



UNIVERSITÀ  
DEGLI STUDI DI BARI  
ALDO MORO



# LE INFEZIONI FUNGINE: UN PROBLEMA EMERGENTE DI SANITÀ PUBBLICA, DALLA EZIOLOGIA ALLA TERAPIA

**SHORT MASTER**

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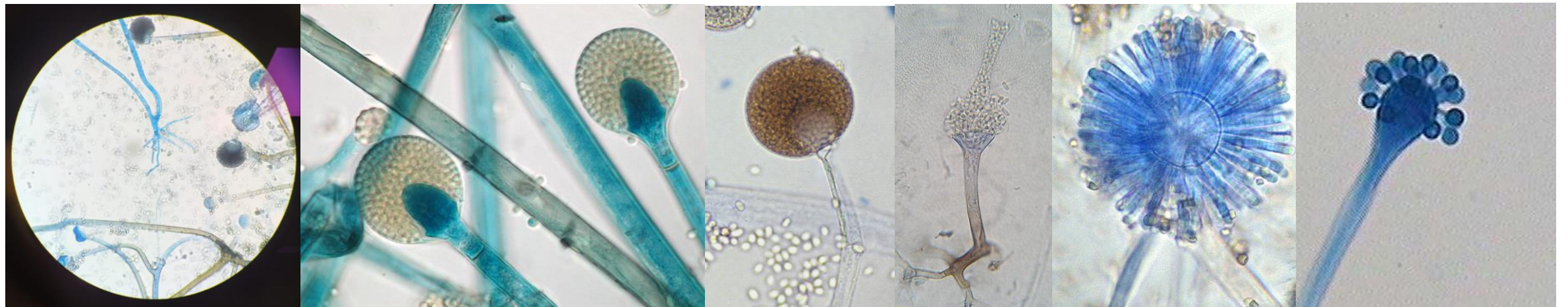
# **Le Mucormicosi e le Entomoftoromicosi nell' uomo**



# Mucormicosi

- Micosi cosmopolita causata da un gruppo di funghi filamentosi opportunisti

Subphylum Mucromycotina Ordine Mucorales



*Rhizopus* , *Lichteimia (Absidia)*, *Rhizomucor*, *Mucor* , *Saksenaea*, *Apophysomyces*, *Cunninghamella*, ....



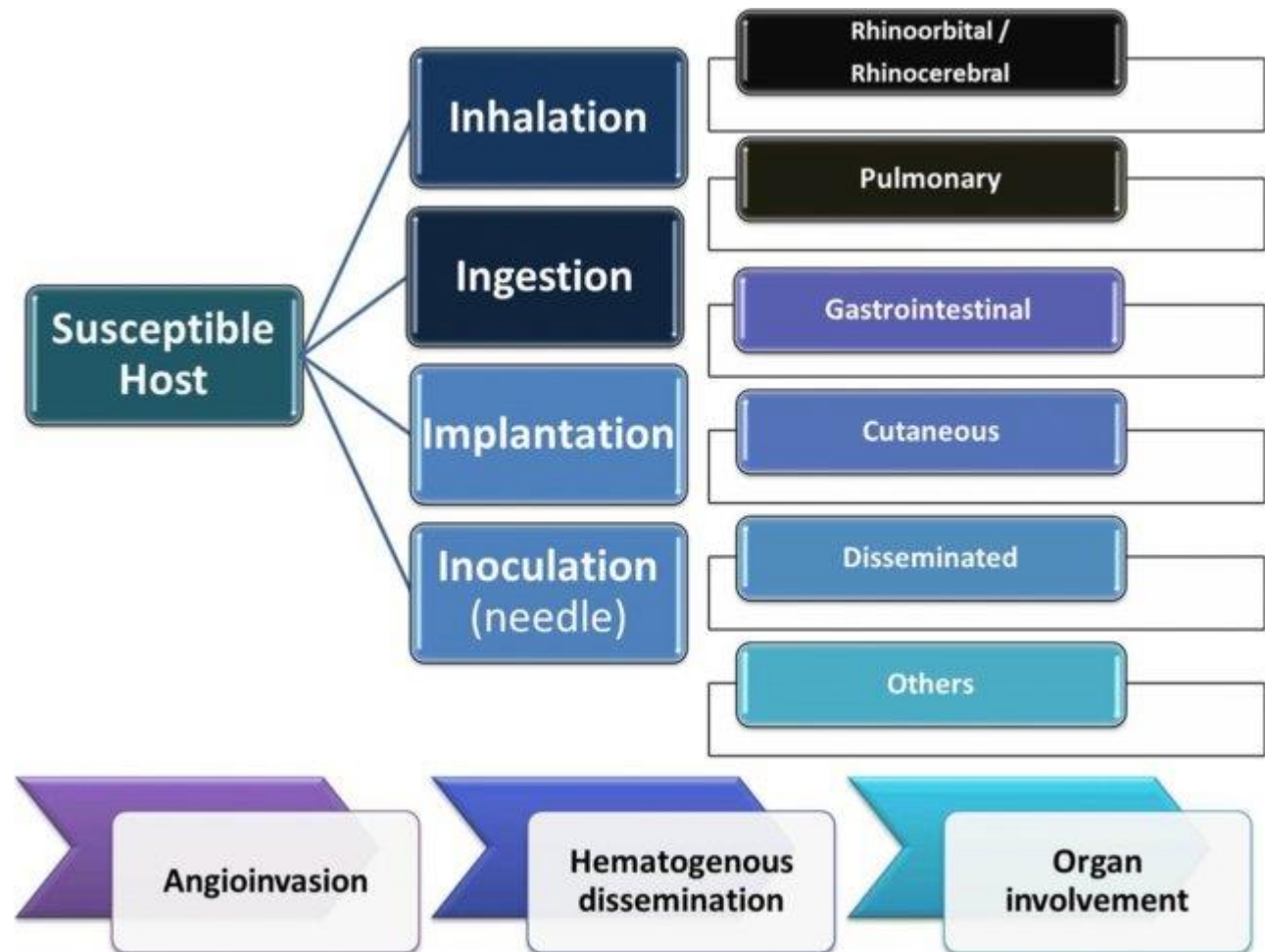
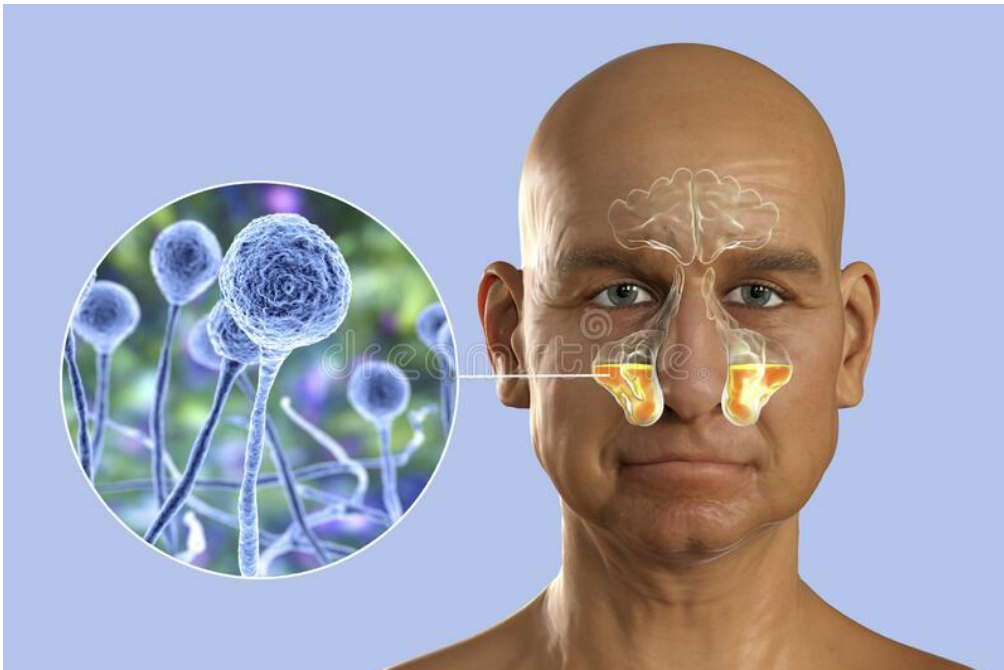
# Mucorales

- Ubiquo (materia organica en descomposizione, aria, .....)





**Vie di infezioni:** respiratoria (inalatoria), contaminazione delle superficie esposte in conseguenza di un alterazione delle barriere anatomiche (EJ: traumatica, ustioni, quirurgica), secondaria a protesi o catetere contaminati, gástrica.



# Mucormicosi

- Infezione invasiva
- Angioinvasiva



trombosi

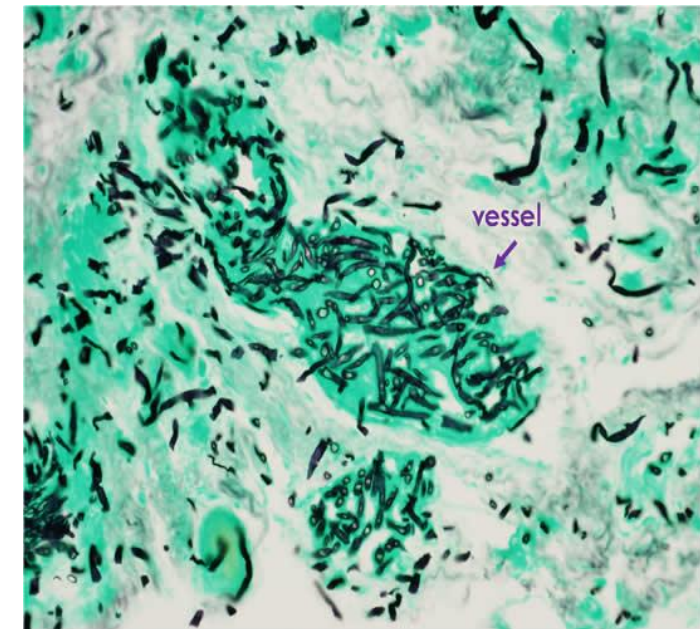
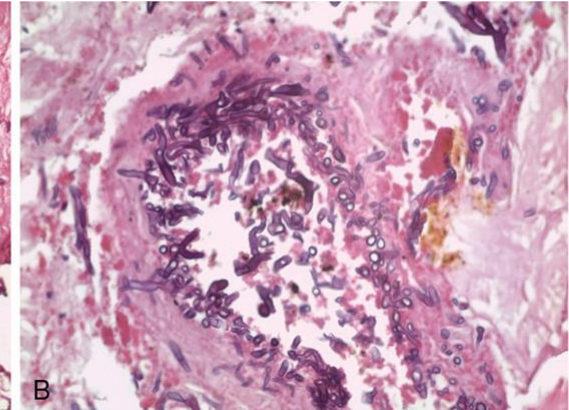
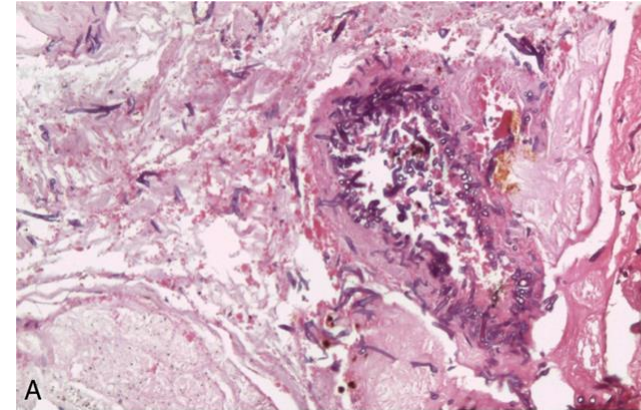


ischemia

infarti



necrosi tissulare





## Fagedenic ulcer

ulcerazione distruttiva veloce del tessuto

Koine Greek φαγεδαινικός (*phagedainikós*) cane famelico

Etiologie possibile:

- Fascite necrotizante
- Infezioni batteriche: *Streptococcus*, *Klebsiella*, *Clostridium*, etc.
- **Mucormicosi**





World Health Organization

Emergenza medica  
Alta mortalit 

# Mucormycosis

Mucormycosis is a serious but rare fungal infection, caused by the 'mucormycetes' group of fungi. It has been incorrectly called 'Black Fungus' recently, but the fungi causing mucormycosis are of a variety of colours.

**1 Who is at risk**  
In most people, the fungi do not cause harm. There is a greater risk of infection in people:

- With diabetes.
- With cancer.
- With HIV/AIDS.
- Who have had treatment with higher doses or longer courses of steroids.
- Who have weak immune systems for other reasons.

Recently many people with COVID-19 have been diagnosed with mucormycosis. It is not currently known if this is due to COVID-19 or some other reason.

**2 How does the infection spread**

- The fungi are found throughout the environment, and most people breathe them in without any effect.
- People with a weak immune system can develop infection in the sinuses and lungs when the fungi enter their airways.
- In rare cases, skin infection occurs, usually only after a skin injury.
- They do not spread from person to person.
- In some rare cases, it has been known to affect the gastro-intestinal system.

**3 How can I recognize it**  
Some common symptoms of mucormycosis are:

- Swelling of the face and around the eye, usually on one side.
- Facial pain or headache, usually on one side.
- Red eye, usually in one eye.
- Black patches on the nose or the roof of the mouth. If you have these, please speak to a health care provider urgently.
- Fever.

Many of these symptoms, such as fever and headache, are also common symptoms of other diseases, including COVID-19. Mucormycosis needs to be confirmed through a laboratory test. If you are at greater risk (refer to section 1) and have these symptoms consult your health care provider.

**4 How is mucormycosis detected**  
The usual way to confirm is for a health care provider to:

- Take a sample from the inside of the nose or a sinus for laboratory testing.
- See the fungus under a microscope or grow it using 'fungal culture'.
- Also conduct scans or camera-based (endoscopy) tests of the sinuses, head and lungs if necessary.

**5 What is the treatment**  
Strictly follow your health care provider's advice.

- Mucormycosis is treated with antifungal medicines. These must only be used as advised by a health care provider.
- Surgery may also be needed around the nose and eye sometimes.
- Do not self-medicate - these drugs can have harmful effects if they are not used properly.

**6 How can we protect ourselves**  
Most healthy people are at very low risk of this disease. There is no vaccine for mucormycosis. Those at greater risk (refer to section 1) could reduce their risk by protecting themselves from the fungi in the environment:

- Avoid areas with a lot of dust, like construction sites.
- Avoid damp buildings or those damaged by water, for example due to floods and cyclones.
- Avoid close contact with soil.
- Wear clothes that cover arms and legs while working outdoors.
- If you cut your skin, clean the injury area with soap and water.



Dr. Alexandro Bonifaz

06/04/15

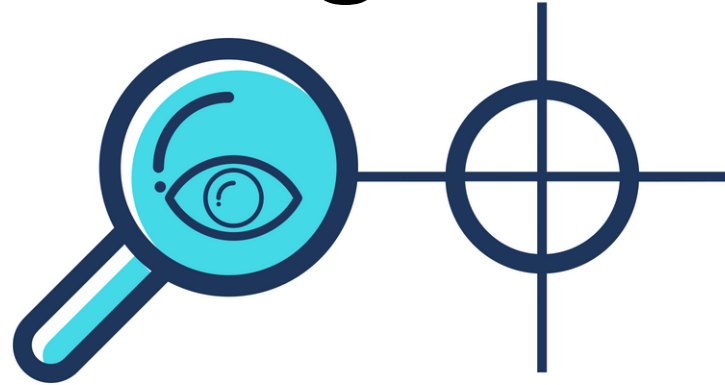
07/04/15



# Mucormicosi – Soggetti a rischio - fattori predisponenti

- ❖ Diabete non controllata / chetoacidosi (≈ 85%)
- ❖ Sovraccarico di ferro
- ❖ Malattie oncoematologiche
- ❖ Trapiantati (TOS - cellule staminali ematopoietiche )
- ❖ Collagenopatie (LES)
- ❖ Terapie steroidee e quelle immunosoppressive
- ❖ alte immunocompromissione
  
- ❖ Ustionati
- ❖ Traumatismi
- ❖ Interventi chirurgici
- ❖ Pazienti con gravi alterazioni della motilità intestinale o dell'attività naturale della mucosa.

# Micologia Medica



Mucomicosi – essenzialmente necrotizzante





SPUTNIK

Covid, primo caso di "fungo nero"  
in Messico: giovane ricoverato con  
sintomi



**BLACK FUNGUS**  
MUCORMYCOSIS SYMPTOMS



FEVER



HEADACHE



COUGHING



SHORTNESS  
OF BREATH



BLOODY  
VOMIT



BLURRED OR  
DOUBLE VISION



ALTERED  
MENTAL STATUS



PAIN, REDNESS  
AROUND EYES  
AND/OR NOSE

# *Mucorales*



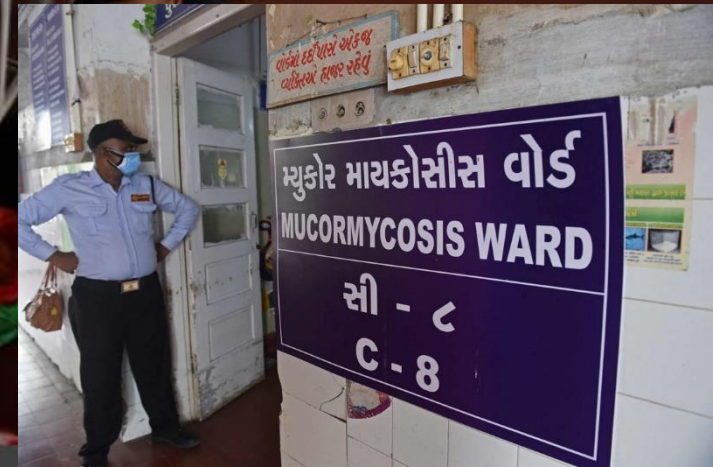




Mata Ambar Tripathi, 65, who lost his eye due to Mucormycosis, also known as black fungus, gestures after a doctor's examined him at hospital in Ghaziabad on the outskirts of New Delhi, India June 27, 2021. Picture taken June 27, 2021. REUTERS/Adnan Abidi



Patients suffering from Mucormycosis, also known as black fungus, are seen inside a hospital ward in Ahmedabad, India, June 25, 2021. Picture taken June 25, 2021. REUTERS/Amit Dave



## THE TIMES OF INDIA

India Ram Temple In Ayodhya LAC Face-Off #MaskIndia Coronavirus Outbreak Opinions And Features Times Evoke Maharashtra Delhi

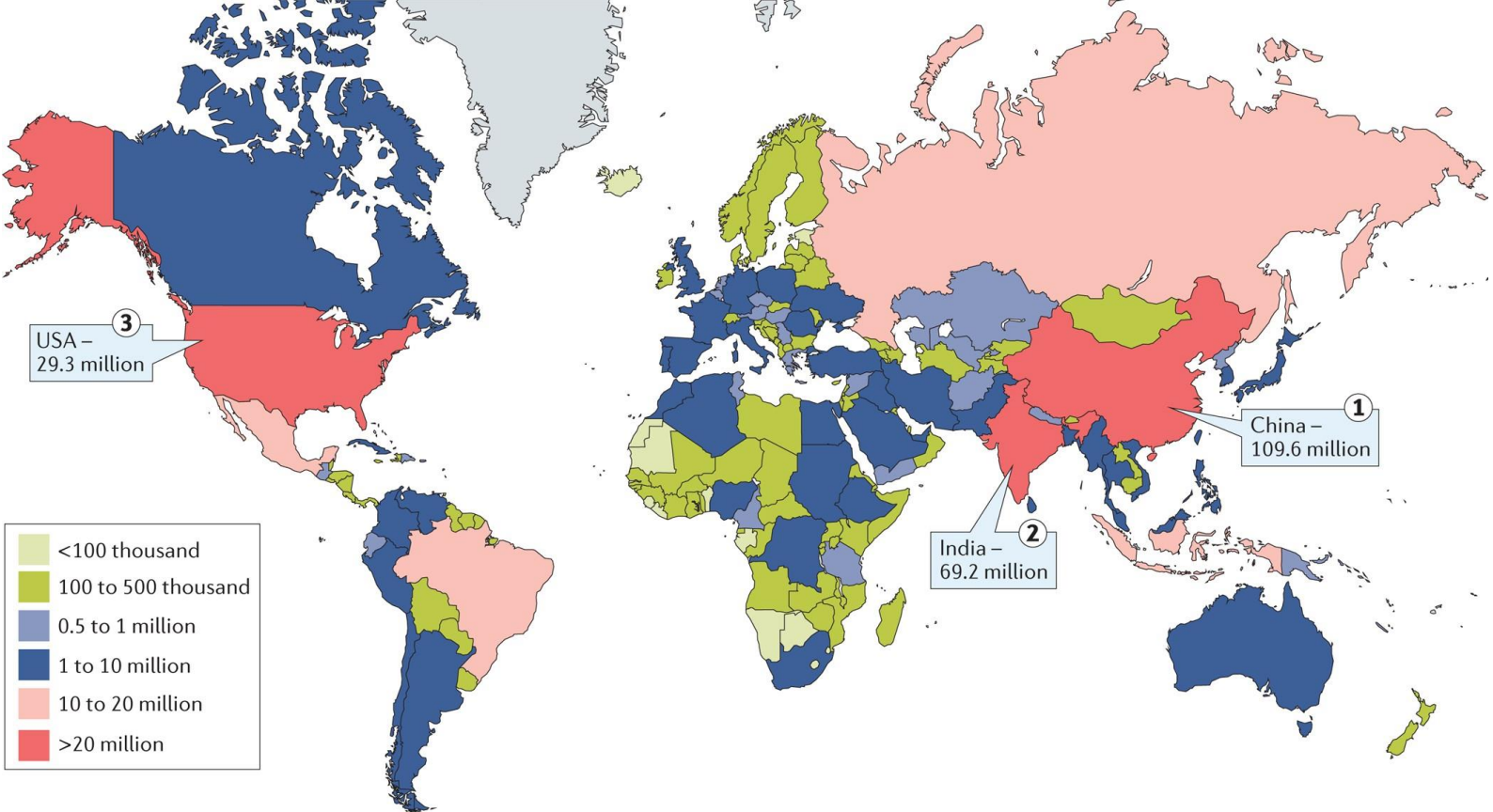
TOP SEARCHES Coronavirus in India Gulab Cyclone Covid Cases in India Pegasus Snooping Row PM Modi Covaxin vaccine Elections 2021 Covid vaccine re

NEWS / INDIA NEWS / India Reports 45,374 Black Fungus Cases, 4,332 Deaths So Far, Says Health Ministry

# India reports 45,374 Black fungus cases, 4,332 deaths so far, says health ministry

ANI / Updated: Jul 22, 2021, 14:34 IST

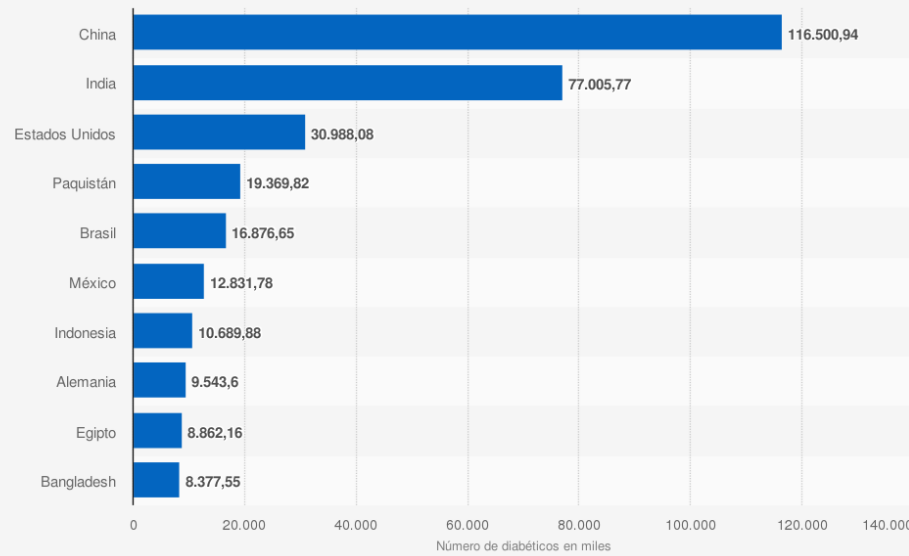




Nature Reviews Endocrinology vol 14, pages 88–98 (2018)

Nature Reviews | Endocrinology

Ranking de los países con mayor número de enfermos de diabetes en 2019 (en miles)



Fuente: International Diabetes Federation © Statista 2020

Información adicional: Mundial; 2019; 0-79 años

acidosi = pH basso  
aumento del ferro libero



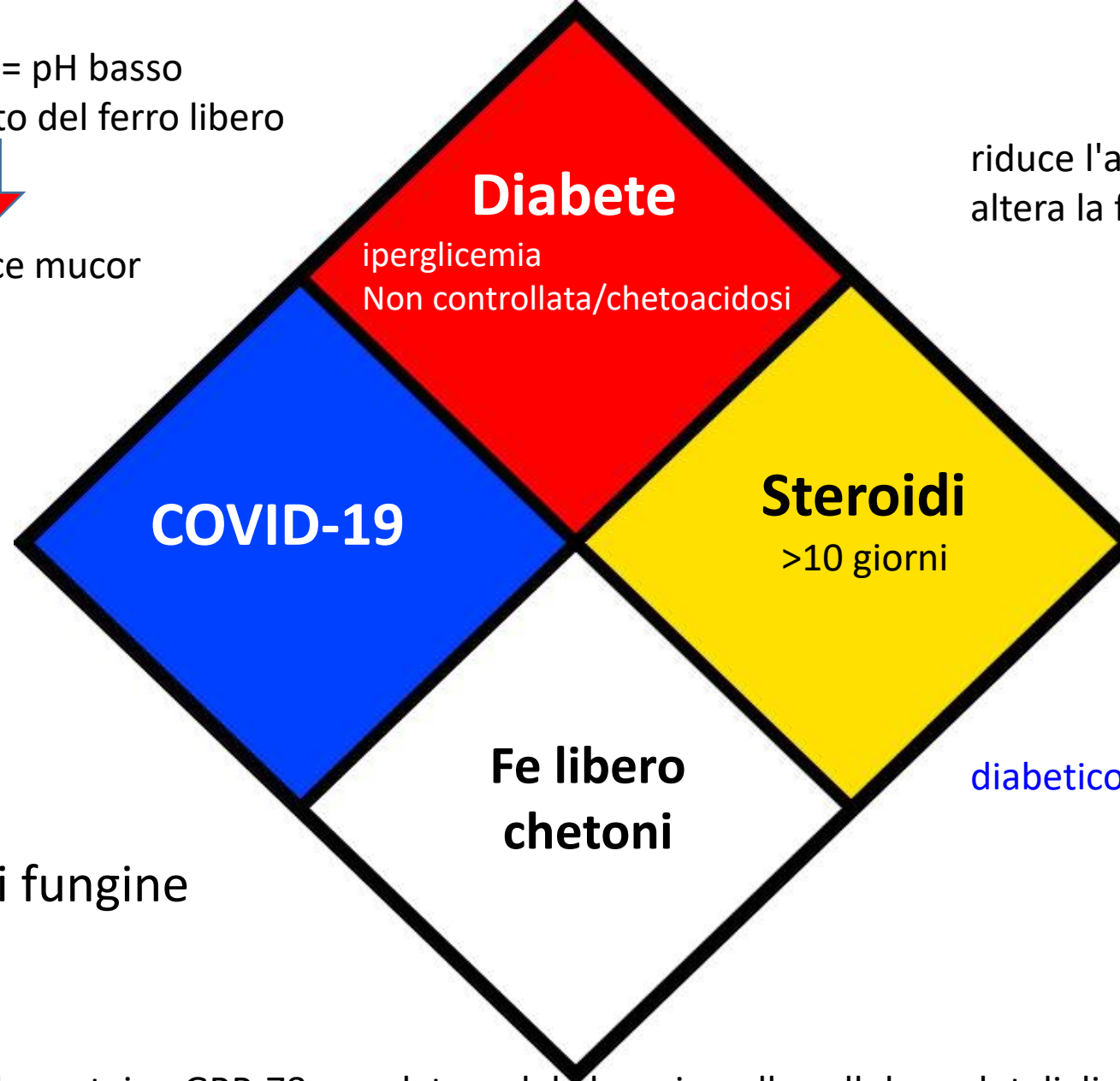
favorisce mucor

riduce l'attività fagocitaria dei GB  
altera la funzione dei macrofagi

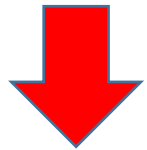


Azione immunosoppressiva

Aumentano i livelli di glucosio  
e la tendenza alla chetoacidosi



danno endoteliale  
Trombosi  
Linfopenia  
Riduzione di CD4 + / CD8 +  
Aumento della ferritina



Predisporre a infezioni fungine

diabetico = eccezionalmente vulnerabile



espressione della proteina GRP-78, regolatore del glucosio nelle cellule endoteliali e la proteina omologa nel rivestimento delle spore (CoH),

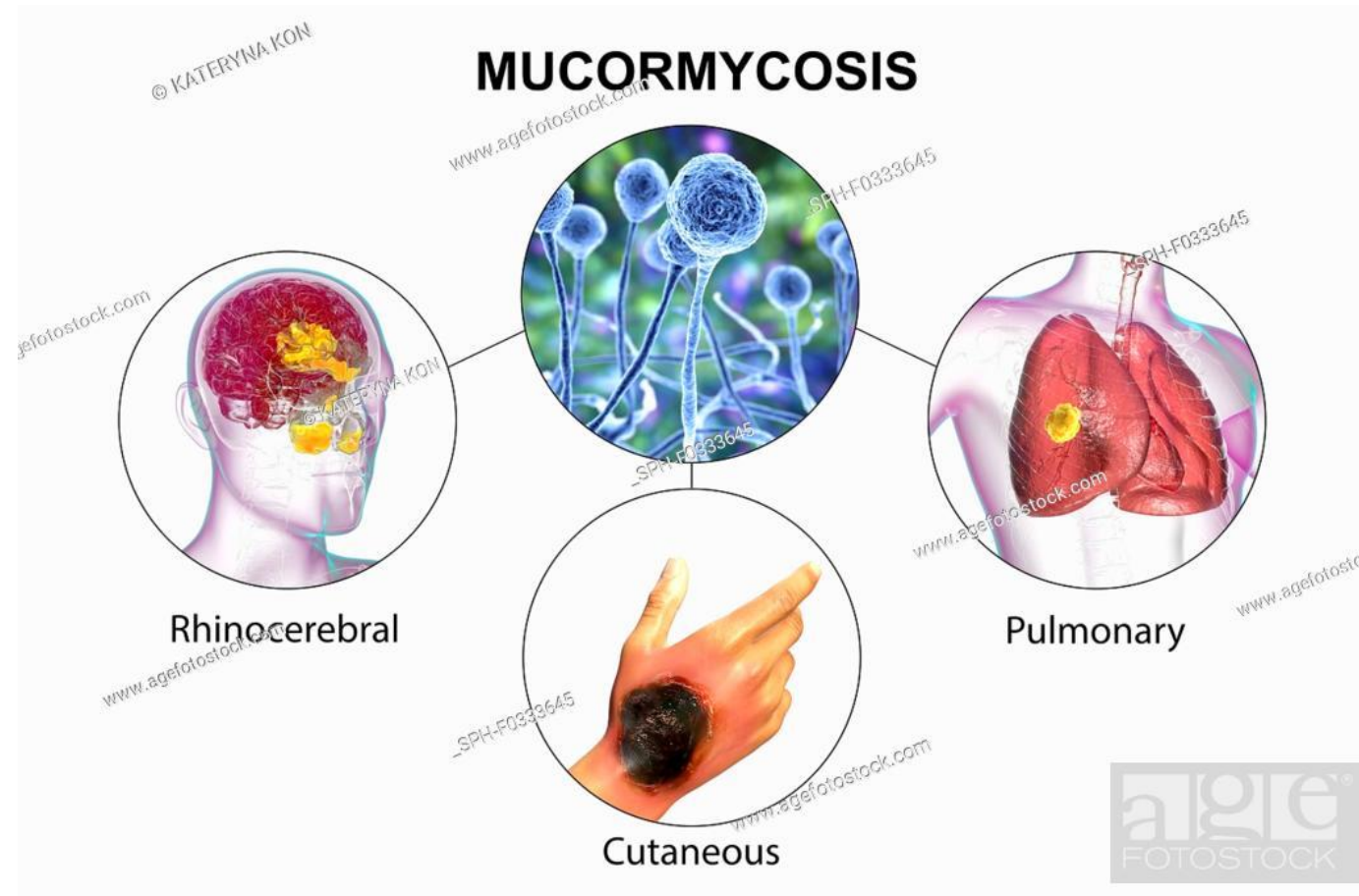


Favorisce angi invasione, la disseminazione ematogena e la necrosi



# Forma clinica

- Rino-cerebrale (80-85%)
- Polmonare (10%)
- Sinusale
- Cutanee
- Gastrointestinali
- Disseminate
  - Immunocompromesi
- Altre
  - otomicosi / cheratite



# Rino-cerebrale



shutterstock.com · 1982714276

- Sinusite
- Edema palpebrale / possibile necrosi
- Perdita unilaterale della visione
  - Ptosì / esoftalmia
- Fistola palpebrale
- Febbre / cefalea



Gentileza Dr. Alexandro Bonifaz



# Rino-cerebrale

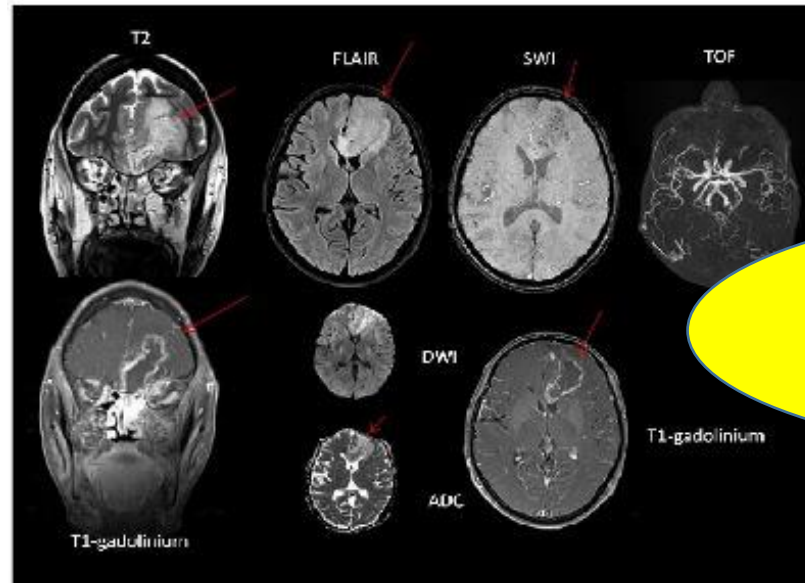
- Sinusite
- Setto nasale coinvolto
- Mucosa nasale necrotica
- Secrezione nasale
  - scura / purulenta/ maleodorante
- Febbre / cefalea



# Rino-cerebrale



- Sinusite - Febbre / cefalea
- Mucosa nasale necrotica
- Secrezione scura / maleodorente
- Afecções pares craneales
- Ulcera palatina / progresso rapido/ necrosi
- Osteomielite



**Fare TAC!!  
Non ci sono biomarcatori**

**Figure 1:** Gingival necrosis at the right maxilla and a violaceous and edematous plaque at the hard palate.

*Our Dermatol Online 4.2020*

*A. Bonifaz et al. / Enferm Infecc Microbiol Clin. 2020;xxx(xx):xxx-xxx*

Vilalta et al., J Infect Dis Ther 2014, 2:4

Ajith Kumar AK; Vikas Gupta. NCBI Bookshelf. 2021



# Polmonare (10%)

- + frequente neutropenici, trapiantati, cancro
- Manifestazione respiratorie non specifiche
  - Febbre, dispnea, tosse, emottisi
- Radiologia



atoll sign

## segno dell'alone inverso

### Spectrum of Diseases with the Reversed Halo Sign (RHS)

#### Fungal infections

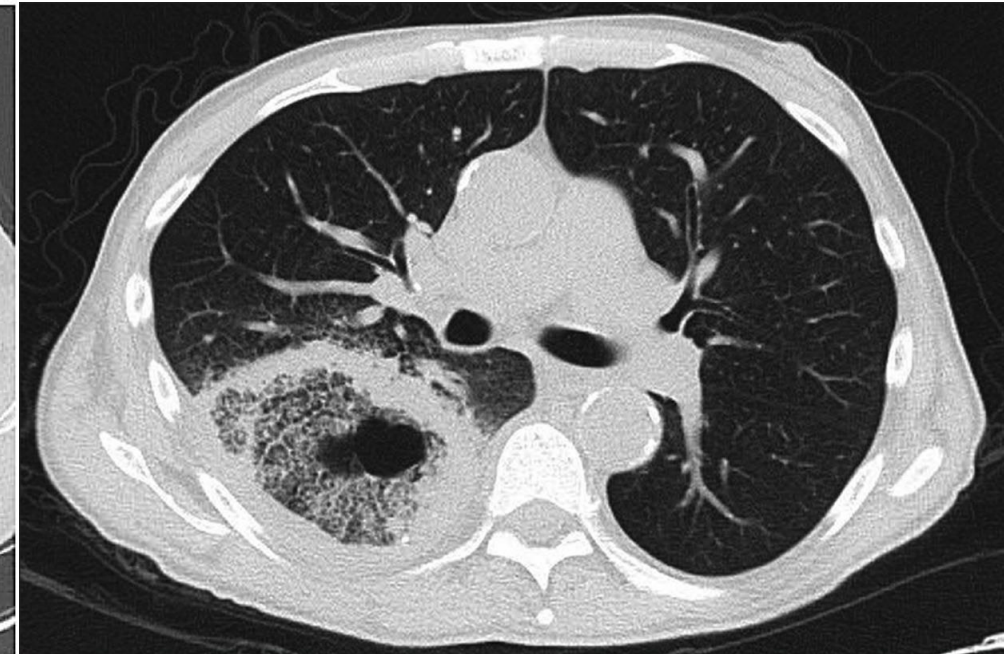
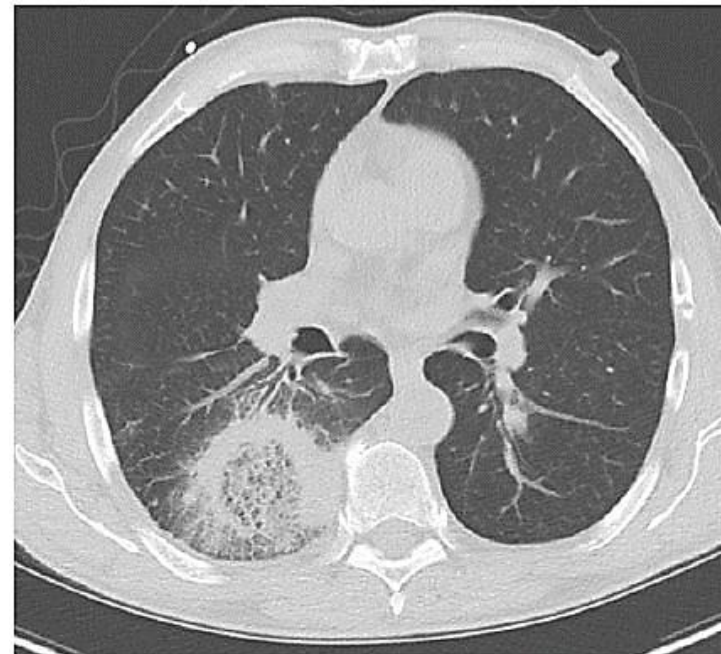
Mucormycosis  
Invasive aspergillosis  
Paracoccidioidomycosis

#### Bacterial infections

Slow-resolving pneumococcal pneumonia  
Chlamydia psittaci  
Legionella pneumophila  
Mycobacterial infections  
Mycobacterium tuberculosis

#### Systemic diseases

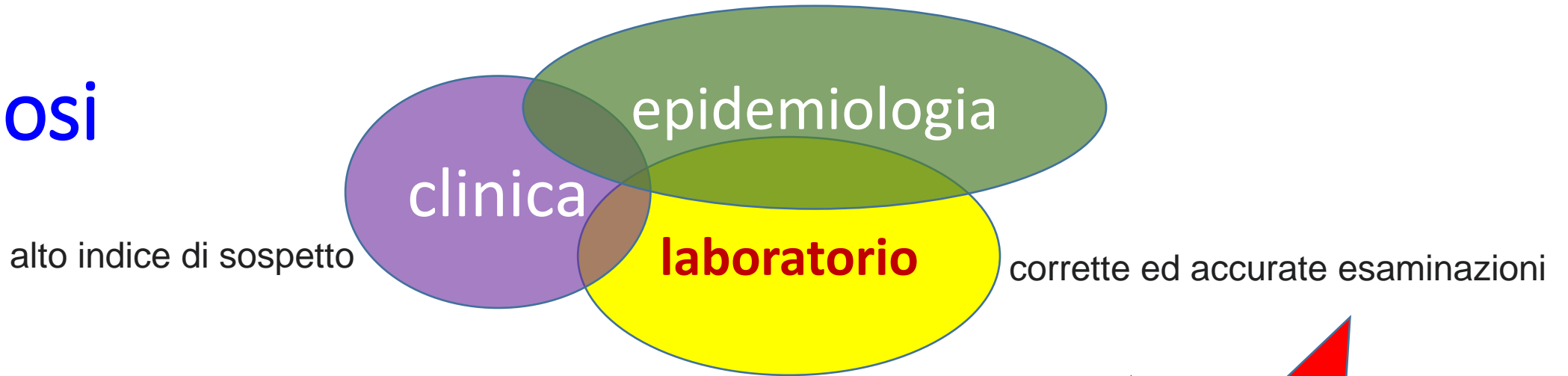
Wegener granulomatosis  
Sarcoidosis  
Churg–Strauss syndrome  
Dermatomyositis  
Neoplastic diseases  
Lymphomatoid granulomatosis  
Various pulmonary diseases  
Cryptogenic organizing pneumonia  
Acute fibrinous and organizing pneumonia  
Lipoid pneumonia



Q J Med 2014; doi:10.1093/qjmed/hcu031

Lancet Infect Dis 2019; 19: 1379  
Clin Infect Dis.2011 May 1; 52(9): 1144–1155

# Diagnosi

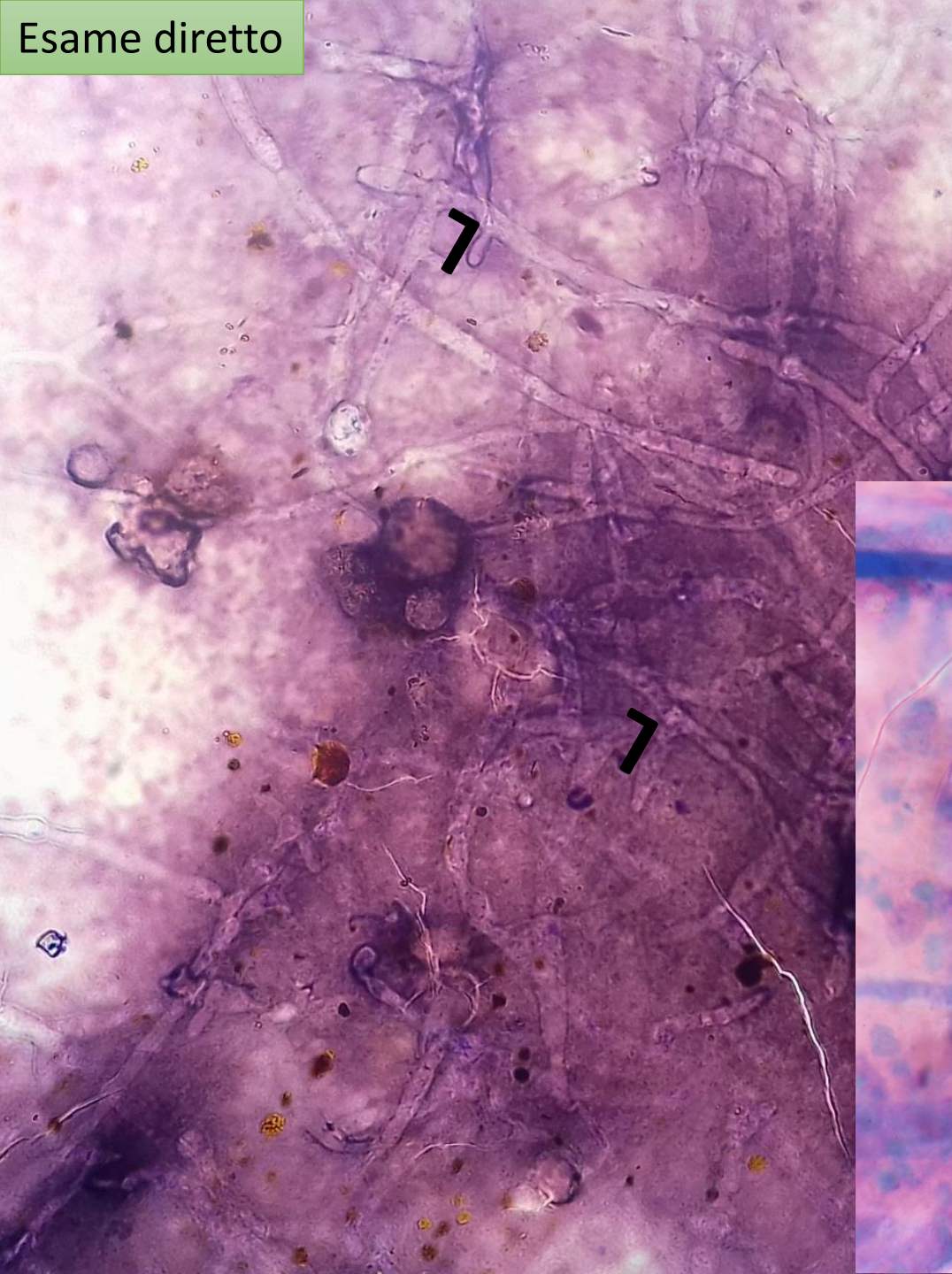


1. Microscopia – Esame diretto
2. Coltura
3. Istopatologia
4. Imaging (RX – TAC - RMN)
5. ~~Biomarcatori~~
6. Detección por PCR

**Invasive mucormycosis  
is a medical emergency  
condition,  
early diagnosis,  
surgery  
and antifungal therapy**

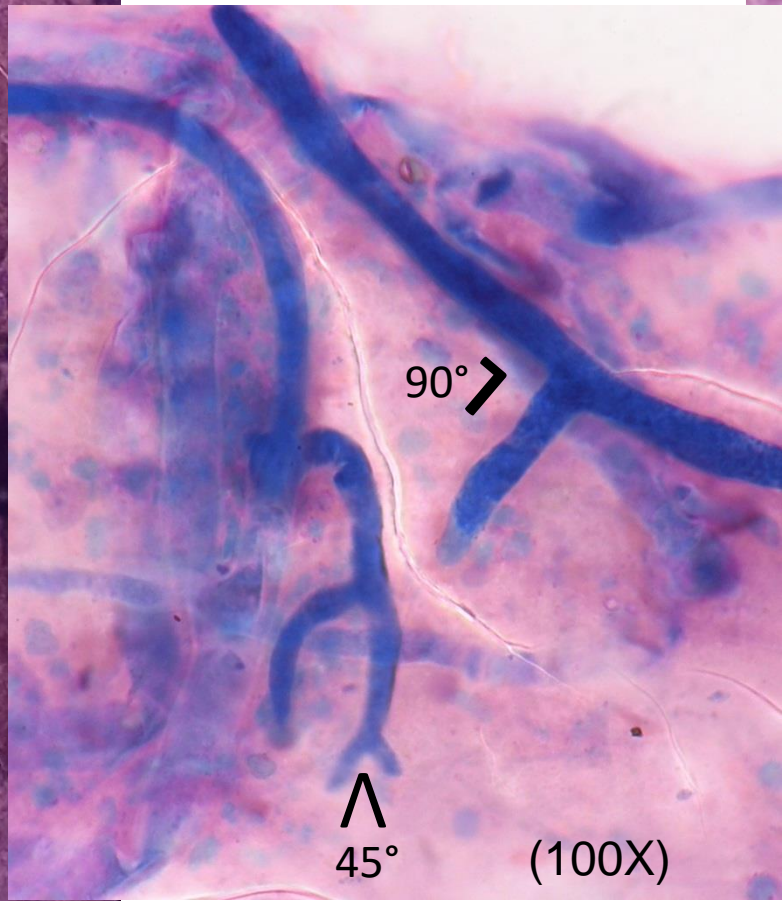
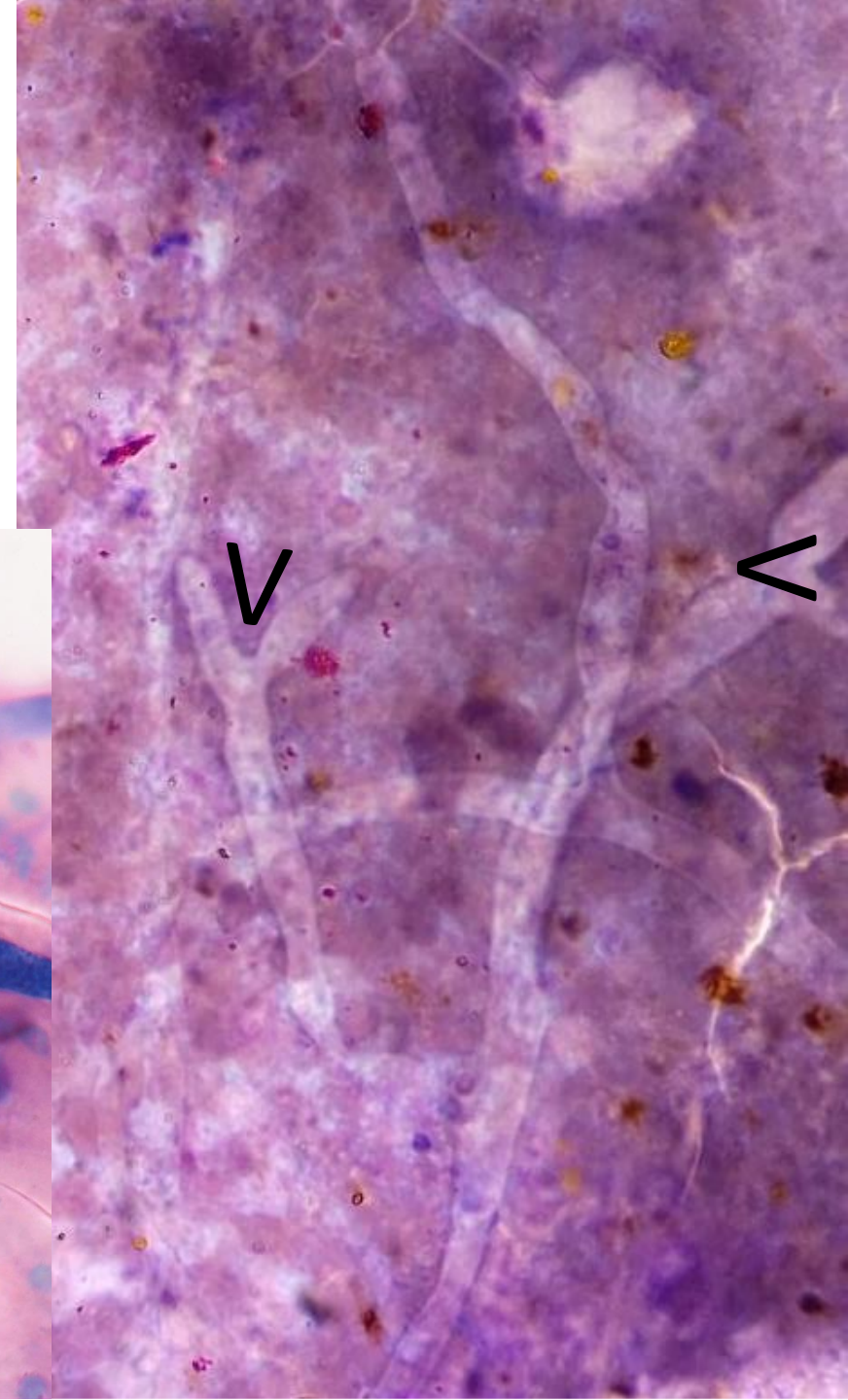


Esame diretto

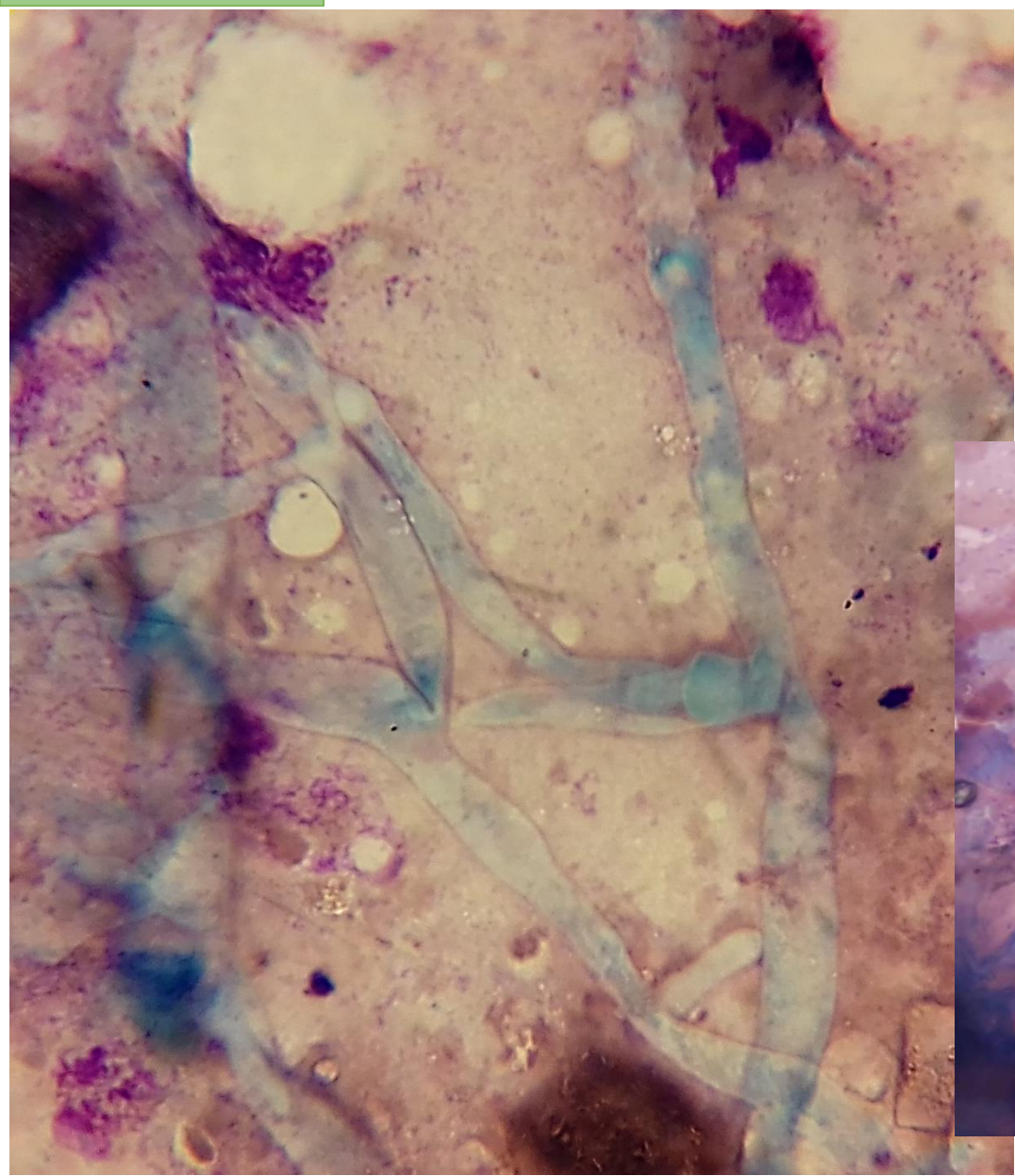


Ife ialinee cenocitiche  
Nos settate (o sporadicche)  
5-25 micre

Giemsa

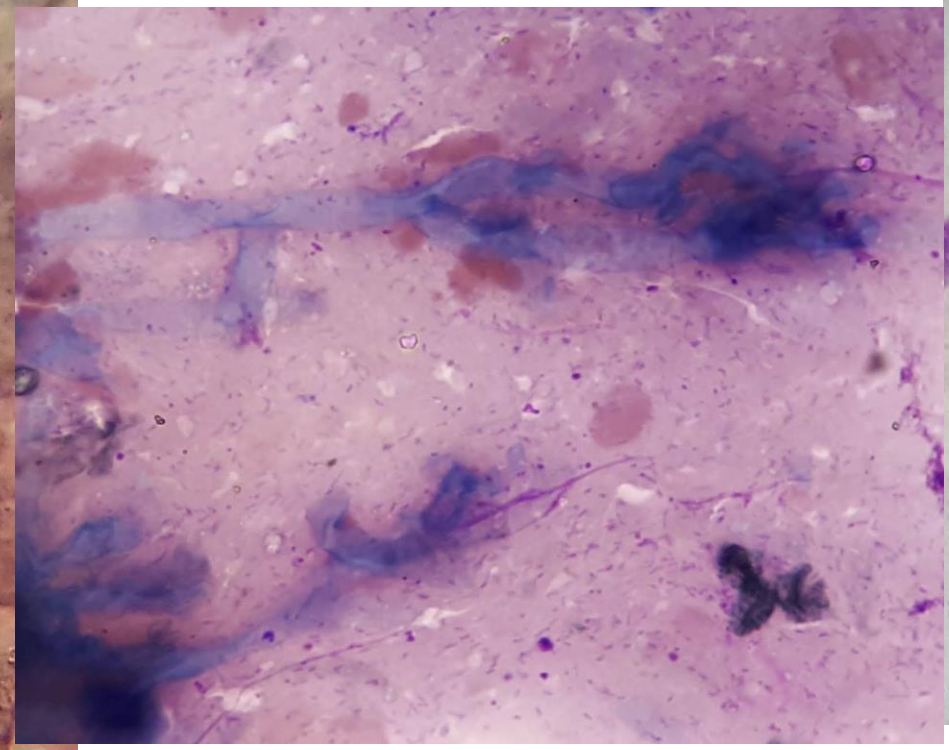






(100X)

Aspetto irregolare / piegato



Giemsa

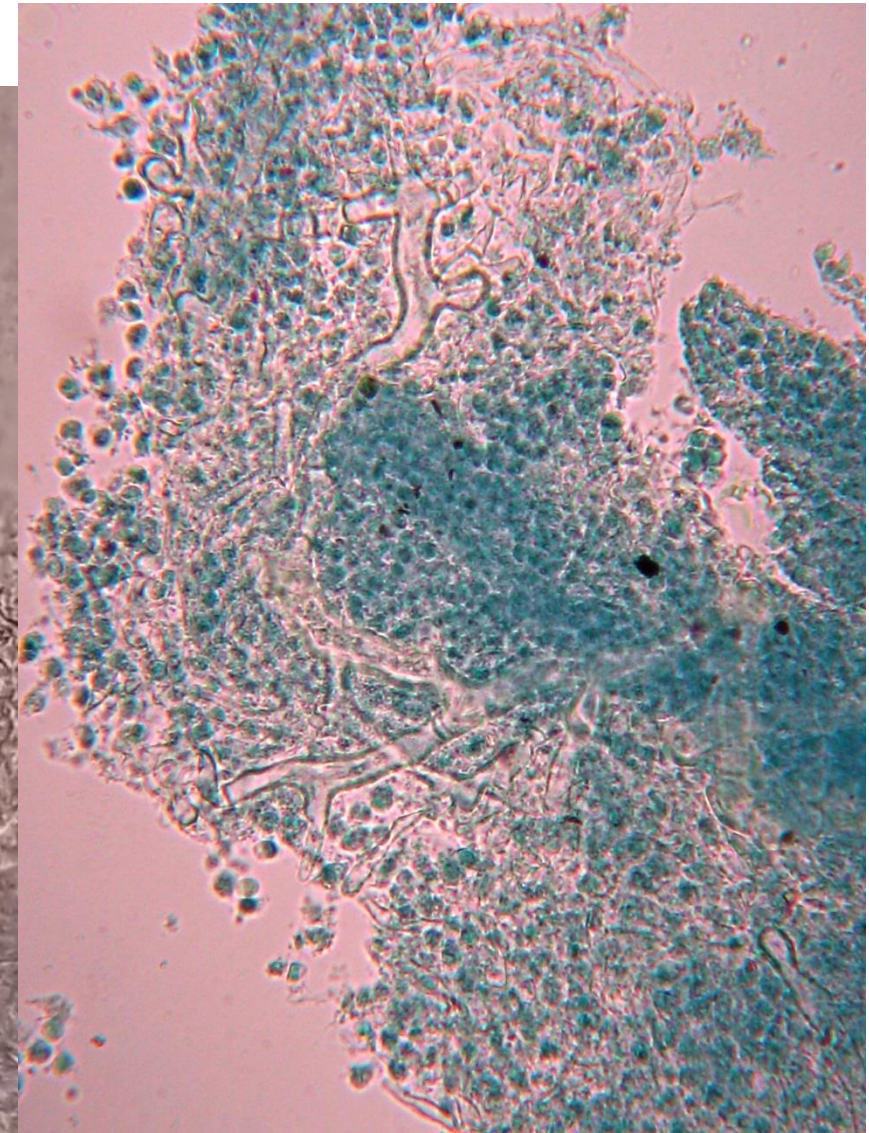
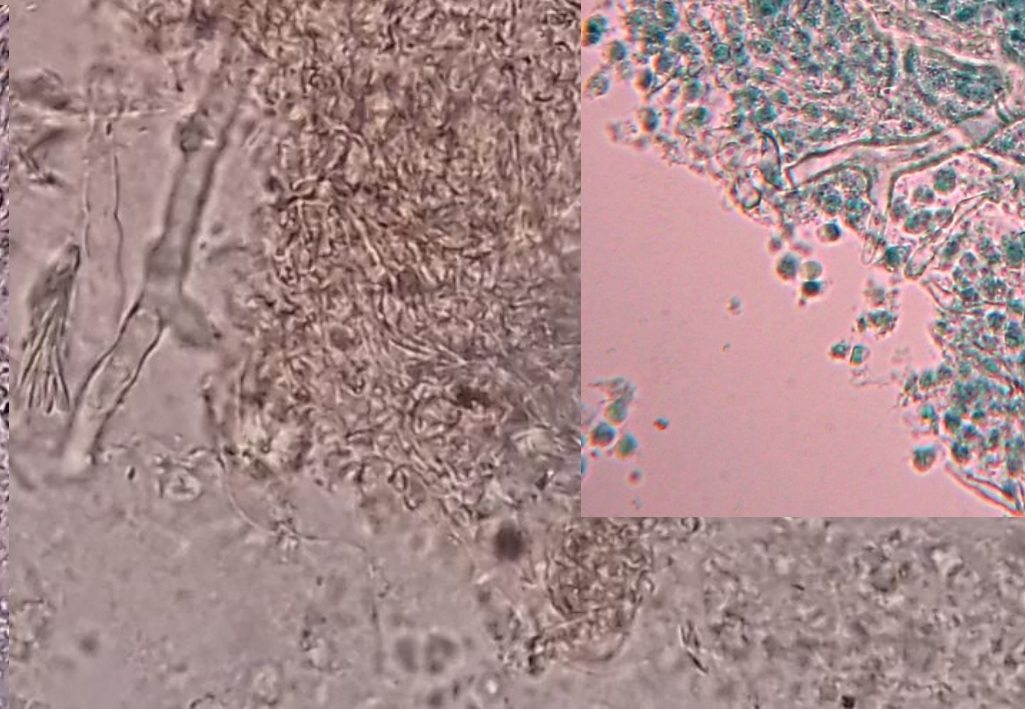
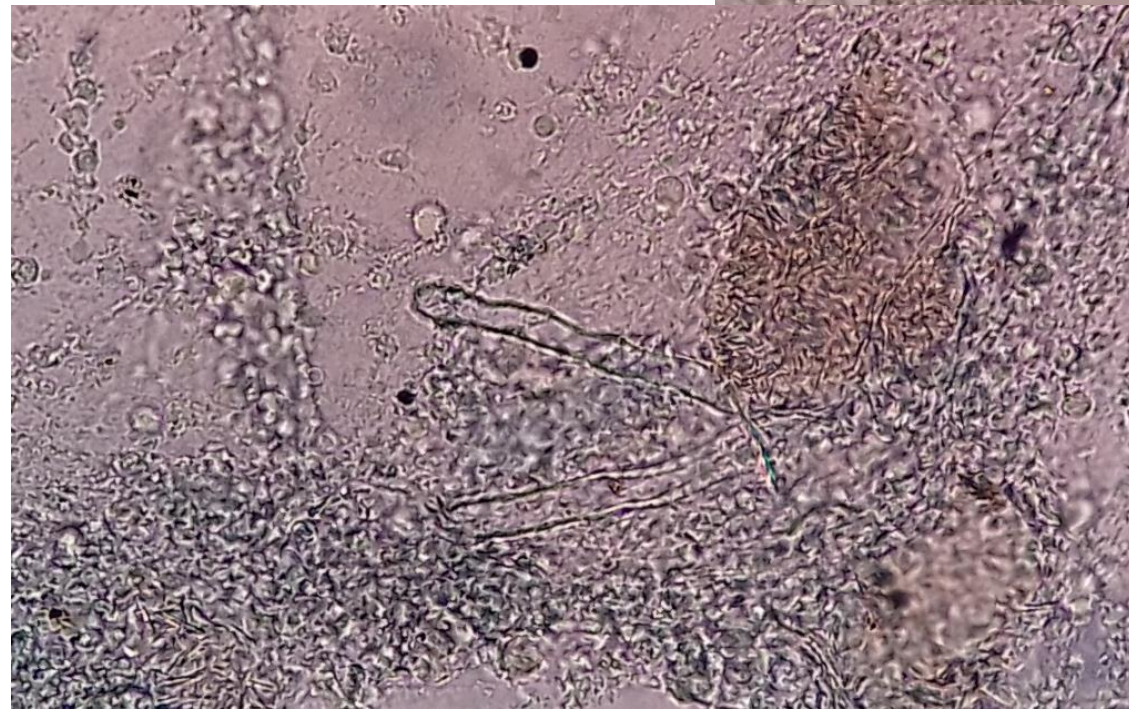
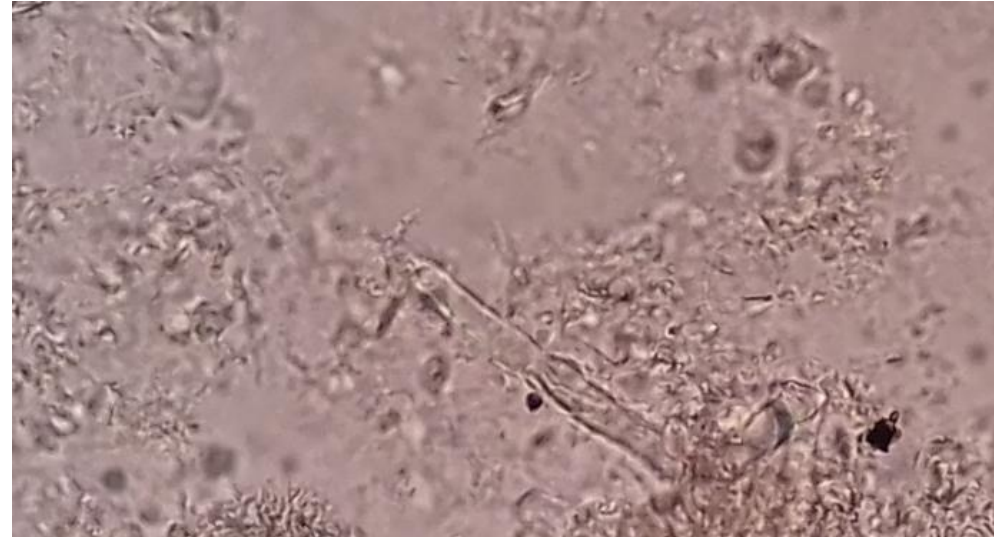


(40X)

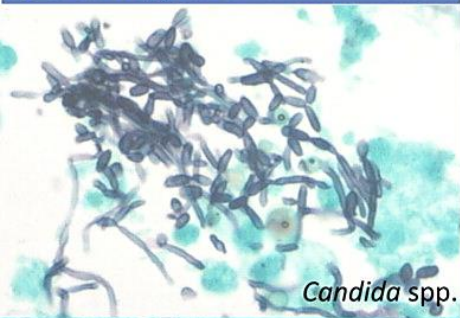
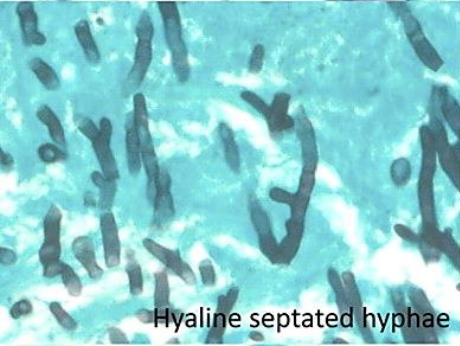
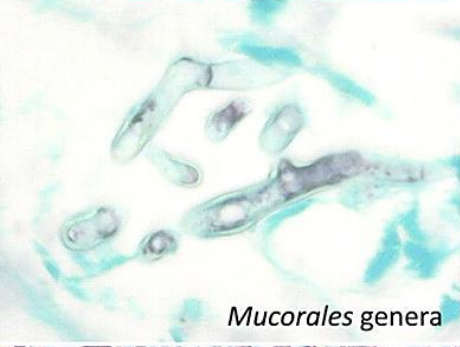
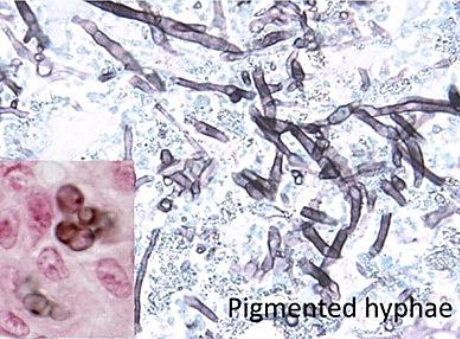


Esame diretto

Esame a fresco (40X)

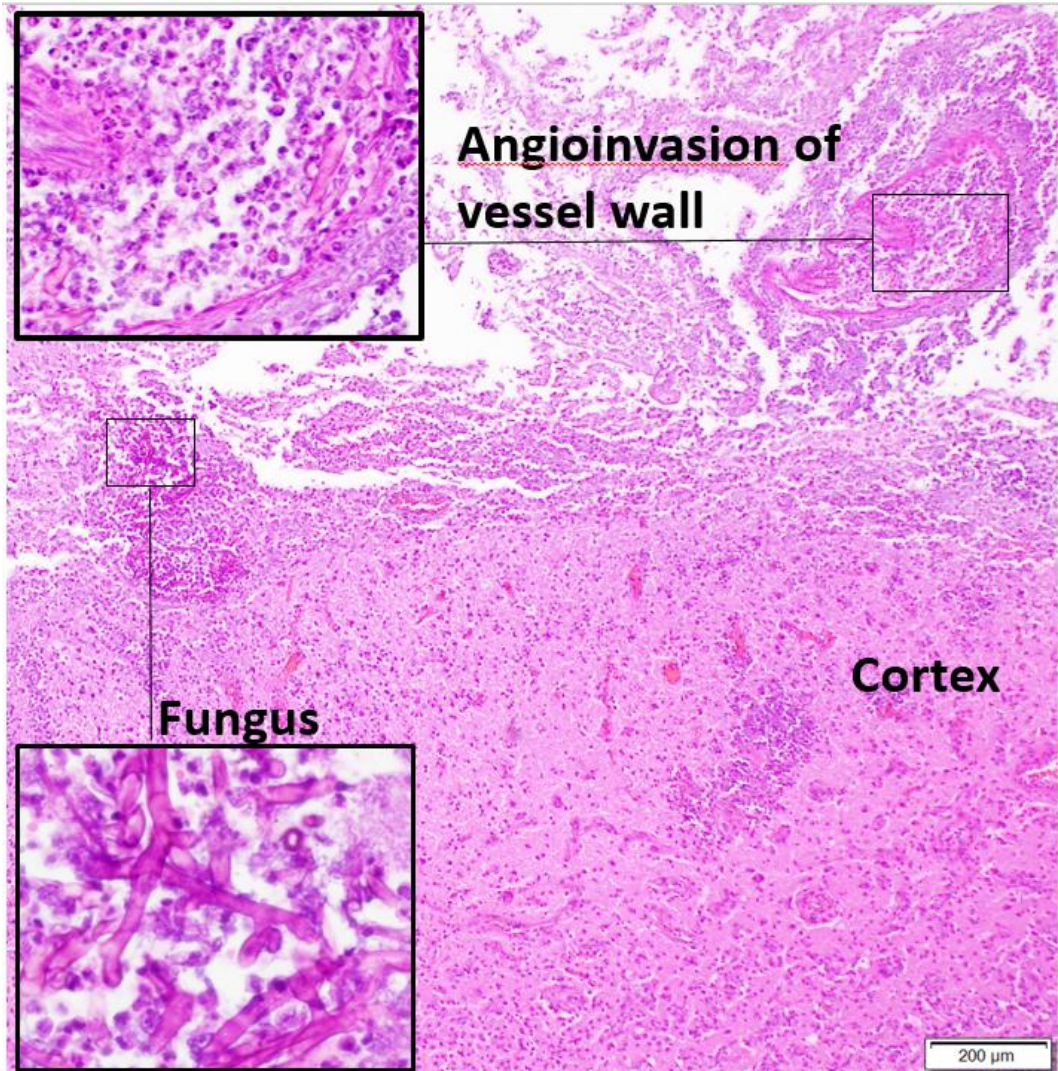
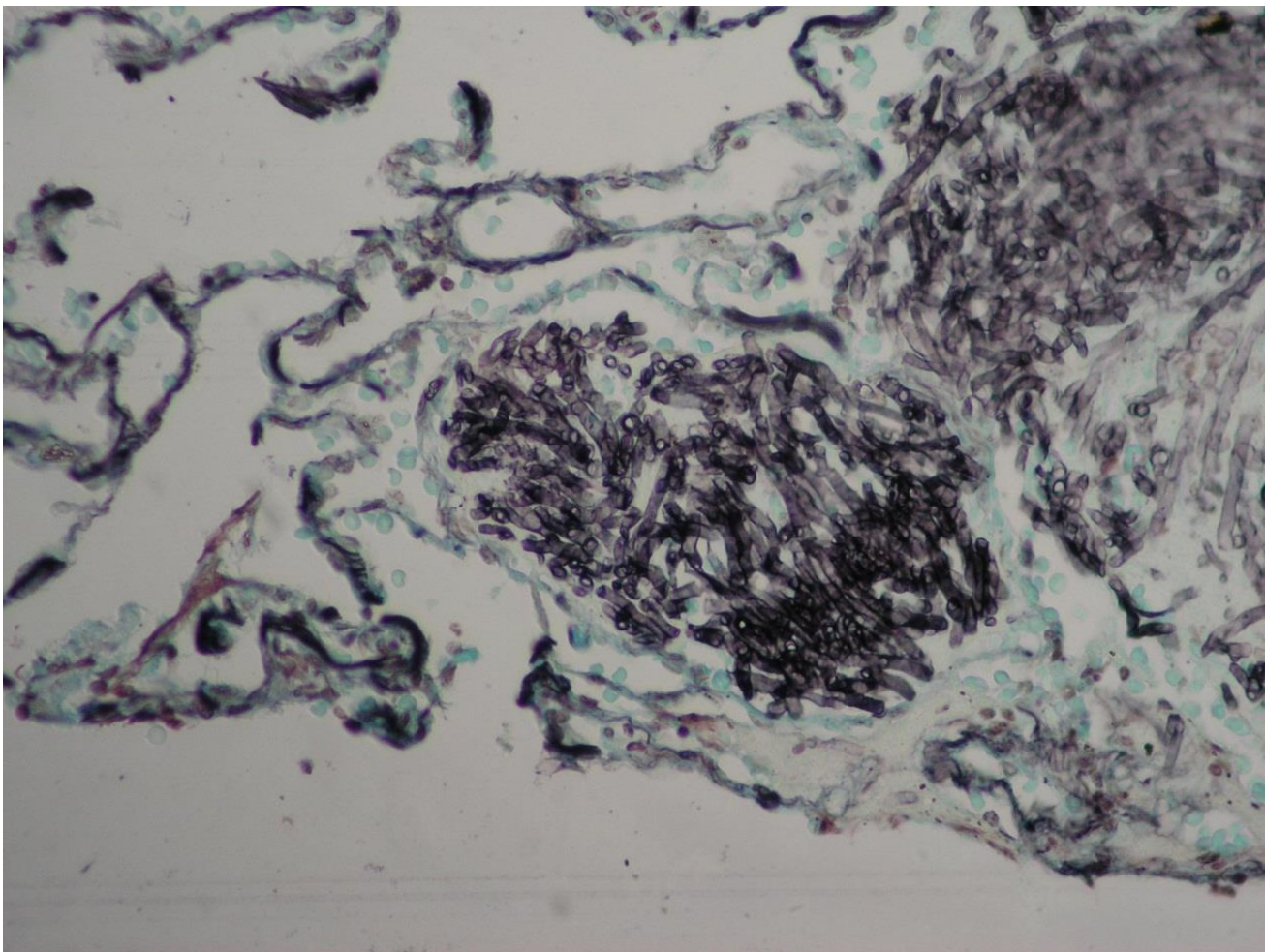




Morphology of hyphae and pseudohyphae	Description, diagnosis and comment
 <p><i>Candida</i> spp.</p>	<p><b>Description:</b> Small yeasts (3- 5 microns in size) intermingled with pseudohyphae and hyphae.</p> <p><b>Diagnosis:</b> Yeasts with pseudohyphae.</p> <p><b>Comment:</b> The morphology is consistent with <i>Candida</i> spp.; however, <i>Aspergillus</i> spp. and other hyaline fungi can be confused histologically.</p>
 <p>Hyaline septated hyphae</p>	<p><b>Description:</b> Non-pigmented (hyaline), septated hyphae with acute angle branching.</p> <p><b>Diagnosis:</b> Non-pigmented (hyaline), septated hyphae.</p> <p><b>Comment:</b> The morphology is consistent with <i>Aspergillus</i> spp., <i>Fusarium</i> spp., <i>Scedosporium</i> spp., <i>Trichoderma</i> spp., <i>Paecilomyces</i> spp. and others. Mucorales genera can sometimes have this morphology.</p>
 <p><i>Mucorales</i> genera</p>	<p><b>Description:</b> Non-pigmented (hyaline), pauciseptate ribbon-like hyphae with right angle branching.</p> <p><b>Diagnosis:</b> Non-pigmented (hyaline), pauciseptate hyphae.</p> <p><b>Comment:</b> The morphology is consistent with <i>Mucorales</i> genera; however, <i>Aspergillus</i> spp. and other septated hyaline hyphae can sometimes have this morphology.</p>
 <p>Pigmented hyphae</p>	<p><b>Description:</b> Pigmented irregular hyphae and yeast-like structures both with septations.</p> <p><b>Diagnosis:</b> Pigmented yeasts and hyphae with septations.</p> <p><b>Comment:</b> The morphology is consistent with dematiaceous fungi including: <i>Madurella</i> spp, <i>Fonsecaea</i> spp, <i>Cladophialophora</i> spp, <i>Exophiala</i> spp, <i>Curvularia</i> spp, <i>Bipolaris</i> spp, and others.</p>



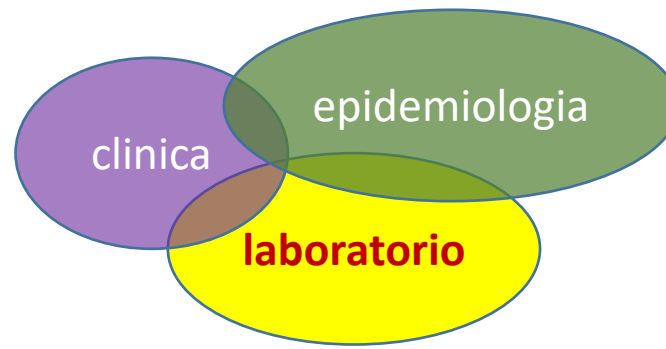
Istopatologia





# Diagnosi

# Coltura



Campioni freschi - preferibilmente da siti sterili

**Sviluppo di mucorales**

**Sito sterile** : diagnosi

**Sito NO sterile**: valutare clinica - escludere colonizzazione / contaminazione

Aspirazioni/punzioni dal seno nasale

Mucosa nasale

Biopsie

Scarificazioni

Secrezioni

Punzioni

Altre

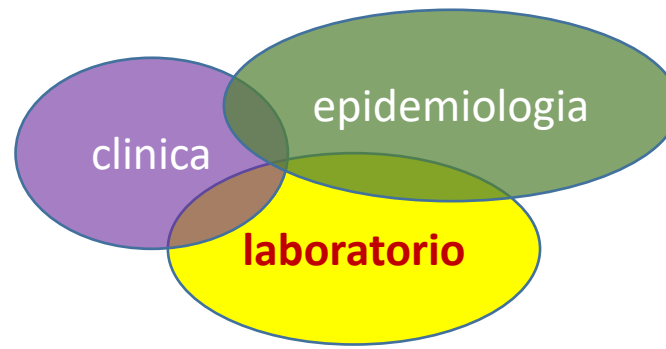


Essudati, tessuti necrotici  
resa inferiore – meno organismi vitali

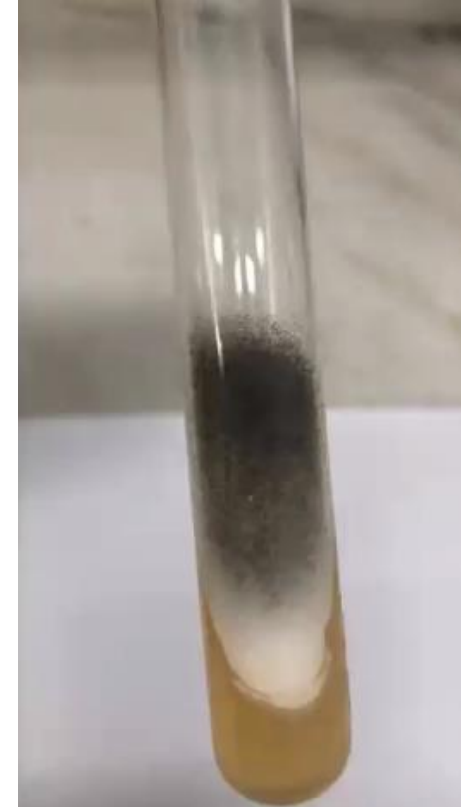
**Attenzione:** MACERARE I CAMPIONI **NO** - SEZIONARE **SI**

# Diagnosi

## Coltura

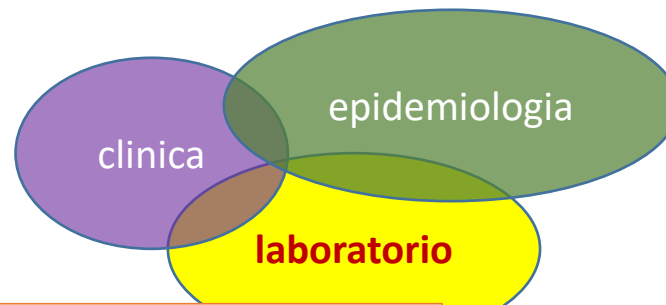


- Sviluppano nei piú comune terreni di coltura per i funghi **con ATB senza inibitori** (compresi terreni batteriologici)
  - Agar Sabouraud / APD/ BHI /
- Temp. 37 °C
- Sviluppo rapido
- Colonie cotonose, bianche, grigie
  
- Alcuni generi hanno bisogno di stimolare la fruttificazione.
- Agar acqua, agar terra, agar estratto de malto, ecc.





# Diagnosi



## Coltura - Identificazione

- Identificazione
  - Macro y micromorfologica
- MALDI-TOF
- Secuenciación ITS

MALDI-TOF mass spectrometry

### Bruker biotyper version 3

- *Rhizopus oryzae*, *R. microsporus*, *R. sexualis*, *R. stolonifer*
- *Rhizomucor pusillus*
- *Absidia caerulea*, *A. glaucas* and *Lichtheimia corymbifera*
- *Mortierella acrotona*, *M. clonocystis*, *M. gamsii*, *M. polygonia*
- *Mucor circinelloides* *M. genevensis*, *M. hiemalis* *M. indicus* *M. lanceolatus*, *M. moelleri*, *M. racemosus*
- *Cunninghamella elegans*
- *Syncephalastrum racemosum*

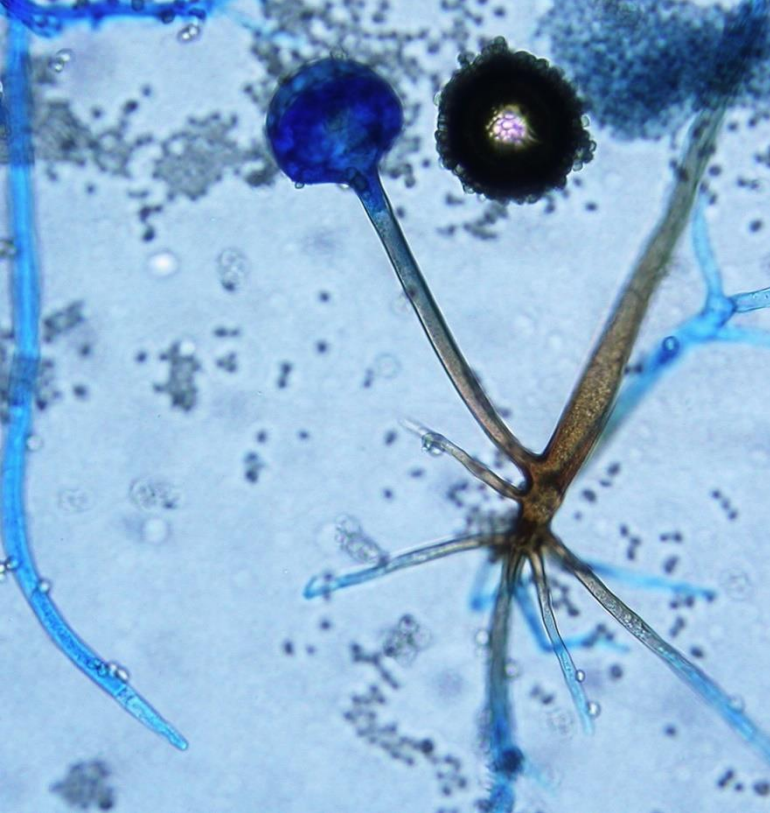
MBT Filamentous Fungi Library 3.0



TABLE 1 Identification of 111 clinical isolates by the Bruker library and the Bruker library plus BMU database

Organism (no. of isolates)	No. (%) of isolates identified at the genus or species level by log(score) value <sup>a</sup>							
	Bruker library				Bruker library plus BMU database			
	≥2.0	≥1.7	<1.7	Mis-ID	≥2.0	≥1.7	<1.7	Mis-ID
<i>R. arrhizus</i> (20)	19 (95)	20 (100)	0 (0)	0 (0)	19 (95)	20 (100)	0 (0)	0 (0)
<i>R. microsporus</i> (27)	24 (88.9)	27 (100)	0 (0)	0 (0)	24 (88.9)	27 (100)	0 (0)	0 (0)
<i>R. stolonifer</i> (1)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
<i>R. pusillus</i> (4)	4 (100)	4 (100)	0 (0)	0 (0)	4 (100)	4 (100)	0 (0)	0 (0)
<i>S. racemosum</i> (2)	2 (100)	2 (100)	0 (0)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)
<i>L. corymbifera</i> (4)	4 (100)	4 (100)	0 (0)	0 (0)	4 (100)	4 (100)	0 (0)	0 (0)
<i>L. ramosa</i> (6)	0 (0)	3 (50)	0 (0)	3 (50)*	0 (0)	3 (50)	0 (0)	3 (50)*
<i>L. ornata</i> (1)	0 (0)	0 (0)	0 (0)	1 (100)†	0 (0)	0 (0)	0 (0)	1 (100)†
<i>M. circinelloides</i> (9)	2 (22.2)	6 (66.7)	0 (0)	3 (33.3)‡	2 (22.2)	6 (66.7)	0 (0)	3 (33.3)‡
<i>M. irregularis</i> (23)	0 (0)	0 (0)	23 (100)	0 (0)	23 (100)	23 (100)	0 (0)	0 (0)
<i>M. hiemalis</i> (5)	0 (0)	0 (0)	5 (100)	0 (0)	3 (60)	5 (100)	0 (0)	0 (0)
<i>M. racemosus</i> (4)	0 (0)	0 (0)	4 (100)	0 (0)	4 (100)	4 (100)	0 (0)	0 (0)
<i>C. bertholletiae</i> (3)	0 (0)	0 (0)	3 (100)	0 (0)	3 (100)	3 (100)	0 (0)	0 (0)
<i>C. phaeospora</i> (1)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
<i>C. echinulata</i> (1)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
Total (111)	55 (49.5)	67 (60.4)	37 (33.3)	7 (6.3)	90 (81.1)	104 (93.7)	0 (0)	7 (6.3)§

<sup>a</sup>Mis-ID, misidentification. Symbols: \*, misidentified as *Lichtheimia corymbifera*; †, misidentified as *Lichtheimia corymbifera*; ‡, misidentified as *Mucor ramosissimus*; §, misidentified at the species level but correctly identified at the genus level.



## Rhizopus

*R. microsporus*

*R. arrhizus (orizae)*

39%

## Mucor

*M. circineloides*

*M. ramossissimum*

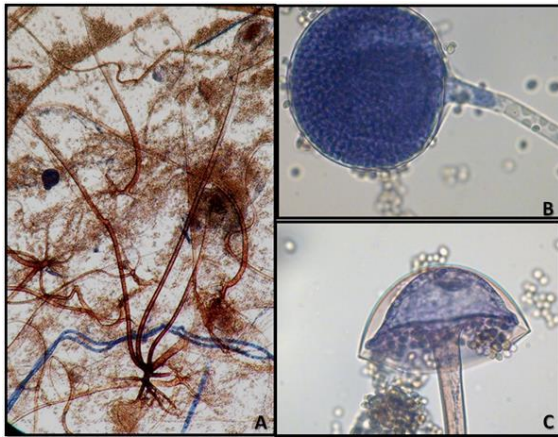
19%

## Lichtheimia

*L. corimbifera*

*L. ramosa*

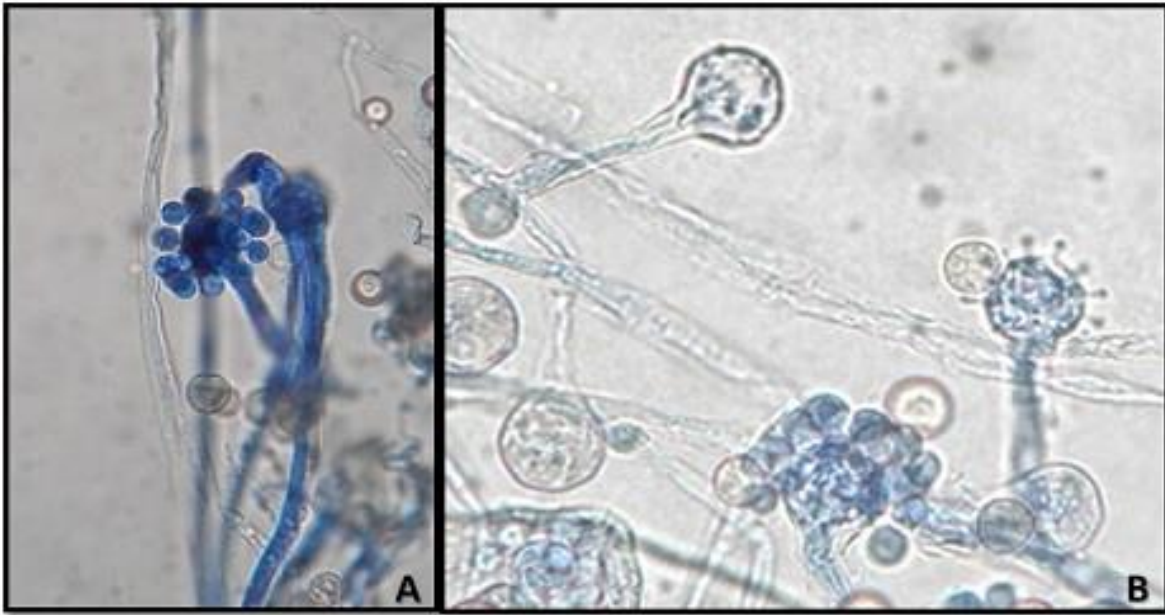
19%



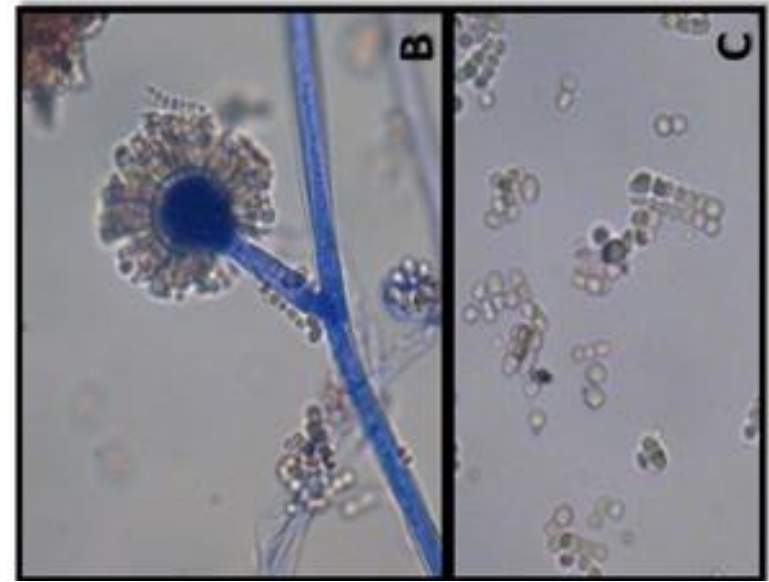
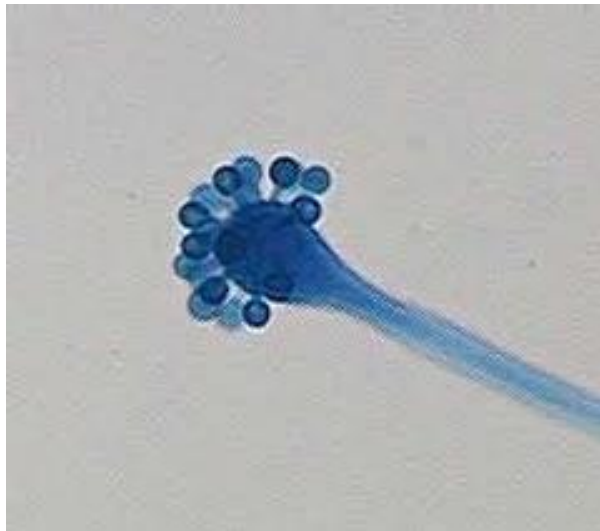
ECMM study from Europe  
*J. Fungi* 2020, 6, 265



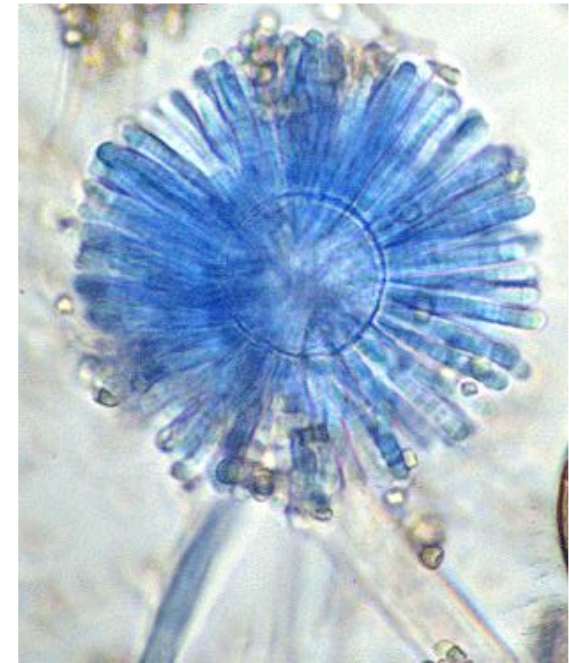




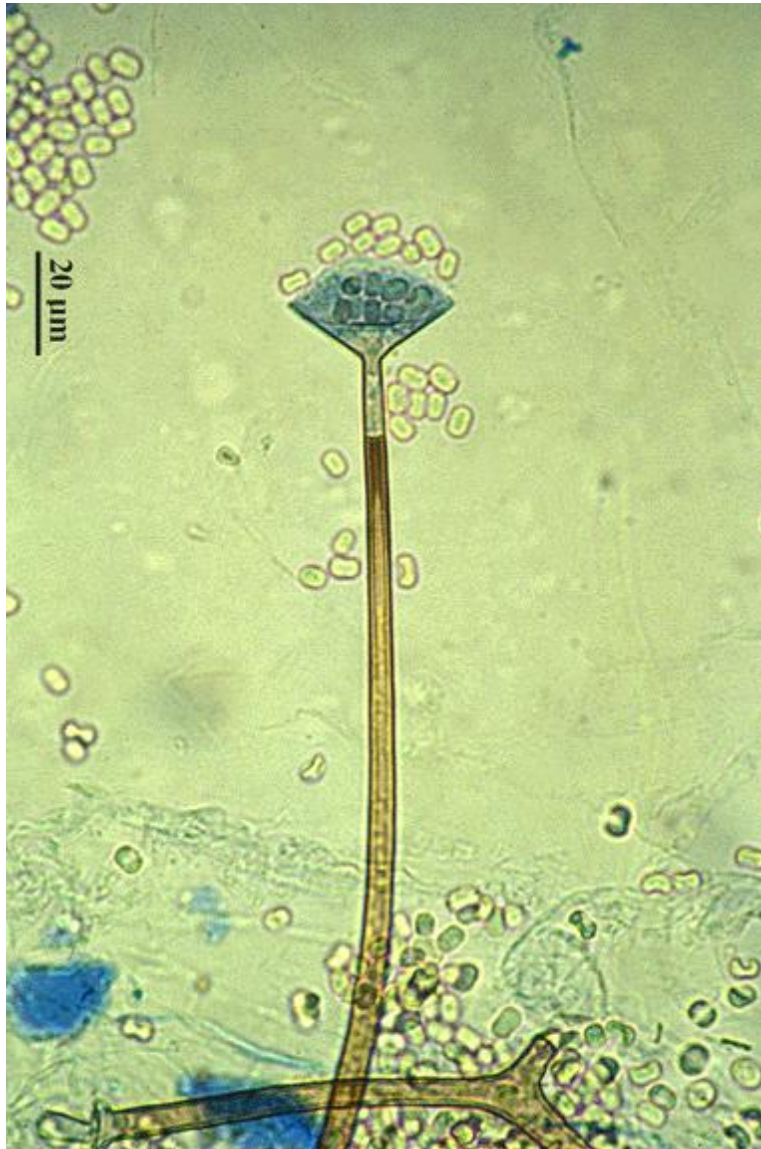
***Cunninghamella* spp.**



***Syncephalastrum* spp.**



***Apophysomyces***



***Saksenaea***



meno frequente in clinica, però sono in grado di provocare infezioni molto aggressive e devastanti - spesso il paziente muore entro pochi giorni



Received: 18 May 2020 | Revised: 11 November 2020 | Accepted: 24 November 2020

DOI: 10.1111/myc.13222

ORIGINAL ARTICLE



## Mucormycosis at a tertiary-care center in Mexico. A 35-year retrospective study of 214 cases

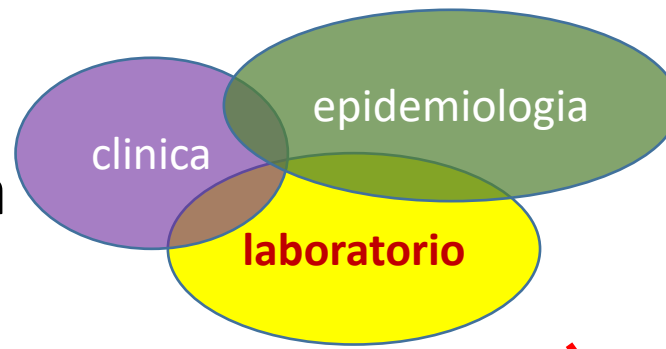
Alexandro Bonifaz<sup>1</sup> | <sup>1</sup> | Andrés Tirado-Sánchez<sup>1</sup> | María L. Hernández-Medel<sup>1</sup> |  
Javier Araiza<sup>1</sup> | Juan J. Kassack<sup>1</sup> | Teresa del Angel-Arenas<sup>1</sup> |  
Jorge F. Moisés-Hernández<sup>1</sup> | Fernando Paredes-Farrera<sup>1</sup> | Erick Gómez-Apo<sup>1</sup> |  
Rogelio de J. Treviño-Rangel<sup>2</sup> | Gloria M. González<sup>2</sup>



TABLE 2 Microbiological characteristics of the patients with mucormycosis

Characteristics	N = 214
Mycological criteria, no. (%)	
Culture	195 (91.0)
Direct microscopy	207 (96.7)
Histology	115 (53.7)
Isolated species	
Rhizopus, no. (%)	
<i>R. arrhizus</i>	114 (58.4)
<i>R. nigricans</i>	11 (5.64)
<i>R. stolonifer</i>	1 (0.51)
<i>Rhizopus</i> sp	13 (6.66)
Lichtheimia, no. (%)	
<i>L. corymbifera</i>	24 (12.3)
Mucor, no. (%)	
<i>M. circinelloides</i>	5 (2.56)
<i>M. ramocissimus</i>	1 (0.51)
<i>Mucor</i> sp	6 (3.07)
Rhizomucor, no. (%)	
<i>R. pussilus</i>	3 (1.53)
<i>R. mihei</i>	1 (0.51)
<i>Rhizomucor</i> sp	4 (2.05)
Apophysomyces, no. (%)	
<i>A. variabilis</i>	2 (1.02)
<i>A. ossiformis</i>	1 (0.51)
<i>A. mexicanus</i>	1 (0.51)
Syncephalastrum, no. (%)	
<i>S. racemosum</i>	3 (1.53)
Cunninghamella, no. (%)	
<i>C. bertholetiae</i>	2 (1.02)
Saksenaia, no. (%)	
<i>S. vasiformis</i>	2 (1.02)
Actinomucor, no. (%)	
<i>A. elegans</i>	1 (0.51)

Diagnosi  
Indipendenti dalla coltura



**Biomarcatori**

~~B-Glucani~~

Negativi

~~Galattomannani~~

**ADN-ARN**

1. Panfungal PCR + secuenciación ITS (in campioni freschi e paraffinati)
2. PCR in house – amplificazione di una regione conservata e successivo sequenziamento e analisi del database.
  - a. Richiede diversi set di primer (molte specie)

**Falsi -** : estrazione del DNA insufficiente - DNA poco rilevabile - inibitori, degradazione o frammentazione del DNA

**Falsi +**: inquinamento



# SENSIBILITÀ AGLI ANTIFUNGINI

non viene eseguito nella routine di laboratorio

- Clinicamente utile in caso di fallimento del trattamento...
  - sebbene il fallimento sia multifattoriale
- Consentono di stabilire conoscenze epidemiologiche e basi per linee guida

Amphotericin B demonstrated the most potent *in vitro* activity, with geometric mean (GM) MICs of  $\leq 0.25$   $\mu\text{g/ml}$  against all genera with the exception of *Cunninghamella* species (GM MIC of  $1.30$   $\mu\text{g/ml}$ ). In head-to-head comparisons, the most active azole was posaconazole, followed by isavuconazole. Differences in azole and amphotericin B susceptibility patterns were observed between the genera with the greatest variability observed with isavuconazole.



**Multicenter Evaluation of MIC Distributions for Epidemiologic Cutoff Value Definition To Detect Amphotericin B, Posaconazole, and Itraconazole Resistance among the Most Clinically Relevant Species of *Mucorales***

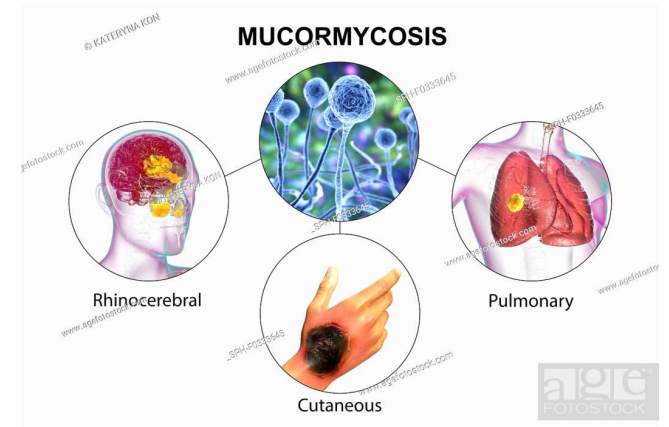
A. Espinel-Ingroff,<sup>a</sup> A. Chakrabarti,<sup>b</sup> A. Chowdhary,<sup>c</sup> S. Cordoba,<sup>d</sup> E. Dannaoui,<sup>e</sup> P. Dufresne,<sup>f</sup> A. Fothergill,<sup>g</sup> M. Ghannoum,<sup>h</sup> G. M. Gonzalez,<sup>j</sup> J. Guarro,<sup>j</sup> S. Kidd,<sup>k</sup> C. Lass-Flörl,<sup>l</sup> J. F. Meis,<sup>m</sup> T. Pelaez,<sup>n</sup> A. M. Tortorano,<sup>o</sup> J. Turnidge<sup>p</sup>

# Mucormicosi - Trattamento

- Rimozione chirurgica dei tessuti infetti (se necessario, dovrebbero essere ripetuti)
- Correzione di iperglicemia, chetoacidosi, terapia steroidea, immunosoppressione
- AMB DO: 0,75-1-1,5 mg/kg/giorno
- AMB liposomal 5 mg/kg/giorno
  - Intolleranza alla AMB: Isavuconazol 6 dose 200mg/8hs e poi 200mg/día
- Posaconazolo 600-800 mg/día
- **NO Voriconazolo**
- Itraconazolo 200-400mg/ giorno
- Equinocandine: “Non efective”



# Forma clinica



- **Cutanea** (riportato principalmente negli immunocompetenti)
  - Impianto traumatico
  - A traverso superficie esposte in conseguenza di un'alterazione delle barriere anatomiche
    - Mucormicosi in ustionati
    - contaminazione nelle procedure chirurgiche
    - secondaria a protesi o cateteri contaminati

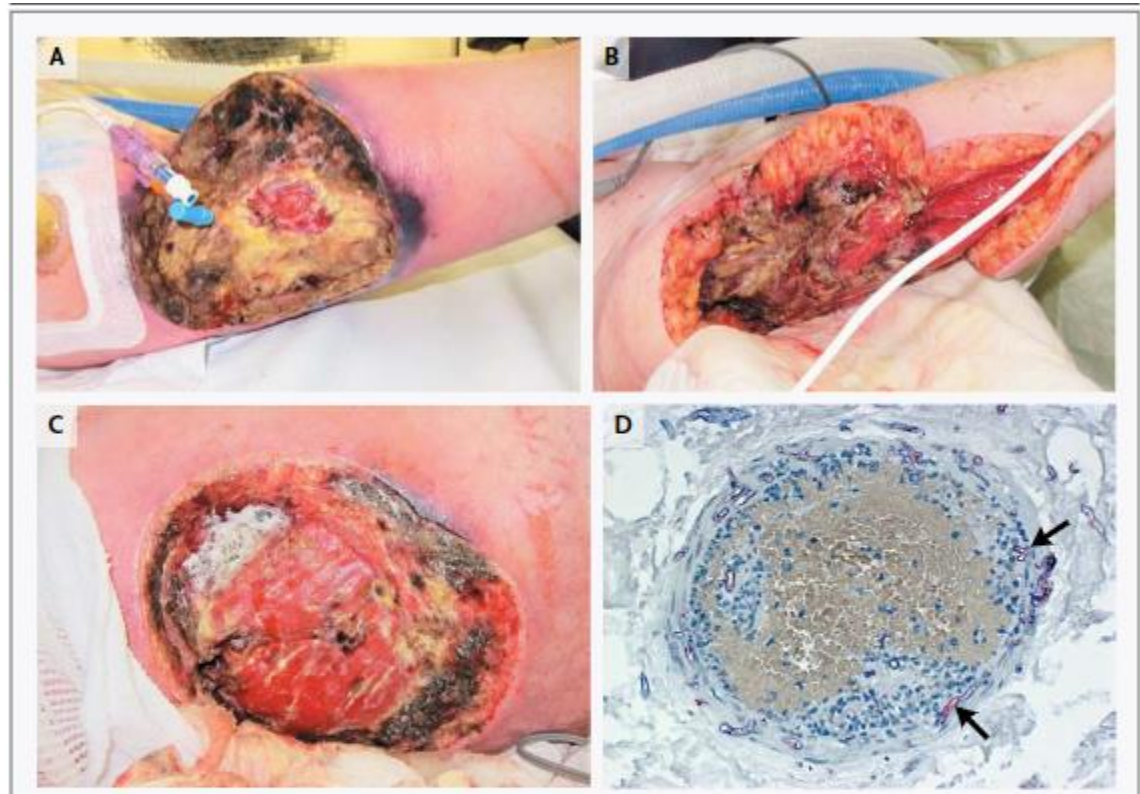
# Mucormicosis in ustionati





**Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011**

N Engl J Med. 2012 Dec 6;367(23):2214-25.



**Figure 1. Necrotizing Cutaneous Mucormycosis.**  
 Panel A shows a left-arm wound with areas of tissue necrosis visible in subcutaneous tissue, with some extension to the muscle layer. Panel B shows the same wound the next day, after surgical débridement, with visible tissue necrosis and soft-tissue extension into muscle layers. Panel C shows a left-flank wound in another case patient, with macroscopical fungal growth (a white, fluffy appearance) and necrotic borders before repeated surgical débridement. Immunohistochemical staining in Panel D shows mucormycetes (arrows) in the vascular wall and lumen of a necrotic vessel with inflammatory microthrombi (immunoalkaline phosphatase staining with naphthol-fast red substrate and a light hematoxylin counterstain).

*Apophysomyces trapeziformis* in 13 case patients  
 Mortality: 5 / 13

**Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka**

Lancet. 2005 Mar 5-11;365(9462):876-8

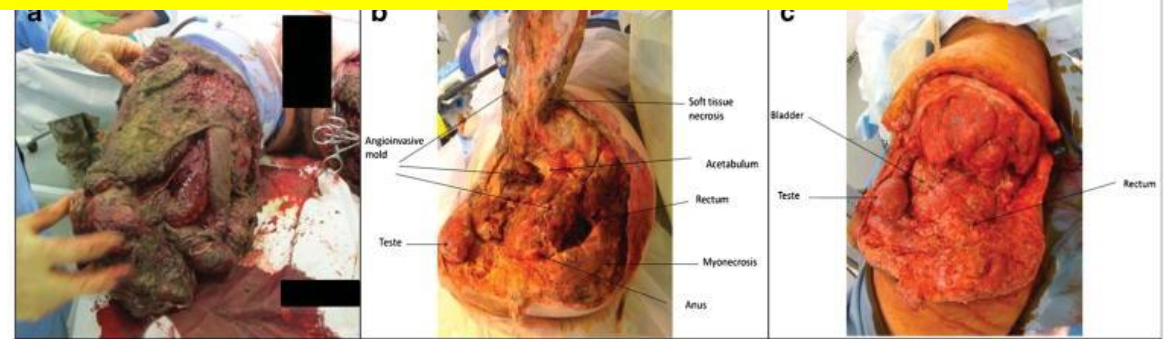


**Figure 1:** New right shoulder skin lesion on day 5 of admission before debridement (A), and previously debrided right thigh lesion on day 5 of admission before subsequent debridement (B). (A) Lesion arose from previously uninfected abrasion. (B) Right popliteal fossa showing necrotic muscle belly and fat. Patient's thigh is to the left and his calf to the right of the image.

**Figure 2:** Debrided popliteal tissue specimen, stained with haematoxylin and eosin  
 A broad, ribbon-like, aseptate filamentous fungus is seen, resembling a zygomycete, 5–12 µm in thickness, with vessel wall invasion (original magnification 200×).

mucormycosis can cause rhinocerebral, visceral, and disseminated infections.<sup>7</sup>  
 Cutaneous mucormycosis is uncommon and can follow either primary inoculation or haematogenous dissemination. Diagnosis on clinical grounds is difficult, and tissue biopsy for histology and culture is usually needed.<sup>5</sup> After a volcanic eruption in Colombia in 1985,<sup>6</sup> 38 patients in Bogotá hospitals developed severe necrotising fasciitis, of whom eight had proven cutaneous mucormycosis. Six of those with this infection died. The best outcomes from cutaneous mucormycosis have been associated with early detection, aggressive surgical debridement, early use of amphotericin B, and correction of predisposing factors.<sup>2a</sup> Hyperbaric oxygen has been used as an adjunctive treatment,<sup>7</sup> but evidence for its effectiveness is scarce.

**Combat-Related Invasive Fungal Wound Infections**



Curr Fungal Infect Rep. 2014 Dec 1; 8(4): 277–286.



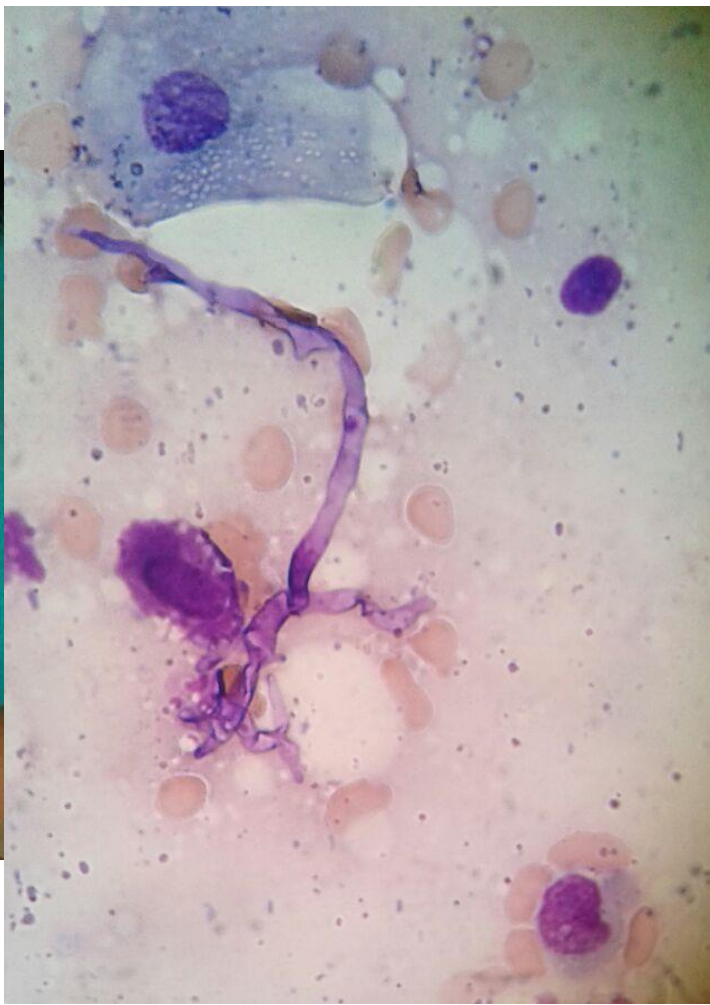


## Hepatic failure and malnutrition as predisposing factors of cutaneous mucormycosis in a pediatric patient

Silvia Colman<sup>a</sup>, Gustavo Giusiano<sup>b,\*</sup>, Carmen Colman<sup>a</sup>, María de los Ángeles Sosa<sup>c</sup>,  
Florencia Rojas<sup>b</sup>







# Mucormycosis

Mucormycosis is a serious but rare fungal infection, caused by the 'mucormycetes' group of fungi. It has been incorrectly called 'Black Fungus' recently, but the fungi causing mucormycosis are of a variety of colours.

## 1 Who is at risk

In most people, the fungi do not cause harm. There is a greater risk of infection in people:



With diabetes.



With cancer.



With HIV/AIDS.



Who have had treatment with higher doses or longer courses of steroids.



Who have weak immune systems for other reasons.

Recently many people with COVID-19 have been diagnosed with mucormycosis. It is not currently known if this is due to COVID-19 or some other reason.

## 2 How does the infection spread



The fungi are found throughout the environment, and most people breathe them in without any effect.



People with a weak immune system can develop infection in the sinuses and lungs when the fungi enter their airway.



In rare cases, skin infection occurs, usually only after a skin injury.



They do not spread from person to person.



In some rare cases, it has been known to affect the gastro-intestinal system.

## 3 How can I recognize it

Some common symptoms of mucormycosis are:



Swelling of the face and around the eye, usually on one side.



Facial pain or headache, usually on one side.



Red eye, usually on one side.



Black patches on the nose or the roof of the mouth. If you have these, please speak to a health care provider urgently.



Fever.

Many of these symptoms, such as fever and headache, are also common symptoms of other diseases, including COVID-19. Mucormycosis needs to be confirmed through a laboratory test. If you are at greater risk (refer to section 1) and have these symptoms consult your health care provider.

## 4 How is mucormycosis detected

The usual way to confirm is for a health care provider to



Take a sample from the inside of the nose or a sinus for laboratory testing.



See the fungus under a microscope or grow it using 'fungal culture'.



Also conduct scans or camera-based (endoscopy) tests of the sinuses, head and lungs if necessary.

## 5 What is the treatment

Strictly follow your health care provider's advice.



Mucormycosis is treated with antifungal medicines. These must only be used as advised by a health care provider.



Surgery may also be needed around the nose and eyes sometimes.



Do not self-medicate – these drugs can have harmful effects if they are not used properly.

## 6 How can we protect ourselves

Most healthy people are at very low risk of this disease. There is no vaccine for mucormycosis. Those at greater risk (refer to section 1) could reduce their risk by protecting themselves from the fungi in the environment:



Avoid areas with a lot of dust, like construction sites.



Avoid damp buildings or those damaged by water, for example due to floods and cyclones.



Avoid close contact with soil.



Wear clothes that cover arms and legs while working outdoors.



If you cut your skin, clean the injury area with soap and water.



World Health Organization



**Non tutte le  
lesioni necrotiche  
sono causate da  
mucorales**



**Celulite /  
Necrosi cutanea causata da  
infezioni batteriche**

**Fascite necrotizzante**



**Linfoma**



Dr. Alexandro Bonifaz

**Aspergilosi**







## Aspergilosi

Tabla 1 >

### Clasificación de las necrosis cutáneas

#### Por agentes exógenos

Químicos: ácidos y álcalis

Físicos: radioterapia, quemaduras, congelación, úlceras por presión, fármacos

#### Por infecciones

Ectima

Gangrena gaseosa

Fascitis necrosante

Meningococemia aguda

#### Por oclusión vascular

Depósito de sustancias:

En la luz del vaso: crioglobulinemia, síndrome antifosfolípido, enfermedad por émbolos de colesterol

En la pared del vaso: calcifilaxia

Vasculitis necrosantes:

Panarteritis nudosa

Granulomatosis de Wegener

Vasculitis alérgica de Churg-Strauss

Vasculitis de la AR y el LES

Alteraciones de la hemostasia:

Por alteración vascular

Por alteración plaquetaria

Por alteración de los factores de la coagulación: déficit de proteínas C y S y antitrombina III; necrosis cutánea por cumarínicos y heparina

#### Otras causas

Pioderma gangrenoso, papulosis atrófica maligna, dermatomiositis, etc.



## Mucormicosi



## Mucormicosi



Palatal mucosal discoloration in a COVID-19 patient with mucormycosis  
J. Maxillofac. Oral Surg. 2021; 20(3):418-425

## Mucormicosi





**Sedosporiosi**



**Mucormicosi causata da *Saksenaea***

**Non tutte le lesioni in rapida evoluzione sono causate da mucorales**



# Conclusioni

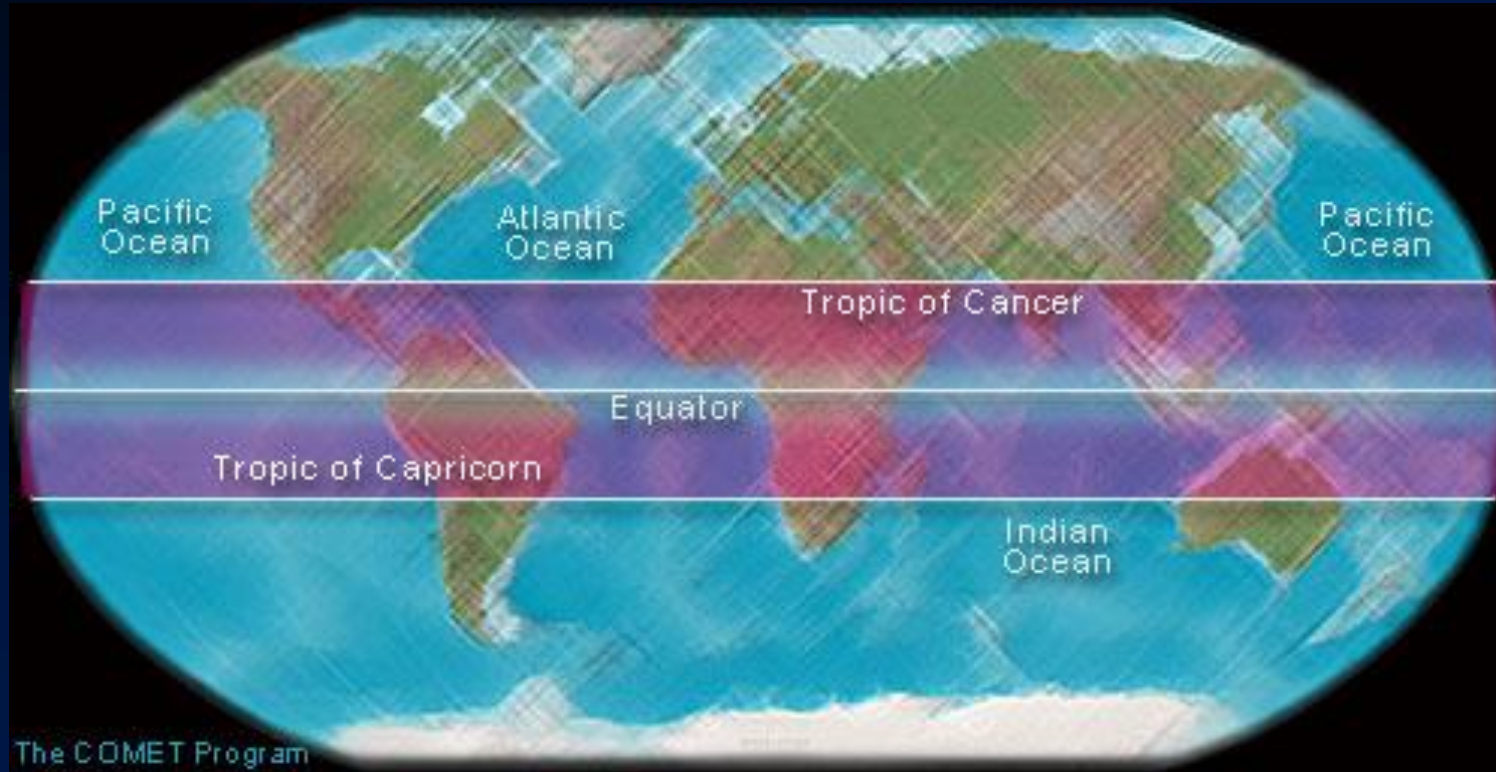
- La mucormicosi è considerata emergente
- Causata da funghi opportunisti ambientali
- Associata maggiormente al diabete (DT2), neutropenia, uso di immunosoppressori
- La principale forma clinica: rino-cerebrale
- **Il laboratorio di microbiologia è fondamentale**
- La risposta dipenderà da :
  - Terapia antimicotica
  - Sbrigliamento chirurgico
  - Controllo dell'iperglicemia e della chetoacidosi
  - Uso giudizioso di steroidi



# Entomoftoromicosi



# Entomoftoromicosi (zigomicosi sottocutanea)



Distribuzione: Regioni umide / tropicali

Africa tropicale – America centrale – America del Sud (Colombia e Brasile) - Asia

Le entomofromicosi sono micosi sottocutanee causate da due tipi di funghi saprofiti in natura, che sono **istologicamente simili** ma producono **entità cliniche diverse**

Agenti: *Entomophthorales*

Generi *Basidiobolus* e *Conidiobolus*

- ❑ *Basidiobolus ranarum*
- ❑ *Conidiobolus coronatus*

Entrambi gli agenti eziologici causano un'infezione granulomatosa cronica



**Basidiobolomicosi**

**Conidiobolomicosi**

saprofiti di vegetazione secca e suoli. Anche dal tratto intestinale di rettili e anfibi

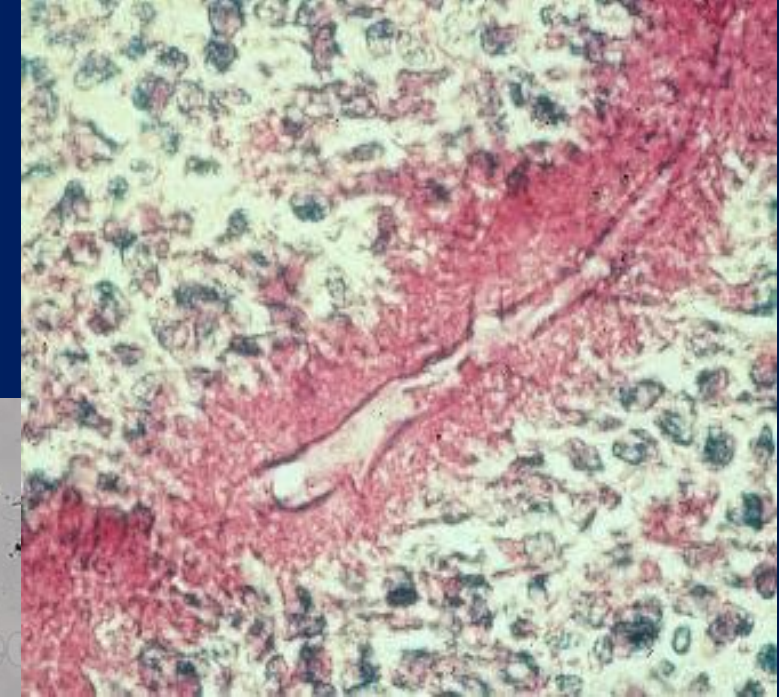
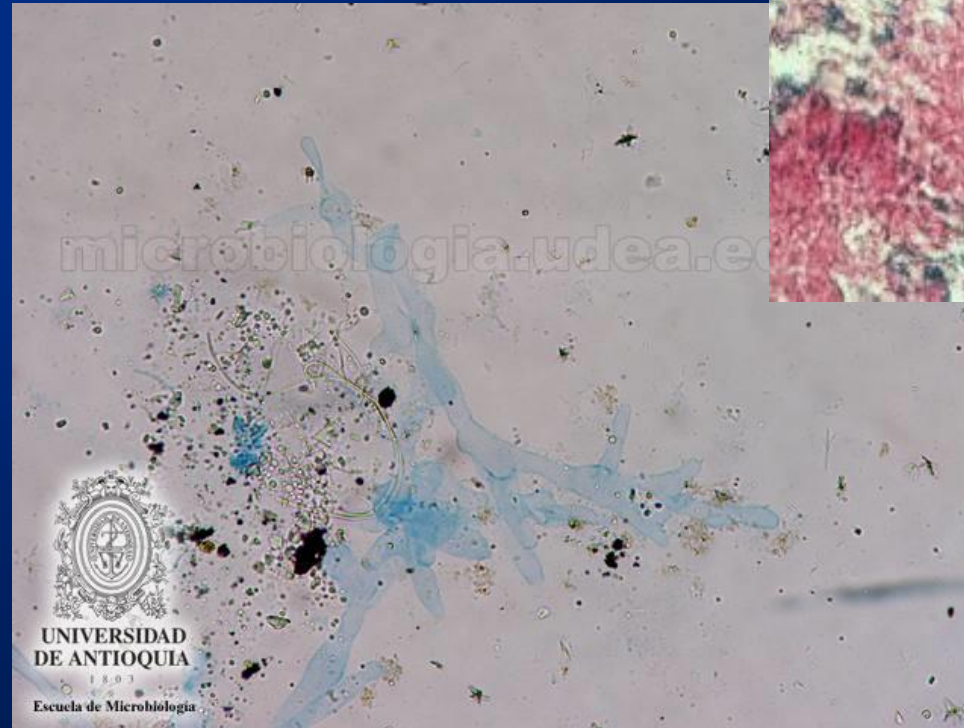
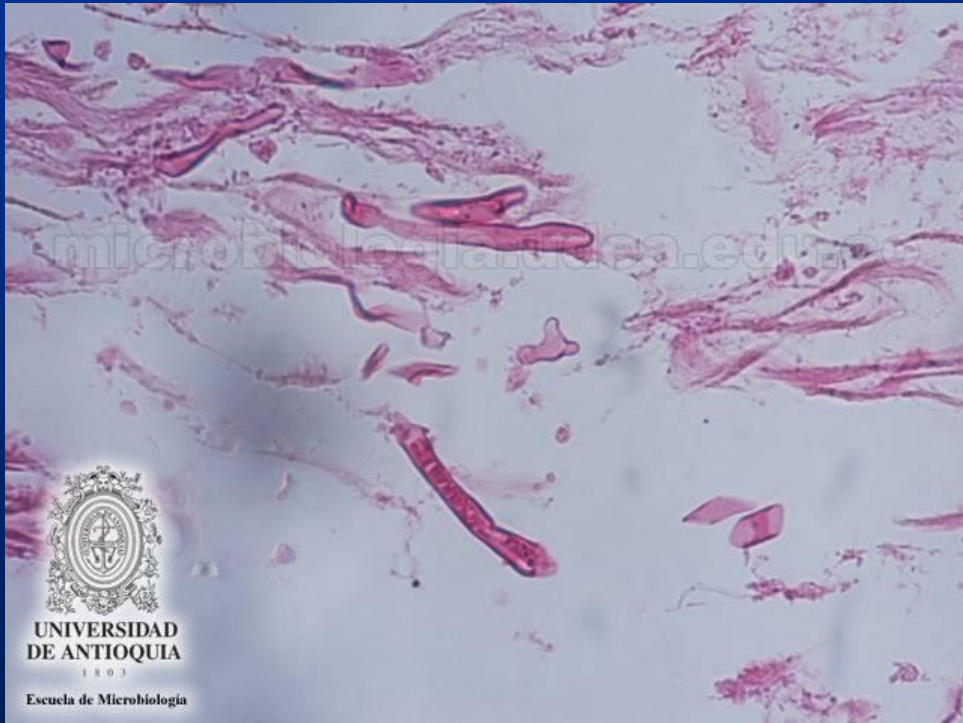


❑ *Basidiobolus ranarum*

❑ *Conidiobolus coronatus*

- Funghi a bassa virulenza
- Microtrauma -
- Pazienti immunocompromessi
- Casi in uomo, cani, delfini, cavalli, scimmie

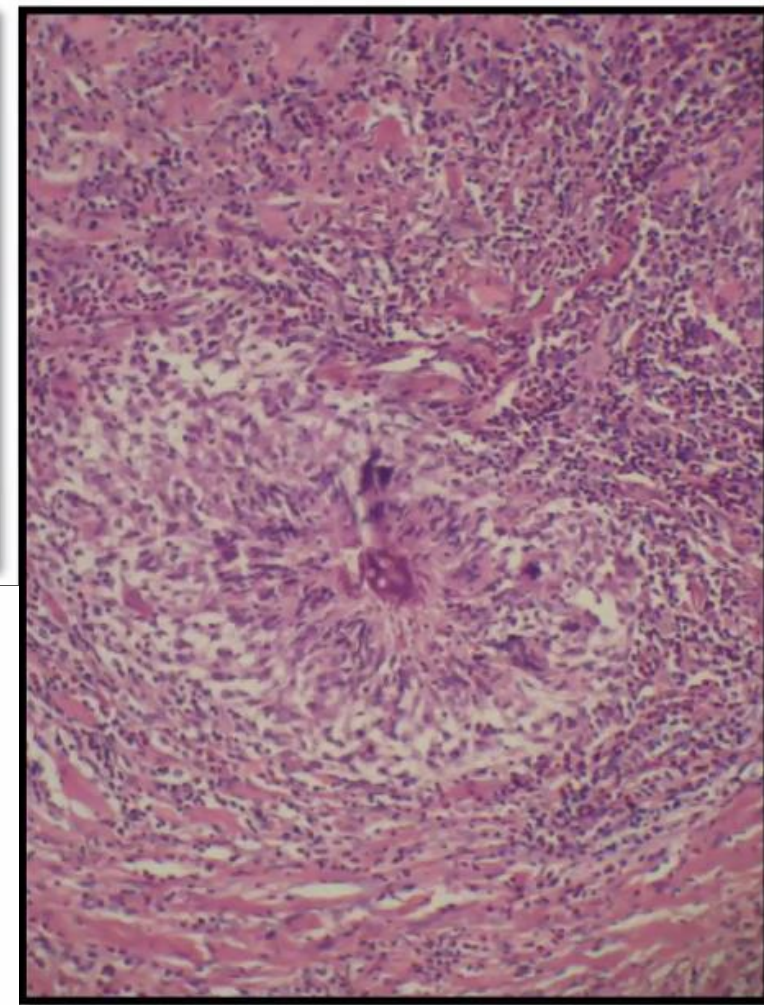
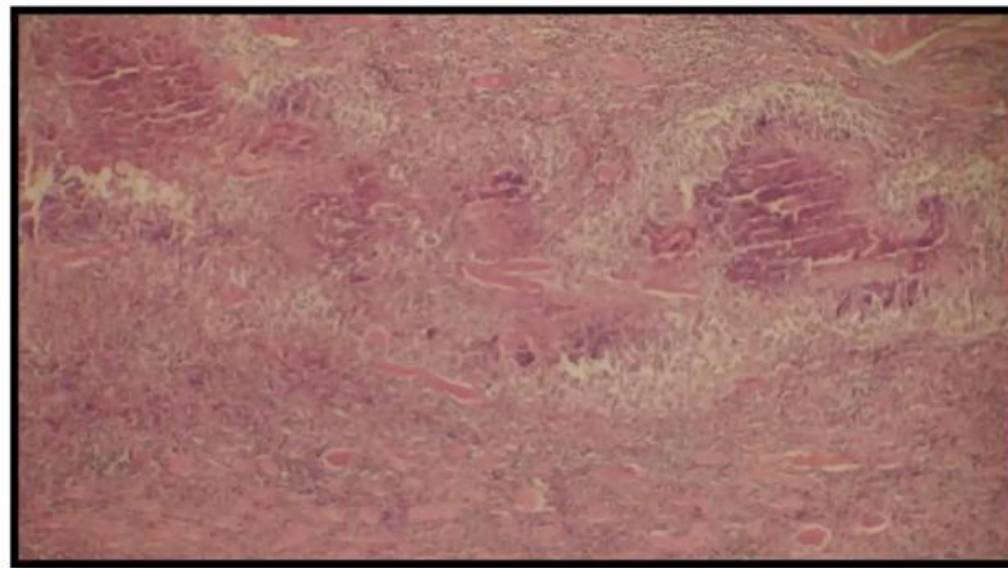
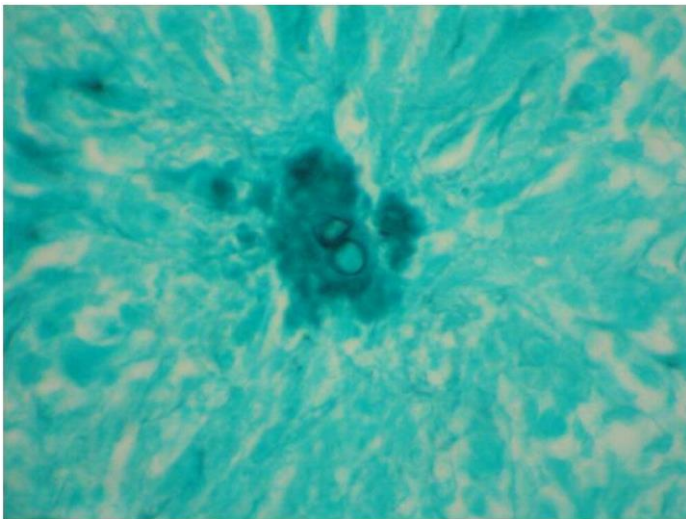
infezioni croniche dei pazienti immunocompetente  
con la presenza di ife non settate o scarsamente settate,  
presenza di alone eosinofilo  
(Fenomeno Splendore-Hoepplii) In istopatologia;



**Conidiobolomycosis y Basidiobolomycosis**, Entrambe sono condizioni croniche e le ife non si infiltrano nelle pareti vascolari o invadono il lume vascolare, la clinica è totalmente diversa dalla zigomicosi causata da Mucorales

*Mucormycosis can also present Splendore-Höeppli phenomenon, but it is exceptional.*





Nonseptated hyphae surrounded by an eosinophilic halo are occasionally visualized (Splendore-Hoeppli phenomenon).

Denso infiltrato infiammatorio misto con abbondanti eosinofili, cellule giganti e necrosi granulare eosinofila circondata da granulomi epitelioidi, tipo Splendori-Hoeppli

Clinics in Dermatology (2012) 30, 409–412



Clinics in Dermatology

### Rhinofacial conidiobolomycosis (entomophthoromycosis)

Rafael Isa-Isa, MD<sup>a</sup>, Roberto Arenas, MD<sup>b,\*</sup>, Ramón F. Fernández, MD<sup>b</sup>, Mariel Isa, MD<sup>a</sup>

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<sup>b</sup>Mycology Section, Department of Dermatology, "Dr. Manuel Gea Gonzalez" General Hospital, Calzada de Tlalpan 4800, Colonia Sección XVI, Mexico, DF 14080, Mexico

### Histopathologic data

In our experience, the biopsy specimen must be taken from the glabella. The fungal structures are easily identified with hematoxylin and eosin, periodic acid–Schiff (PAS) or Gomori-Grocott stain (Figure 6).<sup>4</sup> Biopsy specimens show a suppurative granuloma with lymphocytes, histiocytes, multinucleated giant cells, plasma cells, and eosinophils. Non-septated hyphae surrounded by an eosinophilic halo are occasionally visualized (Splendore-Hoeppli phenomenon).



L'infezione da *C. coronatus* è stata designata con vari nomi:

- Rinoentomoftoromicosi
- Rinoconidiobolomicosi
- Rinozigomicosi
- Rinoficomicosi
- Zigomicosi sottocutanea
- Entomofotomicosi nasale
- Entomoftoromicosi conidiobolae



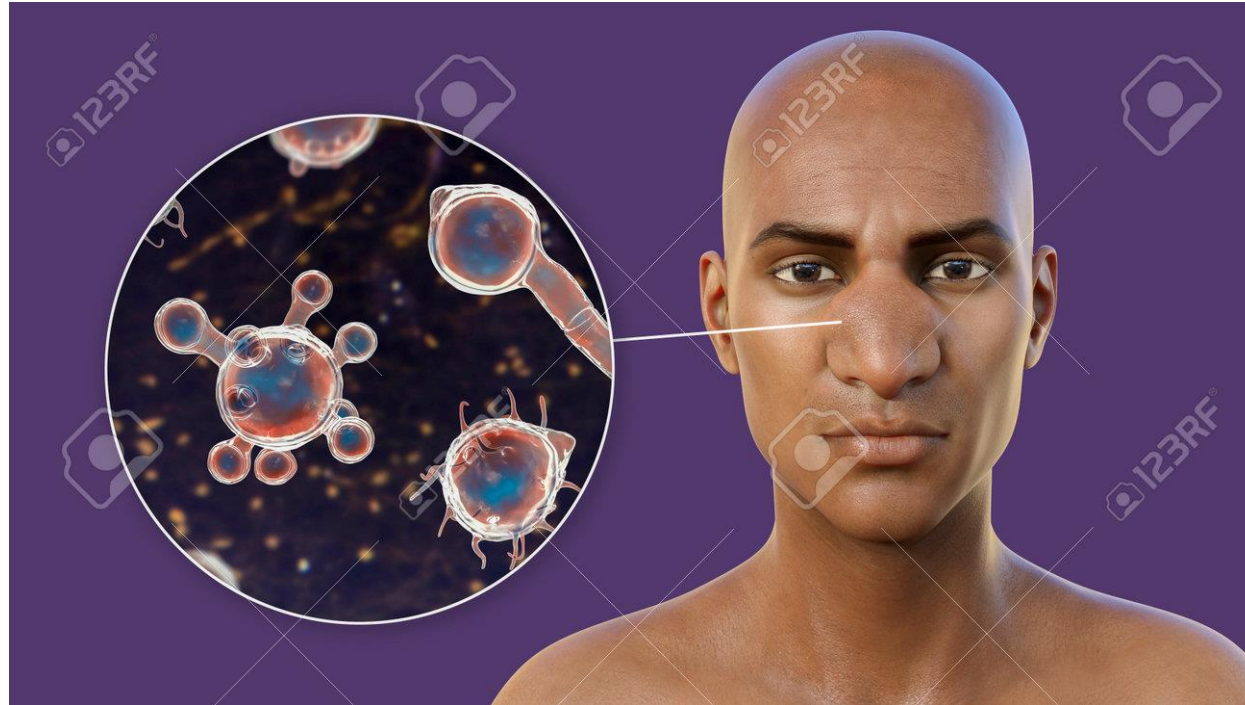
*Conidiobolus* provoca un'**infezione cronica granulomatosa** prevalentemente **facciale**,

Colpisce la **popolazione adulta**

Ha una chiara predilezione per il  **sesso maschile** (10:1)

Produce enzimi: elastasi, collagenasi e lipasi che sono stati coinvolti nella patogenesi della malattia

## Fase 1

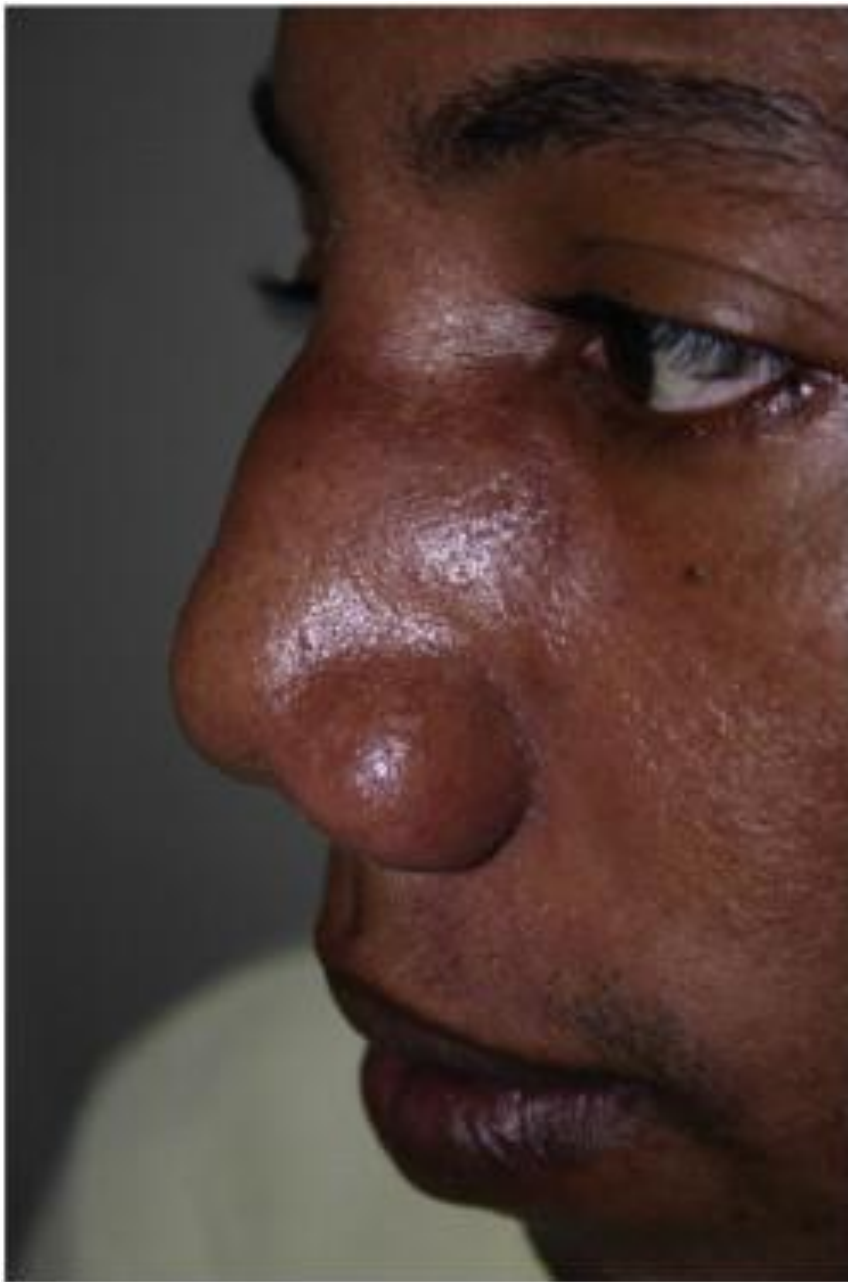


Infezione iniziale della mucosa nasale e della sottomucosa da dove si diffonde al tessuto sottocutaneo del viso con predominanza mediofacciale, area in cui produce lesione necrotizzante con reazione infiammatoria granulomatosa, ricca di eosinofili.



## Fase 1

Narice  
Seni paranasale  
Palato e laringe



Clinics in Dermatology; 2012: 30: 409-412

<https://doi.org/10.1016/j.clindermatol.2011.09.012>



<https://doi.org/10.1111/ijd.12966>

### Conidiobolomicosi

- Rinorrea
- Epistassi,
- Ostruzione nasale
- Dolore
- Infiammazione – deturpamento

Fase 2

## Naso, regione frontale e labbra

volume aumentato  
costituito da noduli ed  
edema con eritema  
superficiale



Clinics in Dermatology; 2012; 30: 409-412

<https://doi.org/10.1016/j.clindermatol.2011.09.012>



Mycoses, 2010; 54: 369-373

<https://doi.org/10.1111/j.1439-0507.2009.01716.x>



### Fase 3

muscoli, ossa e visceri





Colonia ialina, di aspetto cotonoso a polveroso

Coltura mostra colonie satelliti da conidi scaricati forzatamente.

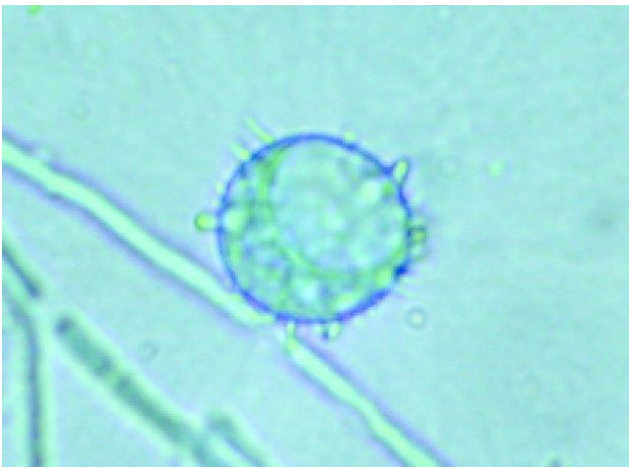
Sabouraud + estratto di lievito + estratto di malto

72 ore

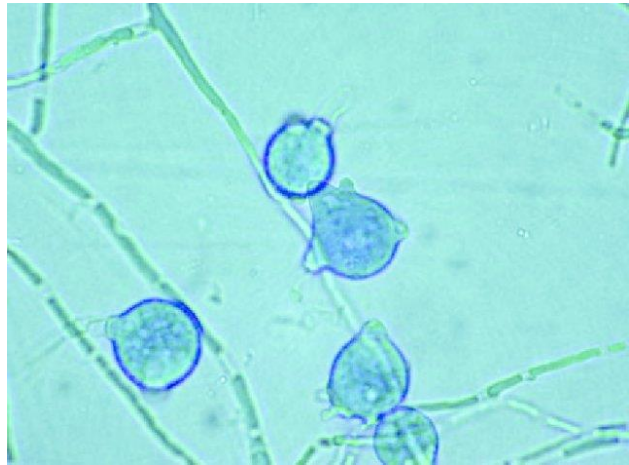
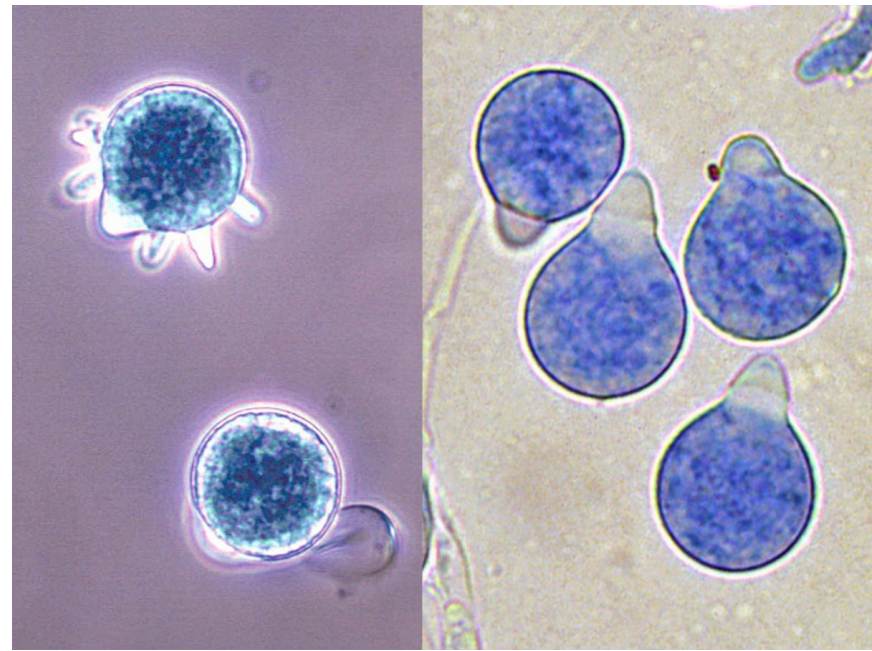
25 – 28 °C





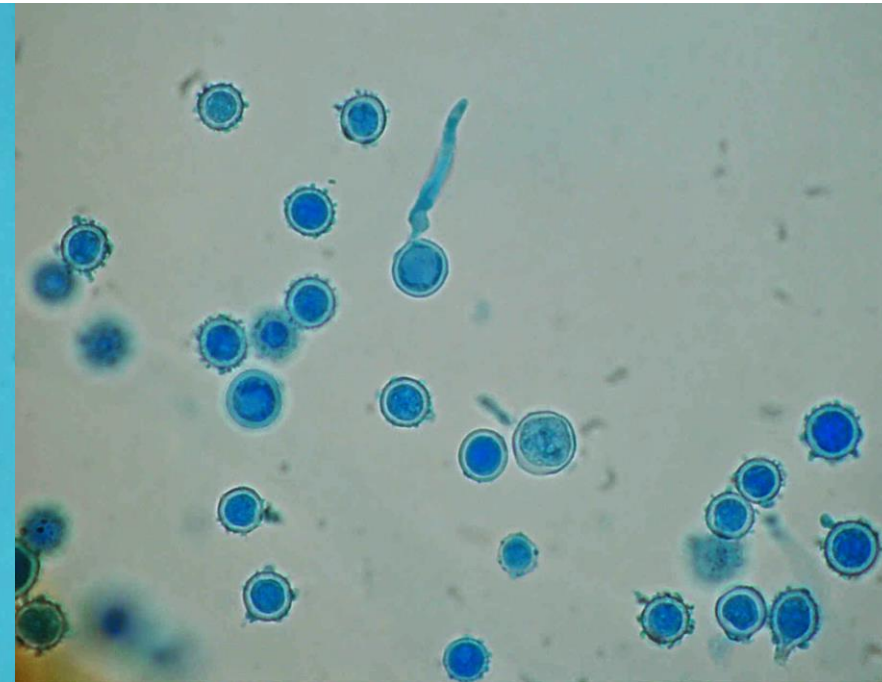


Conidi a forma di corone



Conidi sferici con appendici e papille prominenti

Cienc. Vet. 26 (2): 73-79, 2008



L'infezione da ***Basidiobolus ranarum*** è stata designata con vari nomi:

- Entomophthoromycosis basidiobolae
- Zigomicosi sottocutanea
- Ficomicosi sottocutanea
- Basidiobolomicosi



Kingdom: Fungi  
Phylum: Zygomycota  
Sub - Phylum: Zygomycotina  
Class: Zygomycetes  
Order: Entomophthorales  
Family: Basidiobolaceae  
Genus: *Basidiobolus*



K. Nishimura

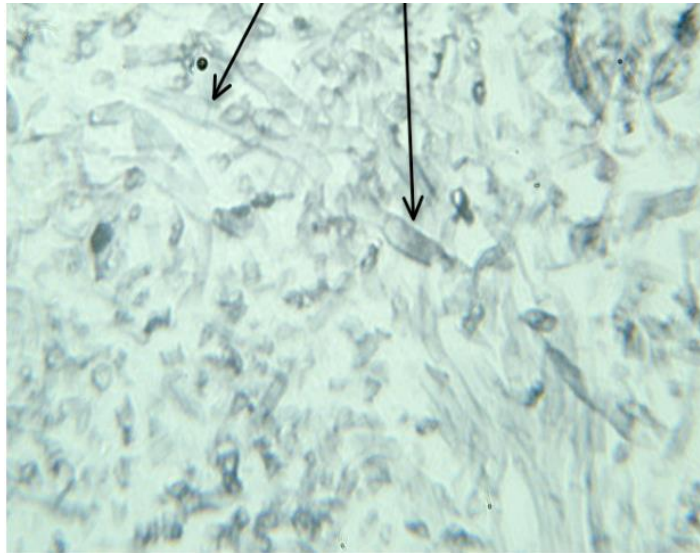
Zigospore a pareti spesse e lisce (cellule tipo orologio).



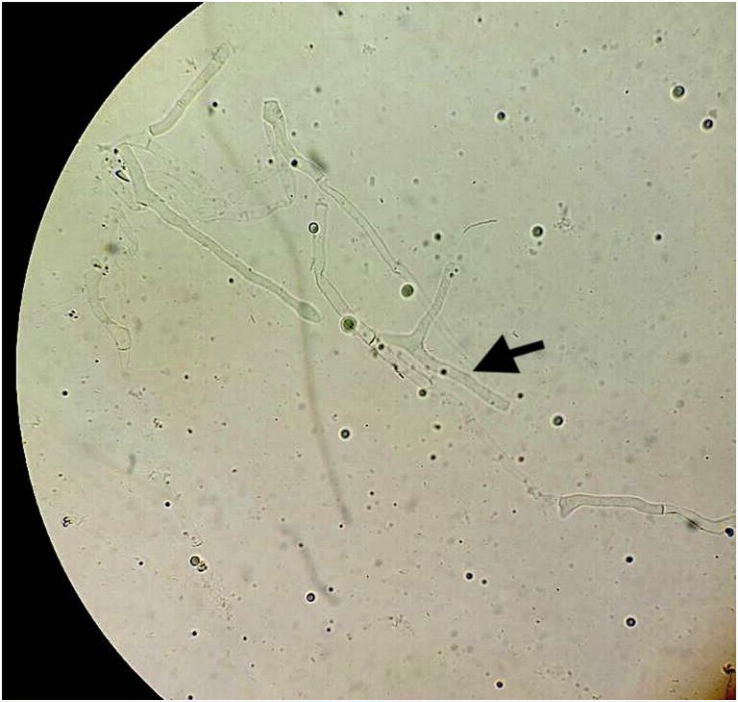
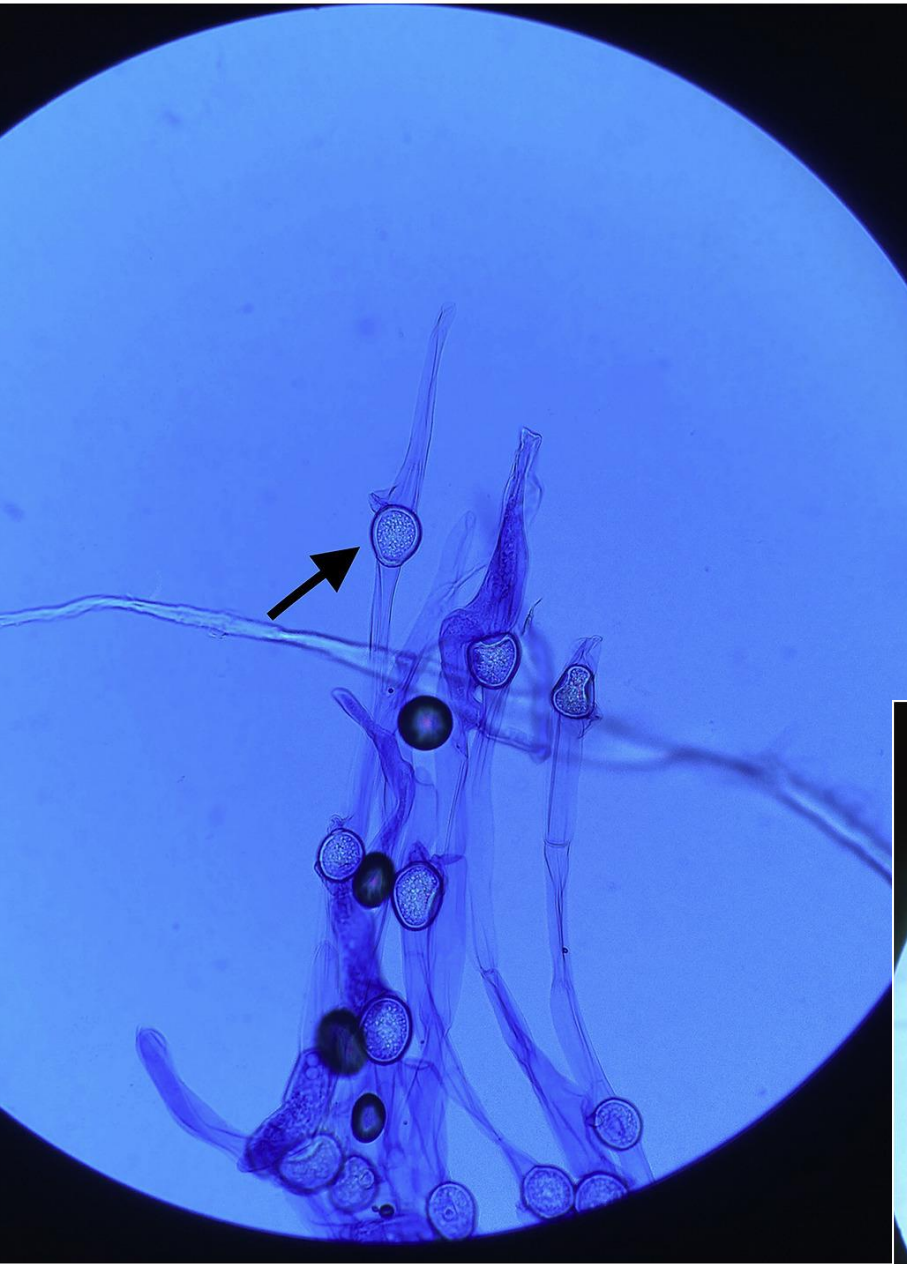
è un'infezione granulomatosa della cute e dei tessuti sottocutanei caratterizzata dalla formazione di tumefazioni sode e non dolenti, generalmente alle estremità, al tronco e raramente in altre parti del corpo

## *Basidiobolomycosis*

Più comune nei bambini e negli adolescenti











Lo sporangioforo ha una zona dilatata appena sotto la spora che partecipa attivamente allo scarico della spora.

grandi ife vegetative (8-20 um Diam)

Esporangiosporas en forma de clava denominadas células adhesivas



Si formano due tipi di spore asexuale: primaria e secondaria.

**Primaria:** spore globose, unicellulari, solitarie e scaricate forzatamente da uno sporangioforo.

**Secundaria:** spore spatolate unicellulari che si liberano passivamente da uno sporangioforo. L'apice della spora rilasciata passivamente ha una punta adesiva



# Trattamento

- Itraconazolo 200-400mg/ giorno – 6 mesi

## Alternativa

- AMB 0,5 mg/kg/giorno 2 a 4 settimane
- Dapsona 1000mg/g
- Terbinafina 250-500mg / g
- Ioduro Potassio 3-6g / g



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**MUCHAS GRACIAS!!**

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