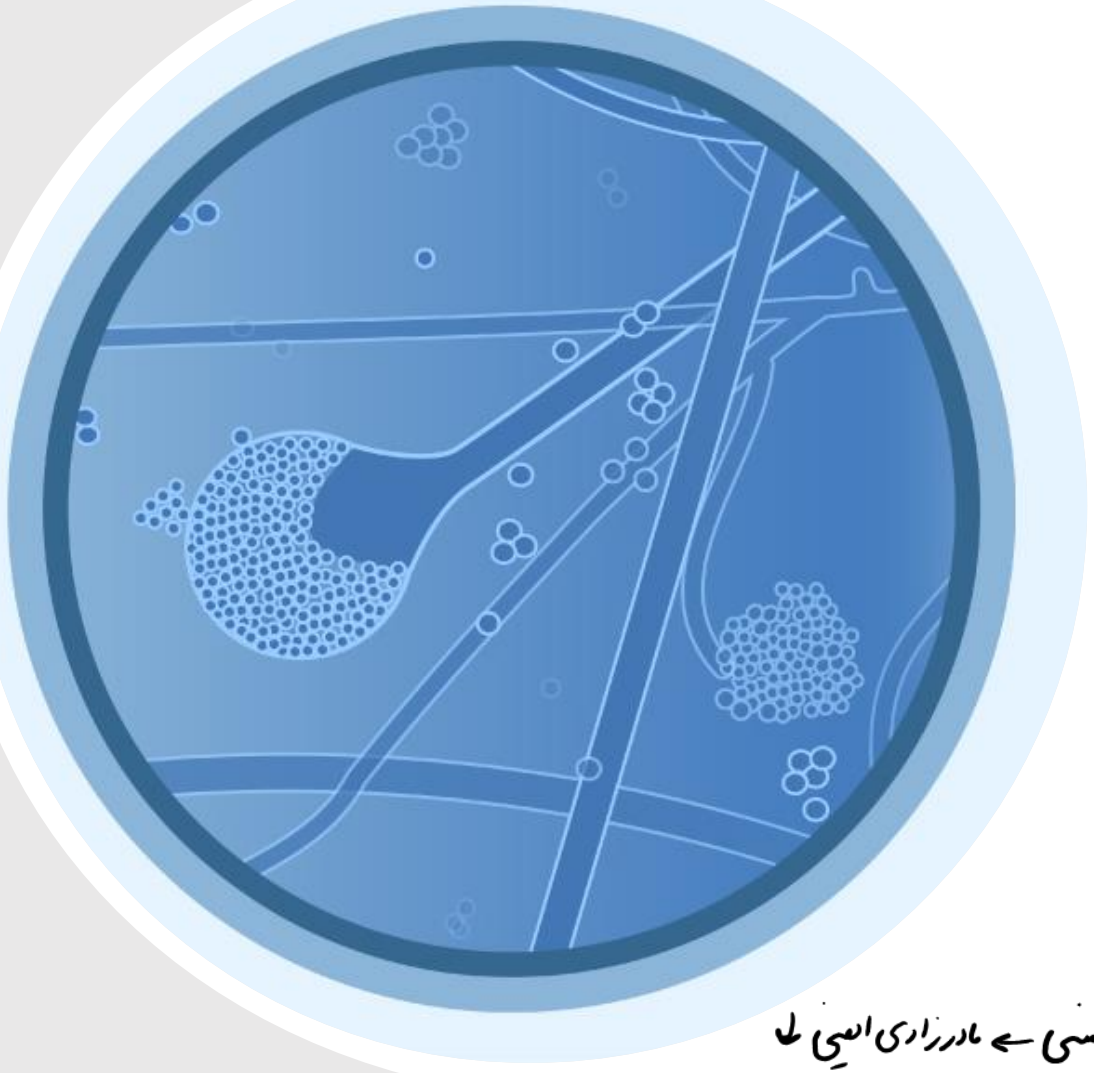

Mucormycosis

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Opportunistic Systemic Mycoses

- These are fungal infections that occur almost exclusively in patients whose normal defense mechanisms are impaired (immunocompromised people).

- Weakened immune function may occur due to inherited immunodeficiency diseases, drugs that suppress the immune system (cancer chemotherapy, corticosteroids, drugs to prevent organ transplant rejection), radiation therapy, infections (e.g., HIV), cancer, diabetes, advanced age, and malnutrition.

The most common infections are:

Disease	Causative organisms	Incidence
Aspergillosis	*Aspergillus* spp. : *A. fumigatus, A. flavus, A. terreus* etc.	Common
Mucormycosis	Order Mucorales: *Rhizopus*, *Mucor*, *Rhizomucor*, etc.	Rare
Cryptococcosis	*Cryptococcus* spp. : *C. neoformans*, *C. gattii*	Rare
Candidiasis	*Candida* spp. : *C. albicans* , *non-albicans Candida* *Candida auris*	The most Common invasive IFI

Recent global outbreaks of mucormycosis during the COVID-19 pandemic highlighted the importance of host immune and metabolic factors such as diabetes and corticosteroid use."

Introduction

→ اسمی کاملاً اشتباه!

اسم گذاشته شده به علت علائم بالینی ← قارچ کاملاً
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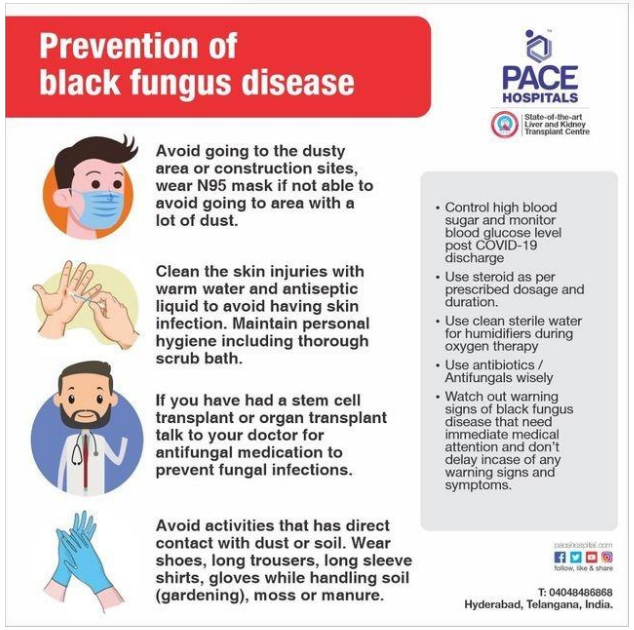
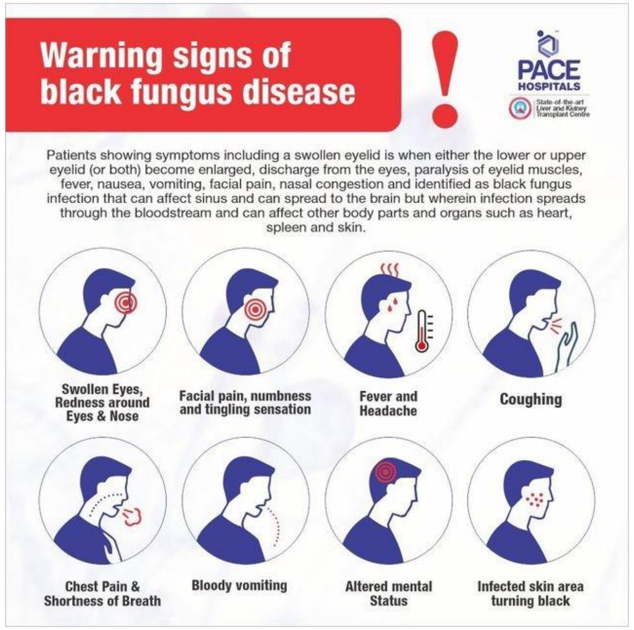




Past	Present
Global incidence rate **0.005** to **1.7** per million population Prevalence in India is around **140** per million population (**80** times that of developed countries) Around **46%** patients with the disease reportedly die with **68%** risk with disseminated and **31%** with cutaneous mucormycosis	Current data (May 5-July 12, 2021) reports **41,512** cases and **3,554** deaths due to mucormycosis in India Around **80%** of patients with COVID-19 associated mucormycosis have diabetes

Introduction

- Mucormycosis has been regarded as a relatively rare mold infection, but recent reports suggest its incidence may increase.
- Mucormycosis (zygomycosis) is the most acute and aggressive fungal infection known.
- Historically, these infections have been seen in immunocompromised hosts in particular, patients being treated for haematological malignancies, where it is the second most common invasive mold infection after invasive aspergillosis.

Clinically relevant species of Mucorales

Human pathogenic Mucorales

✔ 12 genera: 39 species

Family	Genus	Clinically Relevant Species
Rhizopodaceae	*Rhizopus* ~50%	*R. arrhizus* (including var. *arrhizus* and var. *delemar*) *R. homothallicus* *R. microsporus* *R. schipperae*
Saksenaeaceae	*Saksenaea*	*S. erythrospora* *S. loutrophoriformis* *S. trapezispora* *S. vasiformis*
Syncephalastraceae	*Syncephalastrum*	*S. racemosum*
Lichtheimiaceae	*Thamnostylum*	*T. lucknowense*
Mucoraceae	*Actinomucor*	*A. elegans*
Saksenaeaceae	*Apophysomyces*	*A. mexicanus* *A. ossiformis* *A. trapeziformis* *A. variabilis*
Mucoraceae	*Cokeromyces*	*C. recurvatus*
Cunninghamellaceae	*Cunninghamella*	*C. arunalokei* *C. bertholletiae* *C. blakesleeana* *C. echinulata* *C. elegans*
Lichtheimiaceae	*Lichtheimia* ~13%	*L. corymbifera* *L. ornata* *L. ramosa*

~72%

~4%

***Rhizopus arrhizus* (*oryzae*)** remains the most common cause, responsible for approximately **70% of cases**.

Family	Genus	Clinically Relevant Species
Mucoraceae	*Mucor* ~14%	*M. amphibiorum* *M. circinelloides* * *M. griseocyanus* * *M. indicus* *M. irregularis* *M. janssenii* * *M. lusitanicus* * *M. plumbeus* *M. racemosus* *M. ramosissimus* * *M. variicolumellatus* * *M. velutinosus* *
Lichtheimiaceae	*Rhizomucor*	*R. miehei* *R. pusillus*
Mycotyphaceae	*Mycotypha*	*M. microspora*

~22%

Epidemiology

- Agents of mucormycosis are ubiquitous and thermotolerant organisms that usually grow and sporulate abundantly on any carbohydrate-containing source in decaying matter, including bread, vegetables, fruits, and seeds.
- They can also be recovered from soil, compost piles, and animal excreta.
- The spores are easily airborne, and mucorales are readily recovered as contaminants in laboratory cultures.
- COVID-associated mucormycosis (CAM) became an important concern in 2020–2022.

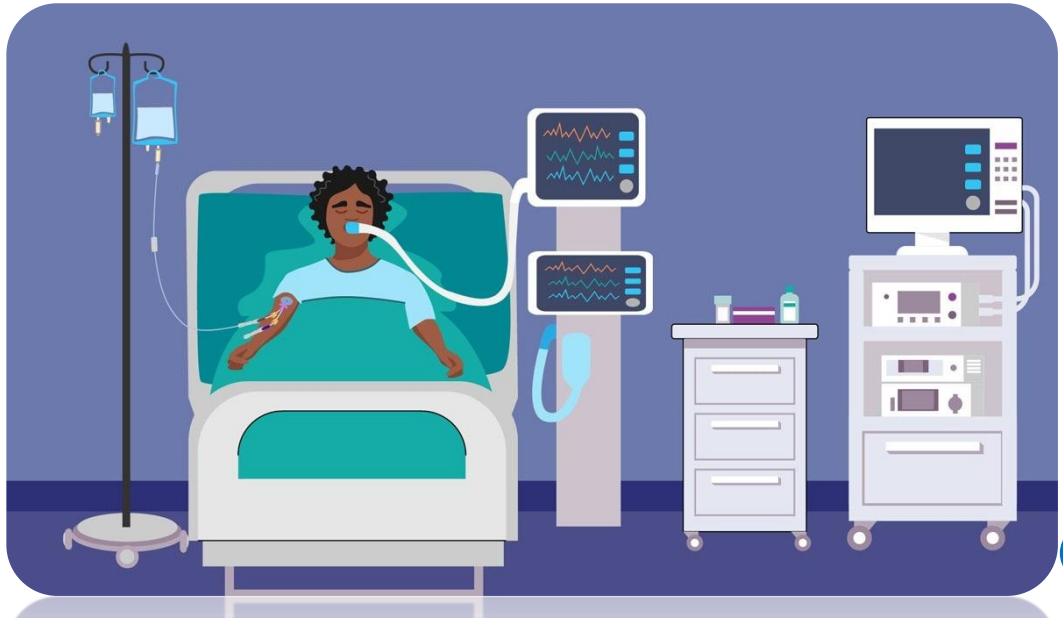
Risk factors

- ❑ Uncontrolled diabetes mellitus and other forms of metabolic acidosis
- ❑ Immunosuppressive therapy especially high-dose corticosteroids
- ❑ Experienced trauma or burns
- ❑ Malignant hematologic disorders
- ❑ Recently COVID-19 particularly among those with diabetes.

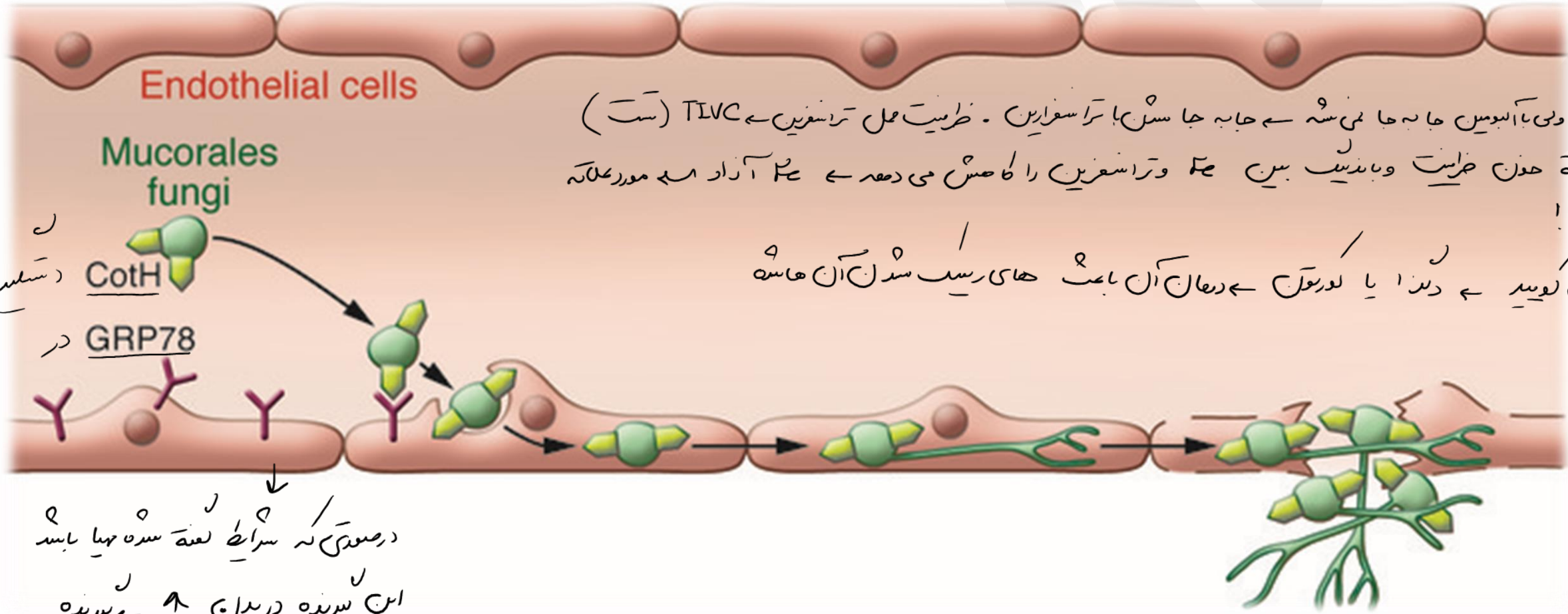
- ➢ Only rare case reports of invasive mucormycosis in apparently normal hosts have been described.
- ➢ Allergic pulmonary disease does occur in immunocompetent hosts and reflects an acute hypersensitivity immune response illness rather than an invasive disease.

Pathogenesis

- The ability of inhaled spores to germinate and form hyphae in the host is critical for establishing infection.
- Findings suggest that neutrophils, but not necessarily T lymphocytes, are critical for inhibiting fungal spore proliferation.
- Both mononuclear and polymorphonuclear phagocytes of normal hosts kill mucorales by generating oxidative metabolites and the cationic peptides, defensins.
- High glucose, acidic pH, and elevated free iron levels promote fungal growth via the CotH protein-mediated endothelial adhesion (GRP78).



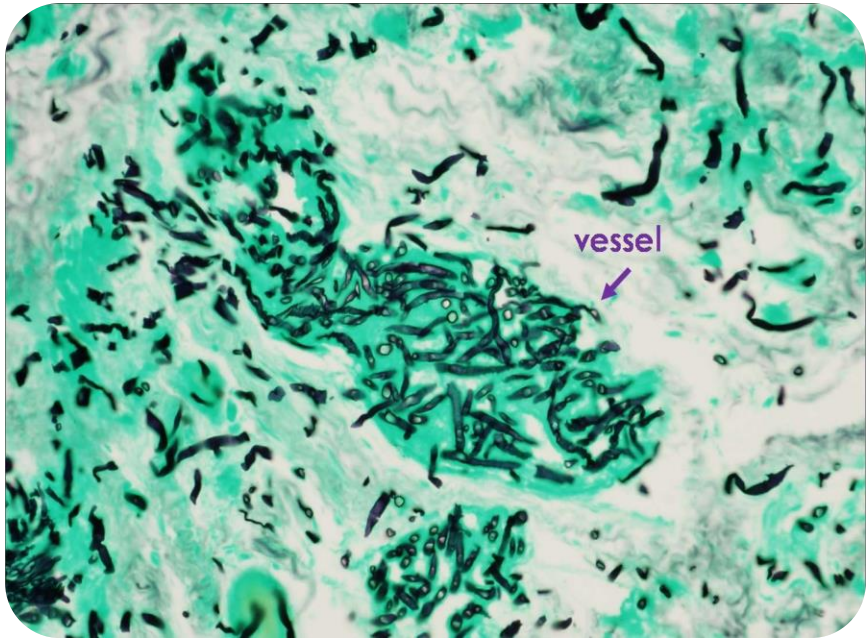
Pathogenesis



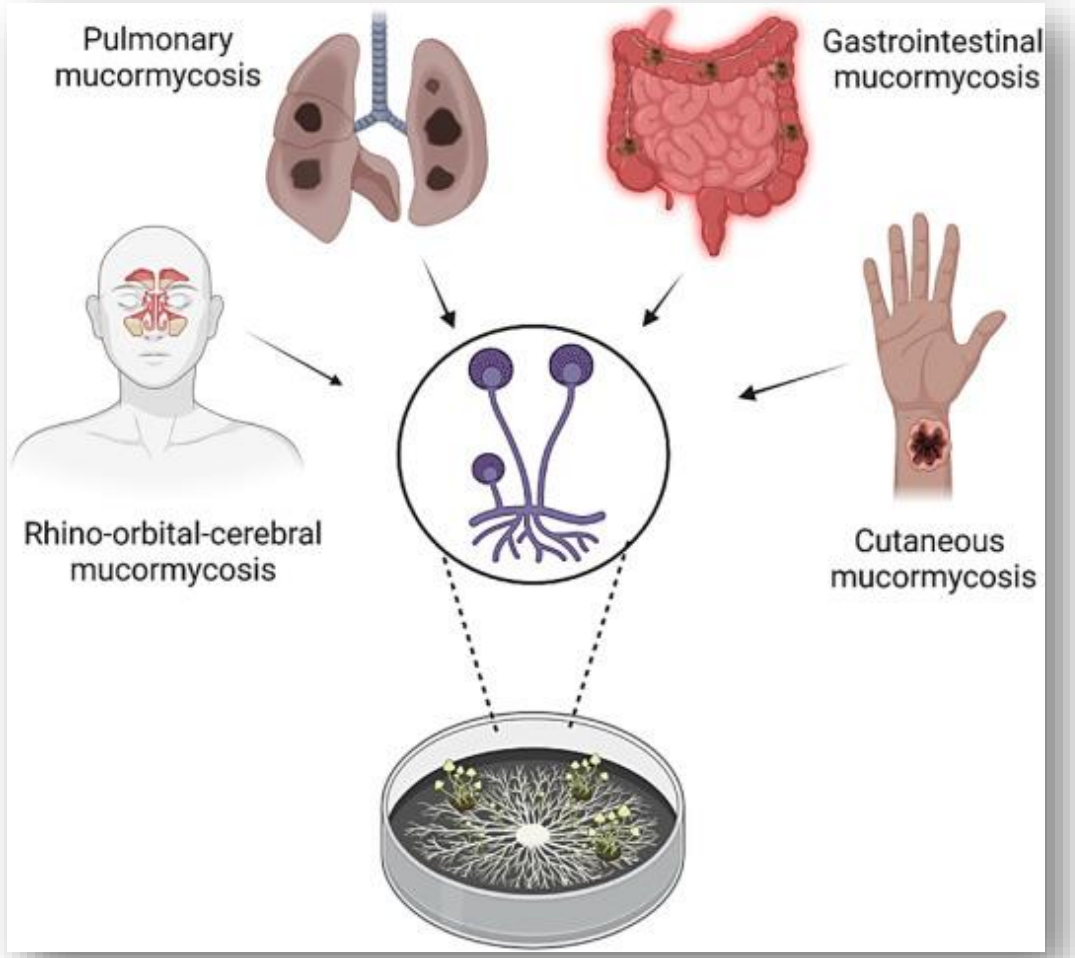
Pathophysiology

- The clinical hallmark of mucormycosis is the rapid onset of tissue necrosis, with or without fever.
- This necrosis is the result of invasion of blood vessels and subsequent thrombosis.
- Unfortunately, the aggressive nature of the infection often means that delayed diagnosis and erroneous treatment decisions often result in significantly higher patient morbidity and mortality.
- As mucoraceous moulds have no septa in their hyphae, allowing more rapid nutrient transport, they can grow faster than many other moulds.

- Angio invasion
- Vessel thrombosis
- Tissue necrosis

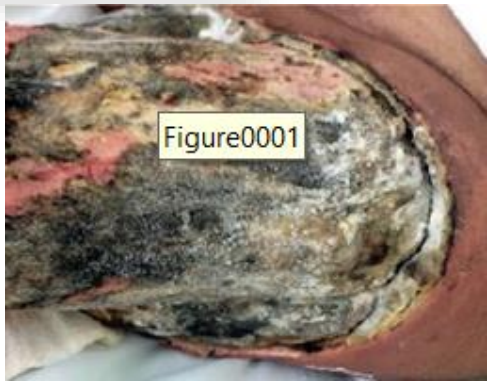


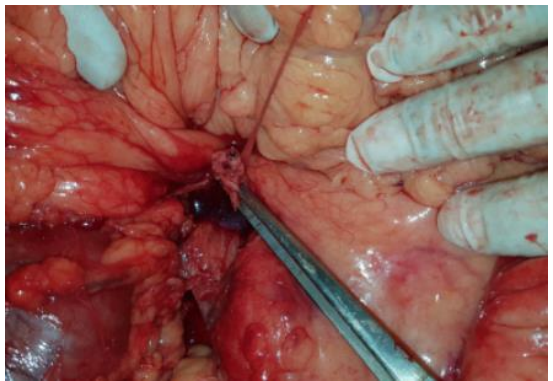
Clinical Manifestations



- ❑Rhino-Orbital-Cerebral (ROCM)
- ❑Pulmonary
- ❑Cutaneouse
- ❑Gastrointestinal
- ❑Disseminated





Major route of infection:

- Inhalation

Both ROCM and pulmonary mucormycosis are acquired through inhalation.

- Ingestion

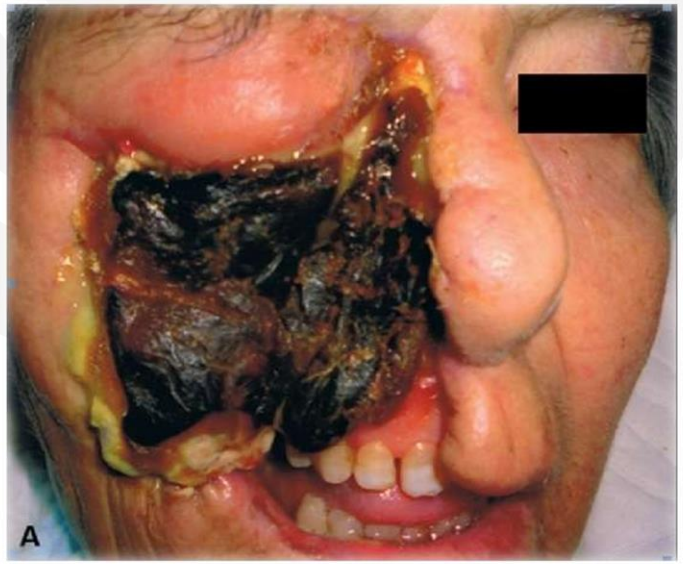
Ingestion of contaminated food, which leads to gastrointestinal mucormycosis in highly immunocompromised patients and premature neonates.

- Traumatic inoculation

Other routes of infection include direct implantation into skin, causing local cutaneous infection.

Rhino-Orbital-Cerebral (ROCM)

- ROCM is the most common form of the disease, representing between one-third to one-half of all cases.
- 70% of cases of ROCM are found in DKA. → ذیابیطس کیتوایسیڈوسس
- The most clinical form observed in COVID-19.
- Beyond classic diabetic ketoacidosis, ROCM now frequently presents in patients on high-dose corticosteroids (for autoimmune conditions or transplant) and those with hematological malignancies.



Clinical Manifestations

- ROCM may present as paranasal sinusitis.
- Delayed recognition and diagnosis may result in rapid progression to involve the orbit, retro-orbital tissues, and brain, with devastating consequences.
- Common Symptoms: Headache, sinus pain, facial swelling, fever, and visual impairment (Ptosis, ophthalmoplegia,…) .
- Early Warning Signs: Unexplained toothache, loosening of teeth, or facial numbness, often appearing before the development of a black eschar.
- A black eschar may appear on the hard palate or nasal mucosa.

Pulmonary mucormycosis

Clinical Manifestations

- Pulmonary mucormycosis occurs most commonly in patients with profound and prolonged neutropenia, such as that noted in patients with leukemia or recipients of a hematopoietic stem cell transplant.
- Patients with DKA can also develop pulmonary mucormycosis.
- Pulmonary mucormycosis may develop as a result of inhalation or by hematogenous or lymphatic spread.
- In immunocompromised or neutropenic patients, pulmonary mucormycosis may mimic invasive aspergillosis; differentiation requires histopathology or molecular confirmation

Cutaneous mucormycosis

Clinical Manifestations

❑ Primary

This form occurs following the direct traumatic implantation of the fungus into the skin, such as in burn injuries, motor vehicle accidents, or contamination of surgical or catheter sites. It can affect immunocompetent individuals if the trauma is severe or the inoculum is large.

❑ Secondary

This form results from hematogenous dissemination from a distant primary infection site (e.g., lungs, sinuses) to the skin. It typically occurs in severely immunocompromised patients, such as those with uncontrolled diabetes, hematologic malignancies, or organ transplantation, and signals widespread, disseminated disease.

Gastrointestinal mucormycosis

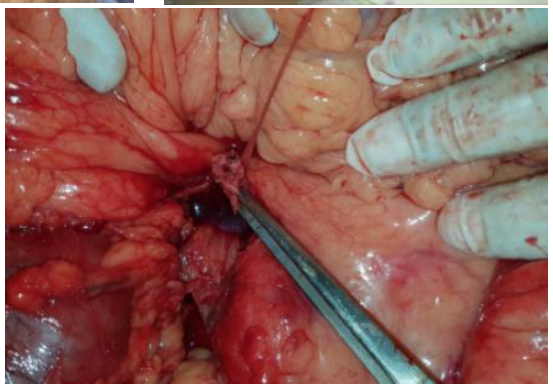
- Mucormycosis of the gastrointestinal tract is rare, but it is increasingly encountered in nosocomial settings occurs mostly in premature infants or malnourished individuals.
- It is thought to arise from ingestion of the fungi.
- The diagnosis is notoriously challenging and is often made only post-mortem, during autopsy.
- This delay occurs because symptoms are non-specific (e.g., abdominal pain, distension, bleeding) and can mimic more common conditions like bowel infarction or bacterial sepsis.

Disseminated mucormycosis

- Hematogenously disseminated mucormycosis may originate from any primary site of infection. Pulmonary mucormycosis in severely neutropenic patients has the highest incidence of dissemination.
- Disseminated infection has a high mortality rate (often >90%), especially with CNS involvement.
- Symptoms are non-specific and depend on the organs involved, often including fever, altered mental status, and multi-organ failure.
- Common Sites of Spread: Brain (most common) - often presenting with abscesses or infarcts, Spleen, Heart, Skin

Clinical Manifestations

Host Factor	Associated Clinical Syndrome
Diabetes mellitus, particularly with ketoacidosis	ROCM
Corticosteroid use	ROCM
Haematologic malignancies	Pulmonary or disseminated infection
COVID-19	ROCM
Haematopoietic cell transplantation	Pulmonary
Solid organ transplantation	Disseminated infection
HIV/AIDS	Disseminated infection
Treatment with deferoxamine	ROCM
Iron overload	ROCM
Injection drug use	Isolated cerebral
Major trauma	Cutaneous
Burns	Cutaneous



Diagnosis

1.Clinical material:

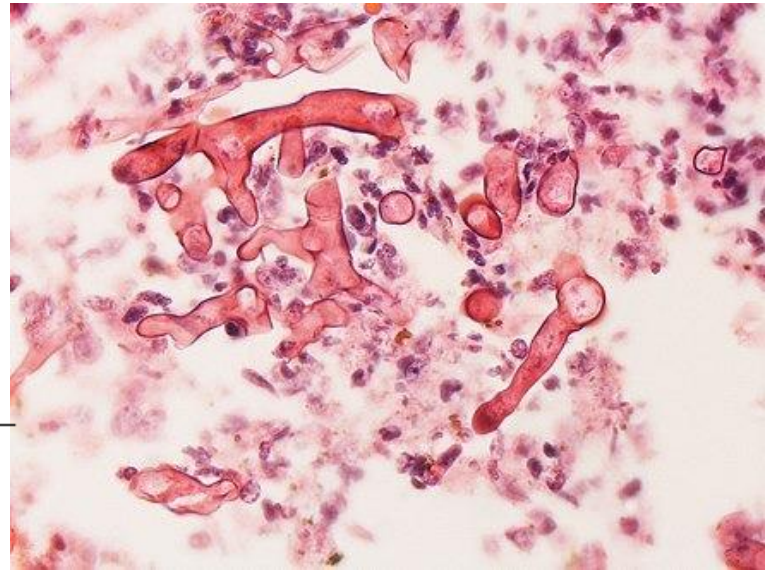
Skin scrapings from cutaneous lesions; sputum and needle biopsies from pulmonary lesions; nasal discharges, scrapings, and aspirates from sinuses in patients with rhinocerebral lesions; and biopsy

2. Direct Microscopy:

(a) Scrapings, sputum, and exudates should be examined using 10% KOH & Parker ink or Calcofluor mounts; and (b) Tissue sections should be stained with H&E and GMS.

Examine specimens for **wide, ribbon-like, coenocytic (mostly aseptate) hyphae that branch at right angles.**

- As a rule, positive direct microscopy, especially from a sterile site, should be considered significant.



Diagnosis

3. Culture:

Clinical specimens should be inoculated onto SDA.

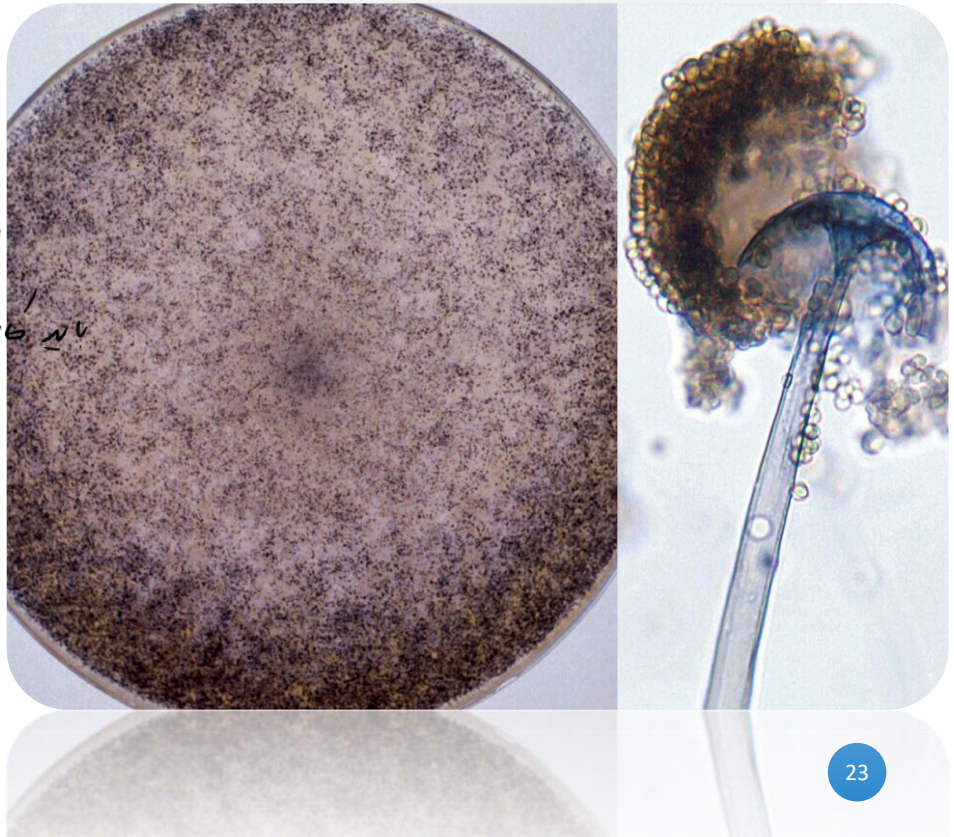
Look for fast-growing, white to grey or brownish, downy colonies.

Because the Mucorales are environmental isolates, establishing a definitive diagnosis requires a positive culture from a **sterile site** obtained by a needle aspirate or a tissue biopsy, or histopathologic evidence of invasive disease.

4. Serology:

There are currently no commercially available serological procedures for the diagnosis of mucormycosis.

- Despite the fact that the mucorales grow quite quickly on laboratory culture media, cultures may be negative in up to half of patients with mucormycosis.
- Due to various factors such as sample collection, storage at 4 °C, and tissue grinding.
- Fungal culture is an essential diagnostic modality for Mucorales identification to genus and species level and antifungal sensitivity testing.



Treatment

- First-line liposomal amphotericin B 5–10 mg/kg per day
- high dose with less nephrotoxicity
- Posaconazole (delayed-release tablets) or isavuconazole can be used for oral step-down therapy.
- Echinocandins (e.g., caspofungin) have no *in vitro* activity against the agents of mucormycosis!
- Adjunctive Surgical Intervention: "Early, aggressive, and repeated surgical debridement of all necrotic tissue is a cornerstone of successful management and is critical for survival.
- "Despite aggressive therapy, mortality remains high (40–80%). Early diagnosis and combined medical–surgical management significantly improve survival."

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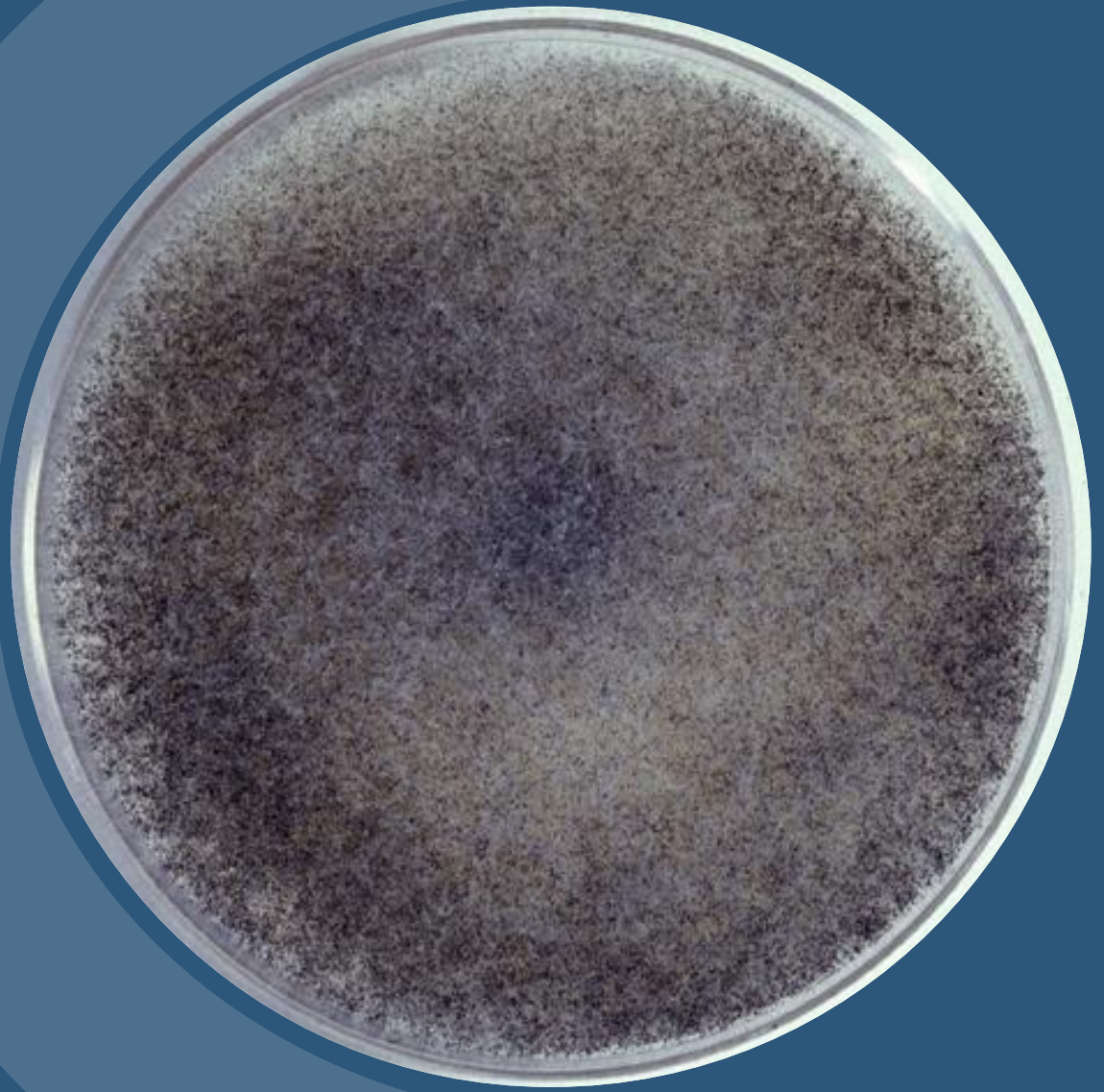

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