEW Open Access

Nanotechnology-based ocular drug delivery systems: recent advances and future prospects

Shiding Li[1,2†], Liangbo Chen[1,2†] and Yao Fu[1,2*]

pharmaceutics

Pharmaceutics 2023, 15, 35 MDPI

Article

Antifungal Combination Eye Drops for Fungal Keratitis Treatment

Victoria Díaz-Tomé [1,2,3,4], Carlos Bendicho-Lavilla [1,2,3], Xurxo García-Otero [1,2,3,5], Rubén Varela-Fernández [1], Manuel Martín-Pastor [6], José Llovo-Taboada [7], Pilar Alonso-Alonso [7], Pablo Aguiar [5], Miguel González-Barcia [8], Anxo Fernández-Ferreiro [4,8,*] and Francisco J. Otero-Espinar [1,2,3,*]

Combinació **voriconazol 1% + natamicina 0,7% en hidrogel**

Ciclodextrines com excipient: milloren la permanència en la superfície ocular i la permeabilitat transcorneal

2.7.1. Preparation of the Hyaluronic Acid Hydrogel (AHNV)

The AHNV was prepared based on previous studies [33,34]. An amount of 0.4% (*w*/*v*) HA was added to the aqueous solution (SNV) and dispersed by magnetic stirring (200 rpm) at room temperature until complete solubilization.

2.7.2. Preparation of the Polyvinyl Alcohol-Based (Liquifilm®) Hydrogel (LNV)

The LNV was prepared based on previous studies where Liquifilm® was chosen as a vehicle for the preparation of a topical ophthalmic formulation of tacrolimus [35]. In addition, Liquifilm® is used in ophthalmic pharmaceutical compounding for the preparation of antibacterial eye drops in the hospital pharmacy department [36]. An amount of 40% (*w*/*v*) HPβCD was added to 50% of the final volume of Liquifilm® and dispersed under low-intensity magnetic stirring (50 rpm) until its complete solubilization for 12 h at room temperature to avoid bubble formation. Afterwards, the formulation was made up to the final volume, and 1% (*w*/*v*) voriconazole and 0.7% (*w*/*v*) natamycin were added under magnetic stirring (200 rpm) until complete dissolution.

Els estudis realitzats van confirmar que les formulacions complien els requisits de qualitat per a l'administració tòpica oftàlmica i d'activitat antifúngica.
Podrien convertir-se en primera línia de tractament de la QF

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International Journal of Pharmaceutics 344 (2007) 150–153
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Note

Liposomal amphotericin B eye drops to treat fungal keratitis: Physico-chemical and formulation stability

K. Morand [a], A.C. Bartoletti [a,b], A. Bochot [b,*], G. Barratt [b], M.L. Brandely [a], F. Chast [a]

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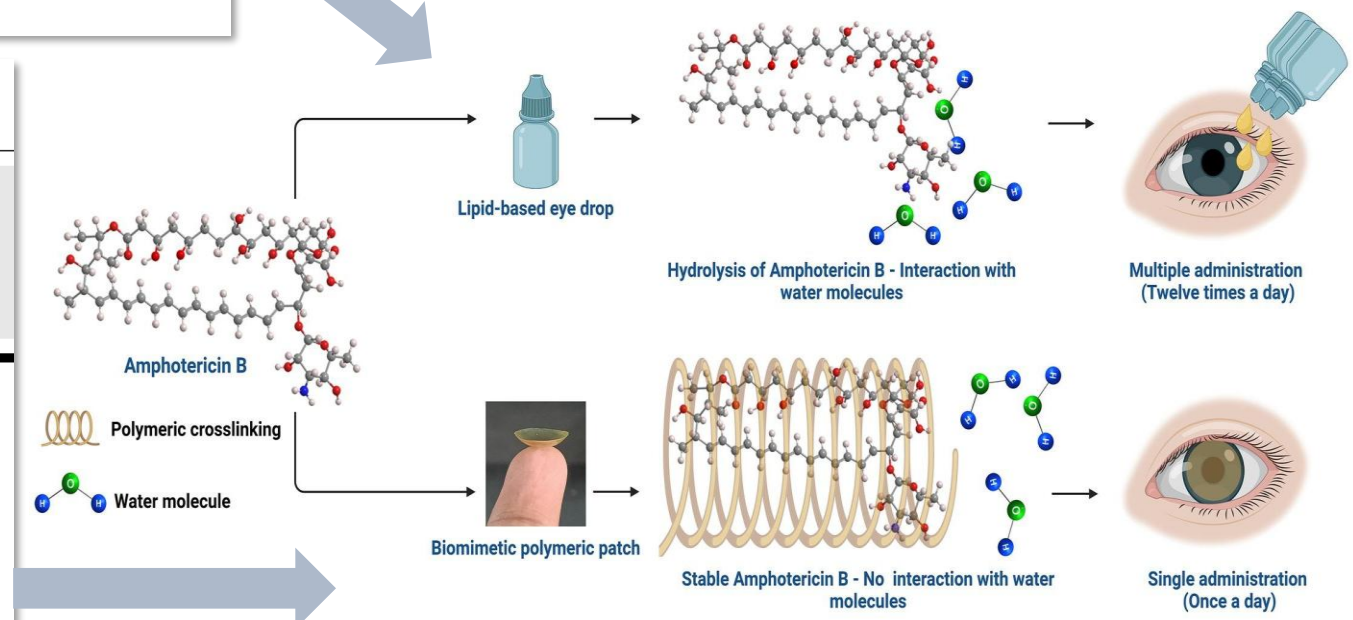
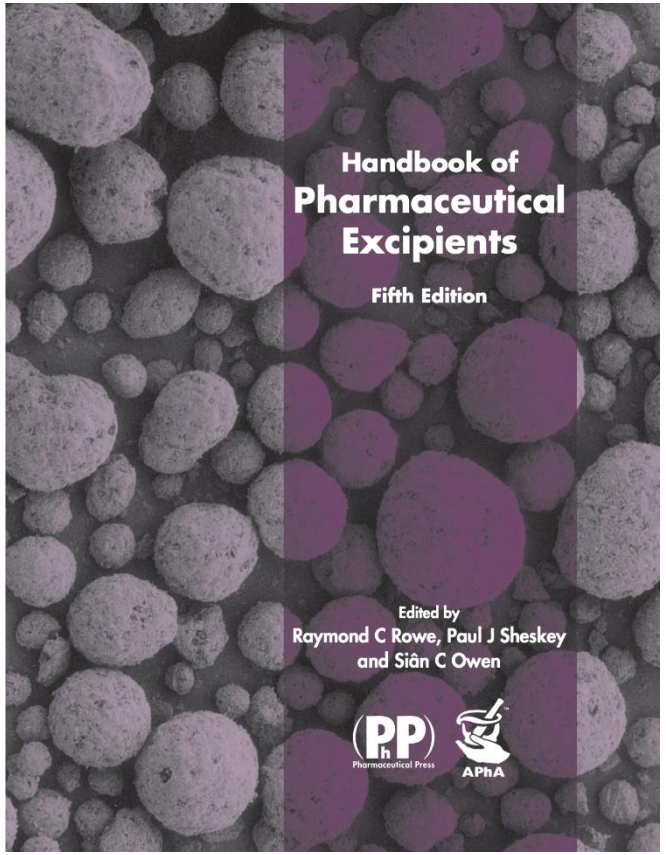
Stability enhancement of Amphotericin B using 3D printed biomimetic polymeric corneal patch to treat fungal infections

Velmurugan Kailasam [a], Manthan S. Hiremath [a], Pandiyan Sudharsan [b], Vasagiri Nagarjuna [c], Prashant Garg [c], Jayabalan Nirmal [a,*]



FORMULACIÓ MAGISTRAL OFTÀLMICA ANTIFÚNGICA

Toxicitat dels excipients de les especialitats farmacèutiques de partida



Cresol

1 Nonproprietary Names
BP: Cresol
JP: Cresol
USPNF: Cresol

2 Synonyms
Cresylic acid; cresylol; hydroxytoluene; tricresol.

3 Chemical Name and CAS Registry Number
Methylphenol [1319-77-3]

4 Empirical Formula and Molecular Weight
C_7H_8O 108.14

5 Structural Formula

m-Cresol

6 Functional Category
Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology
Cresol is used at 0.15–0.3% concentration as an preservative in intramuscular, intradermal, and injectable pharmaceutical formulations. It is also preservative in some topical formulations and as a Cresol is not suitable as a preservative for preparations to be freeze-dried.[1]

8 Description
Cresol consists of a mixture of cresol isomers, phenol, *m*-cresol, and other phenols obtained from petroleum. It is a colorless, yellowish to pale brown or pink-colored liquid, with a characteristic odor phenol but more tarlike. An aqueous solution has taste.

9 Pharmacopeial Specifications
See Table I.

Table I: Pharmacopeial specifications for cresol.

Test	BP 2004	JP 2001	USPNF 23
Identification	+	+	+
Characters	+	–	–
Specific gravity	1.029–1.044	1.032–1.041	1.030–1.038
Distilling range	+	+	195–205°C
Acidity	+	–	–
Hydrocarbons	≤0.15%	+	+
Volatile bases	≤0.15%	–	–
Hydrocarbons and volatile bases combined	≤0.25%	–	–
Phenol	–	–	≤5.0%
Sulfur compounds	+	+	–
Nonvolatile matter	≤0.1%	–	–

10 Typical Properties
Acidity/alkalinity: a saturated aqueous solution is neutral or slightly acidic to litmus.
Antimicrobial activity: cresol is similar to phenol but has slightly more antimicrobial activity. It is moderately active against Gram-positive bacteria, less active against Gram-negative bacteria, yeasts, and molds. Cresol is active below pH 9; optimum activity is obtained in acidic conditions.

14 Safety
Reports of adverse reactions to cresol are generally associated with the use of either the bulk material or cresol-based disinfectants, which may contain up to 50% cresol, rather than for its use as a preservative.

Cresol is similar to phenol although it is less caustic and toxic. However, cresol is sufficiently caustic to be unsuitable for skin and wound disinfection. In studies in rabbits, cresol was found to be metabolized and excreted primarily as the glucuronide.[5]

A patient has survived ingestion of 12 g of cresol though with severe adverse effects.[6]

LD_{50} (mouse, oral): 0.76 g/kg[7]
LD_{50} (rabbit, skin): 2 g/kg
LD_{50} (rat, oral): 1.45 g/kg
See also Sections 17 and 18.

15 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Cresol may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. In the UK, the occupational exposure limit for cresol is 22 mg/m^3 (5 ppm) long-term (8-hour TWA).[8] In the USA, the permissible and recommended exposure limits are 22 mg/m^3 long-term and 10 mg/m^3 long-term respectively.[9]

Polyvinyl Alcohol

1 Nonproprietary Names
PhEur: Poly(vinylis acetas)
USP: Polyvinyl alcohol

2 Synonyms
Airvol; Alcotex; Elvanol; Gelvatol; Gohsenol; Lemol; Mowiol; Polyvinol; PVA; vinyl alcohol polymer.

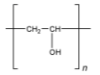
3 Chemical Name and CAS Registry Number
Ethenol, homopolymer [9002-89-5]

4 Empirical Formula and Molecular Weight
$(C_2H_4O)_n$ 20 000–200 000
Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of *n* for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20 000–200 000, *see* Table I.

Table I: Commercially available grades of polyvinyl acohol.

Grade	Molecular weight
High viscosity	~200 000
Medium viscosity	~130 000
Low viscosity	~20 000

5 Structural Formula



6 Functional Category
Coating agent; lubricant; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology
Polyvinyl alcohol is used primarily in ophthalmic formulations. stabilizing agent for emulsions. alcohol is also used as a viscosity formulations such as ophthalmic tears and contact lens solutions. sustained-release formulations transdermal patches.[5] Polyvinyl microspheres when mixed with

8 Description
Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

9 Pharmacopeial Specifications
See Table III.

Table II: Uses of polyvinyl alcohol.

Use	Concentration (%)
Emulsions	0.5
Ophthalmic formulations	0.25–3.00
Topical lotions	2.5

Table III: Pharmacopeial specifications for polyvinyl alcohol.

Test	PhEur 2005	USP 28
Viscosity	–	+
pH	4.5–6.5	5.0–8.0
Loss on drying	≤5.0%	≤5.0%
Residue on ignition	≤1.0%	≤2.0%
Water-soluble substances	–	≤0.1%
Degree of hydrolysis	–	≤0.1%
Organic volatile impurities	–	+
Assay	–	85.0–115.0%

10 Typical Properties
Melting point:
228°C for fully hydrolyzed grades;
180–190°C for partially hydrolyzed grades.
Refractive index: n_D^{20} = 1.49–1.53
Solubility: soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for

14 Safety
Polyvinyl alcohol is generally considered a nontoxic material. It is nonirritant to the skin and eyes at concentrations up to 10%; concentrations up to 7% are used in cosmetics.

Studies in rats have shown that polyvinyl alcohol 5% w/v aqueous solution injected subcutaneously can cause anemia and infiltrate various organs and tissues.[7]

LD_{50} (mouse, oral): 14.7 g/kg
LD_{50} (rat, oral): >20 g/kg

FORMULACIÓ MAGISTRAL OFTÀLMICA ANTIFÚNGICA

Concentració de fàrmac

Gradient de concentració entre la pel·lícula lacrimal i l'epiteli cornial

Perill de toxicitat

ANTIFÚNGICO	PRESENTACIÓN DISPONIBLE	CONCENTRACIÓN EN HUMOR ACUOSO	REF
Anfotericina B	FFMM. Colirio anfotericina B deoxicolato (Fungizone®) 1,5 mg/ml	No penetra sin un desbridamiento epitelial previo.	38 39
Natamicina	Medicamento extranjero Natacyn® 50 mg/ml	No penetra sin un desbridamiento epitelial previo.	40
Econazol	Medicamento extranjero Aurazole® 20 mg/ml	0,504 µg/ml	41
Fluconazol	FFMM. Colirio de fluconazol 2 mg/ml	7,13 µg/ml	42
Voriconazol	FFMM. Colirio de voriconazol (Vfend®) 10 mg/ml	6 µg/ml	43

Tabla 1. Concentración alcanzada por los colirios antifúngicos en humor acuoso.

Susceptibilitat dels microorganismes

	ANFOTERICINA	NATAMICINA	VORICONAZOL	FLUCONAZOL	ECONAZOL
Aspergillus psp	0,09 ~ ≥32	1 ~ 64	0,25 ~ 8	32 ~ ≥256	3,12
Fusarium spp.	0,06 ~ ≥32	2 ~ 32	0,25 ~ 16	0,001 ~ ≥256	0,053
Candida albicans	0,001~ 160	-	0,001~ 16	0,03 ~ ≥256	0,25 ~ 100

Los valores publicados, difieren bastante unos autores a otros y los estudios no tienen un gran casuística 44 - 51

Tabla 2. CMI de los agentes etiológicos más frecuentes en las queratitis fúngicas (µg/ml).

VIES D'ADMINISTRACIÓ

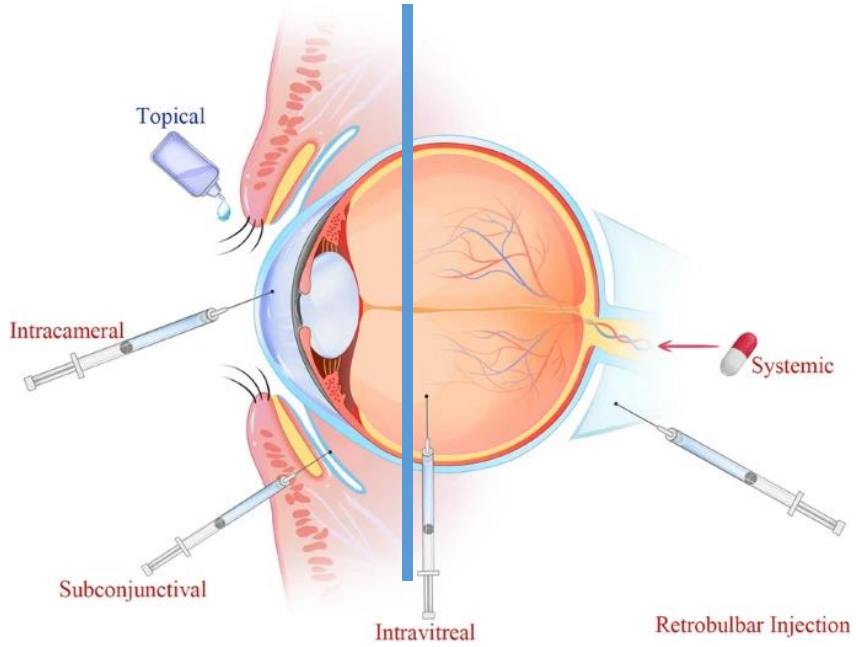


Table 1 Comparison of various routes of ocular drug administration

Delivery routes	Advantages	Disadvantages	Diseases Treated
Topical	High patient compliance, self-administration, noninvasive nature	Corneal barrier, dilution and efflux, low bioavailability, high dosing	Conjunctivitis, keratitis, uveitis, episcleritis, scleritis, blepharitis
Subconjunctival and transscleral administration	Anterior and posterior drug delivery, ideal for depot formation	Choroidal and conjunctival circulation increase toxicity subconjunctival hemorrhage	Glaucoma, AMD cytomegalovirus retinitis,
Intracameral administration	Reduce corneal and systemic side effects. topical steroid use; high anterior chamber drug concentration	Toxic endothelial cell destruction syndrome and toxic anterior segment syndrome	Anesthesia, inflammation, endophthalmitis, pupil dilation
Intravitreal injection	Direct delivery to the vitreous humor and retina, BRB avoidance, high bioavailability and acute dosing	Poor patient compliance, invasiveness, drug toxicity, retinal detachment, cataract endophthalmitis, hemorrhage	AMD, central/branched retinal vein occlusion, diabetic macular edema, cytomegalovirus retinitis
Retrobulbar injection	Selective delivery to both anterior and posterior segments, avoidance of corneal and conjunctival barriers, long duration of action, a site for depot formulations	Poor patient compliance, invasiveness, drug deposition,compliances including pain, bleeding, infection, scarring, eyeball or optic nerve damage	Anesthesia
Systemic administration	High patient compliance	Blood ocular barriers, low bioavailability, systemic toxicity caused by high dosing	Scleritis, episcleritis, cytomegalovirus retinitis

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Tissue Penetration of Antifungal Agents

Timothy Felton,[a,b] Peter F. Troke,[c] William W. Hope[b]

Clinical Microbiology Reviews
January 2014 Volume 27 Number 1

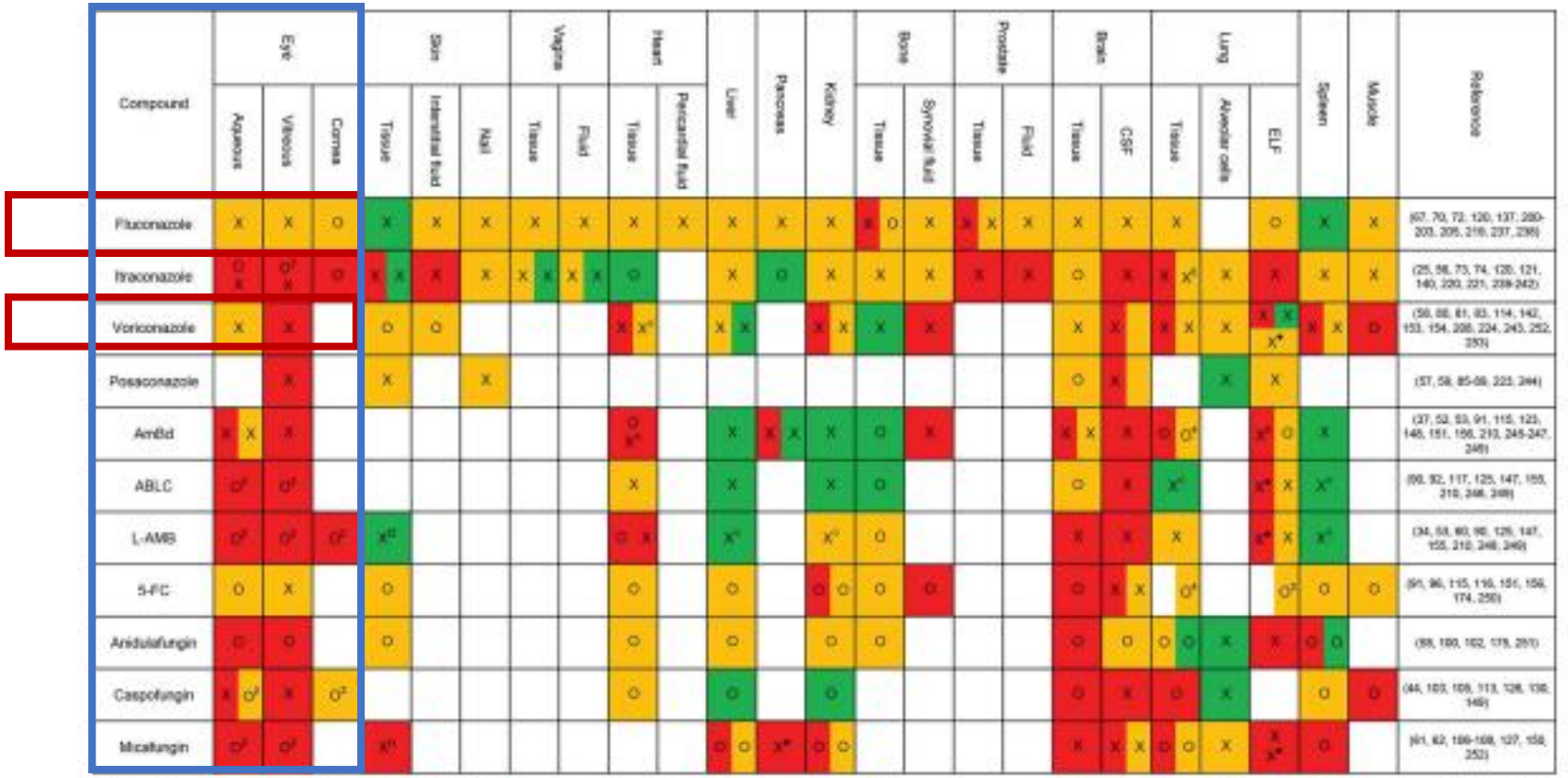


FIG 7 Concentrations in tissues and body fluids for each systemic antifungal agent relative to its concentration in plasma. X, human data; O, animal data. Colors illustrate differing ratios; multiple colors within a column give the range of published data. Red, from below level of detection to ≤0.5 times the plasma concentration; yellow, from >0.5 times to ≤5 times the plasma concentration; green, >5 times the plasma concentration; white, no data. ●, pleural fluid, buccal mucosa, or pancreatic pseudocyst; open diamond, based on autopsy data and human pharmacokinetics; Ω, wound fluid; o^2, only detected in inflamed eyes; o^3, bronchial secretions; x^3, below level of detection in bronchial secretions; o^4, pulmonary lymph; x^5, bronchial biopsy specimen.

Arquivos Brasileiros de Oftalmologia

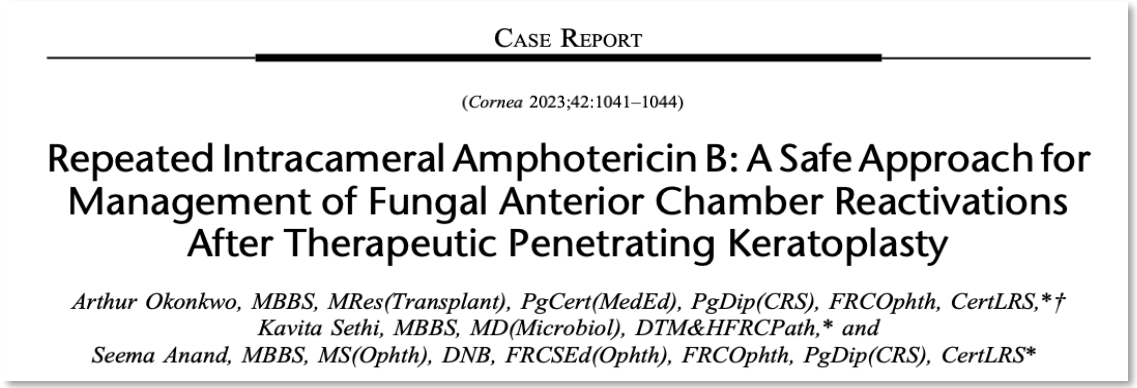
ORIGINAL ARTICLE

Intracameral voriconazole for severe fungal keratitis: a case series

Fernanda M. Bezerra[1], Ludmila N. P. Silva[1], Larissa L. Aguiar[1], Maria Cecília Z. Yu[1], Flavio J. Rocha[2], Luciene B. Sousa[1,3], Ana Luisa Höfling-Lima[1], Lauro A. de Oliveira[1]

50 mcg/0,1 ml

Entre 1 i 4 injeccions interval 72h



CASE REPORT

(*Cornea* 2023;42:1041–1044)

Repeated Intracameral Amphotericin B: A Safe Approach for Management of Fungal Anterior Chamber Reactivations After Therapeutic Penetrating Keratoplasty

Arthur Okonkwo, MBBS, MRes(Transplant), PgCert(MedEd), PgDip(CRS), FRCOphth, CertLRS,† Kavita Sethi, MBBS, MD(Microbiol), DTM&HFRCPath,* and Seema Anand, MBBS, MS(Ophth), DNB, FRCSEd(Ophth), FRCOphth, PgDip(CRS), CertLRS**

5 - 10 mcg/0,1 ml

Dosi acumulada de 35 mcg amb bona tolerància

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Documento de consenso

Consenso sobre preparaciones de medicamentos intraoculares

Gonzaga Garay-Aramburu[a], José María Alonso Herreros[b,*], Marta Núñez Izquierdo[a], Juan Francisco Márquez Peiró[c], Erika Vázquez Cruchaga[d], Fernando González del Valle[e] y José Ignacio Fernández-Vigo[f]

- Revisió material sanitari: xeringues i agulles
- Selecció de productes i proveïdors
- Revisió tècniques de preparació, manipulació i administració
- Revisió períodes de validesa

Tabla 4
Periodo de validez fisicoquímica de preparaciones intravitreas más usuales. El periodo de validez a aplicar estará limitado por los controles microbiológicos descritos en la Guía de Buenas Prácticas de Preparación de Medicamentos en los servicios de Farmacia Hospitalaria, según tamaño del lote o posible fabricación a terceros

Uso	Fármaco	Periodo de validez fisicoquímica (días)	Condiciones (°C)	Material de las jeringas	Referencia	Grado de evidencia (WWW.STABILIS.ORG)
Biológicos	Bevacizumab 25 mg/ml	180	2-8	Policarbonato Polipropileno	[50]	A+
	Ranibizumab 0,5 mg/0,05 ml	28	2-8	Plástico (no especificado)	[51]	
	Aflibercept 2 mg/0,05 ml	28	2-8	Plástico (no especificado)		
	Faricimab 6 mg/0,05 ml	24 horas	2-8	Policarbonato Polipropileno	[52]	
		37	4	Policarbonato	[53]	
	Alteplasa intravitrea 25 µg/0,1 ml	365	-70	Plástico (no especificado)	[54]	
Antiinfecciosos	Cefuroxima 1 mg/0,1 ml	120	-21	Plástico (no especificado)	[55]	A+
		365	-20	Polipropileno	[56]	B
		21	2-8			
	Ceftazidima 2 mg/0,1 ml Vancomicina 1 mg/0,1 ml Moxifloxacino 160 µg/0,1 ml	168	-20	Polipropileno	[57]	
	Amikacina 100-400 µg/0,1 ml	84	2-8	Plástico	[58]	B
		168	-20	(no especificado)		
	Clindamicina 5 mg/ml o 10 mg/ml	68	-10	PVC	[59]	A
		54	5			
	Ganciclovir 200 µg/0,1ml 400 µg/0,1 ml	185	2-8	Polipropileno	[60]	A
	Foscarnet	30	5	PVC	[61]	C
	Voriconazol 0,5 mg/ml	11	2-8	PVC	[62]	B
	0,1 mg/ml	45	-20	Plástico (no especificado)	[63]	
Corticoides	Dexametasona 400 µg/0,1 ml	22	25	Polipropileno	[a][64–66]	

PVC: Cloruro de Polivinilo.
Para detalles concretos de la técnica de preparación se recomienda consultar fuentes especializadas[67–69].
[a] No se disponen de estudios de estabilidad de calidad en las concentraciones y forma de uso descrita para administración intravítrea, aunque la mayoría de los autores consideran que el periodo de validez recomendado es una extrapolación adecuada a lo obtenido por los trabajos originales citados.

POLIENS

	NATAMICINA
MECANISME ACCIÓ	S'uneix a l'ergosterol de la membrana del fong i altera la seva permeabilitat
ESPECTRE D'ACTIVITAT	Ampli espectre incloent *Candida* i *Scedosporium spp* Tractament d'elecció **fongs filamentosos** (*Fusarium* i *aspergillus spp*)
PENETRACIÓ CÒRNIA	Presenta un **elevat PM** que dificulta la penetració. L'eliminació de l'epiteli millora la penetració cornial. En queratitis greus o profundes no es recomana en monoteràpia
POSOLOGIA	1 gota cada hora (dia i nit primeres 48h i després durant el dia) durant 7-10 dies. Continuar 4 cops al dia durant 4 setmanes més
EFECTES ADVERSOS	Bona tolerància irritació ocular, envermelliment, sensació de cos estrany
DISPONIBILITAT PRESENTACIÓ/ VIA ADMINISTRACIÓ	Única especialitat comercialitzada FDA (1960): **Natamicina 5% suspensió oftàlmica** No s'administra via subconjuntival pel potencial efecte tòxic de necrosi conjuntival.

POLIENS

	AMFOTERICINA B LIPOSOMAL
MECANISME ACCIÓ	Unió ergosterol creant pors a la membrana cel·lular fong
ESPECTRE D'ACTIVITAT	Activitat per *Aspergillus*, *Fusarium* i *Candida spp* Tractament d'elecció ***Candida spp***
PENETRACIÓ CÒRNIA	Presenta un **elevat PM** que dificulta la penetració. L'eliminació de l'epiteli permet arribar a concentracions òptimes a l'estroma.
POSOLOGIA	Cada 2 hores fins milloria, després cada 6 h fins resolució
EFECTES ADVERSOS	La forma liposomal millor perfil seguretat que desoxicolat Irritació ocular concentracions > 0,5%
DISPONIBILITAT PRESENTACIÓ/ VIA ADMINISTRACIÓ	**Amfotericina B liposomal (FM):** Tòpica (0,5%) Estabilitat 180 dies refrigerat Intrastromal (5 -10 mcL/0,1 mL) Intracameral (5 – 10 mcL/0,1 mL Subconjuntival (1,5 mg/0,3 mL) més efectes adversos

AZOLS

	VORICONAZOL
MECANISME ACCIÓ	Inhibeix la síntesi de l'ergosterol de les membranes plasmàtiques fúngiques
ESPECTRE D'ACTIVITAT	Ampli espectre incloent *Aspergillus*, *Candida*, *Paecilomyces*, *Fusarium* i *Scedosporium spp* Primera línia si resistències poliens
PENETRACIÓ CÒRNIA	**Bona penetració ocular**, nivells adequats en càmera anterior.
POSOLOGIA	1 gota cada hora 1 setmana – 1 gota cada 2 hores durant el dia 2 setmanes més (MUTT II)
EFECTES ADVERSOS	Via tòpica i local: visió borrosa i canvis a la percepció dels colors (tòpica) Via sistèmica: alteracions visuals, cefalea, edema perifèric, alteracions gastrointestinals i alteració enzims hepàtiques
DISPONIBILITAT PRESENTACIÓ/ VIA ADMINISTRACIÓ	**Voriconazol FM:** Tòpic (**1%** - 2%) Intracameral (50 mcg/0,1 mL) Intraestromal (100 mcg/0,1 mL) rentats càmera anterior? Oral (400mg/12h D1 / 200 mg/12h D2-20 MUTT II)

	CLORHEXIDINA
MECANISME ACCIÓ	Antisèptic amb propietats antibacterianes i antifúngiques
ESPECTRE D'ACTIVITAT	Biocida d'ampli espectre Menys eficaç que natamicina
POSOLOGIA	1 gota cada hora (dia i nit primeres 48h i després durant el dia) durant 7-10 dies. Continuar 4 cops al dia durant 2 setmanes més
DISPONIBILITAT PRESENTACIÓ/ VIA ADMINISTRACIÓ	**Clorhexidina 0,2% col·liri (FM)**

Conclusion Chlorhexidine 0.2% was found to be a useful sequential adjunctive topical antifungal in cases of fungal keratitis not responding to natamycin 5%, which warrants further evaluation.

AMERICAN ACADEMY OF OPHTHALMOLOGY

Topical Chlorhexidine 0.2% versus Topical Natamycin 5% for the Treatment of Fungal Keratitis in Nepal

A Randomized Controlled Noninferiority Trial

Original research

BMJ Open Ophthalmology

Chlorhexidine gluconate 0.2% as a treatment for recalcitrant fungal keratitis in Uganda: a pilot study

Simon Arunga [1,2] Tumu Mbarak,[2] Abel Ebong,[2] James Mwesigye,[2] Dan Kuguminkiriza,[3] Abeer H A Mohamed-Ahmed,[1] Jeremy John Hoffman,[1] Astrid Leck,[1] Victor Hu,[1,4] Matthew Burton[1]

Key messages

What is already known about this subject?
- Microbial keratitis (MK) is a major ophthalmic public health problem, particularly in low-income and middle-income countries.
- MK is a major cause of blindness in sub-Saharan Africa.
- A large proportion of MK is due to fungal keratitis.
- Natamycin 5% eye-drops is the preferred first-line treatment option for fungal keratitis, however, not all cases respond well to natamycin.
- Other options for treatment of fungal keratitis are limited.

What are the new findings?
- Patients with recalcitrant fungal keratitis not responding to natamycin 5% eye-drops responded well to an additional chlorhexidine 0.2% eye-drops.

How might these results change the focus of research or clinical practice?
- Chlorhexidine 0.2% eye-drops could be a viable sequential combination option for patients with recalcitrant fungal keratitis not responding to natamycin 5%.

CASPONFUGINA 0,5% col·liri

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Review

Clinical utility of caspofungin eye drops in fungal keratitis

Chin Fen Neoh[a,b], Mark Daniell[c,d], Sharon C.-A. Chen[e], Kay Stewart[b], David C.M. Kong[b,*]

Formulation and stability of topical caspofungin

Currently, caspofungin acetate is only available in 70 mg and 50 mg injection vials. Therefore, caspofungin eye drops must be extemporaneously prepared by reconstituting the i.v. formulation using aseptic technique. As per the manufacturer's instructions, the vials can be reconstituted with 10.5 mL of water for injection or normal saline to give 7 mg/mL (70 mg vial) or 5 mg/mL (50 mg vial) solutions [148]. A 50 mg vial of caspofungin contains excipients [149], including sucrose (35.7 mg), mannitol (23.8 mg), glacial acetic acid (1.83 mg) and a small quantity of sodium hydroxide to adjust the pH of the formulation (M. Arens, Merck Sharp &

ESTABILITAT:

4 setmanes refrigeració / 72 h TA

DADES HUMANS LIMITATS:

QF per A. Alternata

Natamicina + voriconazol tòpic: progressió

Múltiples injeccions intrastromal voriconazol + caspofungina 0,5% col·liri cada 2 h

CAS 1: EVOLUCIÓ

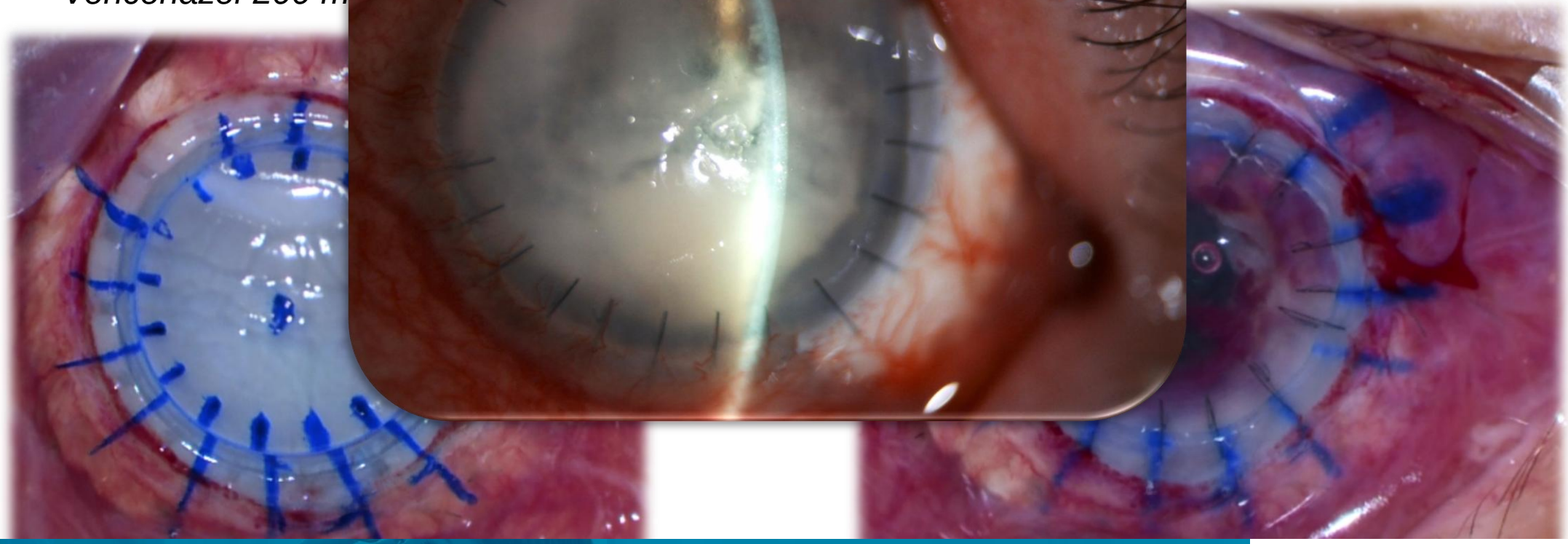
18/12/24 → Escleroqueratoplastia

- *Clorehexidina 0,02% c/*
- *Voriconazol c/3h*
- *Amfotericina B c/3*
- *Ciclosporina 1% c/*
- *Voriconazol 200 m*

11/12/24

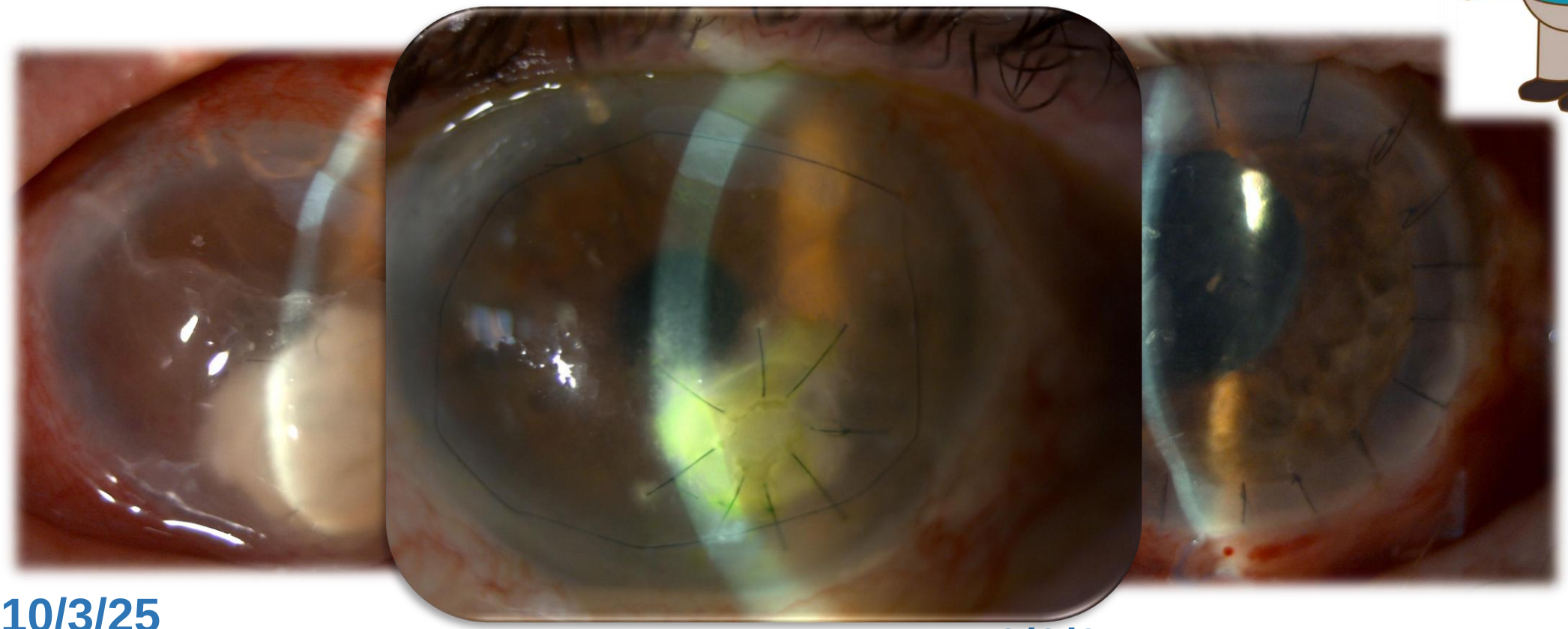
20/03/24

egatius per



CAS 2: EVOLUCIÓ

4/03/25



10/3/25

Evolució ràpida i tórpida

Voriconazol 1% c/2h

Amfotericina B c/3h

13/3/25

Reintervenció queratoplàstia

Queratitis fúngica...

- És una infecció **greu de la còrnia** que suposa un **repte diagnòstic i terapèutic**
- L'abús de **lents de contacte** i **corticoesteroides** han incrementat la incidencia al nostre entorn.
- La primera opció terapèutica són els **antifúngics tòpics** que s'han d'iniciar de forma precoç i la durada del tractament és llarga.
- **L'arsenal terapèutic** és molt **limitat** i l'eficàcia és baixa.
- **Natamicina**, **voriconazol** i **amfotericina B** són els antifúngics amb major evidència científica.
- La **formulació magistral** juga un paper molt important però és necessari desenvolupar **nous sistemes d'administració ocular** d'antifúngics.

QUERATITIS FÚNGICA

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