ME 2491 Medicine and Surgery
Infectious Diseases
20 March 2023

Invasive Fungal Infections

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DMM

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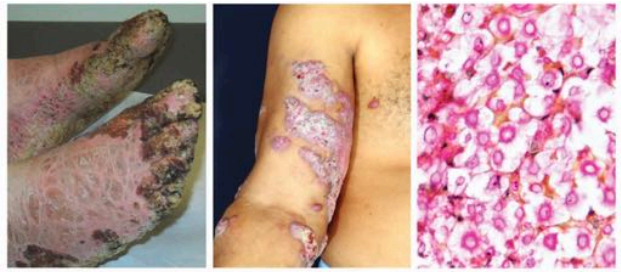
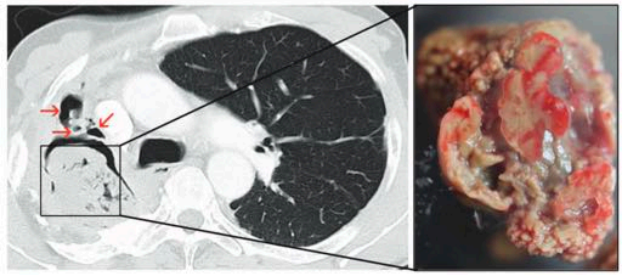
Objectives

- Describe the most common causes and clinical scenarios for opportunistic invasive fungal infections
- Provide general diagnostic recommendations and management/treatment approaches for common invasive fungal infections
- Compare pros/cons of systemic antifungal therapy

Spectrum of human fungal infections

- **Allergies**
  - e.g., hypersensitivity to mold spores
- **Mycotoxicosis**
  - Ingestion of fungal toxins in contaminated food or mushrooms
- **Mycoses**
  - Invasive of living tissue by fungus

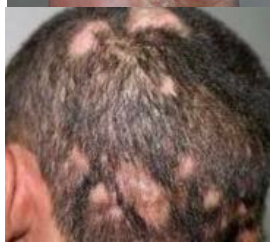


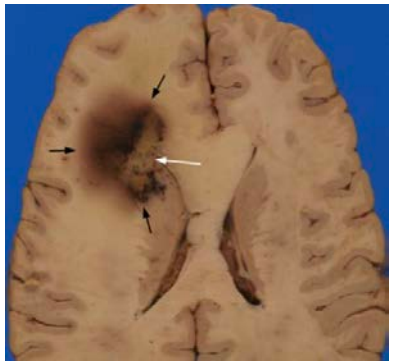


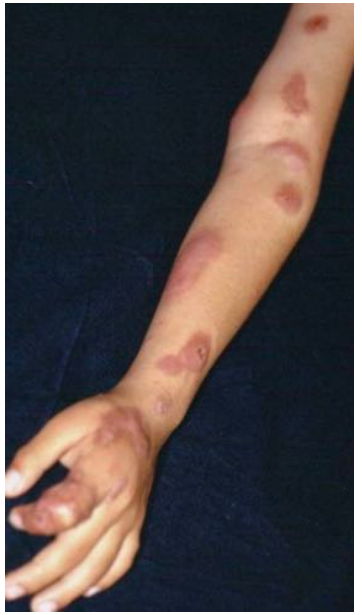
Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med **2012**; 4:165rv13.

Types of mycoses

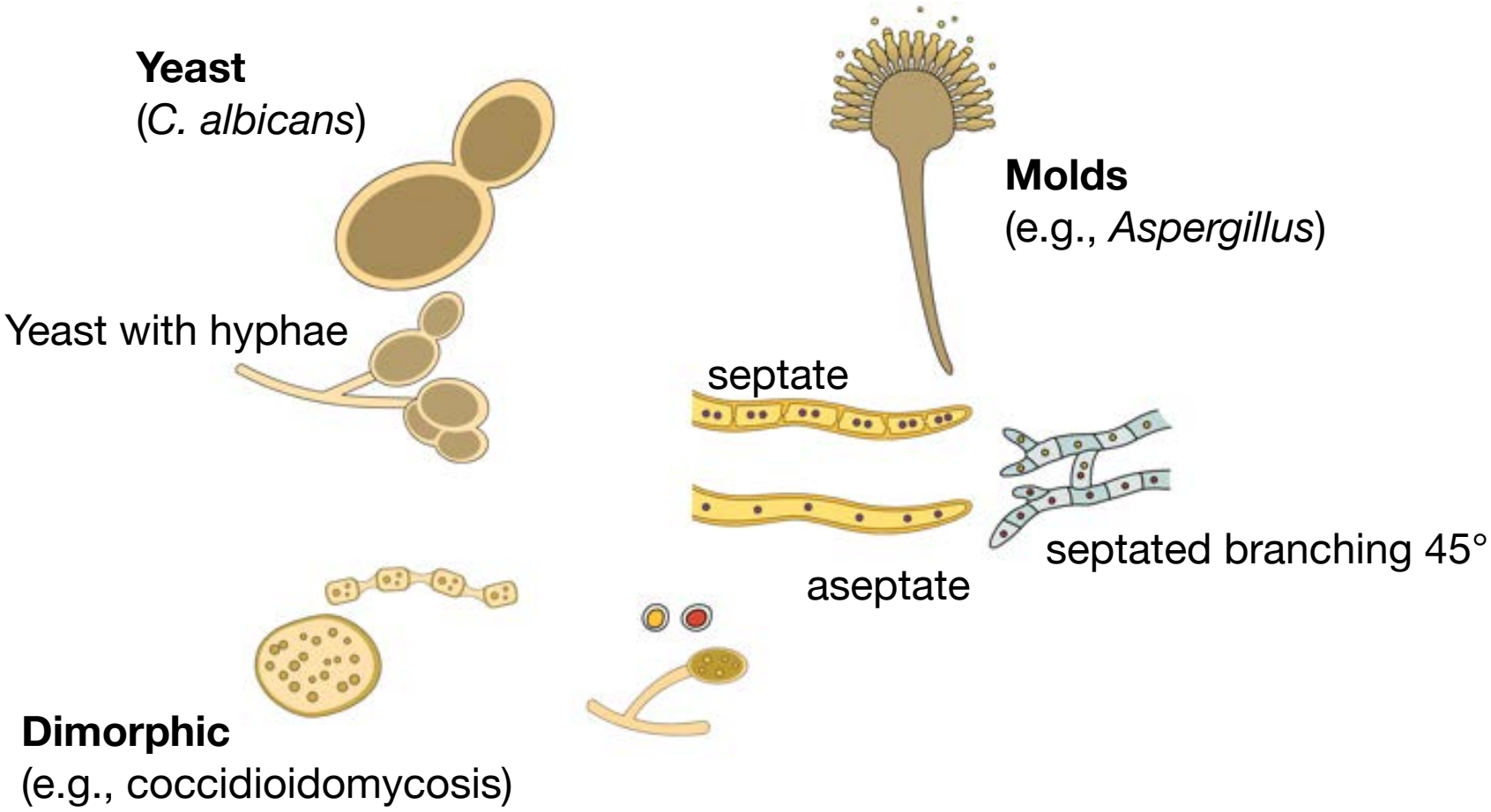
- **Superficial mycoses**
  - Affect skin, hair, nail beds
- **Subcutaneous mycoses**
  - Affect muscle and connective tissue immediately below skin
- **Systemic mycoses**
  - Invade internal organs
  - Primary vs. opportunistic





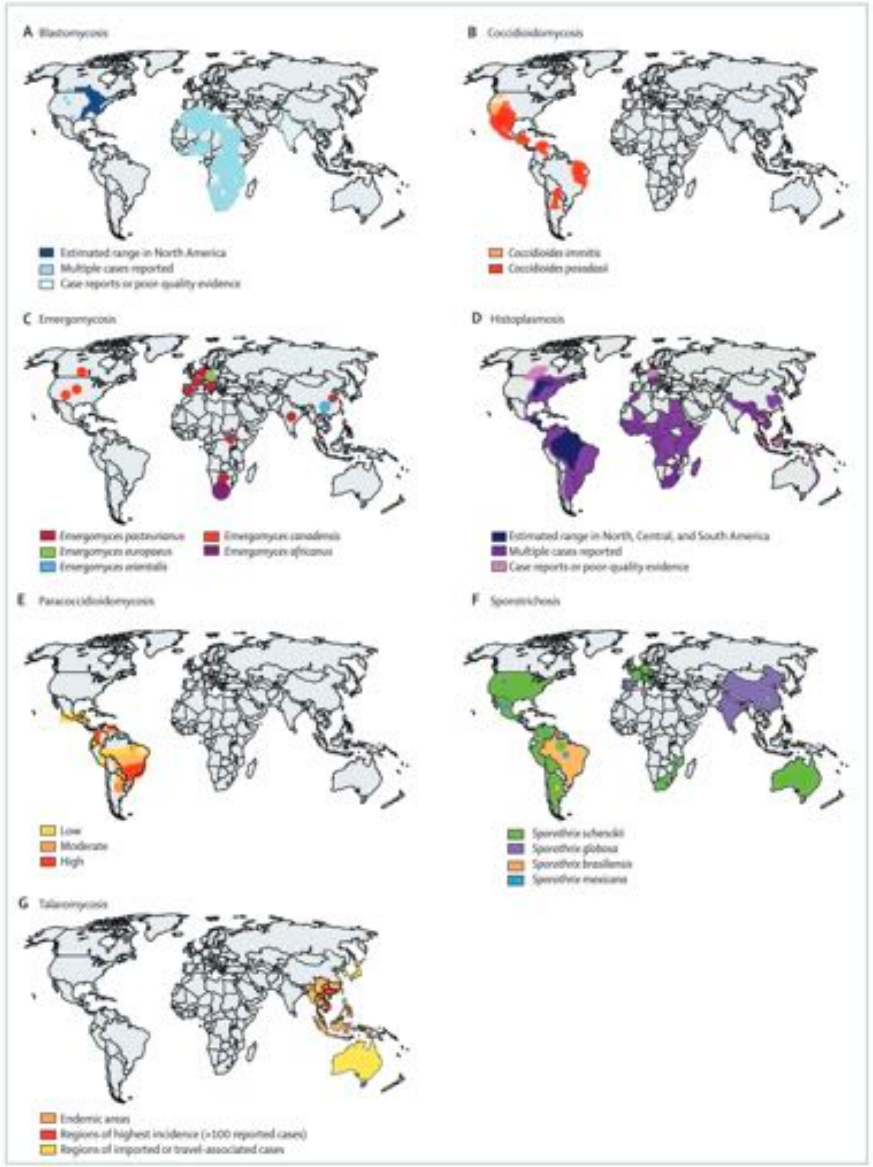


Fungal morphology



Primary endemic fungal infections

Can cause infection in both healthy and immunocompromised hosts

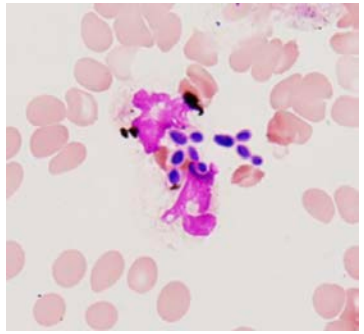


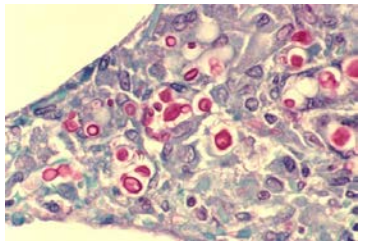
- **Specific ecological niches**
- **Endemic (dimorphic) fungi**
  - "Mold-like" at environmental temperatures
  - "Yeast-like" at 37°C
- **Distribution of pathogens is changing with global warming**

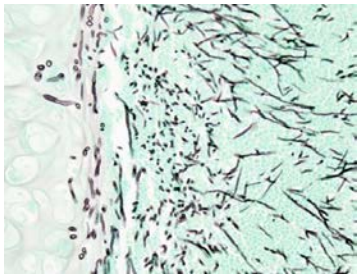
Thompson GR 3rd, Le T, Chindamporn A, et al. Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. Lancet Infect Dis 2021; 21:e364–e374.

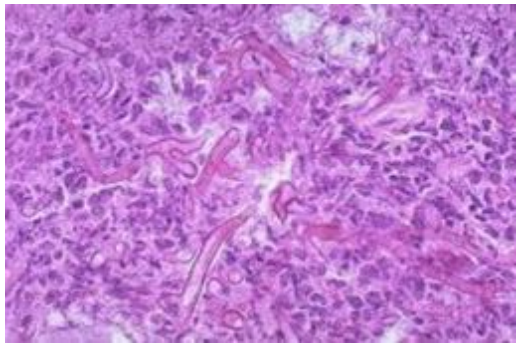
Opportunistic systemic mycoses

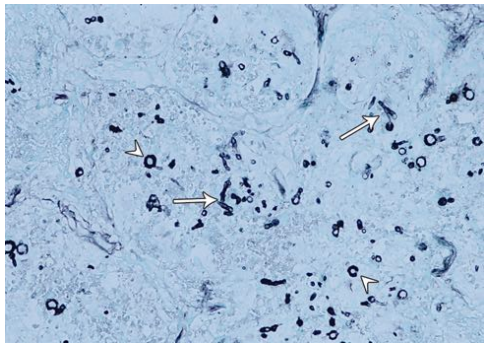
- **Invasive candidiasis**
- **Cryptococcosis**
- **Aspergillosis**
- **Rarer molds**
  - e.g., Mucormycosis, Fusariosis, and Scedosporium

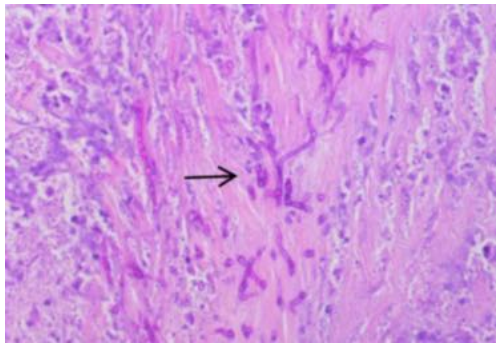




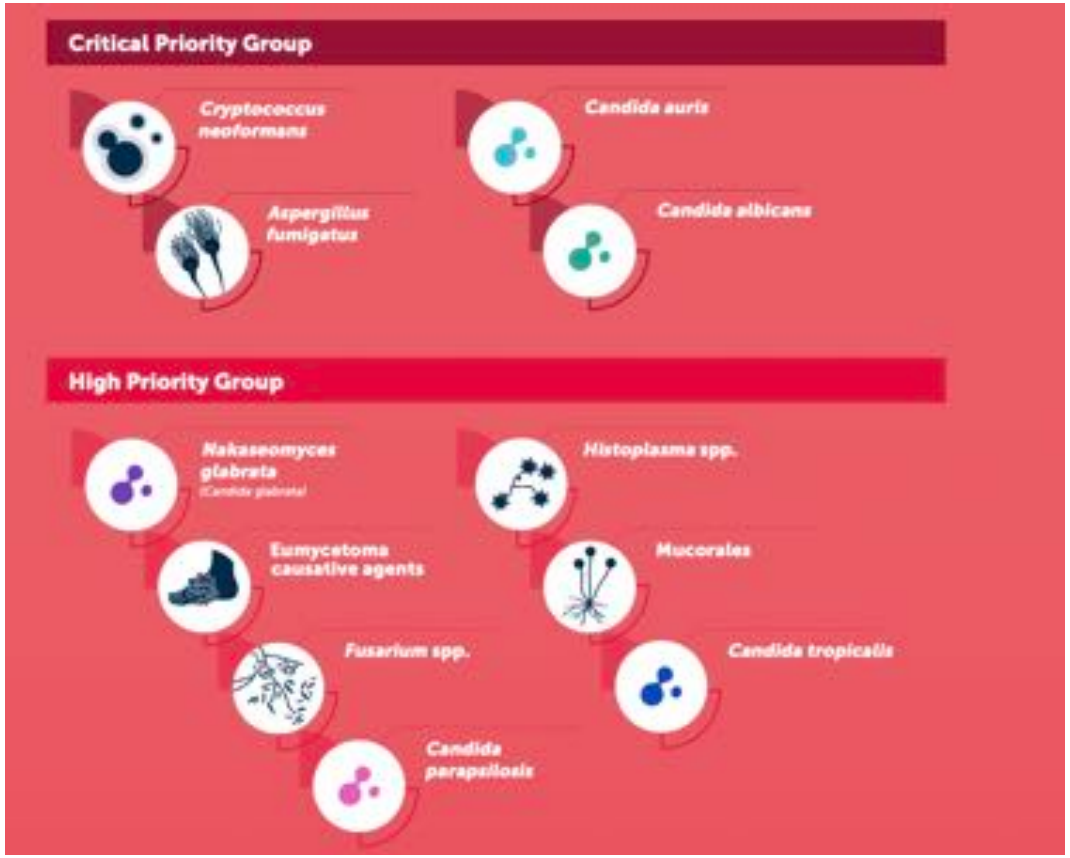


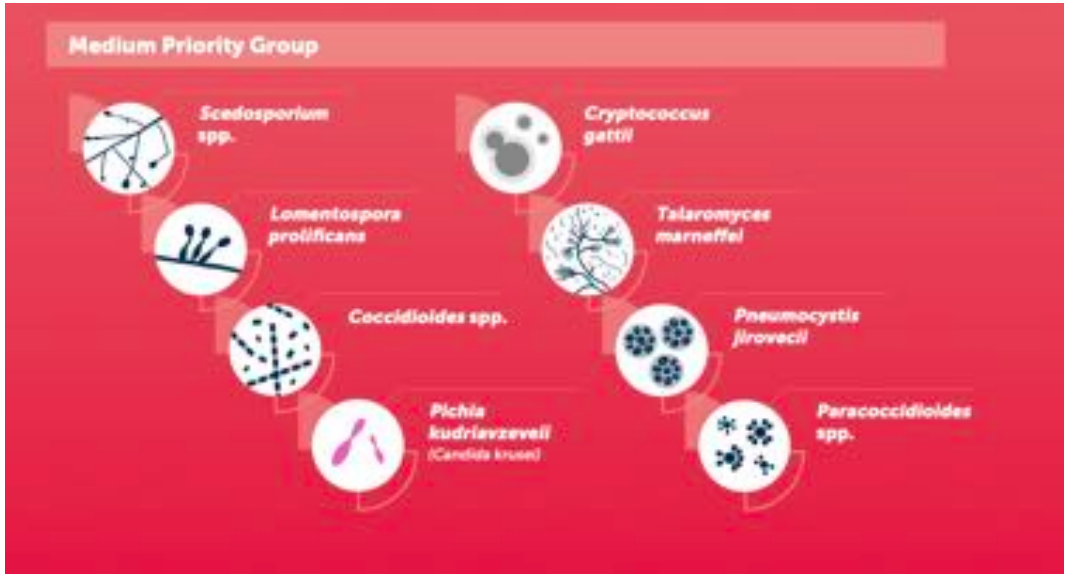






WHO priority fungal pathogens





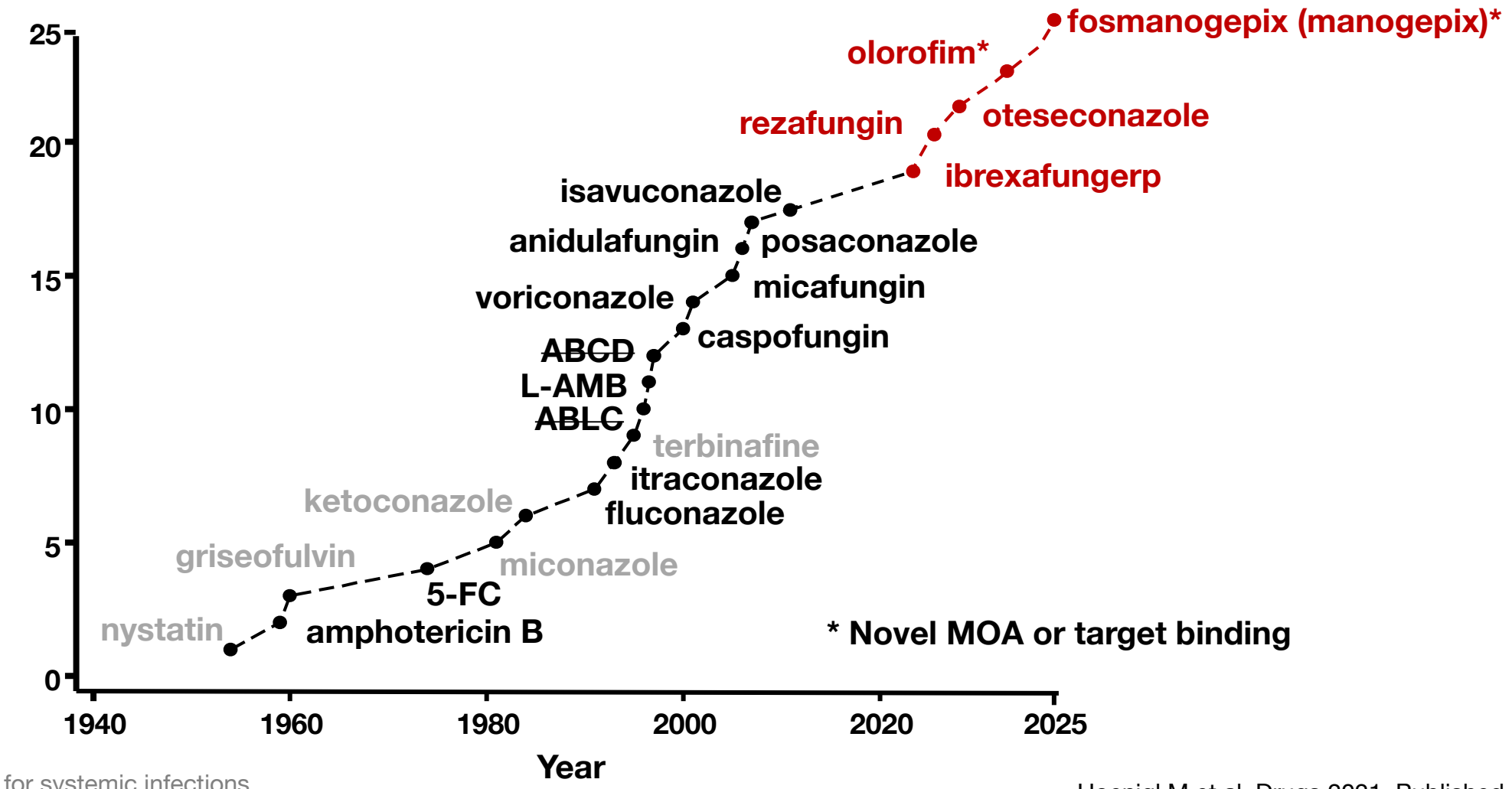
WHO fungal priority pathogens list to guide research, development and public health action. World Health Organization, 2022. Available at: https://www.who.int/publications/i/item/9789240060241. Accessed 17 March 2023.

What is health burden of serious fungal diseases?

- **150-300 million cases per year**
- **>99% of invasive fungal infections caused by 30 species**
- **1.7 million deaths annually**
  - Similar mortality burden as tuberculosis, >3 fold-higher than malaria

Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. J Fungi (Basel) **2017**; 3.

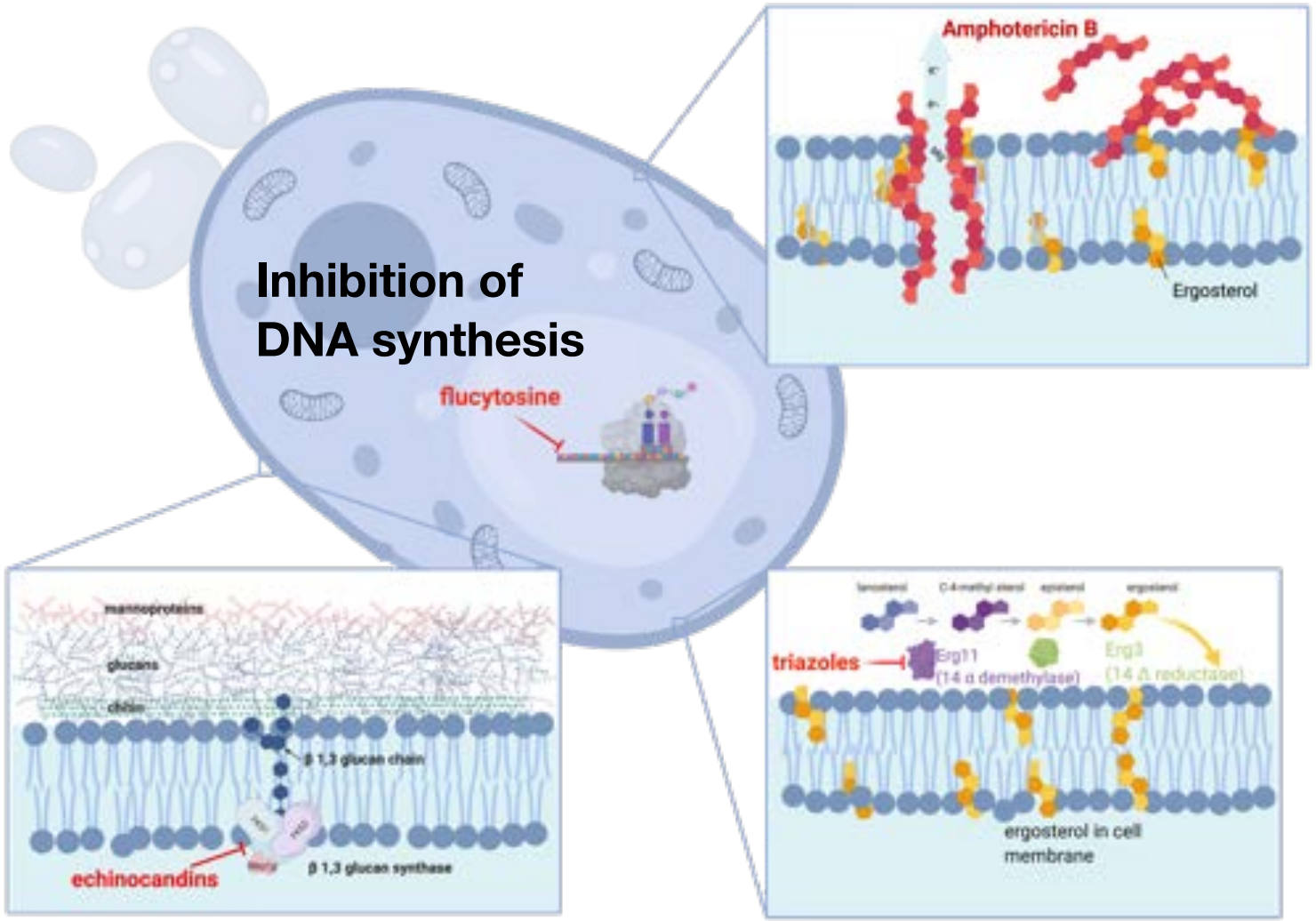
Antifungal therapies



Not used for systemic infections
Investigational

Hoenigl M et al. Drugs 2021. Published Online 9 Oct 2021

Targets of current antifungal agents



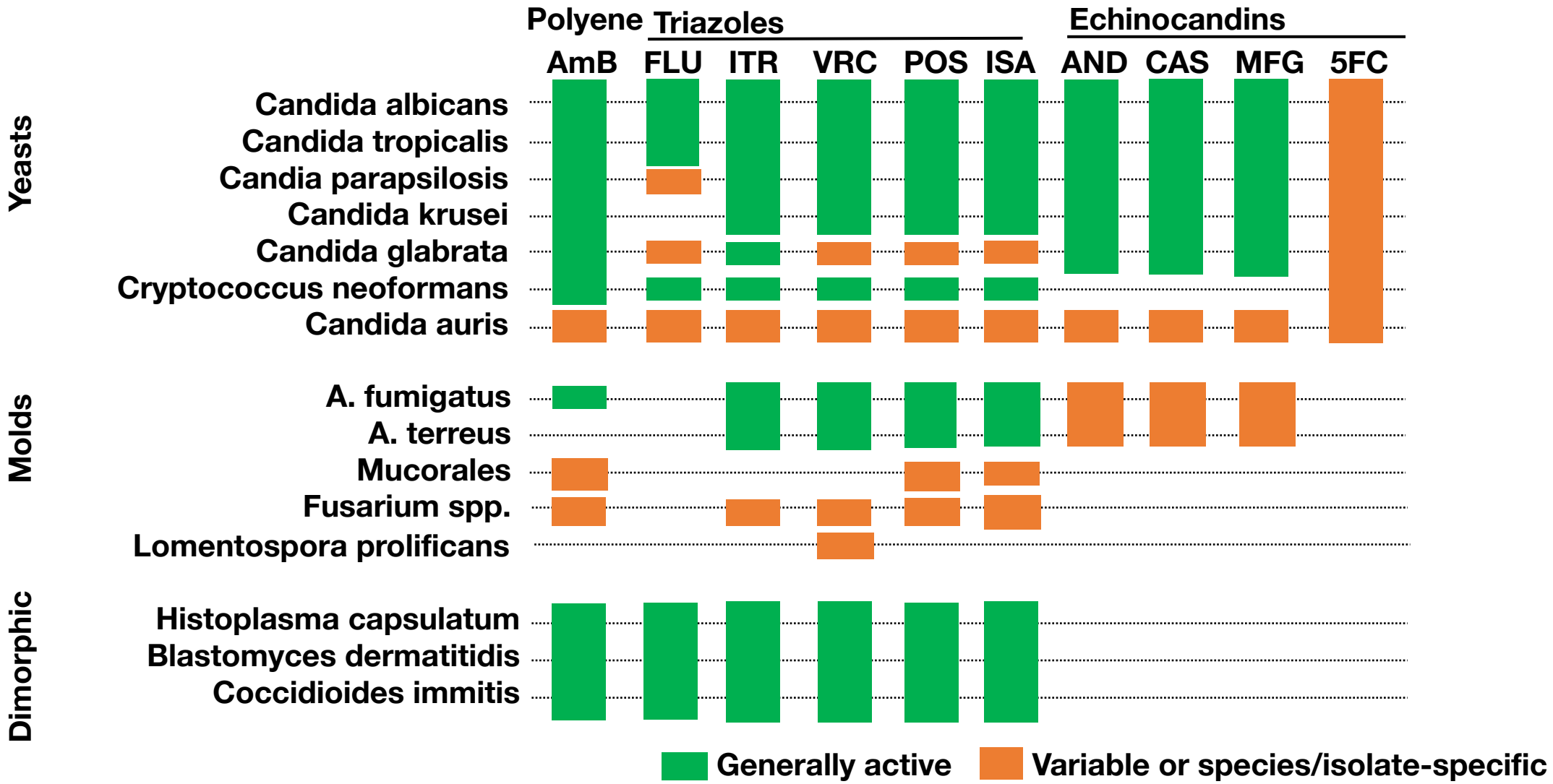
Direct damage to cell membrane

Disruption of cell wall

Disruption of cell membrane

Antifungal spectrum of action

Where are the holes in activity?



AMB- amphotericin B, FLU- fluconazole; ITRA-itraconazole, VRC-voriconazole, POS-posaconazole, ISA-isavuconazole; AND-anidulafungin, CAS-caspofungin, MFG-micafungin, 5-FC-flucytosine

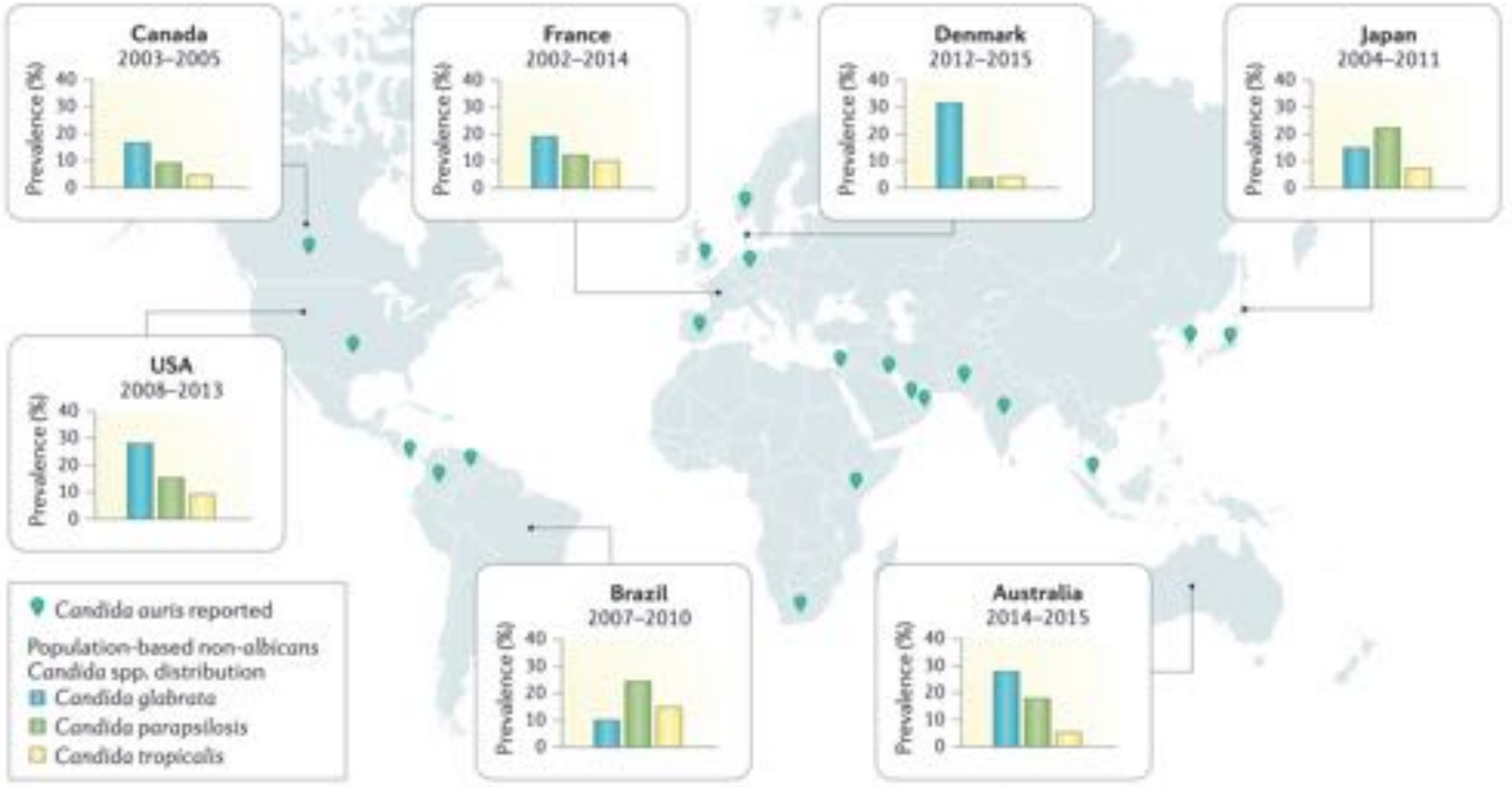
Invasive candidiasis

Invasive candidiasis epidemiology

- **Infection linked to medical progress/ technology**
- **In many developed countries, 3rd-4th most common cause of BSI**
  - 18% of all infections in the ICU
- **Most infections start with colonization (60% of hospitalized patients)**
- **Most infections are caused by 5 species:**
  - ***Candida albicans*** *(most common, high virulence)*
  - ***Candida glabrata*** *(potential MDR, low virulence)*
  - ***Candida tropicalis*** *(high virulence)*
  - ***Candida parapsilosis*** *(biofilm-producer, catheter infection, low virulence)*
  - ***Candida krusei*** *(fluconazole resistant, breakthrough infections)*
  - ***Candida auris*** *(emerging MDR isolate, spreads patient to patient)*

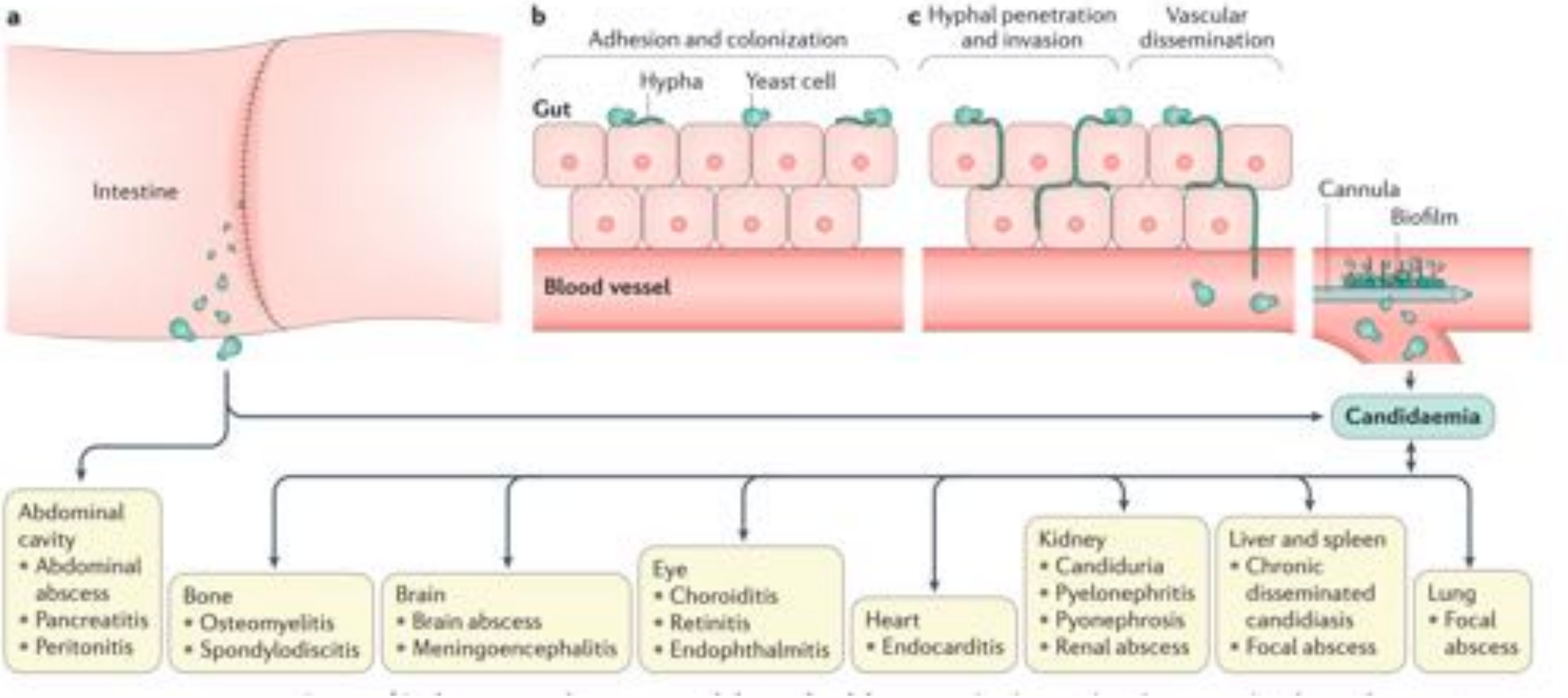
Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.
Vincent J-L, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302:2323–2329.

Geographical variation in non-albicans *Candida* spp.



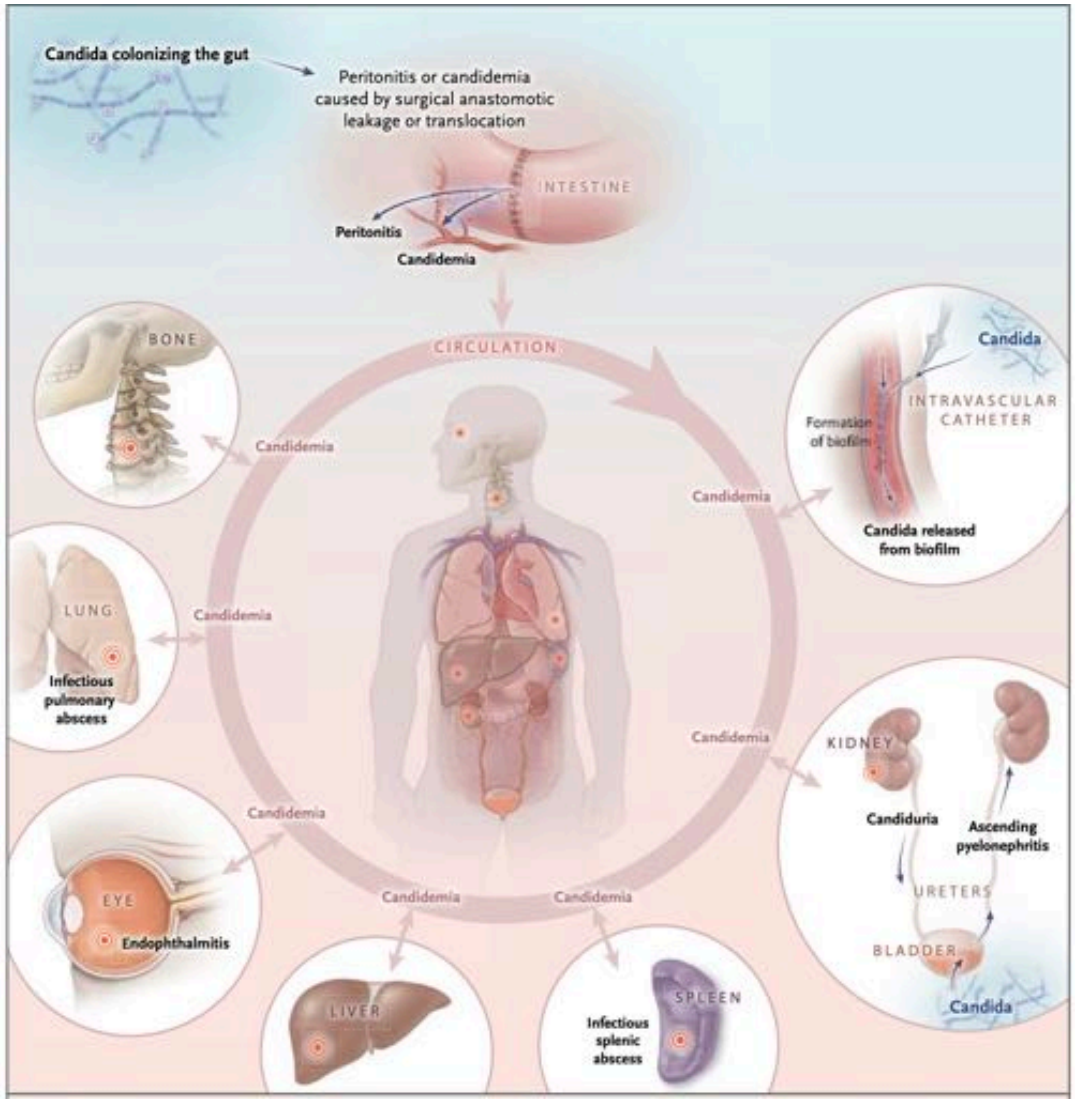
Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

How does invasive candidiasis develop?



Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

Candidemia can spread to virtually any organ



Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med 2015; 373:1445–1456.

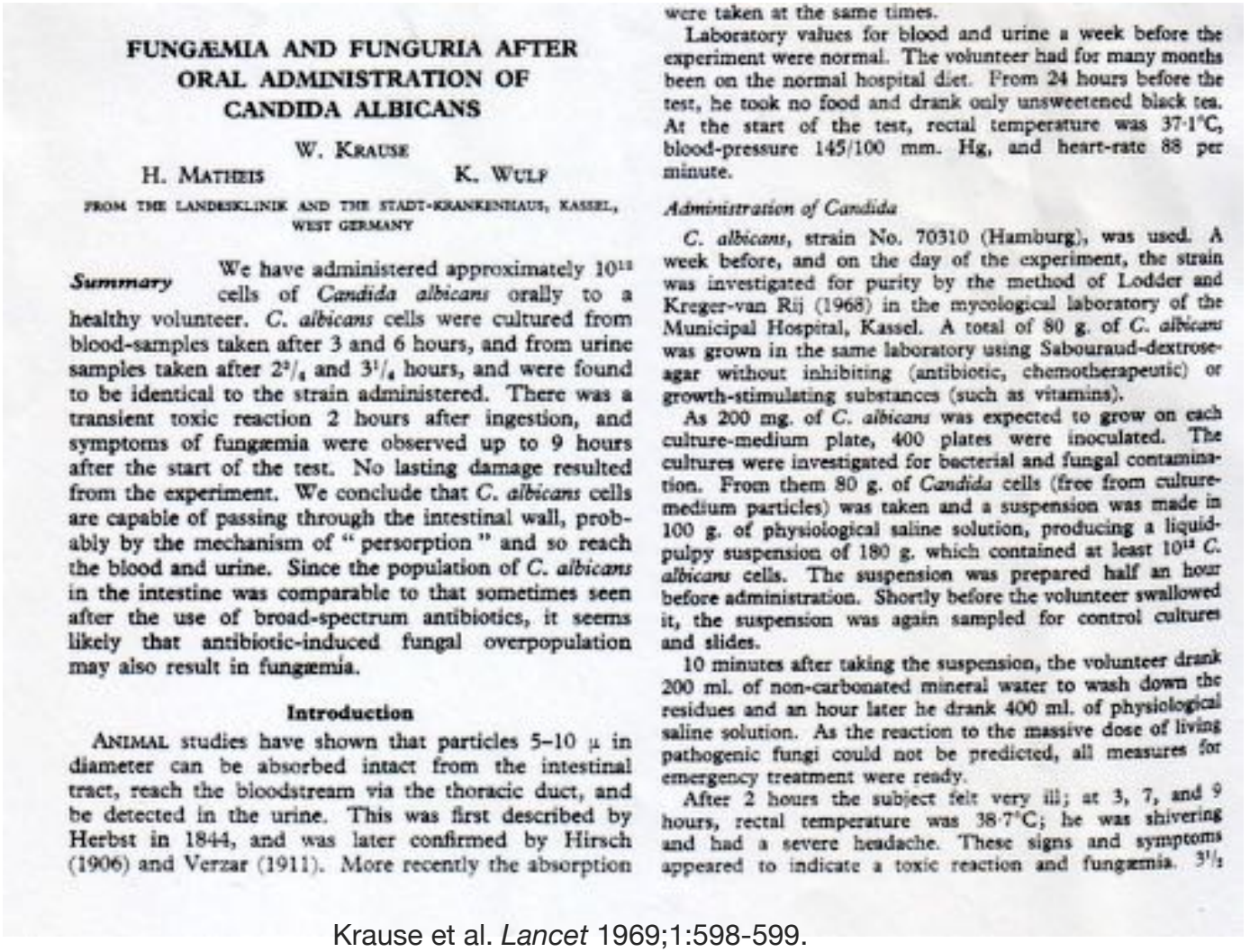
A brave surgical resident!

- Conventional wisdom was that *Candida* was too large to pass intact from the undamaged gut into the bloodstream

- A German surgical resident thought that overgrowth of *Candida* in the bowel during antibiotic therapy may allow sufficient density for “persorption” into the bloodstream

- To test this hypothesis, he recruited two colleagues to watch him **after drinking 10^{12} cells of freshly- prepared *Candida albicans (one trillion cells)***

Candida translocation (persorption) after ingestion of a massive oral inoculum



FUNGÆMIA AND FUNGURIA AFTER ORAL ADMINISTRATION OF CANDIDA ALBICANS

W. KRAUSE
H. MATHEIS K. WULF
FROM THE LANDESKLINIK AND THE STADT-KRANKENHAUS, KASSEL, WEST GERMANY

Summary We have administered approximately 10^{12} cells of *Candida albicans* orally to a healthy volunteer. *C. albicans* cells were cultured from blood-samples taken after 3 and 6 hours, and from urine samples taken after $2^3/_4$ and $3^1/_4$ hours, and were found to be identical to the strain administered. There was a transient toxic reaction 2 hours after ingestion, and symptoms of fungæmia were observed up to 9 hours after the start of the test. No lasting damage resulted from the experiment. We conclude that *C. albicans* cells are capable of passing through the intestinal wall, probably by the mechanism of "persorption" and so reach the blood and urine. Since the population of *C. albicans* in the intestine was comparable to that sometimes seen after the use of broad-spectrum antibiotics, it seems likely that antibiotic-induced fungal overpopulation may also result in fungæmia.

Introduction

ANIMAL studies have shown that particles 5–10 μ in diameter can be absorbed intact from the intestinal tract, reach the bloodstream via the thoracic duct, and be detected in the urine. This was first described by Herbst in 1844, and was later confirmed by Hirsch (1906) and Verzar (1911). More recently the absorption

were taken at the same times.

Laboratory values for blood and urine a week before the experiment were normal. The volunteer had for many months been on the normal hospital diet. From 24 hours before the test, he took no food and drank only unsweetened black tea. At the start of the test, rectal temperature was 37·1°C, blood-pressure 145/100 mm. Hg, and heart-rate 88 per minute.

Administration of Candida

C. albicans, strain No. 70310 (Hamburg), was used. A week before, and on the day of the experiment, the strain was investigated for purity by the method of Lodder and Kreger-van Rij (1968) in the mycological laboratory of the Municipal Hospital, Kassel. A total of 80 g. of *C. albicans* was grown in the same laboratory using Sabouraud-dextrose-agar without inhibiting (antibiotic, chemotherapeutic) or growth-stimulating substances (such as vitamins).

As 200 mg. of *C. albicans* was expected to grow on each culture-medium plate, 400 plates were inoculated. The cultures were investigated for bacterial and fungal contamination. From them 80 g. of *Candida* cells (free from culture-medium particles) was taken and a suspension was made in 100 g. of physiological saline solution, producing a liquid-pulpy suspension of 180 g. which contained at least 10^{12} *C. albicans* cells. The suspension was prepared half an hour before administration. Shortly before the volunteer swallowed it, the suspension was again sampled for control cultures and slides.

10 minutes after taking the suspension, the volunteer drank 200 ml. of non-carbonated mineral water to wash down the residues and an hour later he drank 400 ml. of physiological saline solution. As the reaction to the massive dose of living pathogenic fungi could not be predicted, all measures for emergency treatment were ready.

After 2 hours the subject felt very ill; at 3, 7, and 9 hours, rectal temperature was 38·7°C; he was shivering and had a severe headache. These signs and symptoms appeared to indicate a toxic reaction and fungæmia. $3^1/_2$

Krause et al. *Lancet* 1969;1:598-599.

C. albicans cells were cultured from blood-samples taken after 3 and 6 hours, and from urine samples taken after 2 3/4 and 31/4 hours, and were found to be identical to the strain administered. There was a transient toxic reaction 2 hours after ingestion, and symptoms of fungæmia were observed up to 9 hours after the start of the test. No lasting damage resulted from the experiment.

What are the risk factors for invasive candidiasis?

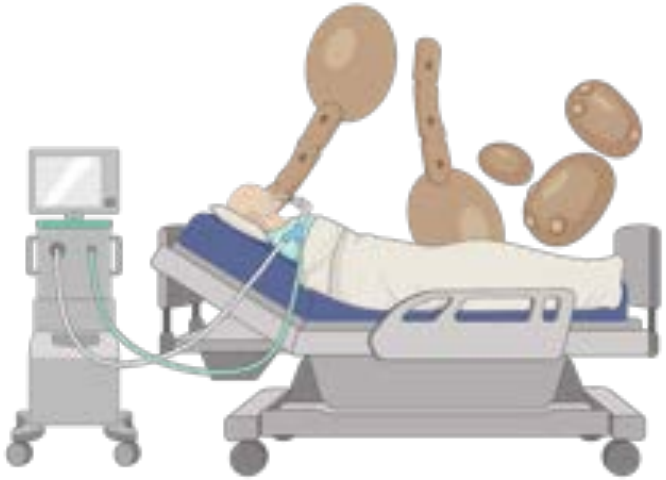
- **General risk factors**
  - **Intrinsic:** Colonization with *Candida* spp., diabetes mellitus, gastrointestinal perforation, increased age, pancreatitis, sepsis, severity of illness (e.g., high APACHE-II, or SOFA)
  - **Iatrogenic:** Any type of dialysis (esp. hemodialysis), broad spectrum antibiotics, central venous catheter, corticosteroids or other immunosuppression, GI surgery or other major surgery, left ventricular assist device, long-term stay in hospital or ICU, mechanical ventilation, total parenteral nutrition
- **Additional risk factors in immunocompromised**
  - **Intrinsic:** Graft versus host disease, mucositis and profound neutropenia (ANC < 500 cells/mm^3)
  - **Iatrogenic:** Solid organ transplant and stem cell transplant

Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

Screening and diagnosis

My patient is colonized, will they develop candidemia?

Candida risk scores: Many different versions, require internal validation



Candida score = 0.908 x (total parenteral nutrition) + 0.997 x (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 x (total parenteral nutrition) + 1 x (surgery) + (multifocal *Candida* species colonization) + 2 x (severe sepsis).

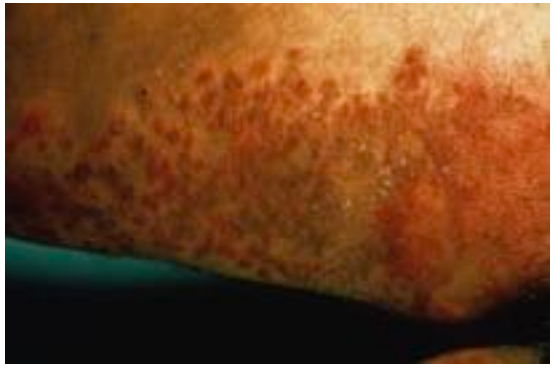
All variables coded as follows: absent, 0; present, 1.

A score > 2.5 should prompt use of antifungal therapy

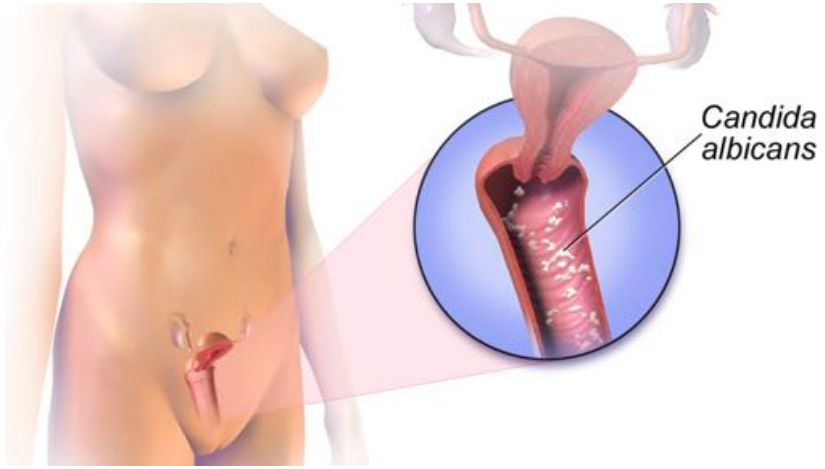
León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ('Candida score') for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med 2006; 34:730–737.

Mucocutanous Semi-invasive forms

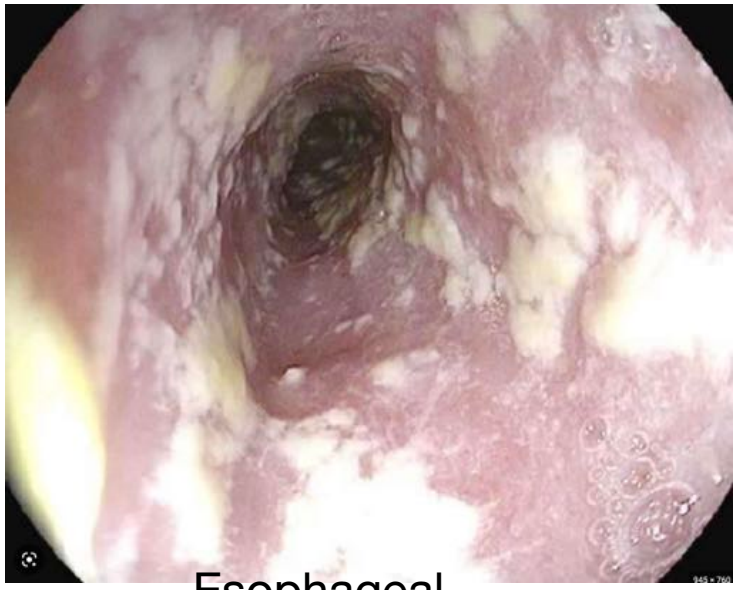
Thrush



Cutaneous



Vulvo-Vaginal candidiasis



Esophageal

Clinical presentation

Invasive candidiasis

- **Fever and hemodynamic instability, as with bacterial sepsis**
- **Skin lesion in neutropenic patients**
- **Chorioretinitis**
- **Endocarditis (uncommon but consider in patients with prosthetic valves, injection drug users, patients with persistently positive cultures)**

Perform within 1 week of diagnosis, or in Neutropenic patients, within 1 week of PMN recovery

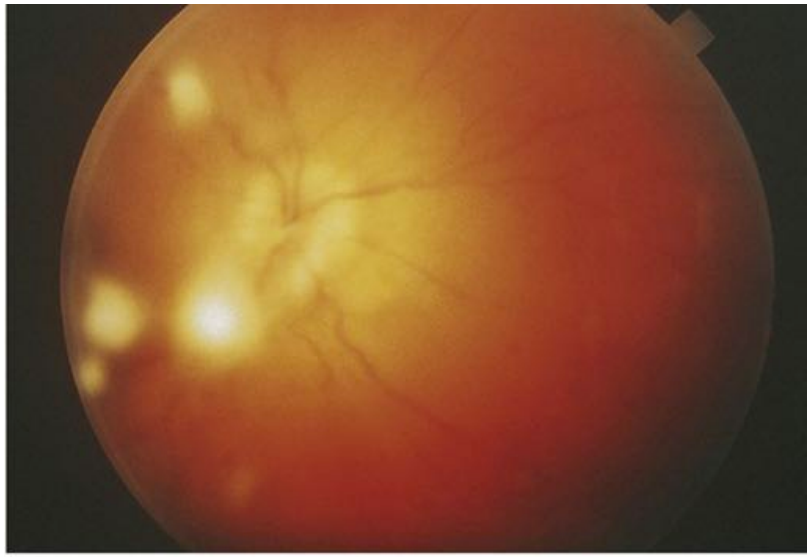
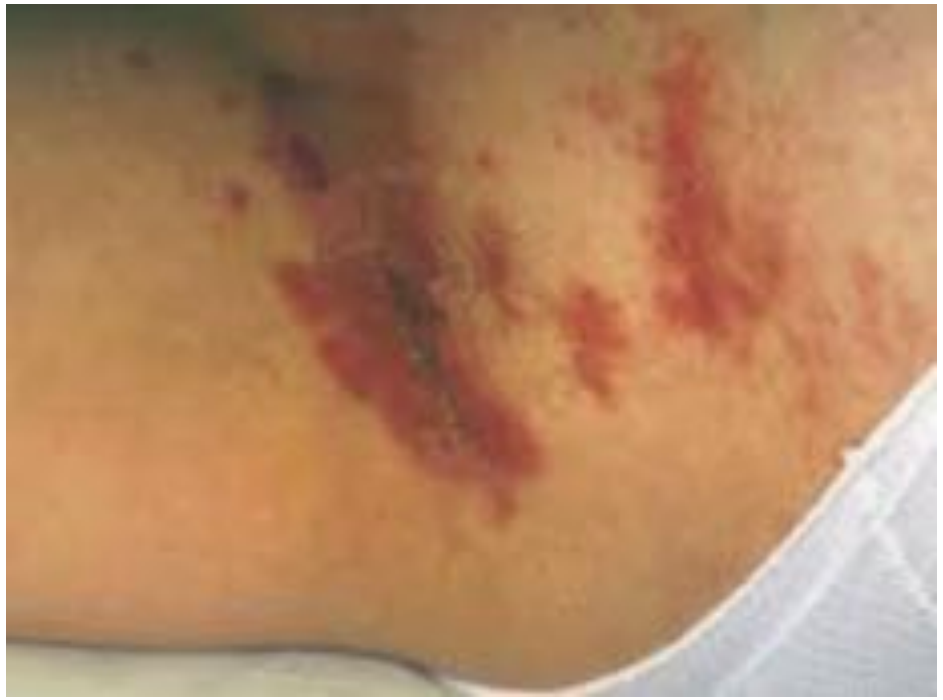
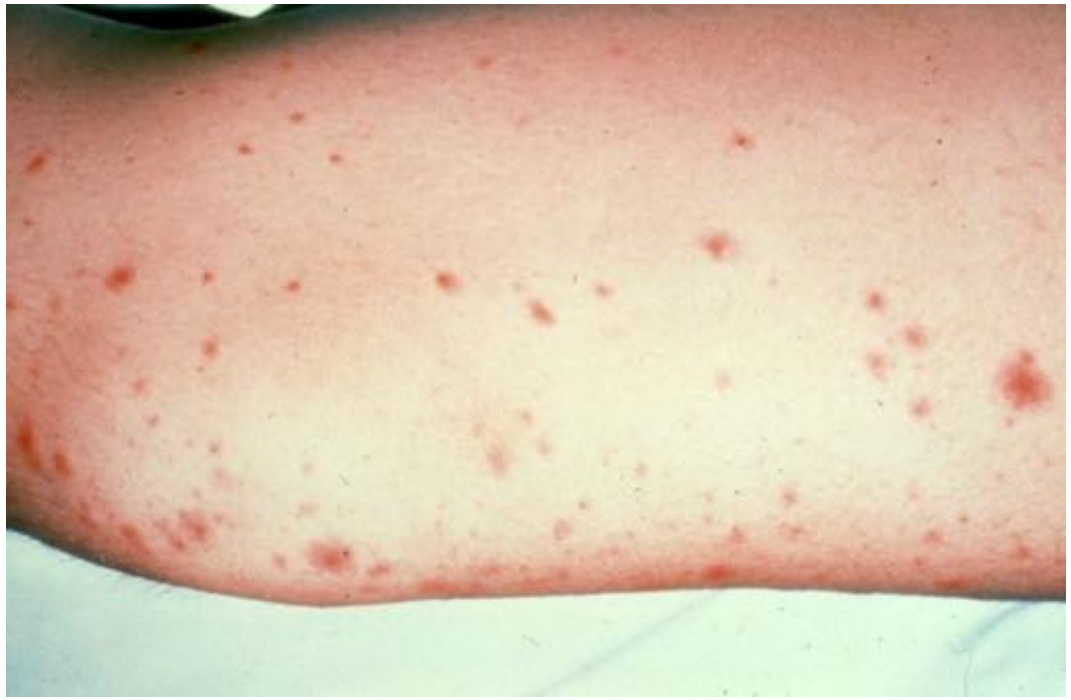


FIG. 27.10 *Candida* endophthalmitis. All candidemic patients should be examined for such well-demarcated, white chorioretinal lesions.

Candida infection- cutaneous signs



Not disseminated

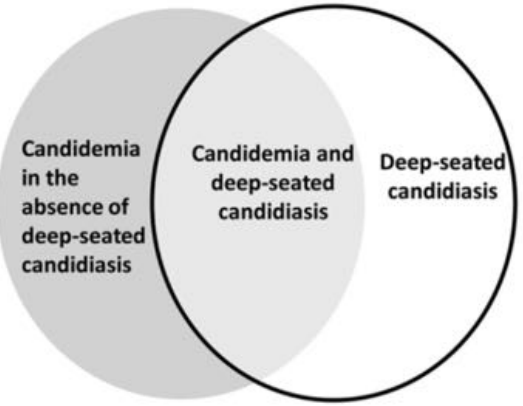


Disseminated (neutropenic patient)

Invasive candidiasis
Classical diagnosis

- **Blood cultures or histopathology**
  - Blood cultures insensitive (positive in 21-71% of patients)
  - Circulating yeast <1 CFU/mL of blood
  - Longer time to positivity (2-5 days days)
  - Techniques to improve sensitivity:
    - High-volume cultures (> 40 -60 mL/day), frequent sampling if febrile
    - Specialized culture techniques (lysis centrifugation)
  - Positive cultures from sterile sites (e.g., intraabdominal or intrathoracic sites) or newly placed drains
  - Isolates are identified by commercial ID systems, MALDI-TOF
    - *Candida auris* often misidentified by commercial systems (*C. famata, Rhodotorula glutinous, Candida sake, Saccharomyces cerevisiae*)

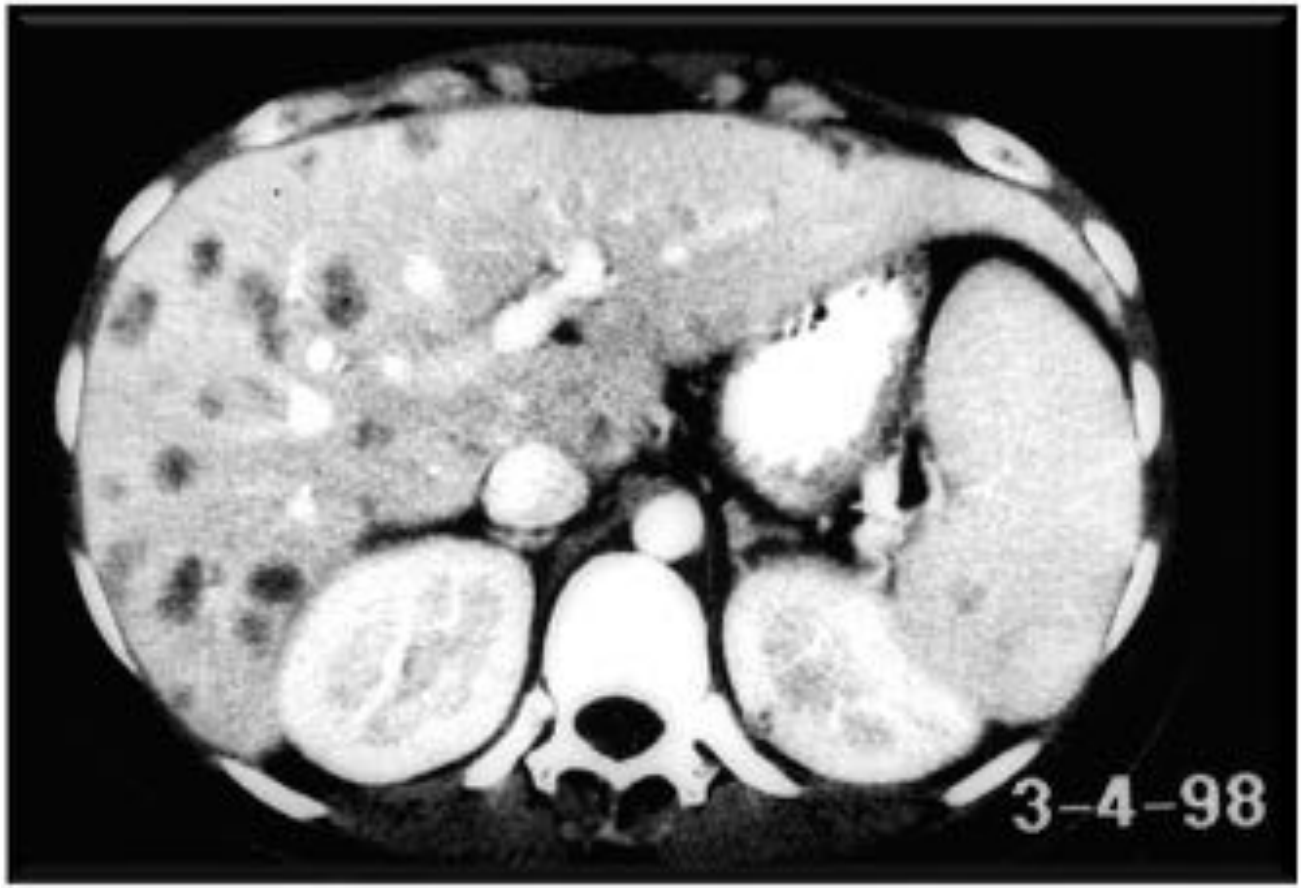
Blood cultures miss 50% of cases



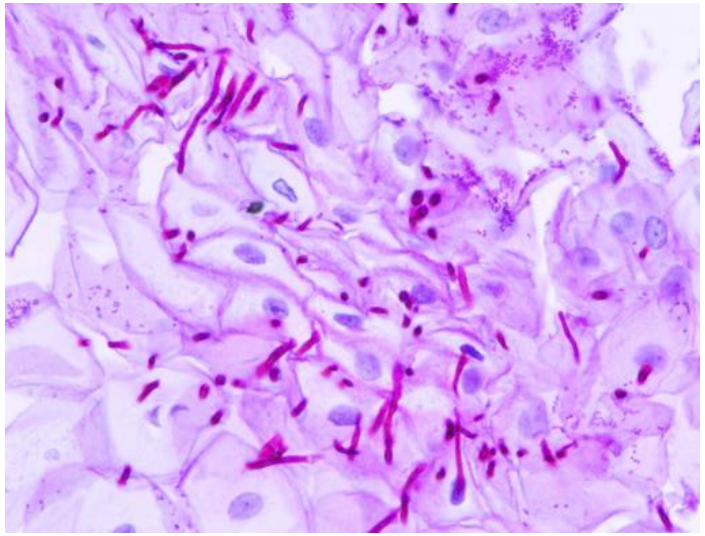
Clancy CJ, Nguyen MH. Clin Infect Dis 2013; 56:1284–1292.

Hepatosplenic candidiasis with neutrophil recovery

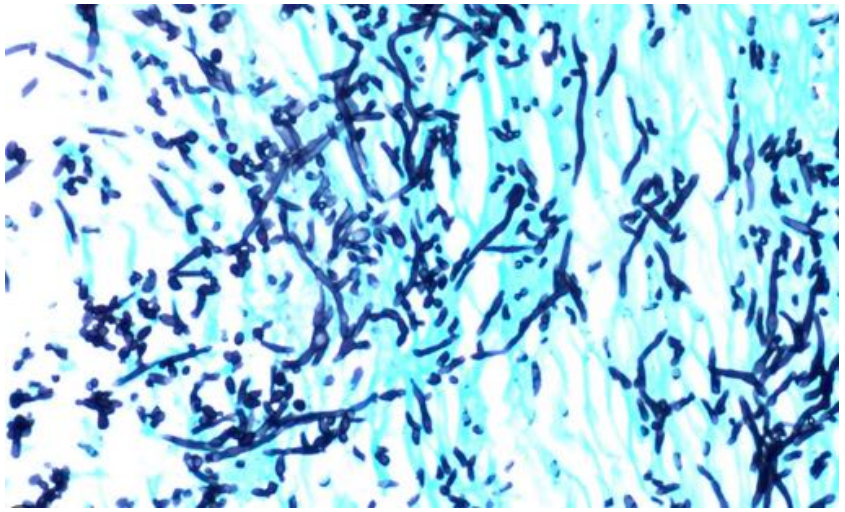
increasing
alkaline phosphatase,
fever as neutrophils
recover



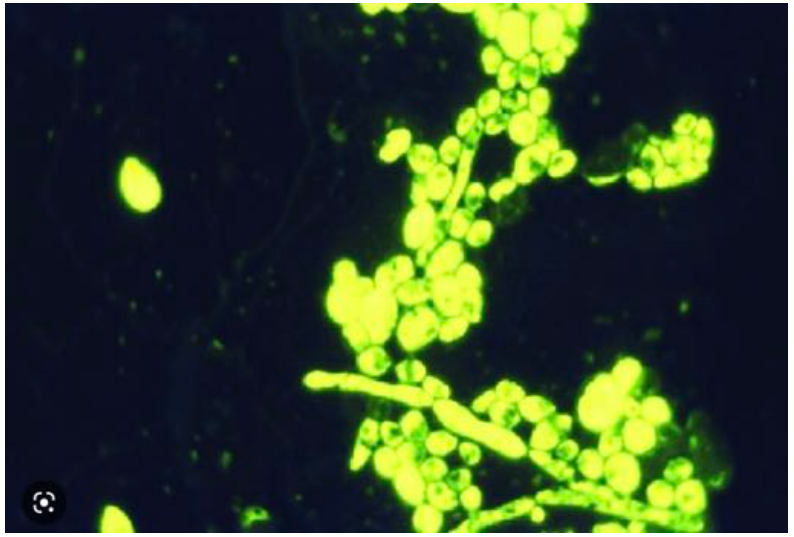
Histology



Candida, PAS stain



Candida, GMS stain



Candida, Calcafluor

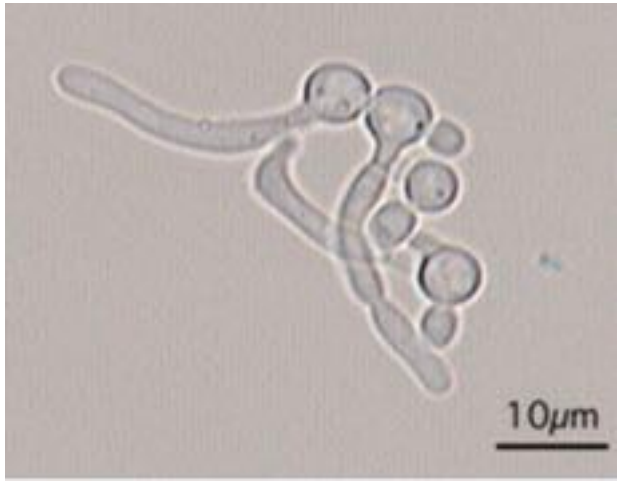
Invasive candidiasis
Antigen detection

- **β-D-glucan**: Pan-fungal marker detects fungal cell wall from *Candida, Aspergillus* and *Pneumocystis jirovecii* infections
  - High sensitivity (76-100%)
  - Low specificity (40-92%)
  - Multiple causes of **false-positive** results
    - Heavy *Candida* colonization
    - Hemodialysis with cellulose membranes
    - Human blood products (immunoglobulin, albumin)
    - Antibiotics
    - Serious bacterial infections
    - Surgical sponges and gauzes
    - Severe mucositis
  - Usually relied on as a “screening-out” test: the high negative predictive value (NPV) makes invasive candidiasis unlikely if the test is negative

Limulus amebocyte lysate (LAL) used

Invasive candidiasis
Other tests

- **Mannan antigen and anti-mannan antibody**
  - Poor sensitivity (55%) and specificity (60%)
- ***C. albicans* germ tube antigen (CAGTA) test**
  - Sensitivity (53-74%) and specificity 56.5% to 92.0%)
- **PCR tests**
  - Do not detect all *Candida spp. Including C. auris)*
  - Septifast platform
  - T_2Candida Panel-rapid, direct from blood, but more clinical trials needed for validation)



C. albicans germ tube formation in serum

Diagnostic test	Specimen(s)	Advantages	Disadvantages
Fungal culture	Blood	• Enables species identification and subsequent susceptibility testing	• Slow (median detection time 2–3 days) • Sensitivity suboptimal, particularly if high volume (≥60 ml) and a fungal blood culture bottle are not employed
	Tissue and sterile body fluids	• Enables species identification and subsequent susceptibility testing	• Selective media, proper spreading of the sample and 3 days of incubation required for optimal performance
Microscopy	Cerebrospinal fluid, tissue and sterile body fluids	• Highly sensitive, particularly if using fluorescent brightener staining	• No species identification • Lower sensitivity in absence of fluorescent brightener staining
Histopathology	Tissue and sterile body fluids	• Enables evaluation of tissue invasion and inflammation	• No species identification • Lower sensitivity in absence of fluorescent brightener staining
Mannan antigen and antimannan antibody detection	Serum or plasma (EDTA) or cerebrospinal fluid	• Increased diagnostic sensitivity when combined antigen and antibody testing is performed (although in neonates (in any sample) and in cerebrospinal fluid, antigen testing suffices)	• Heavy colonization (many non-sterile body sites culture positive for *Candida* spp. and/or with heavy growth in semi-quantitative culture) could cause positivity for blood testing
β-D-glucan detection	Serum or plasma (EDTA)	• Pan-fungal marker	• No separation between *Candida* spp. and other fungi • Many sources for false positivity
PCR	Blood (EDTA)	• Rapid tests • Some commercial tests are FDA approved	• Commercial tests are expensive • May not detect all species

Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

Treatment of invasive candidiasis

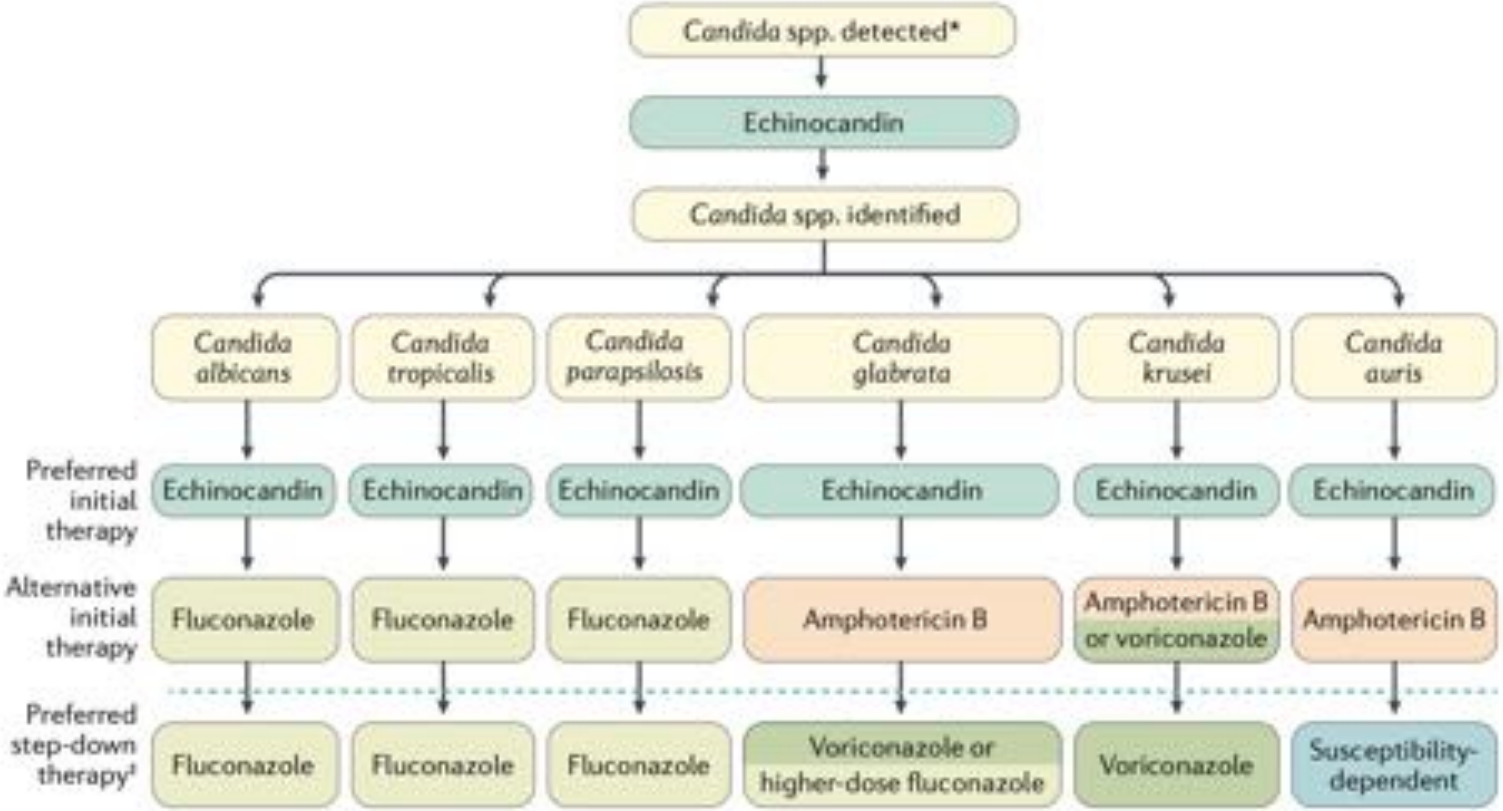


Figure 5 | **Algorithm for the management of invasive candidiasis.** For candidaemia, the total duration of therapy is 14 days from the first negative blood culture. *As yet unknown species. ‡Step-down therapy to fluconazole is usually based on documented susceptible minimum inhibitory concentrations to fluconazole (<2 μg/ml for *C. albicans*, *C. parapsilosis* and *C. tropicalis* and <32 μg/ml for *C. glabrata*) and clinical stabilization of the patient. Higher-dose fluconazole consists of 12 mg/kg per day. The information in the presented figure is based in part on Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines[106,107].

A note of caution:
Echinocandins do not cover *Cryptococcus neoformans* or other rare yeast (e.g., *Geotrichum*, *Saprochaete* spp.) that may occur as breakthrough infections on echinocandin prophylaxis/therapy.

Caution is warranted in patients prior echinocandin therapy or profound lymphopenia/steroids

Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

Management issues

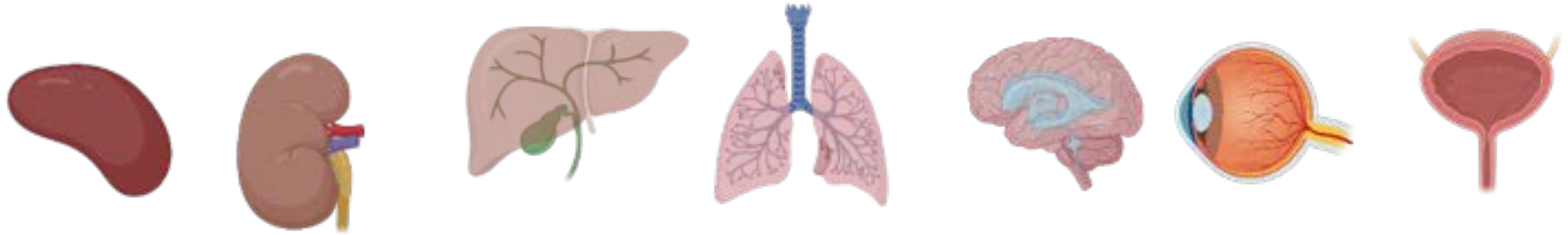
- Source control important. CVC should be removed as soon as safely possible, abscess drainage
- Repeat blood cultures daily to document date of clearance of fungemia→ At least 2 weeks from clearance of fungemia, longer therapy administered if infection has spread to internal organs (complicated diseases)
- Dilated ophthalmologic exam for all cases of candidemia within 1 week of diagnosis (except in neutropenic patients who should be examined within a week of neutrophil recovery)
- Patients with *C. auris* must be isolated→risk of spread to other patients
- Transition to oral fluconazole if patients are stable, **infected by fluconazole-sensitive *Candida* isolates**, who have negative blood cultures

Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nature Reviews Disease Primers 2018; 4:18026.

Antifungal susceptibility testing

- **Susceptibility profile should be confirmed by microbiology laboratory**
- **Intrinsic resistance defined by species (e.g., *C. krusei* resistance to fluconazole)**
  - **Problematic pathogens:**
    - ***Candida glabrata*** (fluconazole resistance → cross resistance to other triazoles)
    - ***Candida tropicalis*** (fluconazole resistance increasing in some centers)
    - ***Candida parapsilosis*** (intrinsically less susceptible to echinocandins, increasing fluconazole resistance, infection control problems- healthcare worker hands, think biofilms and catheters)
    - ***Candida lusitaneae*** (rare species, but potential amphotericin B resistance)
    - ***Candida auris*** (fluconazole resistance, potential amphotericin B and echinocandin resistance)

Antifungal drug distribution



	Spleen	Kidneys	Liver/ Biliary	Lung/ELF	Brain/ CSF	Eye	Urine/ Bladder
L-AmB	+	+	+	+/-	+/-	–	–
5FC	+	+	+	+	+	+	+
FLU	+	+	+	+	+	+	+
ITR	+	+	+	+	–	–	–
VOR	+	+	+	+	+	+	–
POS*	+	+	+	+	–	–	–
ISAV	+	+	+	+	+/-	–	–
Echinocan.	+	+	+	+	–	–	–

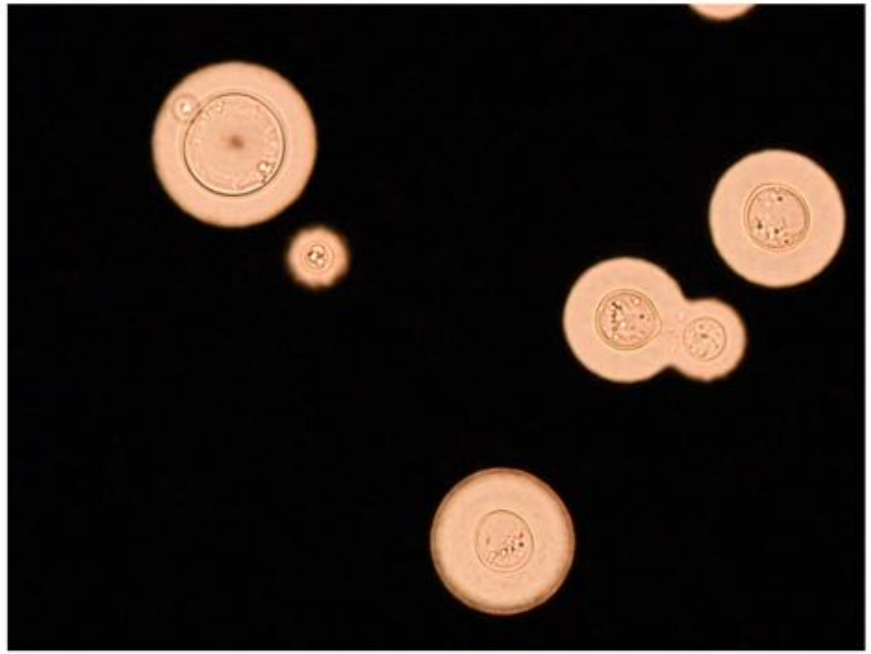
+ ≥50% of serum concentrations
– <10% of serum concentrations
* predicted

Felton, Troke & Hope. Clin Microbiol Rev 2014,27:68

Cryptococcosis

Microbiology

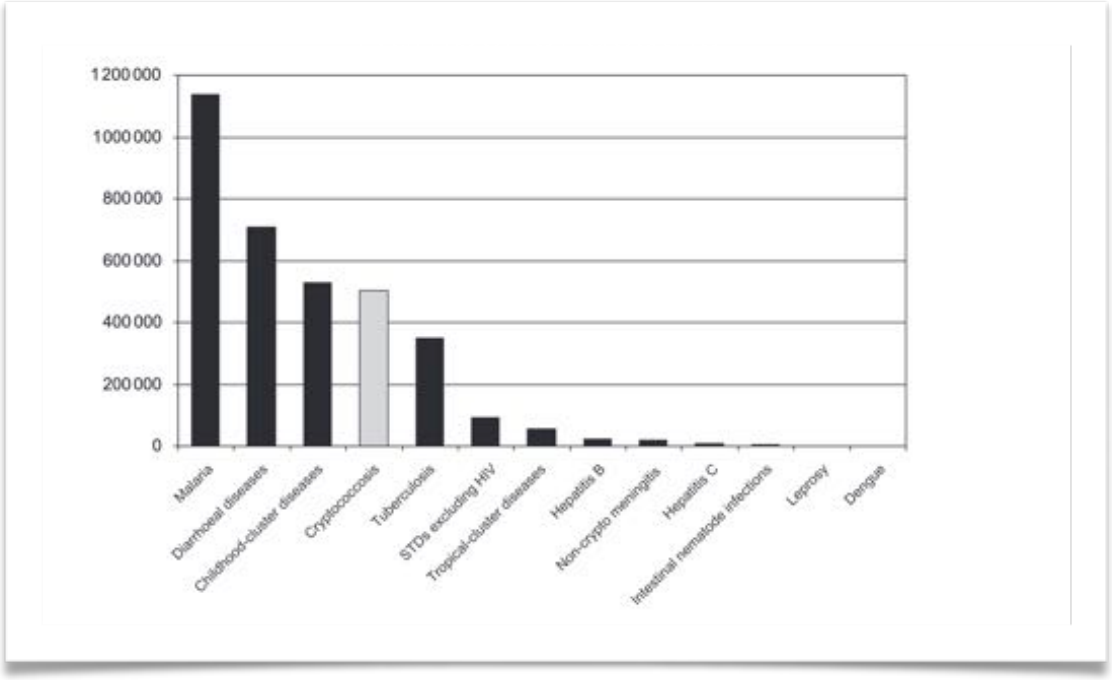
- ***C. neoformans* and *C. gatti***
  - *Now recognized to be at least 7 cryptic species within these*
  - *C. neoformans* associated with pigeon guano, rotting trees → global distribution
  - *C. gatti* associated with eucalyptus trees in endemic areas (British Columbia, Canada, Pacific NW US, Australia)
- **Large polysaccharide capsule is defining feature of fungi**
  - Required for virulence



India ink stain of CSF

Epidemiology of cryptococcosis

- **Usually associated with immunocompromised conditions**
  - > 90% of cases associated with advanced HIV (CD4 <100 cells/μL, transplantation, long-term corticosteroids, cirrhosis)
  - In western countries, HIV-associated cases compromise a minority of cases; HIV the dominant cause in resource-poor settings
    - Sub-Saharian Africa
    - South and Southeast Asia
  - **Incidence has dropped with widespread availability of ART in Western countries**



Cryptococcal infections cause 15% of AIDS-related deaths globally

Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS. 2009;23:525-530.

Box 2 | **Predisposing genetic and other conditions in non-HIV CM**

Syndromes and autoantibodies

- Idiopathic $CD4^+$ lymphopenia[22,23]
- Pulmonary alveolar proteinosis with autoantibodies to GM-CSF[24–26]
- Autoantibodies to IFN-γ[27]

Monogenic disorders

- Primary immunodeficiency owing to *GATA2* mutations[28–30]
- Chronic granulomatous disease
- Hyperimmunoglobulin E recurrent infection syndrome (also known as Job syndrome)[31,32]
- X-Linked CD40L deficiency (also known as hyper-IgM syndrome)[33,34]

Polygenetic modifiers

- FCg receptor II polymorphism[35]

Comorbidities[18,19]

- Sarcoidosis, autoimmune disease, steroid treatment
- Hepatic disease
- Solid organ transplant conditioning

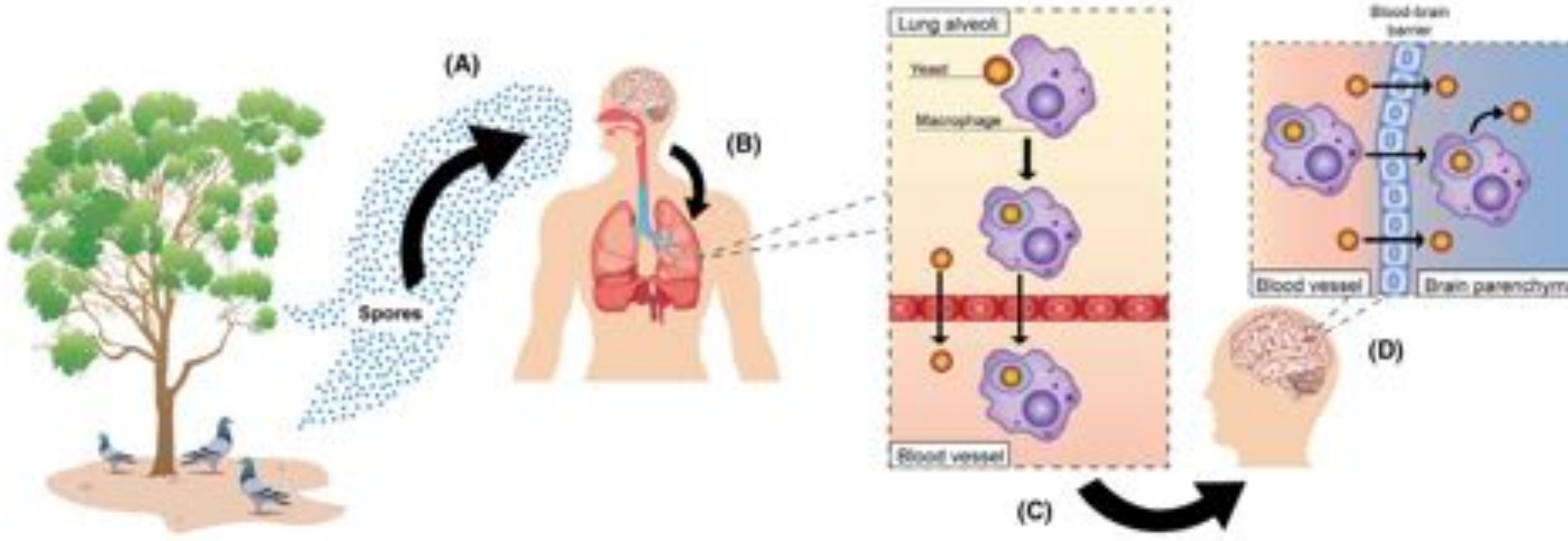
CM, cryptococcal mengitis; GM-CSF, granulocyte-macrophage colony stimulating factor.

Williamson PR et al. Nat Rev Neurol 2017; 13:13–24.

Pathogenesis

Infection is typically dormant for years, reactivates during immunosuppression

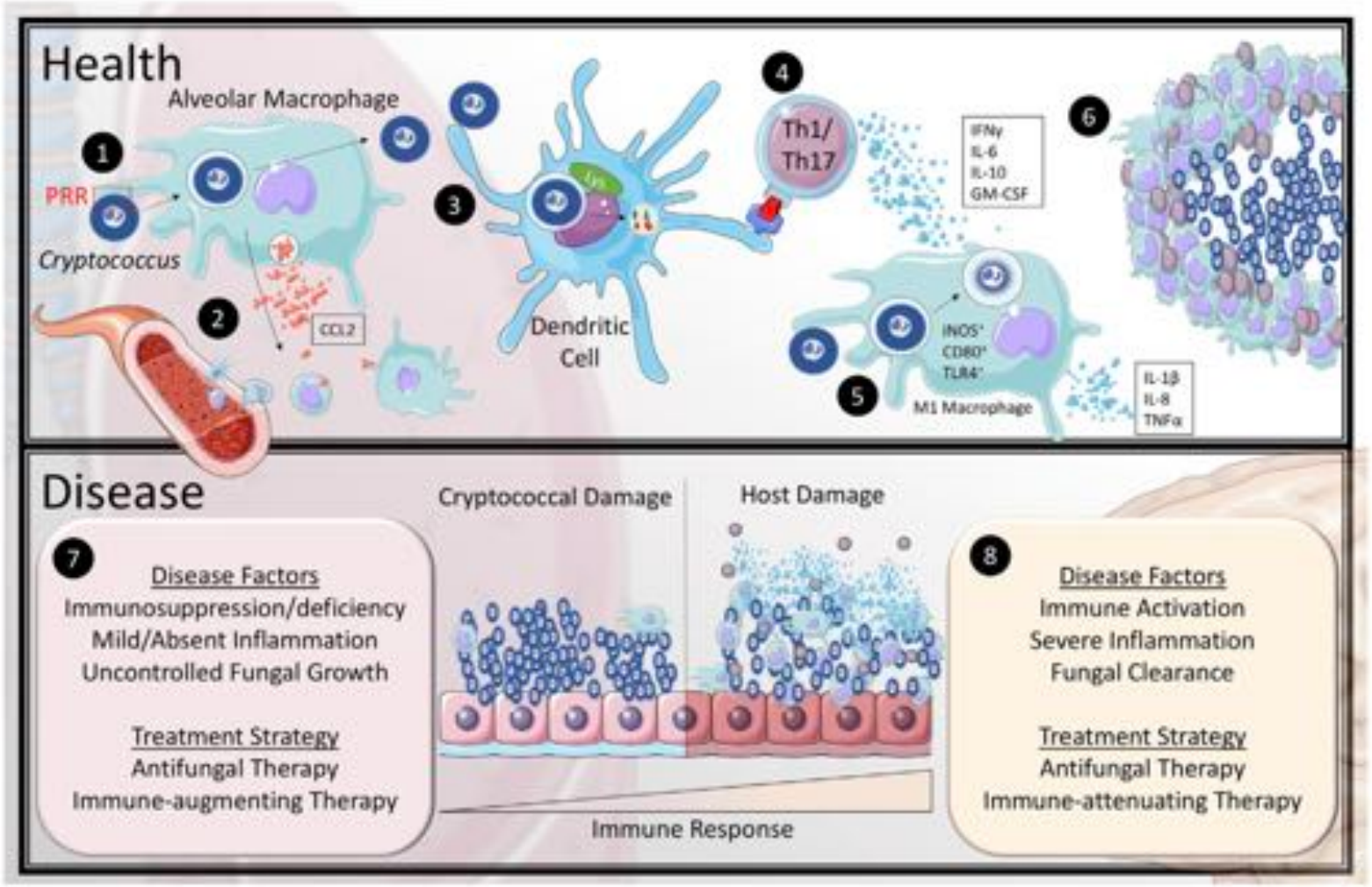
Meningoencephalitis → involvement of brain parenchyma



Nematollahi S, Mycoses 2020; 63:1033–1046.

Immune response to cryptococcosis

A double-edged sword



Granuloma

IRIS
(immune-related inflammatory syndrome)

Elsegeiny W et al. Front Immunol 2018; 9:651.

Clinical manifestations

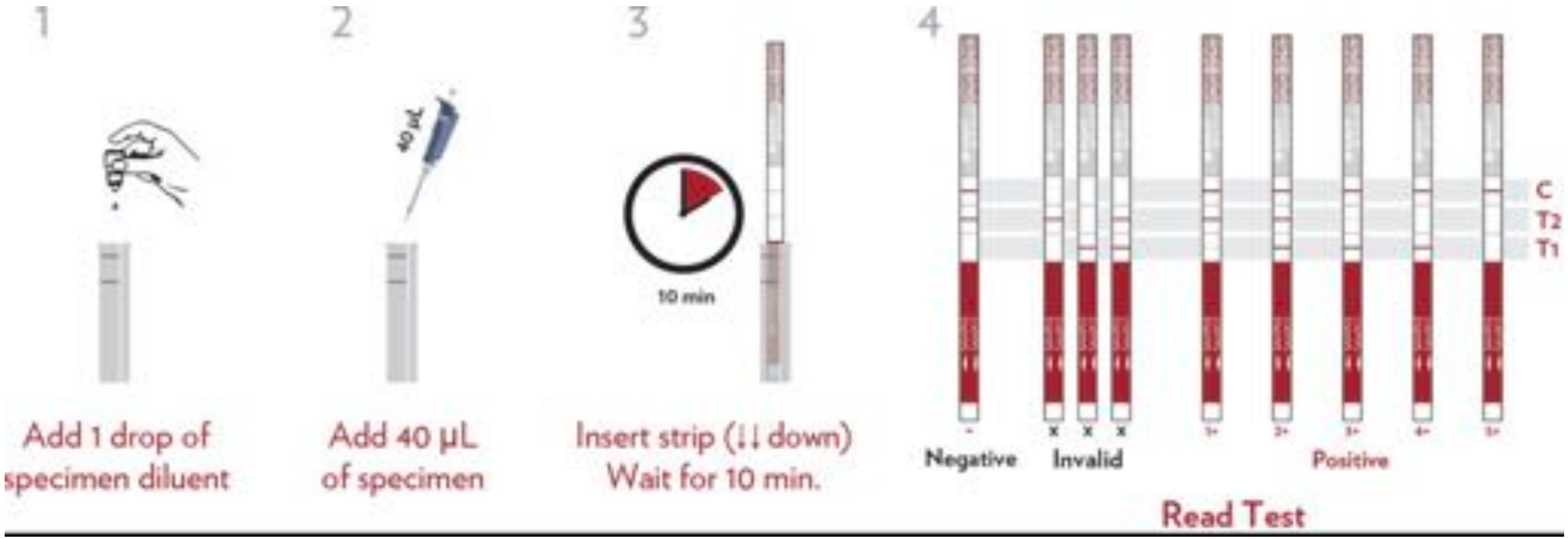
- **Indolent onset over 1-2 weeks**
  - Fever
  - Malaise
  - Headache
  - Confusion, Clouding of sensorium
  - Visual, Haring loss
  - Classic meningeal signs 25-33% (stiff neck, photophobia, vomiting)
  - Focal neurological deficits (cranial neuropathies)
  - Tachypnea and skin lesions (like molluscum contagiousum)
  - Increased diastolic hypertension (indicative of increased ICP)

Patient work-up

- **High suspicion for disease:**
  - Advanced HIV disease (CD4 < 100 cells/μL)
  - Fever and headache
- **Careful history**
  - Neurologic exam (Cranial nerve VI-abducens nerve-horizontal eye movements)
  - **Serum cryptococcal antigen (CrAg)**

Cryptococcal serum antigen (CrAg)

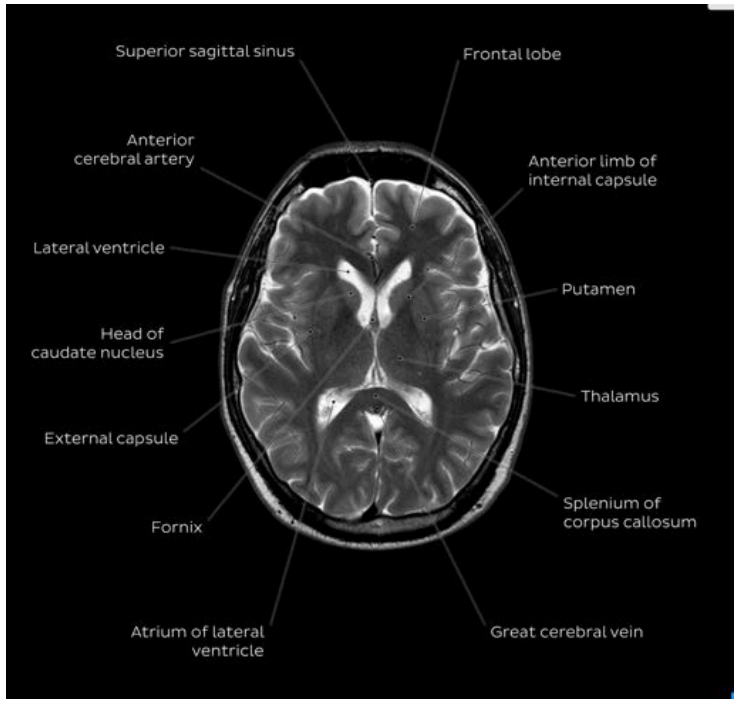
- **Detectable in serum and CSF months before any signs/ symptoms of cryptococcal meningitis**
- **Reported 99% sensitivity and specificity**

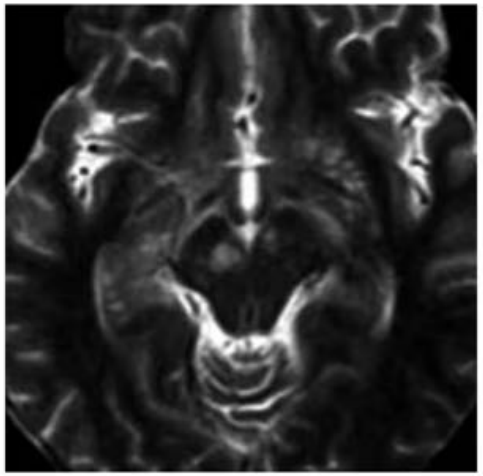


Neuroimaging

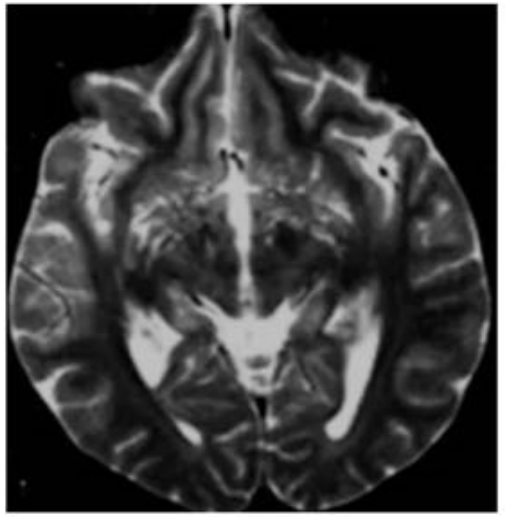
- **CT or MRI**
  - Important for detecting increased intracranial pressure (ICP) due to enlarged ventricles, herniation, or mass effect from causes such as tumors, abscesses, and hematomas etc.
    - Risk of LP in patient with ICP (cerebral herniation)
  - Mass lesions may suggest alternative diagnosis:
    - Toxoplasmosis
    - Lymphoma
    - Tuberculosis
    - Syphilis
    - Progressive multifocal leukoencephalopathy (PML)
    - Mass lesions more common in patients receiving active retroviral therapy, *C. gattii* infection, or “unmasked” cryptococcosis in the setting of IRIS.

Williamson PR et al. Nat Rev Neurol 2017; 13:13–24.

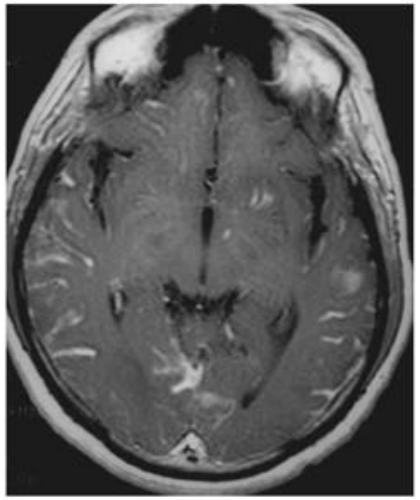




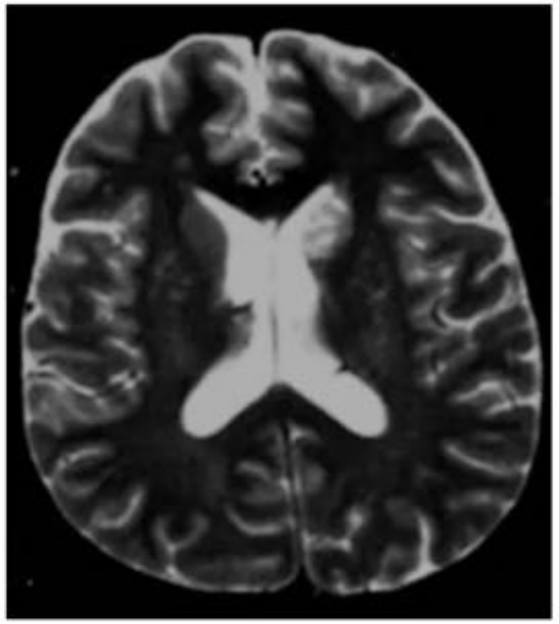
T2-weighted axial magnetic resonance image demonstrates hyperintense cryptococcomas in the midbrain.



T2-weighted axial magnetic resonance image demonstrates linear and punctate hyperintensities in the basal ganglia; these represent dilated perivascular spaces caused by small cryptococcomas. Cryptococcomas vary in size from several millimeters to several centimeters.



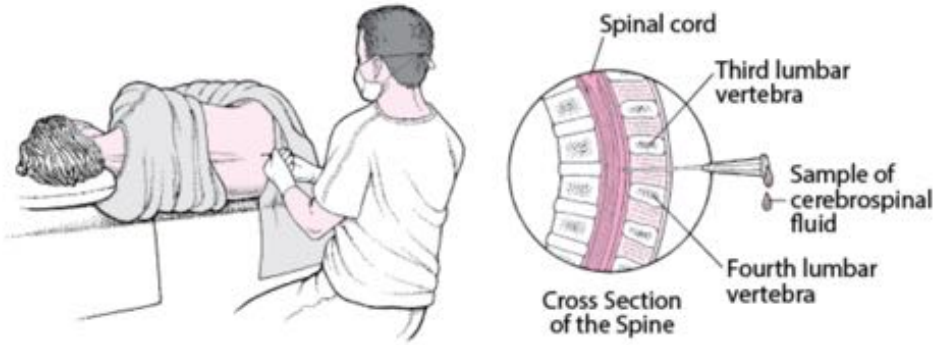
Axial contrast-enhanced T1-weighted magnetic resonance image shows diffuse, gyriform leptomeningeal enhancement. Enhancing lesions in the left basal ganglia, left temporal lobe, and left occipital lobe correspond to intraparenchymal cryptococcosis.



Axial T2-weighted magnetic resonance image shows clustered hyperintensities in the left caudate; these are consistent with enlarged Virchow-Robin spaces caused by small cryptococcomas.

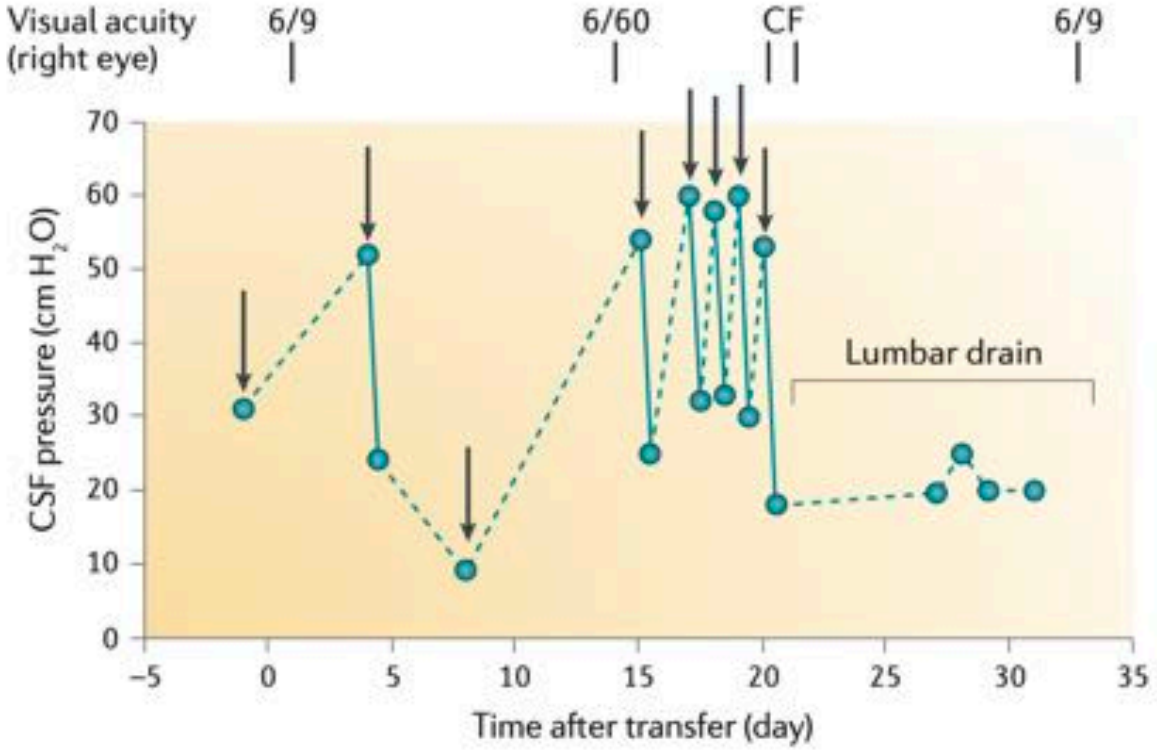
Lumbar puncture

- **Confirmatory test for cryptococcal meningioencephalitis**
  - Low WBC (< 50 cells/μL)
    - **CSF WBC count <20 cells/μL poor prognostic sign**
  - Mononuclear predominance
  - Elevated CSF protein
  - Glucose low or normal
  - Elevated intracranial pressure (ICP) (> 20 cm CSF)
  - Confirmed positive CrAg test
    - Measuring antigen titre
  - India ink stain
  - Cultures (for identification and susceptibility testing if available, usually positive in 3-7 days)
    - Resistance generally rare, but fluconazole resistance increasing in some areas
- 20-30% of patients will have a normal CSF profile
- **CSF Antigen titer > 1:4000 by lateral flow) independent predictor of poor outcomes in first 2 weeks**



Intracranial pressure

- **50% of HIV-infected patients: CSF opening pressure of >25 cm CSF**
- **25% very high pressure of >35 cm CSF**
- **High pressure is associated with worse symptoms, including headache, nausea, diplopia secondary to sixth nerve palsies, and altered mental status.**
- **Careful therapeutic lumbar punctures are recommended to control high CSF pressure (< 20 cm, or < 50% if initial pressure was > 50 cm)**
  - The safe maximum volume of CSF that can be drained at one lumbar puncture is unclear, but up to 30 ml are frequently removed in patients with high pressure, with checking of pressure after each 10 ml removed.
  - Daily LPs may be required until patient asymptomatic and CSF pressure normal/stable → lumbar or ventricular drain may be required
- **General timing:**
  - After initial LP, 2 week after induction therapy finished
  - A earlier repeat LP recommended in patients with persistent or worsening symptoms
  - A repeat LP and measurement of ICP should be performed in any patients with recurrent symptoms after initial improvement



Time after transfer (day)	21	22	23	24	25	26	27	28	29	30	31	32	33
CSF drained (ml)	250	231	227	205	174	185	143	113	170	172	51		

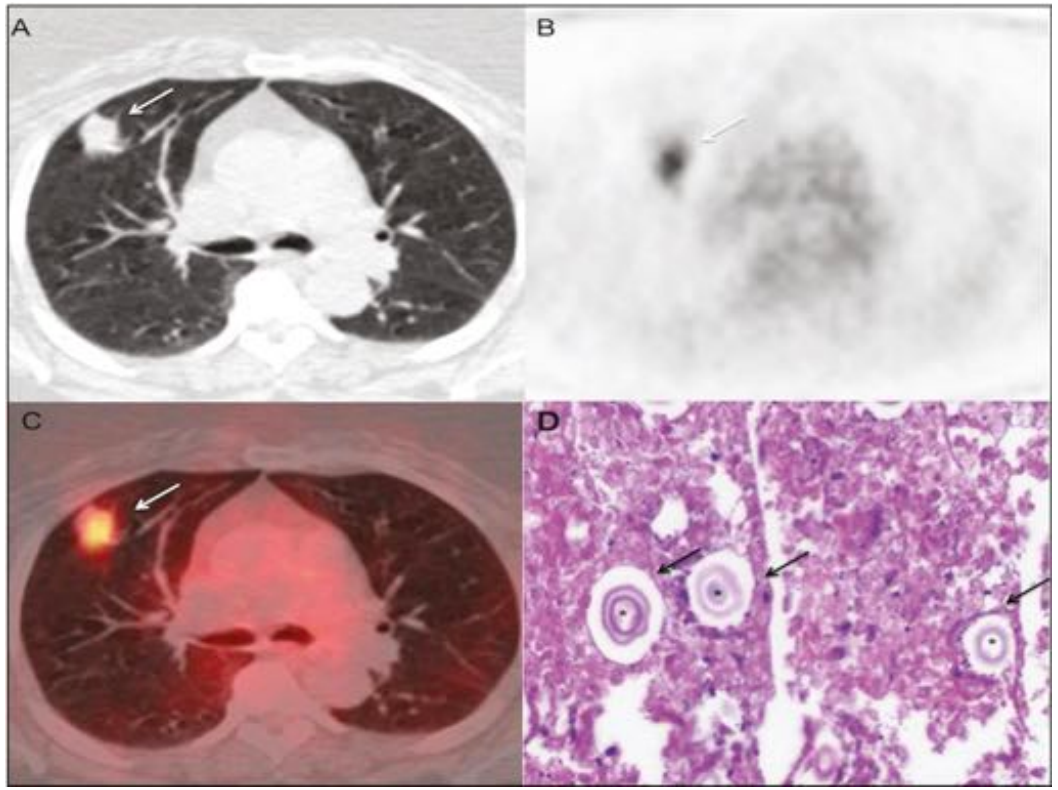
Drain clamped overnight

Drain clamped, then removed

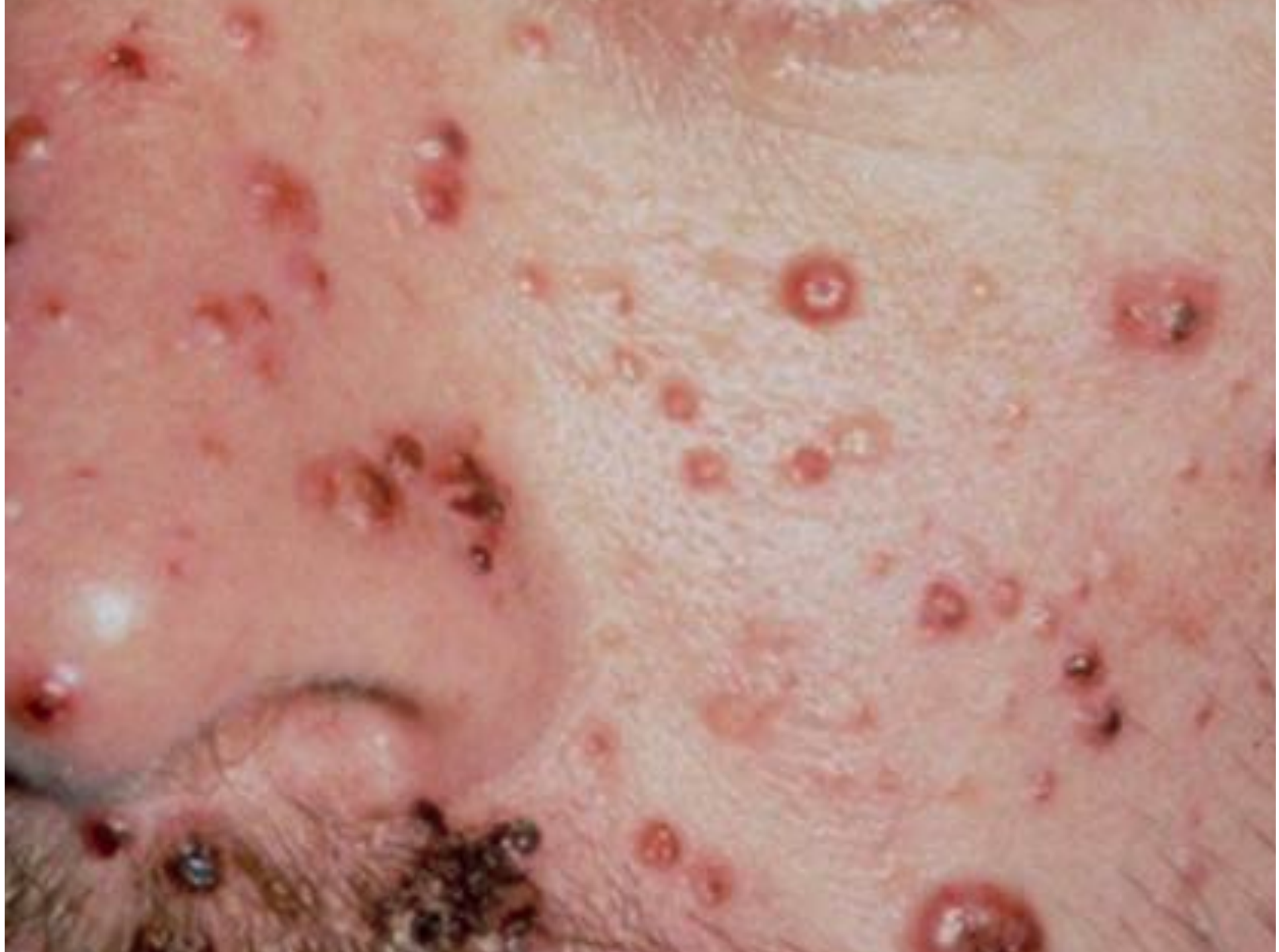
Depicted here is time course of changes in cerebrospinal fluid
(CSF) pressure, visual acuity, and volume of CSF drained through a temporary lumbar drain *in situ* over 11 days. Arrows indicate times of lumbar puncture. During the third week of antifungal therapy, and despite the fact that CSF cultures had become negative, the patient developed severely raised CSF pressure that was unresponsive to repeated daily lumbar punctures, but did respond to CSF drainage via a temporary lumbar drain. Symptoms of high CSF pressure recurred when the drain was clamped after 6 days, but did not recur when it was clamped and then removed after 10 days. CF, counting fingers (indicating severely reduced visual acuity).

Extraneural sites of cryptococcus

Positive histopathology or culture



- Isolated lung nodules, lymphadenopathy, cavitations
- Chronic prostatitis
- Bone and soft tissue (< 10%)



Prognostic factors

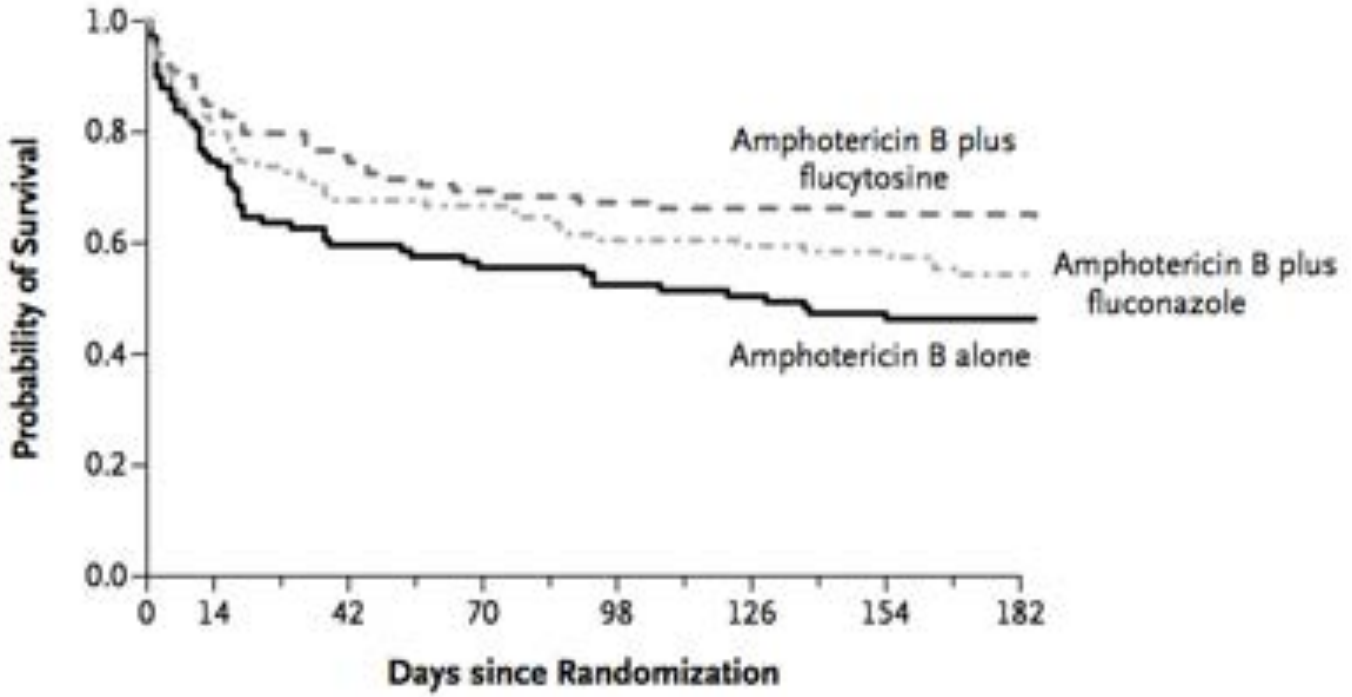
- Uniformly fatal if untreated
- Acute mortality (high-income countries) 6-16%
- Resource limited settings: 24-35% acute mortality, higher mortality if suboptimal treatment regimens are used
- Key for long-term survival is to start and maintain effective anti-retroviral therapy

Antifungal therapy

- **Induction therapy (2 weeks)**
  - Liposomal amphotericin B, 3-4 mg/kg daily *plus* flucytosine (100 mg/kg day in 4 divided doses)
  - Amphotericin B deoxycholate 0.7-1 mg/kg IV daily can be substituted but limited to 7 days
  - Single-dose liposomal amphotericin B 10 mg/kg with 14 days of flucytosine and fluconazole (1200 mg/day)
- **Consolidation therapy (8 weeks)**
  - Fluconazole, 400-800 mg/day
- **Maintenance therapy (at least 1 year)**
  - Fluconazole 200 mg/day

Combination therapy for cryptococcal meningitis improves survival

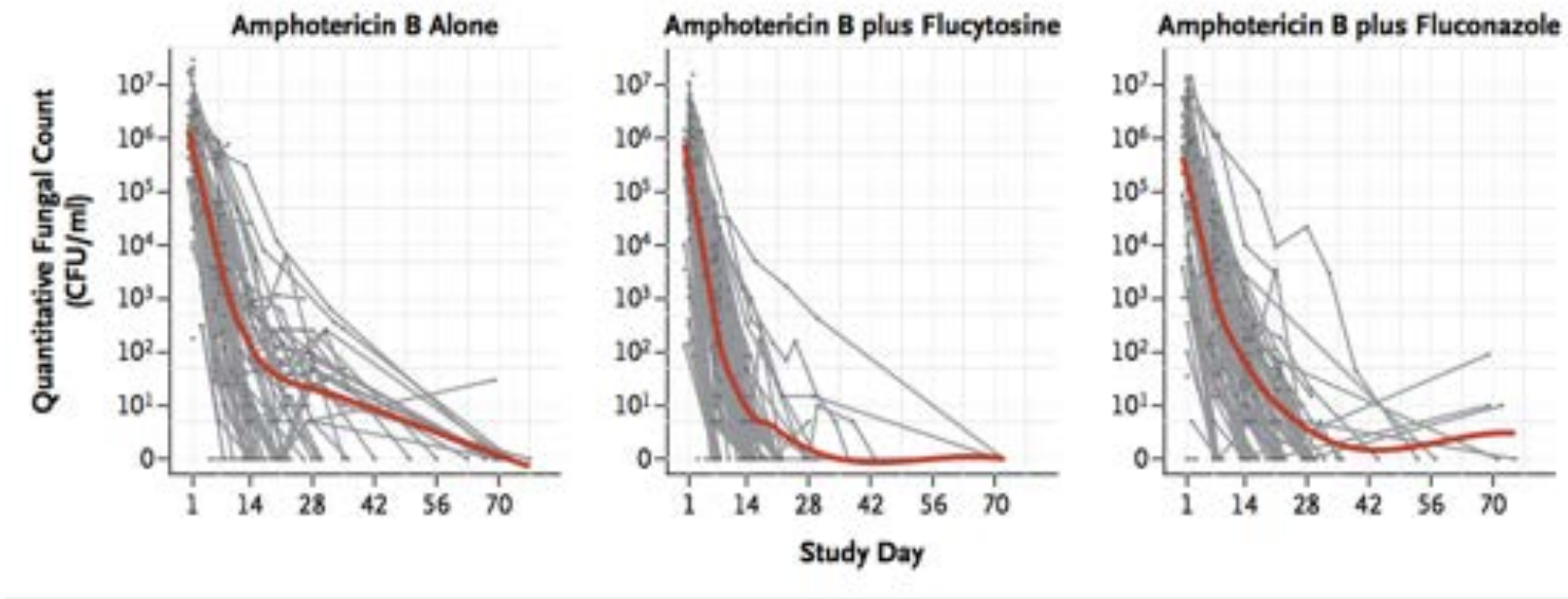
Day 70:
AMB + 5FC vs. AMB
HR 0.61 (0.39-0.97)
unadjusted P = 0.04

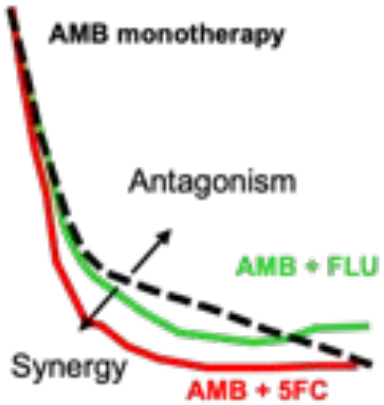


No. at Risk								
Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67	65	59	58	57	39

Day et al. N Eng J Med 2013;368:1291-1302

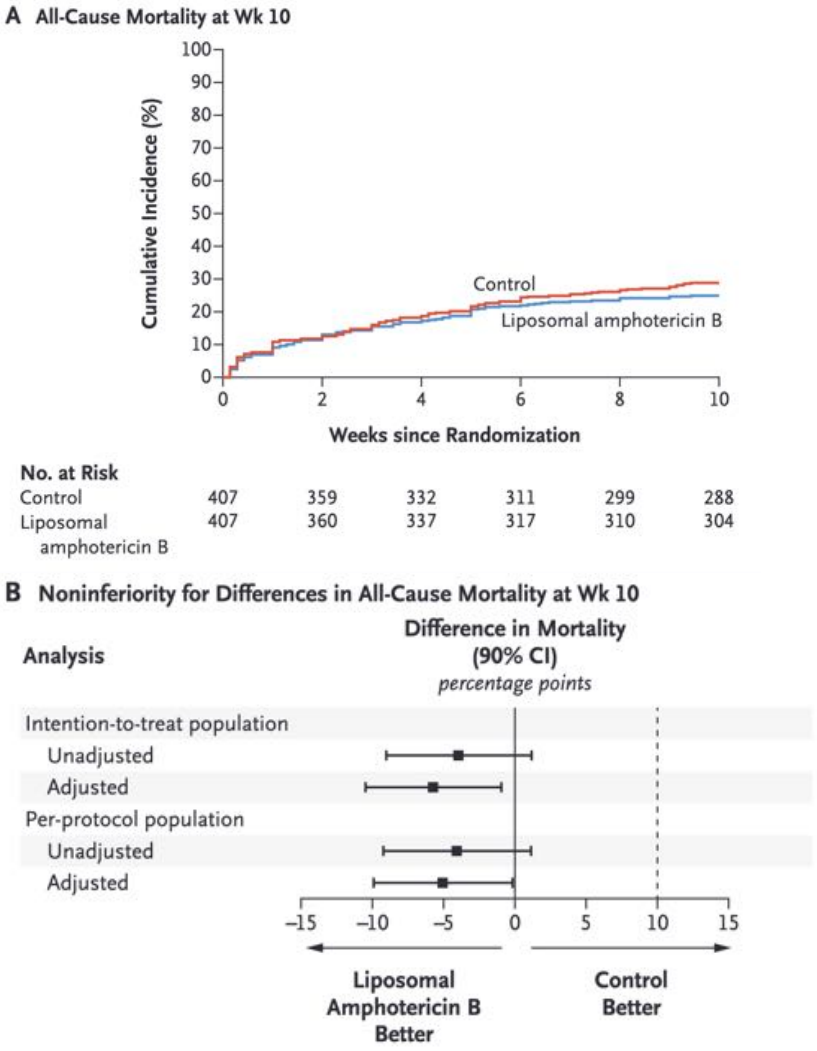
Amphotericin B + 5FC is Synergistic In the Treatment of Cryptococcal Meningitis





Day et al. N Eng J Med 2013;368:1291-1302

Single 10 mg/kg liposomal AMB is as effective as 7 days of amphotericin B deoxycholate



- **Liposomal AMB** (10 mg per kilogram of body weight) of liposomal amphotericin B plus 14 days of flucytosine (100 mg/kg/per day) and fluconazole (1200 mg per day)

- **Control:** WHO-recommended regimen, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) on days 8 through 14 (the control group)

Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med 2022; 386:1109–1120.

Table 3. Laboratory-Defined and Clinical Adverse Events Occurring within 21 Days after Randomization.*

Event	Liposomal Amphtericin B (N=420)	Control (N=422)	P Value†
Grade 3 or 4 adverse events — no. of events	382	579	
Any grade 3 or 4 adverse event — no. of participants (%)			
Grade 3 or 4	210 (50.0)	263 (62.3)	<0.001
Grade 3	173 (41.2)	225 (53.3)	<0.001
Grade 4	91 (21.7)	127 (30.1)	0.005
Anemia — no. of participants (%)‡			
Grade 3	44 (10.5)	108 (25.6)	<0.001
Grade 4	12 (2.9)	62 (14.7)	<0.001
Mean change in hemoglobin level from baseline to day 7 — g/dl§	−0.3±1.39	−1.9±1.8	<0.001
Receipt of blood transfusion — no. of participants (%)	32 (7.6)	76 (18.0)	<0.001
Neutropenia — no. of participants (%)¶			
Grade 3	27 (6.4)	21 (5.0)	0.36
Grade 4	20 (4.8)	16 (3.8)	0.49
Thrombocytopenia — no. of participants (%)‖			
Grade 3	9 (2.1)	17 (4.0)	0.11
Grade 4	4 (1.0)	6 (1.4)	0.75
Creatinine increase — no. of participants (%)**			
Grade 3	17 (4.0)	22 (5.2)	0.42
Grade 4	5 (1.2)	3 (0.7)	0.51
Mean relative increase in creatinine level from baseline to day 7 — %††	20.2±48.1	49.7±70.8	<0.001
Hypokalemia — no. of participants (%)‡‡			
Grade 3	6 (1.4)	27 (6.4)	<0.001
Grade 4	0	3 (0.7)	0.25
Elevated ALT — no. of participants (%)§§			
Grade 3	6 (1.4)	4 (0.9)	0.52
Grade 4	1 (0.2)	1 (0.2)	1.0
Thrombophlebitis requiring antibiotic therapy — no. of participants (%)	8 (1.9)	28 (6.6)	<0.001
Other grade 3 or 4 adverse event — no. of participants (%)¶¶	167 (39.8)	173 (41.0)	0.72

Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med 2022; 386:1109–1120.

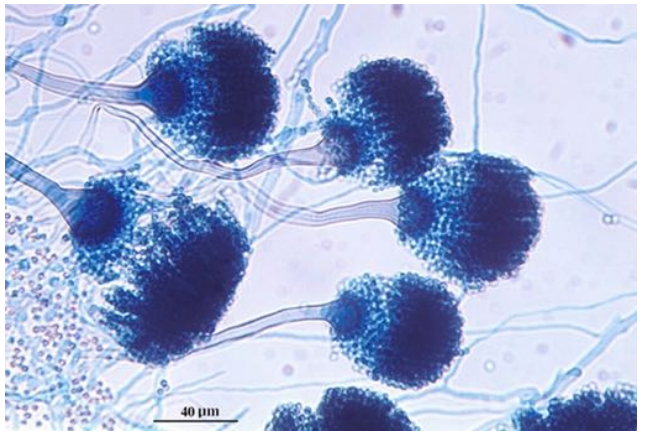
Key difference from other meningitis

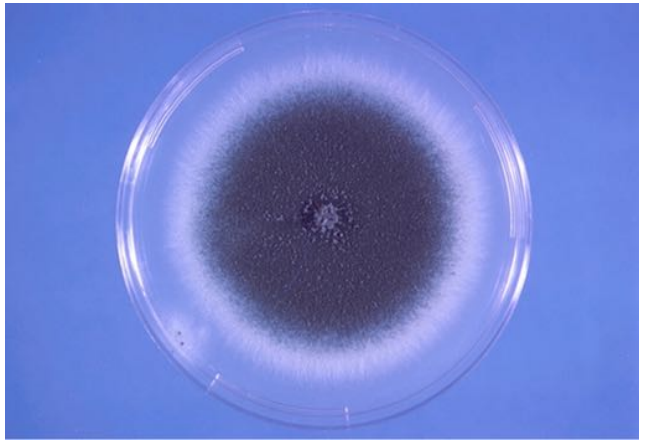
- **No role for empiric glucocorticoids during initial induction therapy**
- **Antiretroviral therapy should be started between 2-10 weeks after antifungal therapy initiated**
  - Benefit vs. risk: Early immune recovery vs. IRIS
  - Later may minimize the risk of drug interactions/IRIS
- **Glucocorticoids may be considered in patients with IRIS with symptomatic increases in ICP (i.e. prednisone 0.5-1 mg/kg daily then taper over over 2-6 weeks**

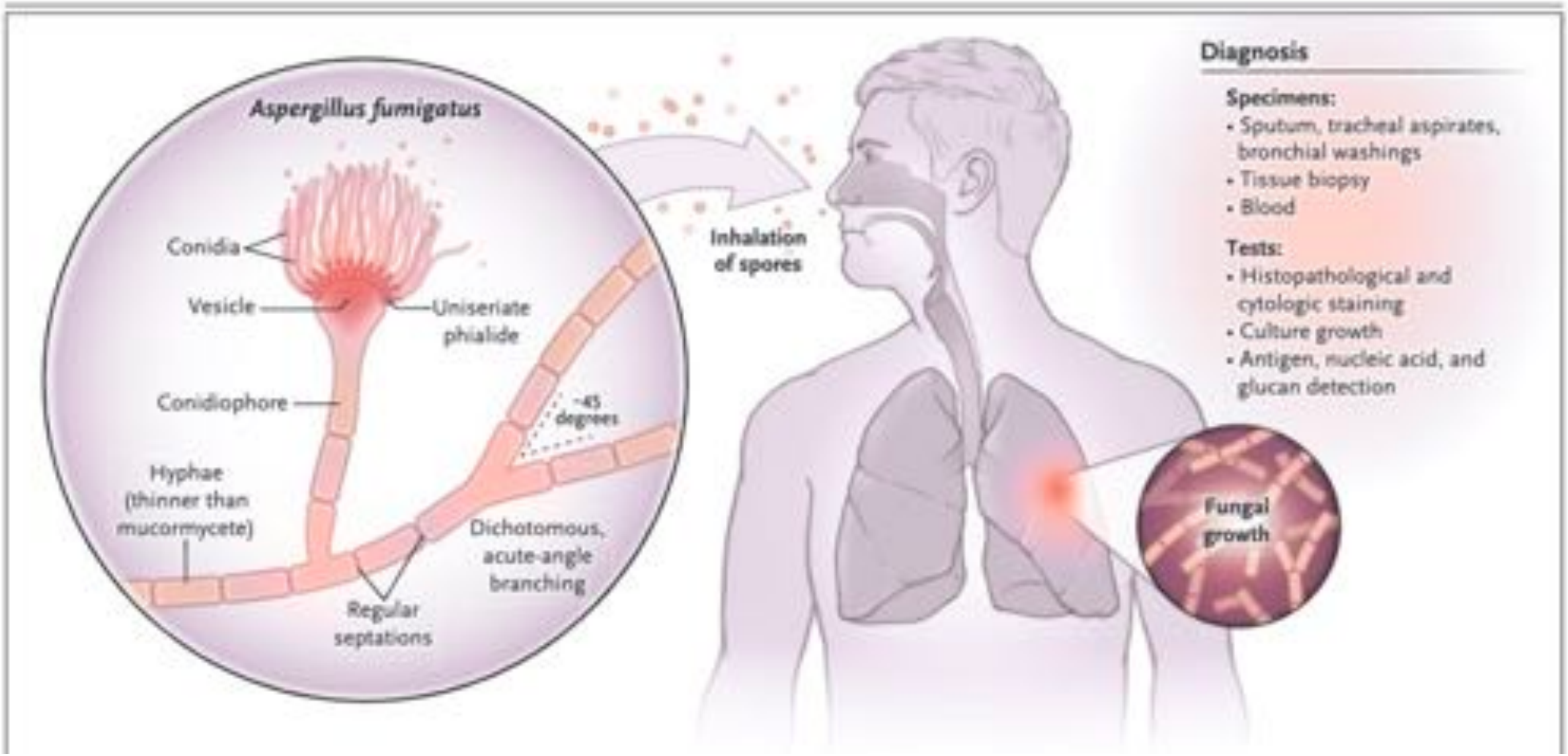
Invasive aspergillosis

Key difference from other meningitis

- **Ubiquitous, environmental mold**
- **Most common species:**
  - *Aspergillus fumigatus*
  - *Aspergillus flavus (can be less susceptible to amphotericin B)*
  - *Aspergillus niger*
  - *Aspergillus terreus (amphotericin B resistance)*







Thompson GR 3rd, Young J-AH. Aspergillus Infections. N Engl J Med **2021**; 385:1496–1509. Available at: http://dx.doi.org/10.1056/NEJMra2027424.

Spectrum of disease due to *Aspergillus* spp.

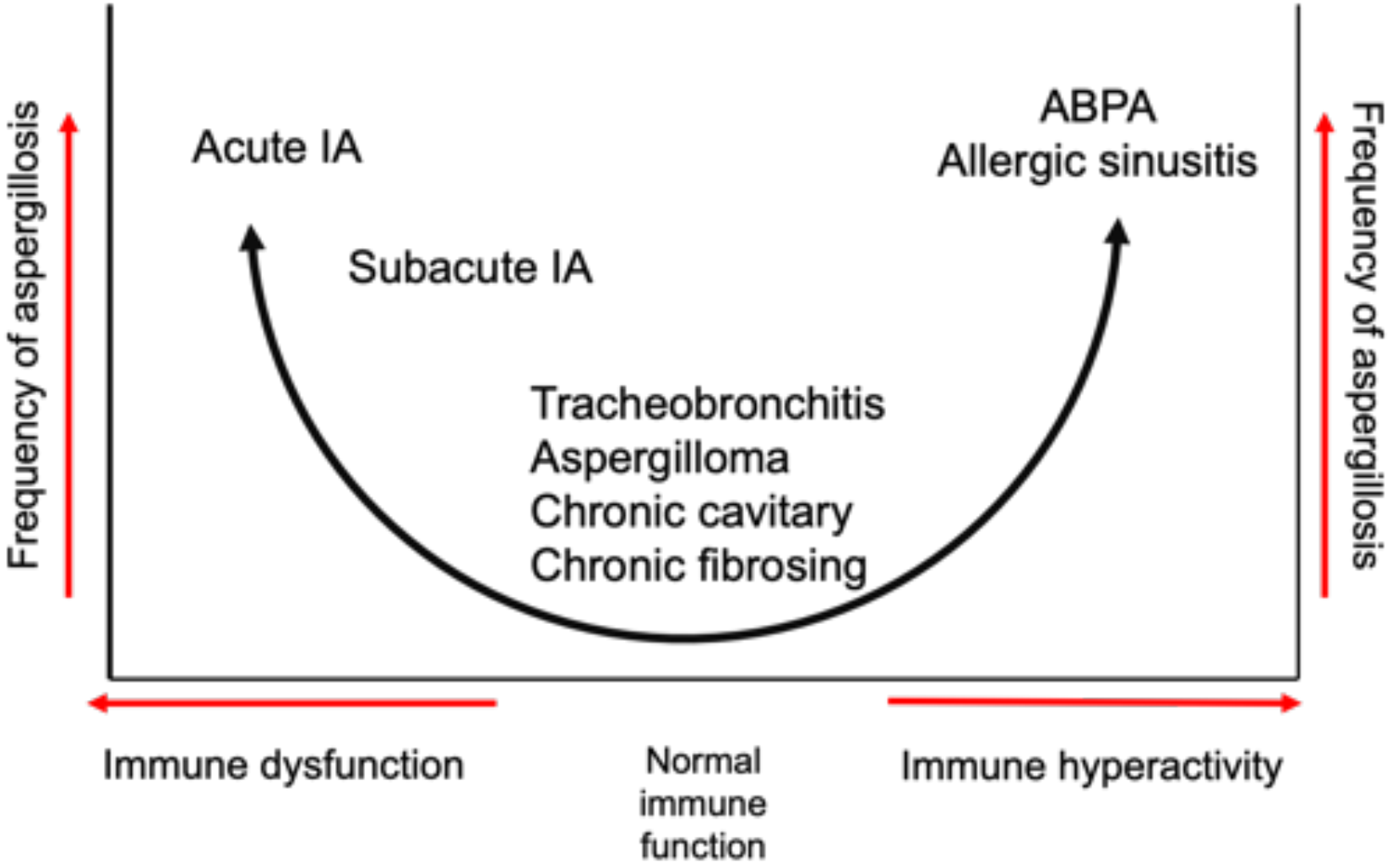


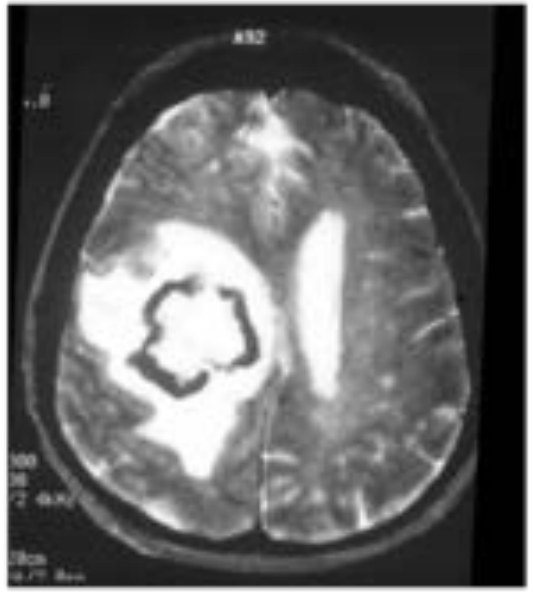
Table 1. Risk Factors for and Clinical Manifestations of Aspergillus Infections.*

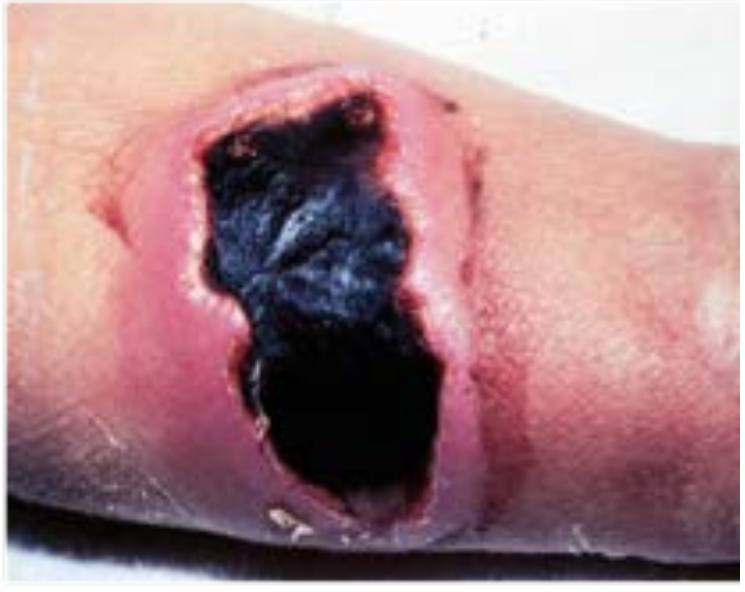
Clinical Syndrome	Risk Factors	Clinical Elements of Infection
Allergic bronchopulmonary aspergillosis	Reactive airway conditions, cystic fibrosis	Hypersensitivity to inhaled airborne conidia causes allergic bronchopulmonary aspergillosis or asthma exacerbations with fungal sensitization
Aspergilloma	Structural lung disease	Fungus balls develop inside lung cavities (e.g., from tuberculosis)
Colonization of the pulmonary tree	Inhaled glucocorticoids, bronchiectasis, cystic fibrosis	Recurrent recovery in culture without compatible symptoms or radiographic findings
Cutaneous disease	Tissue damage, inoculation, burn wounds	Primary site or secondary dissemination; iatrogenic infection of wounds (e.g., through contamination in an operating room or contaminated medical products)
Eye disease	Tissue damage, surgery, foreign body	Topical keratitis, endophthalmitis, or extension of sinus disease
Tracheobronchitis	Develops most commonly in lung transplant recipients but may be seen in other patient groups as well	Cough, hemoptysis, wheezing, and dyspnea are observed clinically. Although radiographic imaging may be normal or show only airway thickening, various patterns have been described: obstructive tracheobronchitis with prominent mucous plugs and hyphae in the airways, ulcerative tracheobronchitis with focal invasion of the mucosa, and a pseudomembranous form with extensive inflammation and necrosis of the tracheobronchial tree; in lung transplant recipients, invasion by hyphae may develop at the site of anastomosis and suturing
Chronic pulmonary aspergillosis	Structural lung disease, underlying cancer, receipt of glucocorticoids, malnutrition, impaired mucociliary clearance after recent pulmonary infection, ICU stay	Fever, cough, and shortness of breath, with or without chest pain and hemoptysis (signs of angioinvasion)
Sinus disease	Neutropenia, diabetes, excessive alcohol use, tropical residence, prolonged immunocompromised state	Sinus disease may be difficult to differentiate from other infections, including mucormycosis; clinical findings may be subtle in patients who have neutropenia, with nasal congestion, fever, and facial pain most commonly encountered; cacosmia is a concerning signal, suggesting necrosis of the nasal or sinus tissue and requiring urgent evaluation; extension from the sinus into the surrounding bony or soft tissues may develop, requiring surgical debridement; patients with the orbital apex syndrome, characterized by impairment of extraocular muscles, present with ophthalmoplegia and visual loss
Disease of the central nervous system	Develops with hematogenous dissemination from a primary site (pulmonary or cutaneous inoculation) or contiguous extension from a sinus source; common with brain-lung therapy	Neurologic deficits consistent with the region of involvement are seen on examination, and imaging studies show mass lesions or nodules
Invasive infection	Exogenous immunosuppression, often related to chemotherapy, transplantation, or small-molecule kinase inhibitors Severe respiratory viral infection (SARS-CoV-2 infection or influenza)	Small foci of growth are unchecked, and vegetative hyphae invade through tissue planes into blood vessels (i.e., angioinvasion), with the opportunity for contiguous or hematogenous spread and fatal infection of multiple organ systems, including endocarditis

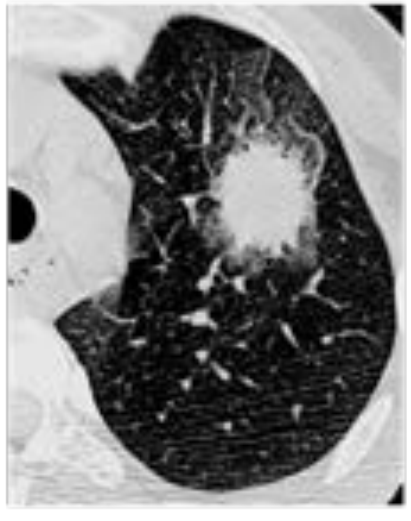
* ICU denotes intensive care unit, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

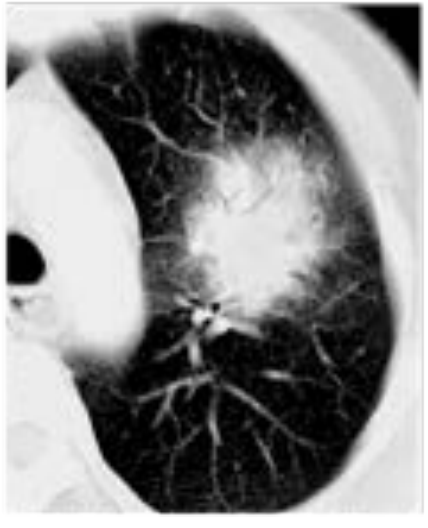
Thompson GR 3rd, Young J-AH. Aspergillus Infections. N Engl J Med 2021; 385:1496–1509.

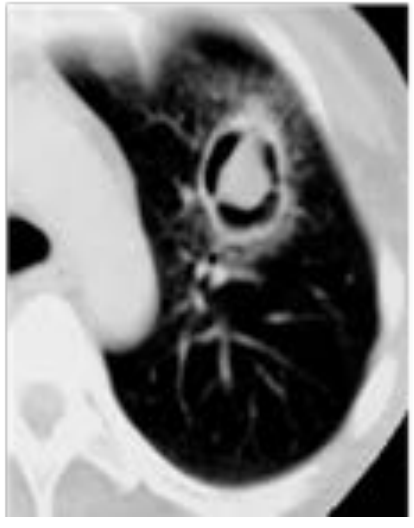
Multiple clinical manifestations of aspergillosis



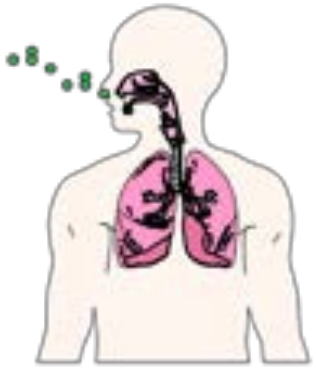




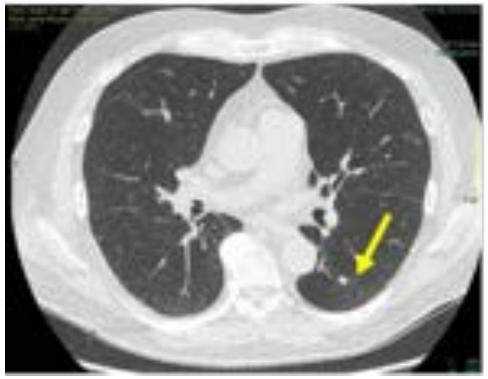


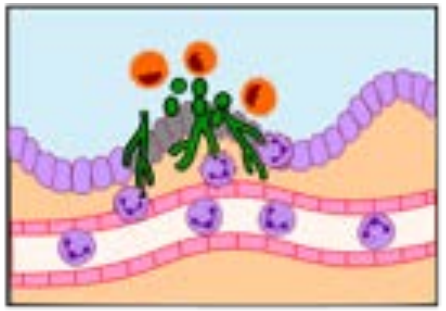


Invasive aspergillosis pathophysiology

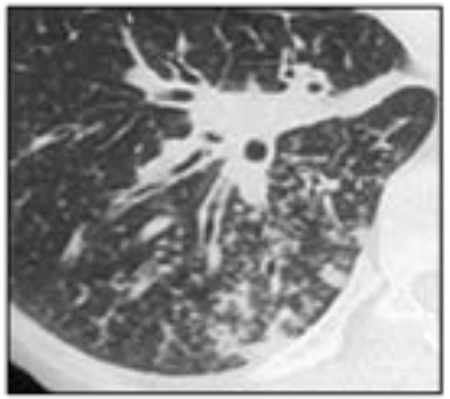


Inhalation of fungal spores





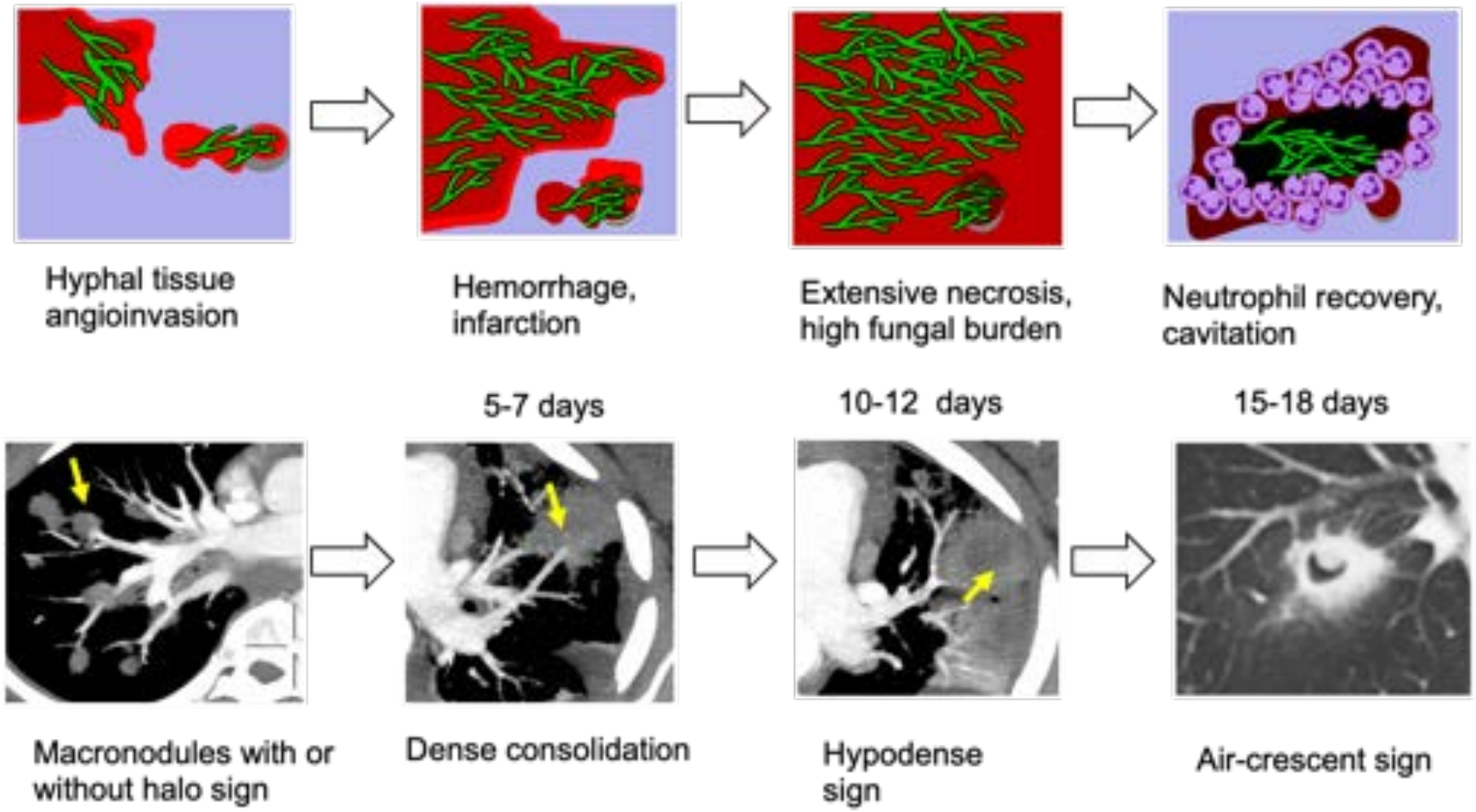
Invasion through bronchial and alveolar walls with associated inflammation



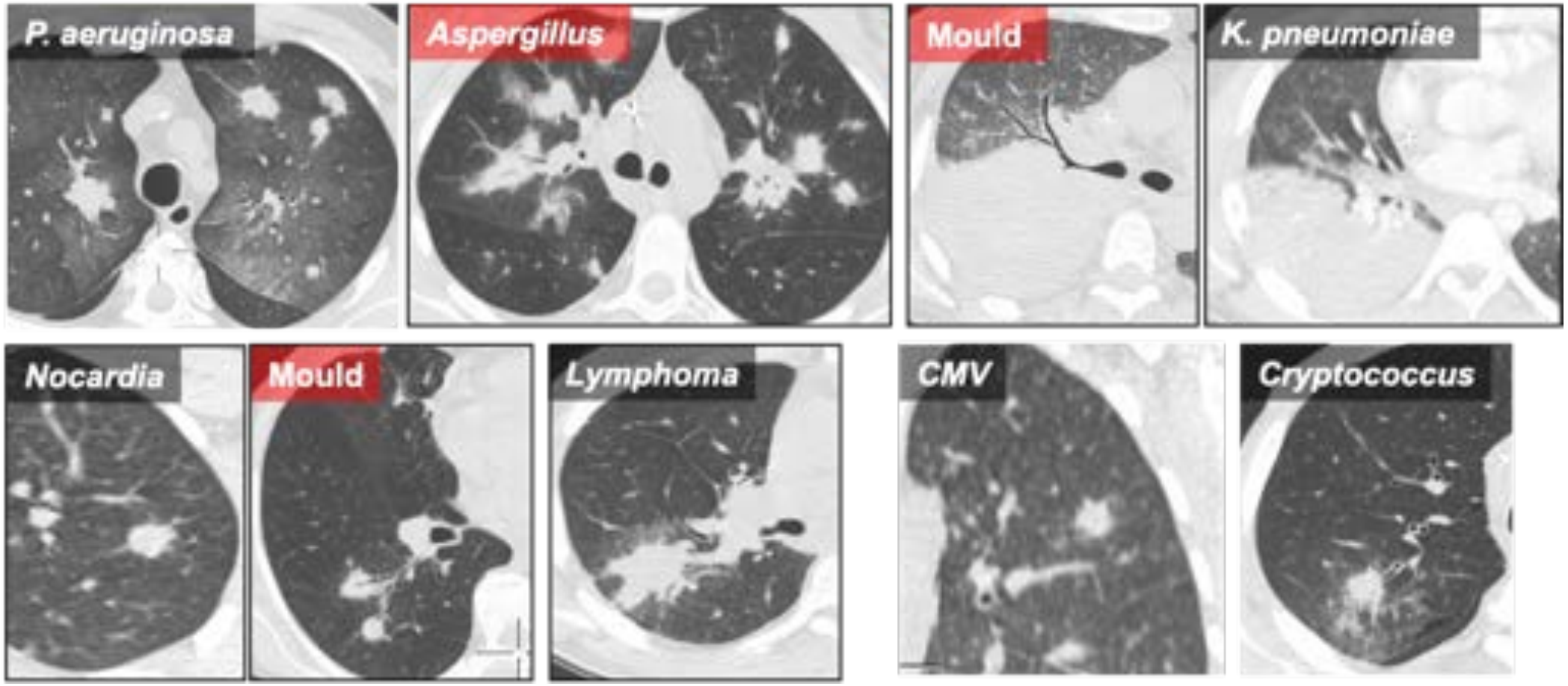
Centrilobar nodules bronchiolitis, tree in bud

Fungal burden: low
Serum galactomannan: undetectable
BAL culture/ galactomannan: detectable

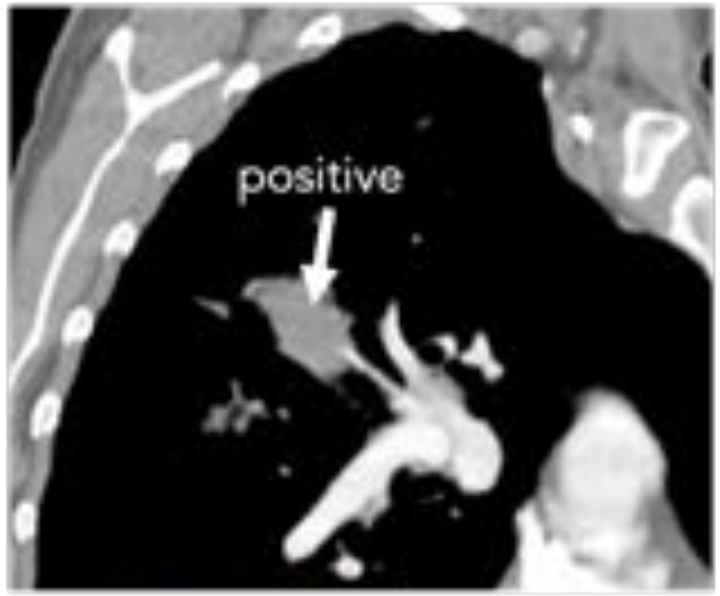
Disease progression of aspergillosis



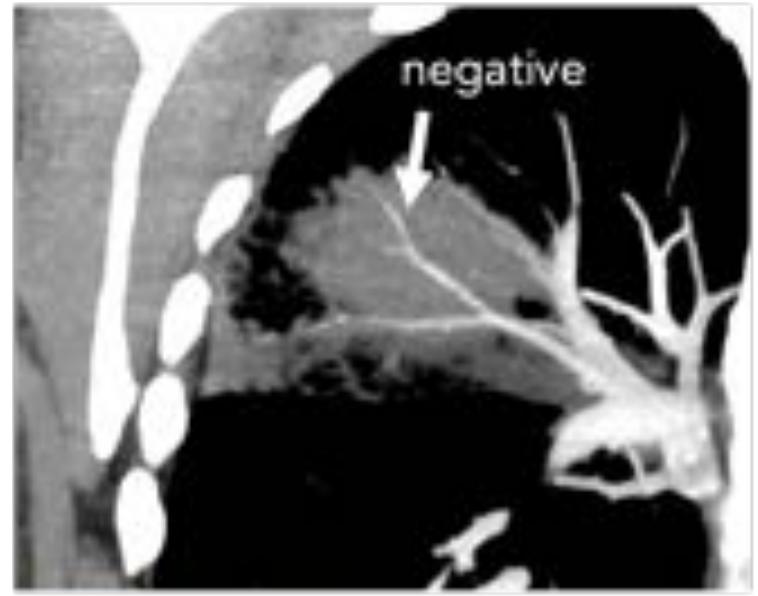
Suggestive CT findings for pulmonary aspergillosis



CT pulmonary angiography (CTPA) can differentiate mold vs. bacterial pneumonia in patients with acute leukemia



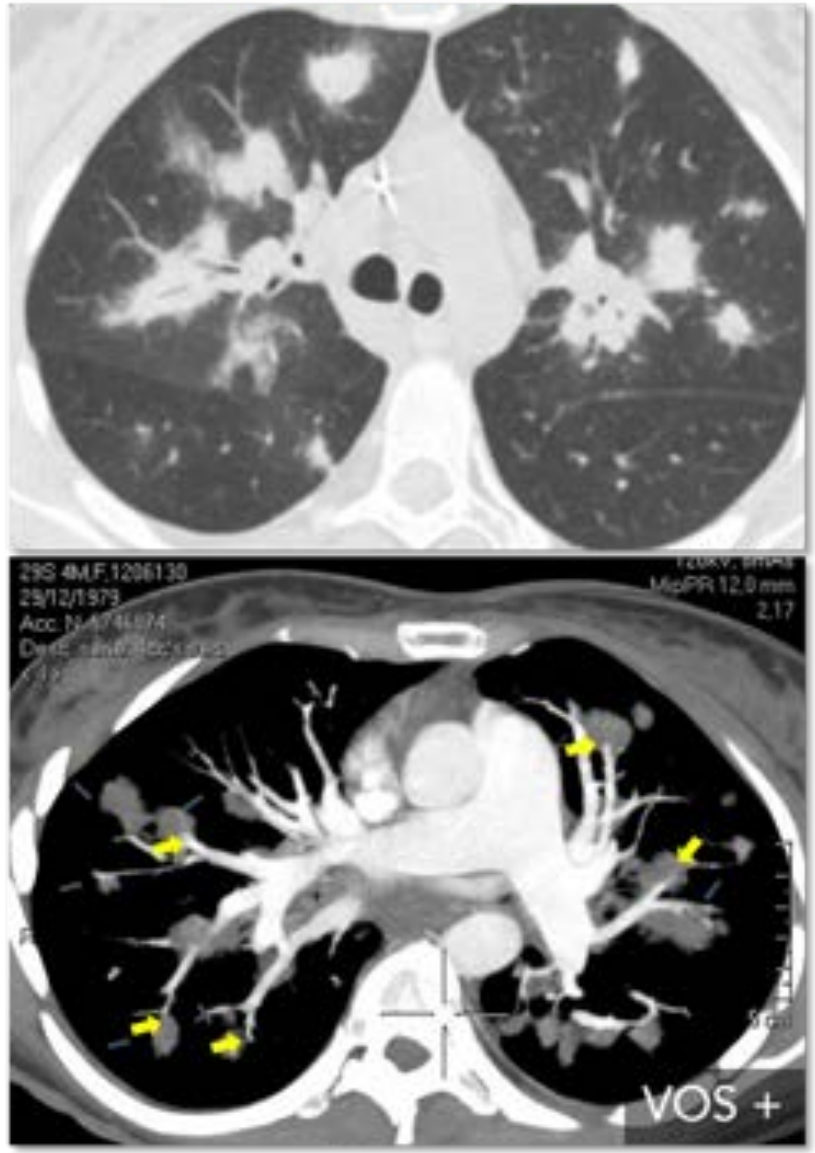
VOS positive,
proven mold
disease by autopsy



VOS negative,
bacterial pneumonia

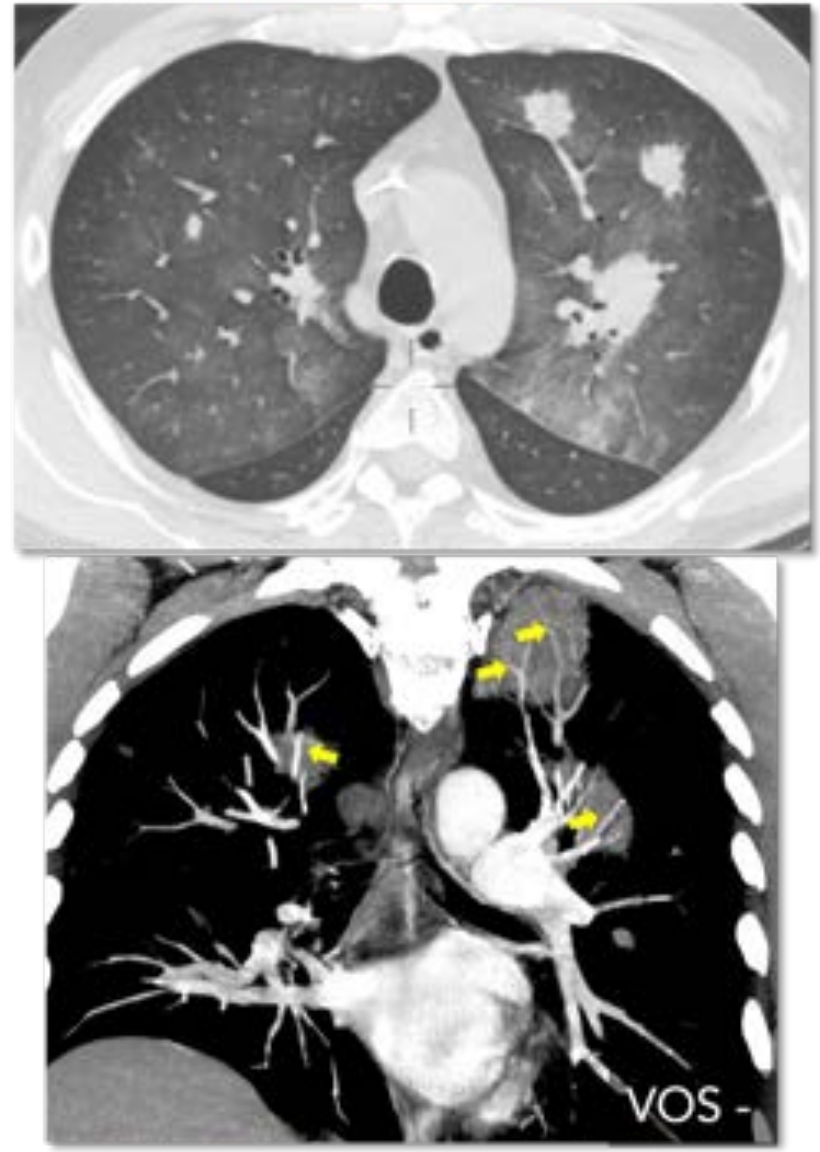
VOS- Vessel occlusion sign

Resistant CML; neutropenia;
posaconazole prophylaxis;
serum GM negative



BAL: Galactomannan 1.5

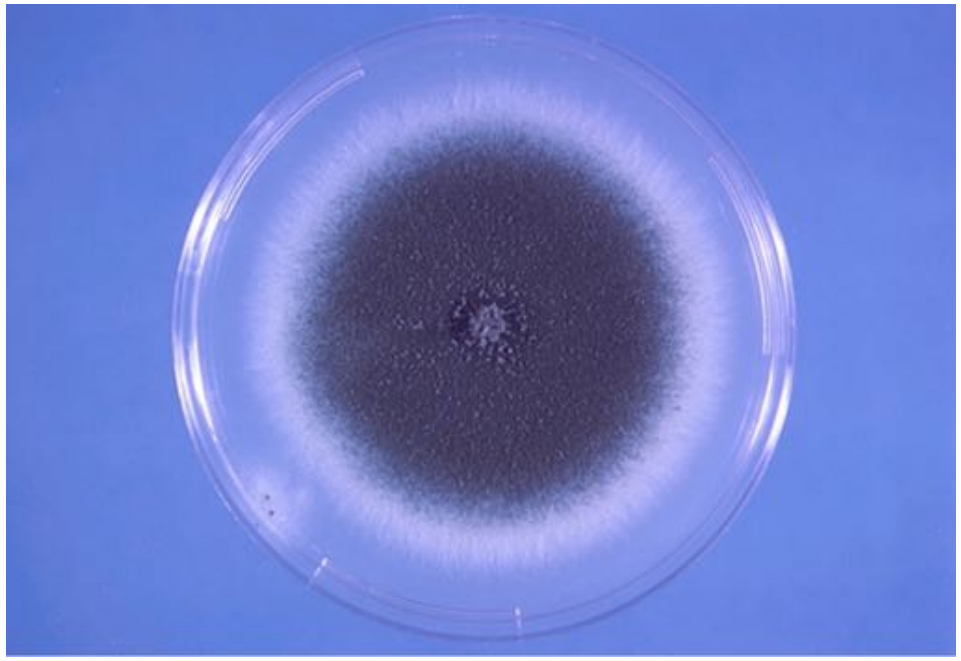
AML consolidation; neutropenia;
posaconazole prophylaxis;
serum GM negative

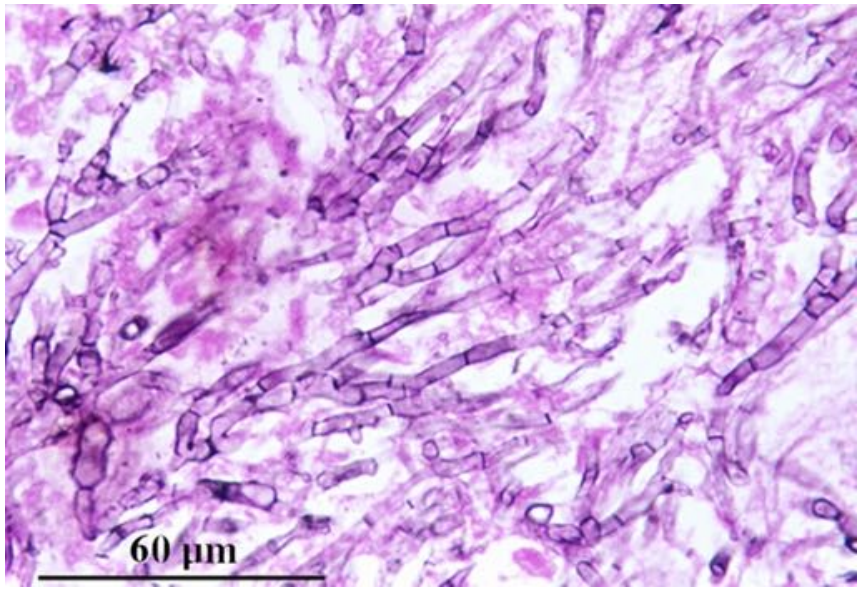


BAL: MDR *P. aeruginosa* +, GM-

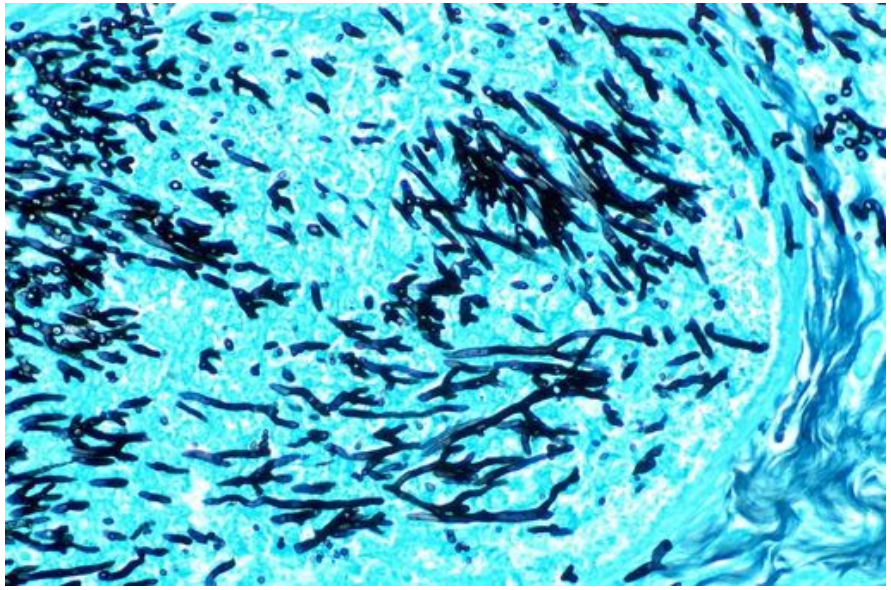
Diagnosis

Culture + Histopathology





PAS stain



GMS stain

Diagnosis
Non-culture based diagnostics

- **Serum galactomannan**
  - Galactomannan is a polysaccharide that is major constituent of cell wall
    - Cross-reactive with some species; e.g., *Fusarium spp.*
  - Reported as an optimal read-out- Index 0.5-0.7 “positive”
    - Average sensitivity 82%, specificity 81% in high-risk patients
    - Test performs better in neutropenic vs. non-neutropenic patients
    - Sensitivity is reduced by antifungal therapy
      - Testing in bronchial alveolar lavage fluid may improve sensitivity in patients on antifungals
    - False positives 6-10% esp. in patients with mucositis + some foods
    - Can be performed in CSF, abdominal fluid
- **PCR testing, β-D-glucan test**

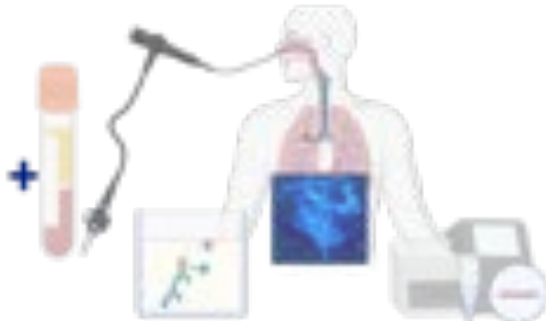
EORTC/MSG definitions of invasive fungal disease

"Direct" evidence of fungal tissue invasion

Proven disease

Host factors

Clinical factors



"Indirect" mycological evidence (e.g., galactomannan)

Probable disease

Host factors

Clinical factors

Possible disease

Invasive aspergillosis

Main risk factors

- **Severe and prolonged neutropenia (≥ 3 weeks)**
  - Especially in the setting of only fluconazole prophylaxis
- **Receipt of high-dose corticosteroids**
  - 0.5 mg/kg/day prednisone equivalent within 30 days
- **Other drugs or conditions that lead to chronically-suppressed immune responses**
- **Ibrutinib (Bruton-tyrosine kinase inhibitors used for CLL)**
- **Hematopoetic stem cell or solid organ transplant**
- **Airway colonisation in lung transplant patients (cystic fibrosis)**
- **COPD with glucocorticoid therapy, ICU admission**
- **Influenza, SARS-CoV2; especially in the setting of other risk factors**

Influenza and COVID-associated aspergillosis

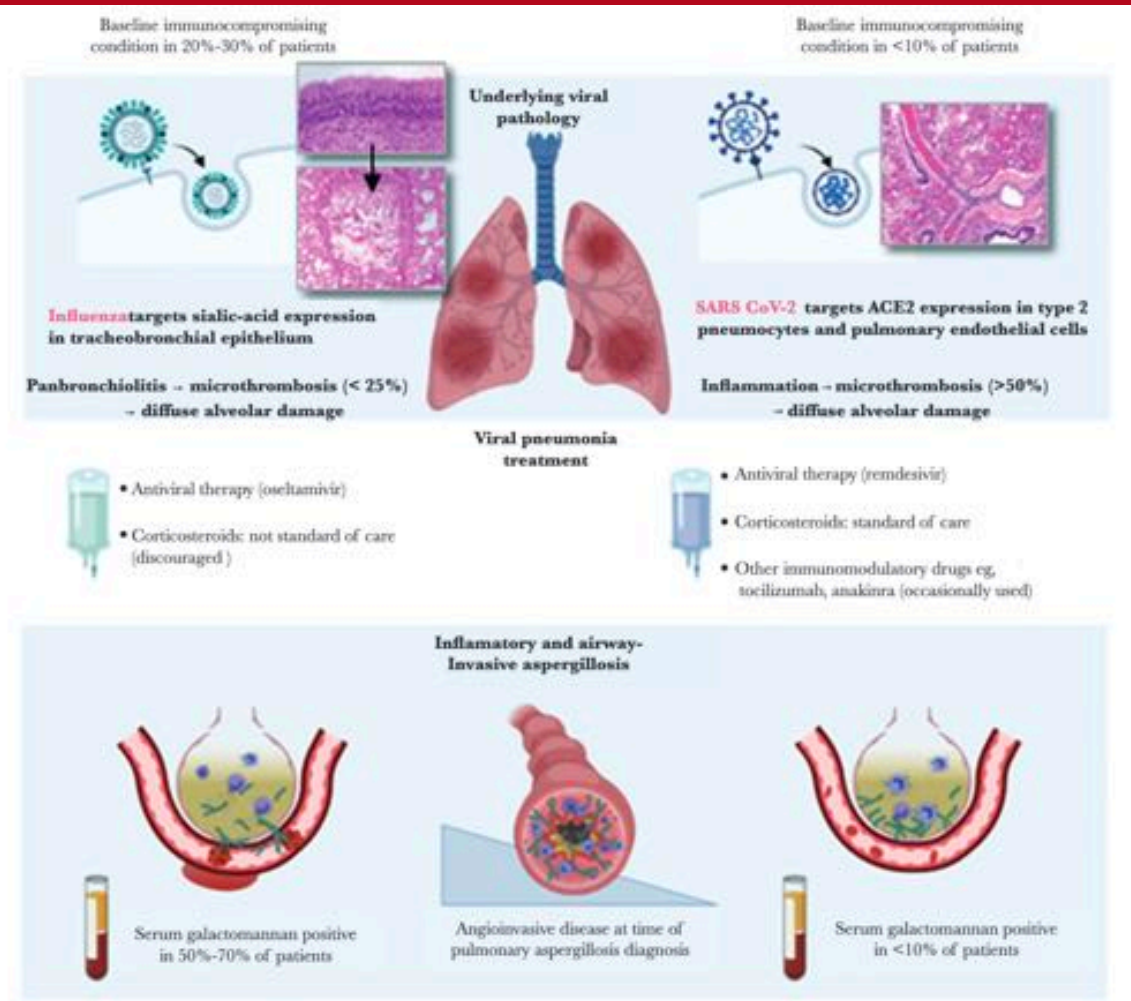


Figure 1. Comparative pathophysiological features of influenza-associated pulmonary aspergillosis (IAPA) and coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA).

Lamoth F et al. Navigating the uncertainties of COVID-19 associated aspergillosis (CAPA): A comparison with influenza associated aspergillosis (IAPA). J Infect Dis **2021**; 224:1631–1640.

Prognostic risk model for invasive aspergillosis in newly admitted hematology patients

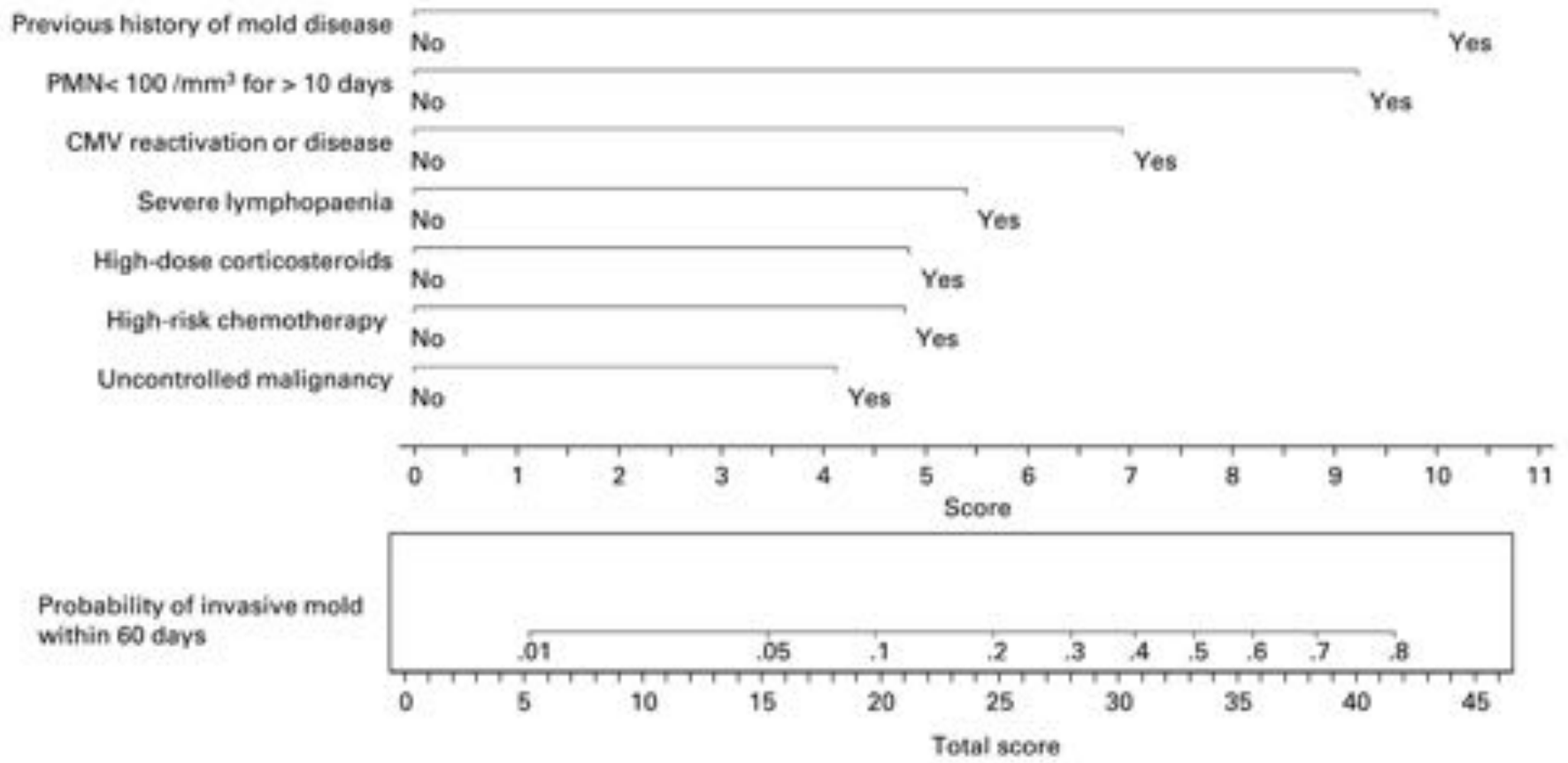
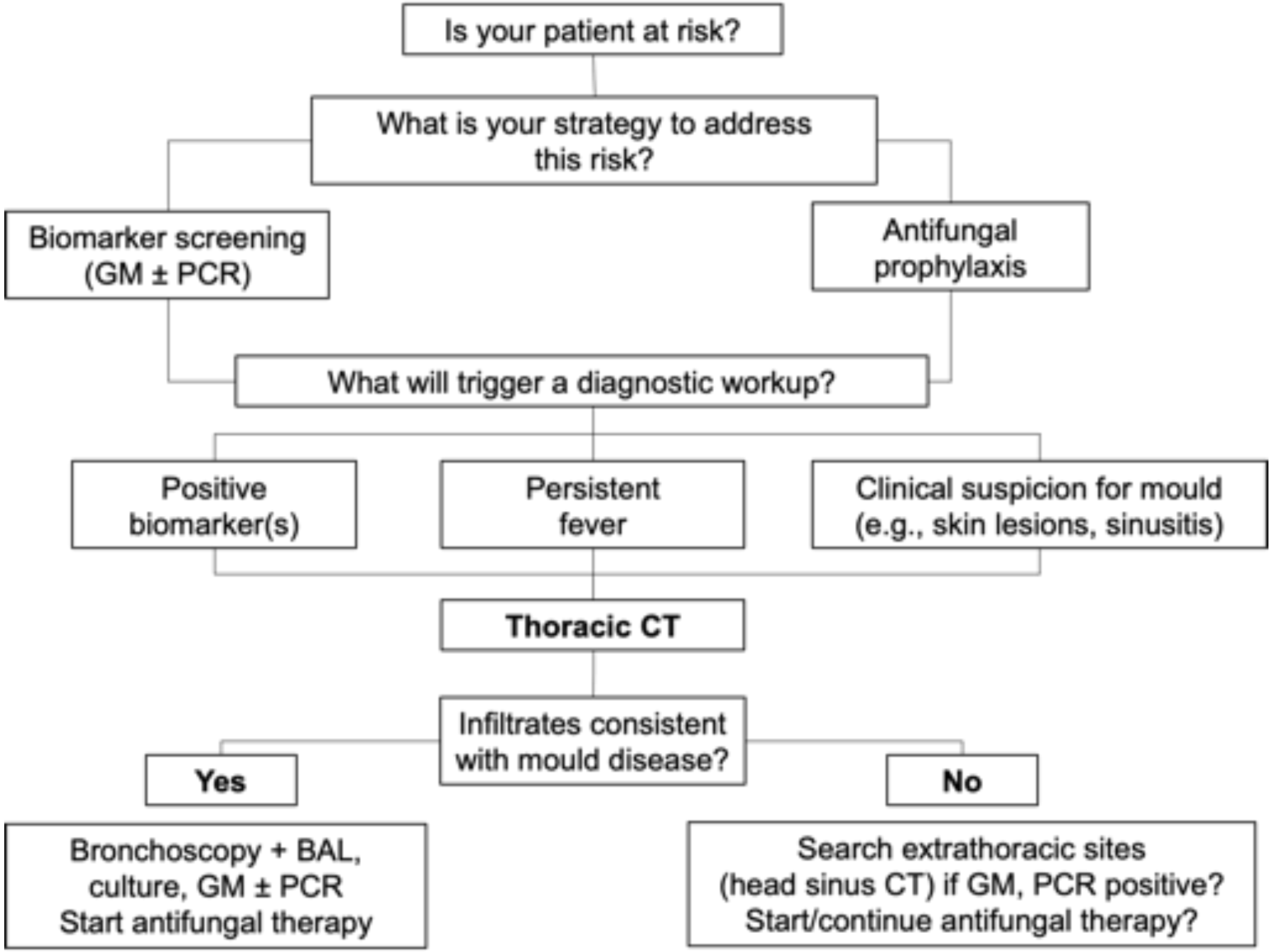
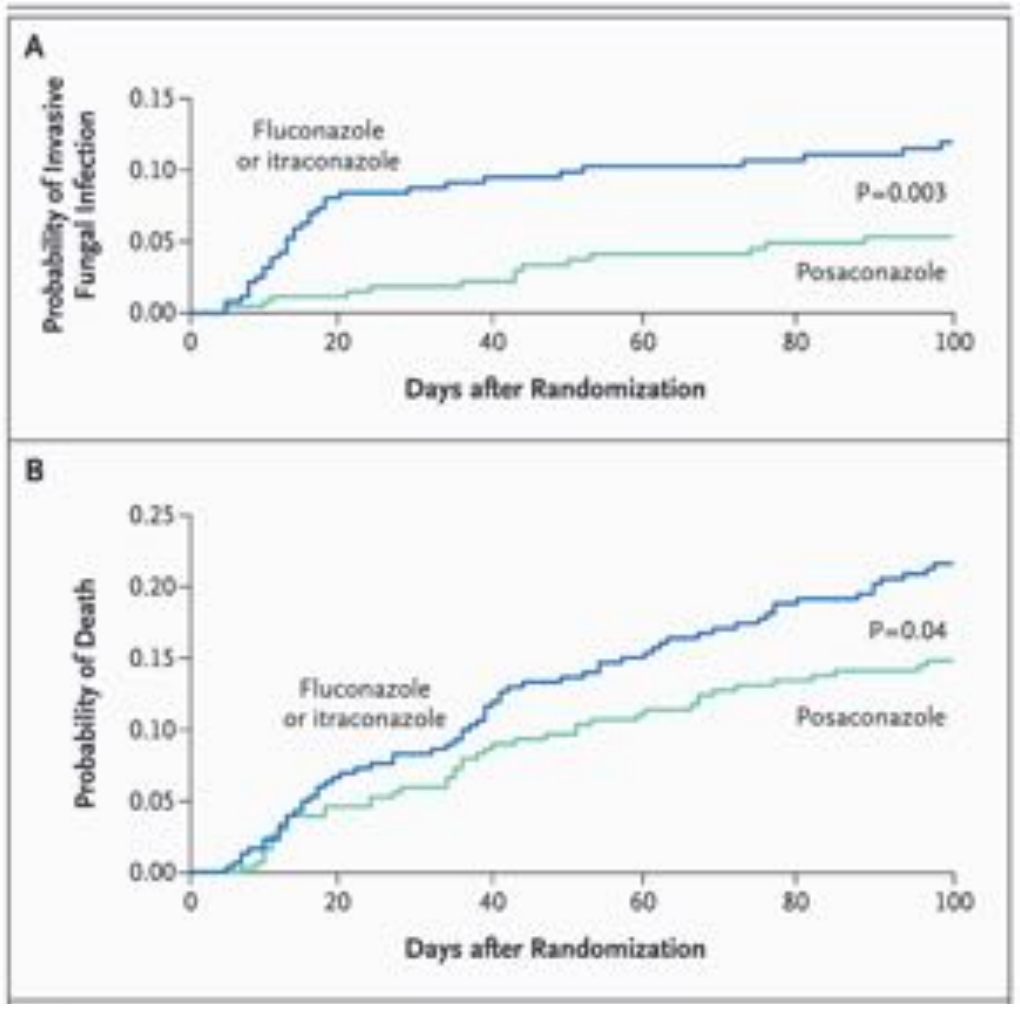


Fig. 3. Nomogram for estimating patient 60-day risk of invasive mould disease. Patients are screened for seven risk factors listed above. The user assigns a score to each risk factor (to the nearest 0.5 points) by drawing a line directly down from the end of the line (at "yes") for each risk factor to the scale labelled "score." The scores for risk factors present are then summed to calculate a total score, which is used to estimate 60-day estimated probability of invasive mould disease from the scale inside the lower box. See text for sample patient calculation.

Stanzani M, Vianelli N, Cavo M, Kontoyiannis DP, Lewis RE. Development and internal validation of a model for predicting 60-day risk of invasive mould disease in patients with haematological malignancies. J Infect **2019**; 78:484–490. Available at: http://dx.doi.org/10.1016/j.jinf.2019.04.002.


Is your patient at risk?
What is your strategy to address this risk?
Biomarker screening (GM ± PCR)
Antifungal prophylaxis
What will trigger a diagnostic workup?
Positive biomarker(s)
Persistent fever
Clinical suspicion for mould (e.g., skin lesions, sinusitis)
Thoracic CT
Infiltrates consistent with mould disease?
Yes
No
Bronchoscopy + BAL, culture, GM ± PCR Start antifungal therapy
Search extrathoracic sites (head sinus CT) if GM, PCR positive? Start/continue antifungal therapy?

Posaconazole prophylaxis



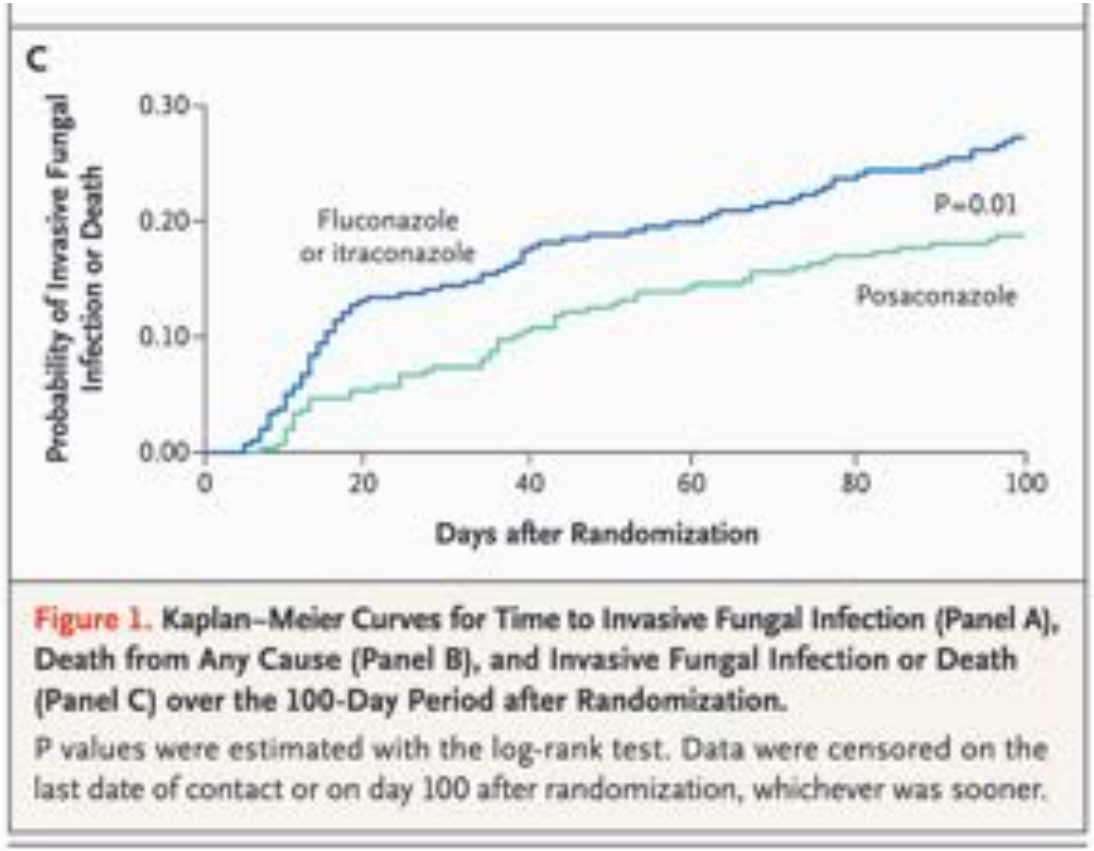


Figure 1. Kaplan–Meier Curves for Time to Invasive Fungal Infection (Panel A), Death from Any Cause (Panel B), and Invasive Fungal Infection or Death (Panel C) over the 100-Day Period after Randomization.

P values were estimated with the log-rank test. Data were censored on the last date of contact or on day 100 after randomization, whichever was sooner.

Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia. N Engl J Med 2007; 356:348–359.

Table 3. Current Medication Options for the Treatment of Aspergillosis.*

Antifungal Agent	Advantages	Disadvantages	Comments
Voriconazole	Superior to amphotericin B deoxycholate†; treatment with voriconazole is based on decades of data and experience with multiple clinical forms of invasive aspergillosis	Need for therapeutic drug monitoring; trough drug levels should be monitored within the first 7 days after initiation of therapy, with a goal of 1 to less than 5.5 μg/ml Multiple drug–drug interactions Risk of periostitis or cutaneous cancer with long-term use Hepatotoxicity, transient visual disturbance or visual hallucinations, rash, alopecia and nail changes, QTc prolongation	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Isavuconazole	Noninferior to voriconazole in a randomized, prospective trial, with fewer side effects; no clear indication for therapeutic drug monitoring; no QTc prolongation	Common adverse effects are nausea, vomiting, and diarrhea Multiple drug–drug interactions Hepatotoxicity QTc shortening of unclear clinical relevance Infusion reactions with IV administration	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Posaconazole	Noninferior to voriconazole in a randomized, prospective trial, with fewer side effects	Need for therapeutic drug monitoring Multiple drug–drug interactions Hepatotoxicity, potential for QTc prolongation Possibility of hypertension during treatment	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Itraconazole	Associated with good clinical responses in patients with ABPA when itraconazole was the only oral azole available; it decreased the fungal burden and reduced the need for glucocorticoid courses	A strong inhibitor and substrate of CYP3A; drug–drug interactions occur	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Lipid amphotericin B formulations (liposomal amphotericin B, amphotericin B lipid complex)	Release of amphotericin from synthetic phospholipids at the site of infection, based on affinity for fungal ergosterol rather than exposure of kidney tissues to amphotericin, which occurs with IV administration of nonlipid amphotericin B deoxycholate	With dose escalation of liposomal amphotericin B, a dose that exceeds 5 mg/kg/day results in increased toxic effects	Dose-related reactions: nephrotoxicity and electrolyte disturbances Infusion-related reactions: fever, rigors, and nausea Both dose-related and infusion-related reactions are much less frequent with lipid formulations than with amphotericin B deoxycholate
Amphotericin B deoxycholate	IV administration is limited to situations in which lipid formulations of amphotericin B or mold-active azole antifungals are unavailable; inhaled or nebulized antifungal therapy may be an option in patients with neutropenia and lung-transplant recipients; agent of choice for intrathecal or irrigant use	Clinical outcomes severely limited by toxic effects that preclude robust IV dose escalation	Dose-related reactions: nephrotoxicity and electrolyte disturbances Infusion-related reactions: fever, rigors, and nausea Both dose-related and infusion-related reactions are much less frequent with lipid formulations than with amphotericin B deoxycholate
Echinocandin (anidulafungin, caspofungin, micafungin)	Daily IV infusion has an acceptable side-effect profile	Sporadic cases of aminotransferase elevations Sporadic cases of infusion or hypersensitivity reactions	Should not be used as initial monotherapy

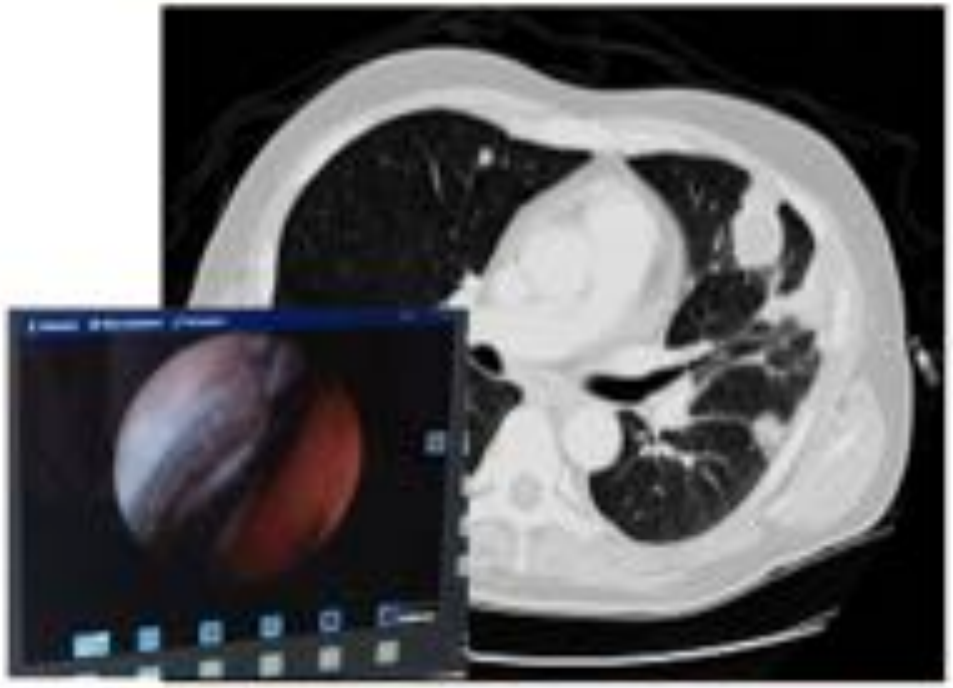
* ABPA denotes allergic bronchopulmonary aspergillosis, CYP cytochrome P-450, IV intravenous, and QTc corrected QT interval.
† In a 2002 randomized trial, primarily involving patients treated with allogeneic HCT and those with hematologic diseases,[44] successful outcomes at 12 wk were more common in the voriconazole group than in the amphotericin B group (53% vs. 32%), with a survival benefit in the voriconazole group (71% vs. 58%); voriconazole-treated patients also had fewer severe drug-related adverse events.

Thompson GR 3rd, Young J-AH. Aspergillus Infections. N Engl J Med 2021; 385:1496–1509.

Prognosis

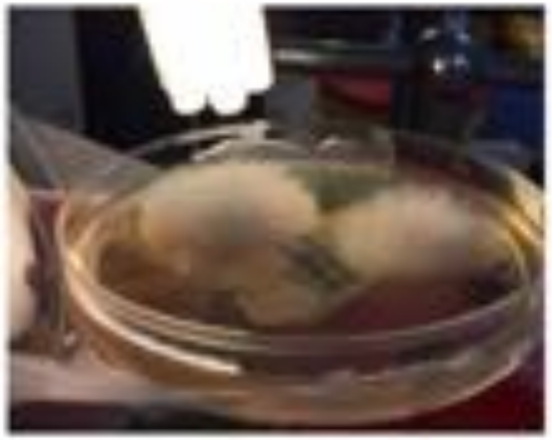
- **Key factors:**
  - Early diagnosis, prompt effective antifungal therapy
  - Recovery of underlying immune suppression (e.g., neutropenia)
  - Status of underlying condition/disease

Breakthrough fungal infections



Stanzani M et al. Mycoses 2019; 62:1100–1107.

Resistant
Aspergillus?



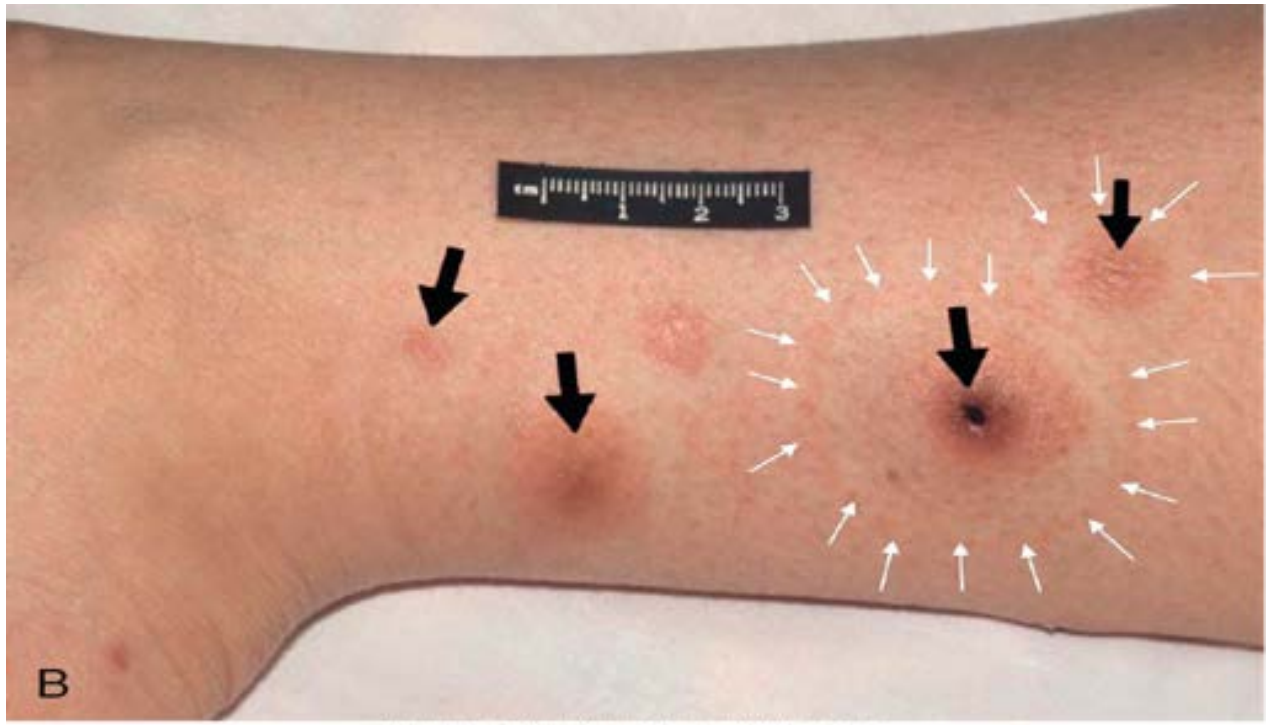
Mucorales

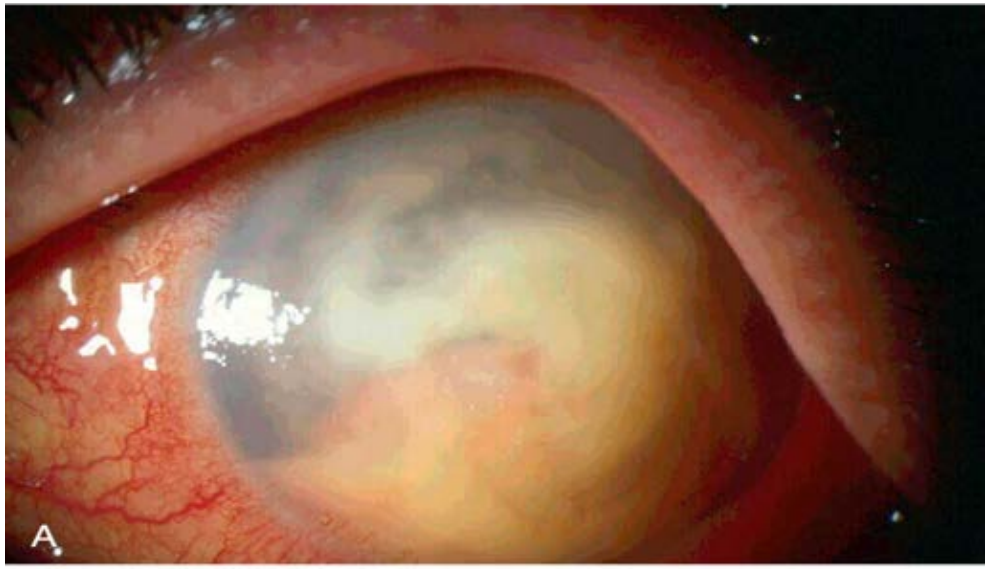
Fusarium spp.

Scedosporium spp.

Rare yeast
(e.g., *Saprochaete clavata*)

Metastatic skin lesions in fusariosis

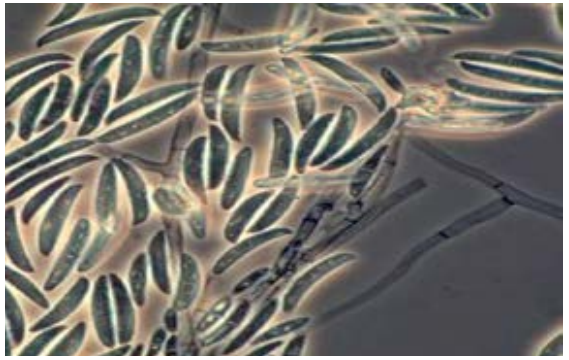




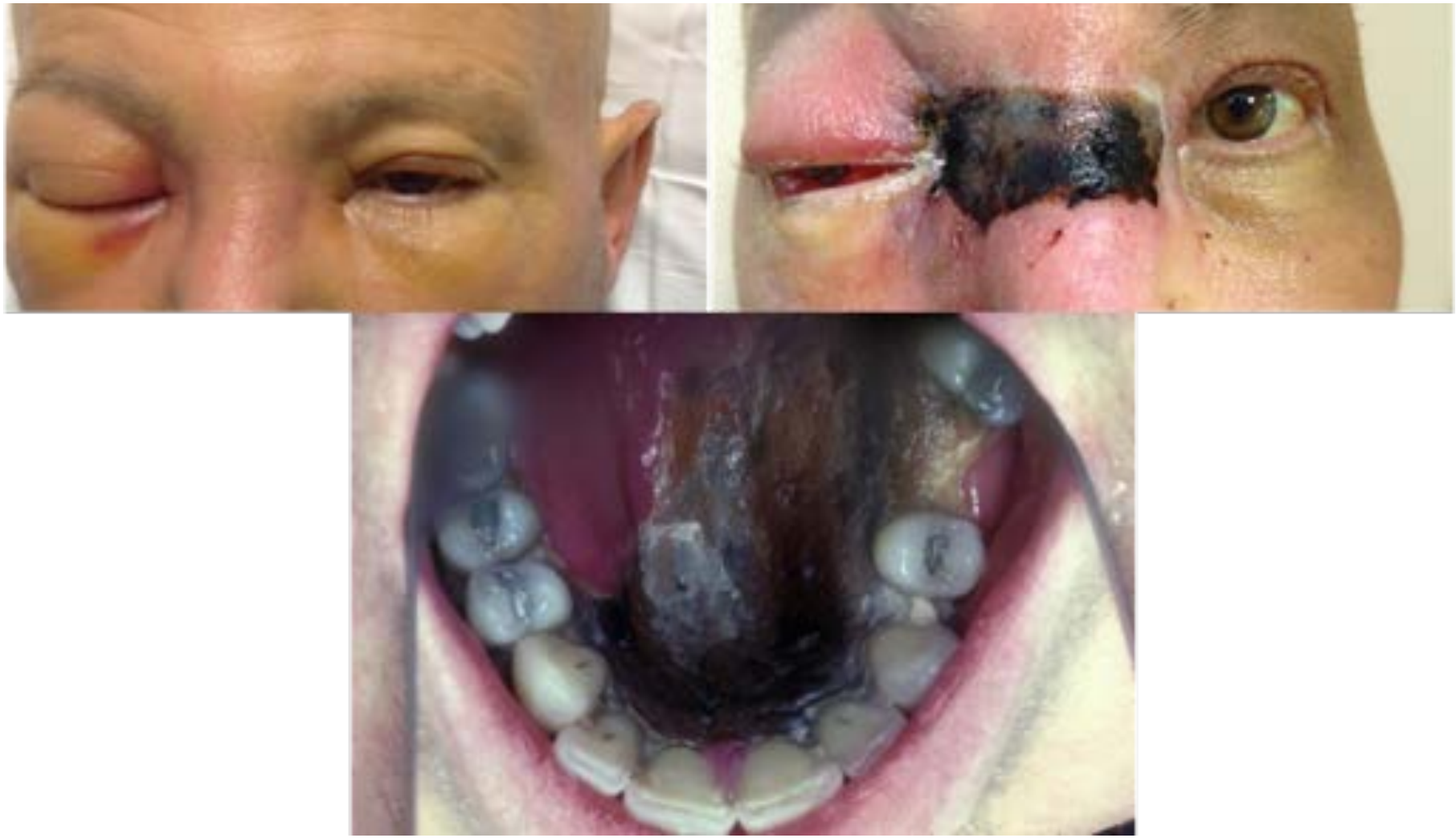
Fusarium fungal keratitis

Fusarium spp.

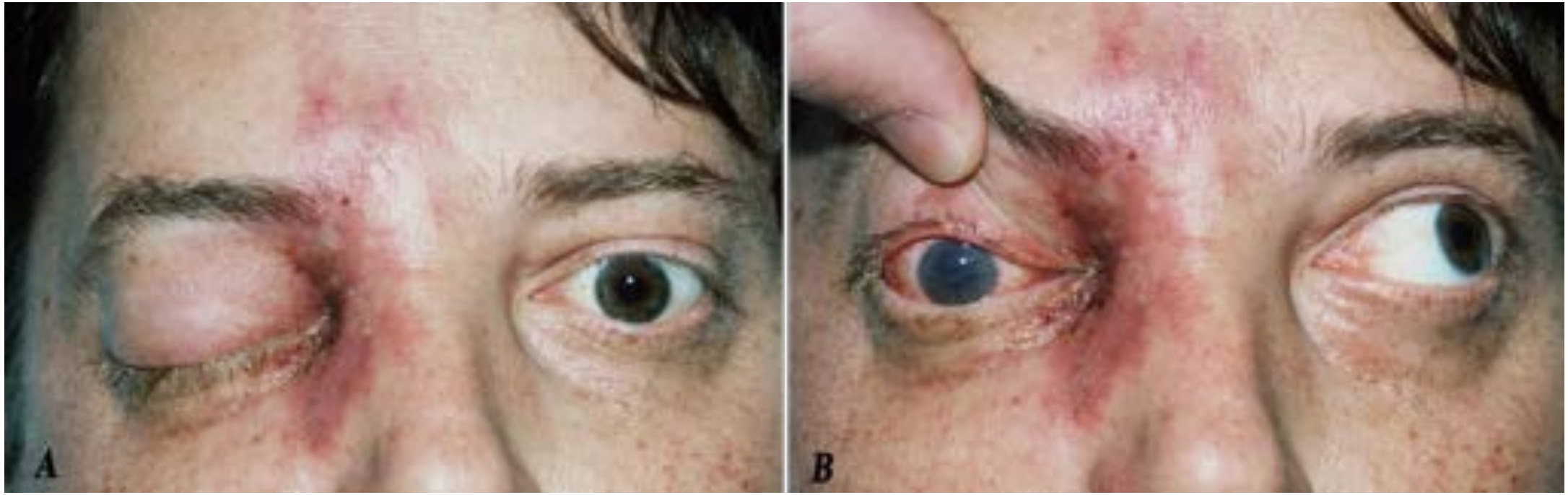
- Most common scenario: Persistent neutropenia
- Most common species: *F. solani* complex (50%), *F. oxysporum* (14%), *F. verticillioides* (10-11%)
- Macroconidia are classic (banana-shaped)
- PCR, rRNA in situ hybridization available, still investigational
- Positive blood cultures in 30-50% of cases
- Can be recovered from urine in disseminated infection
- Combination L-AMB+ VRC drugs of choice



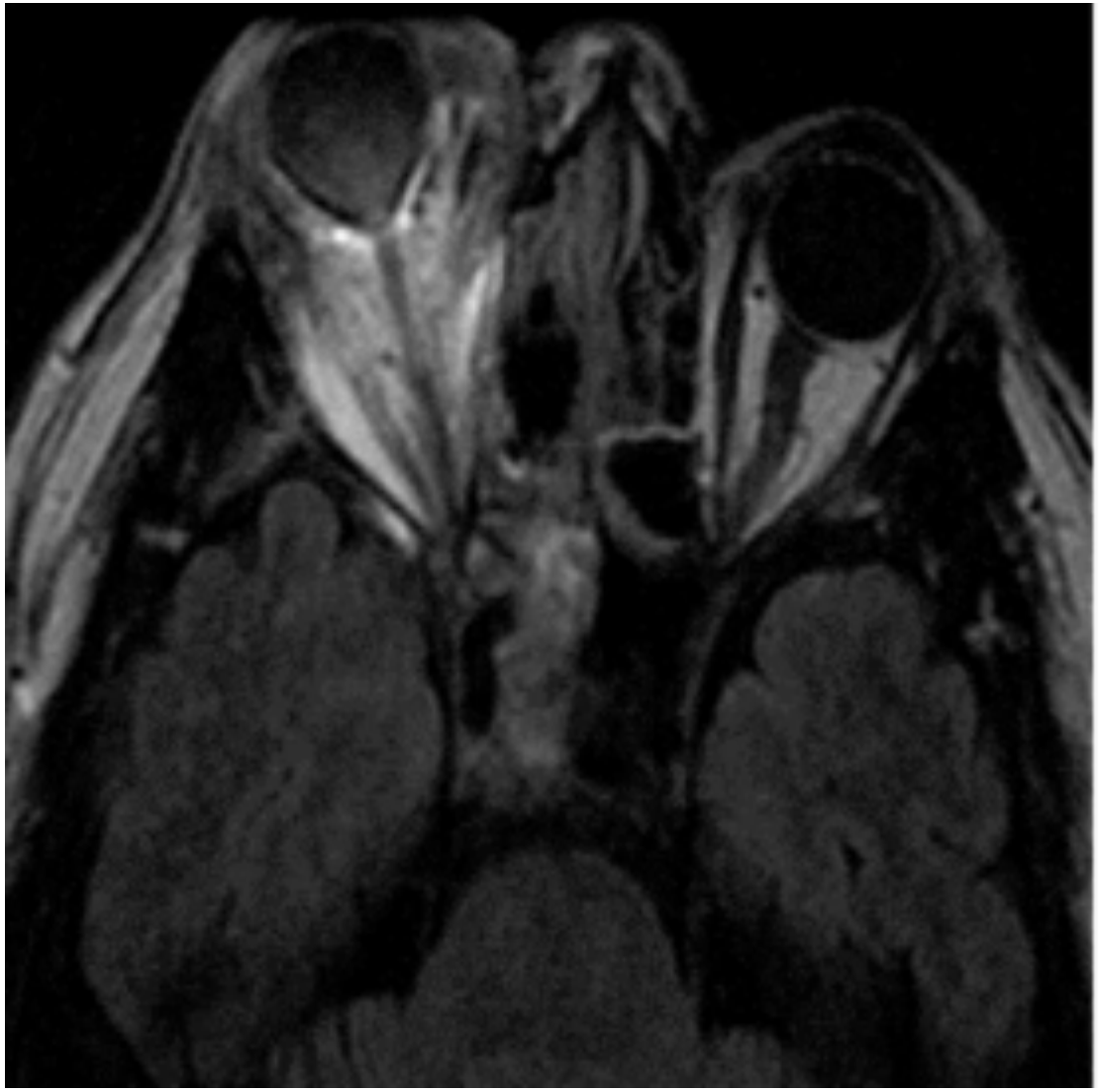
Rapid progression with necrosis of the nasal bridge in a neutropenic patient in less than 24 hours

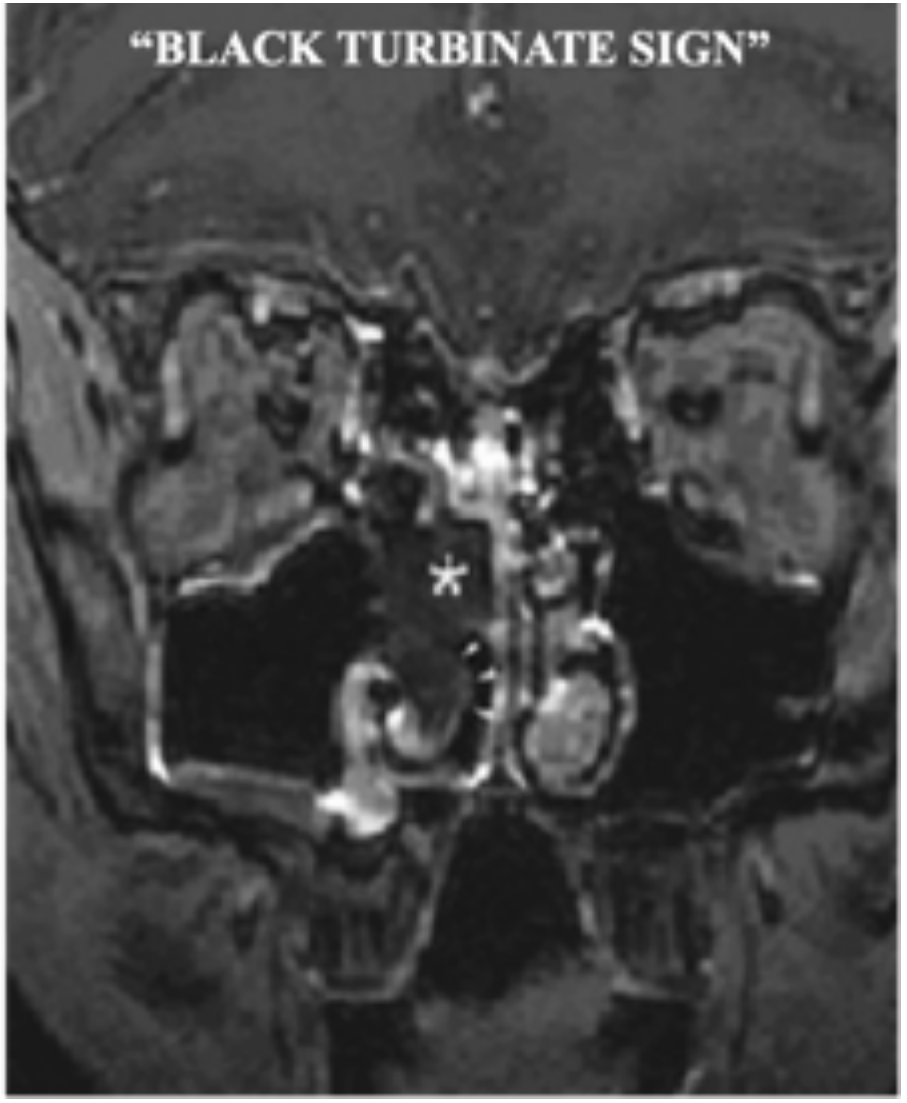


Cavernous Sinus Invasion via the Sphenoid Sinus

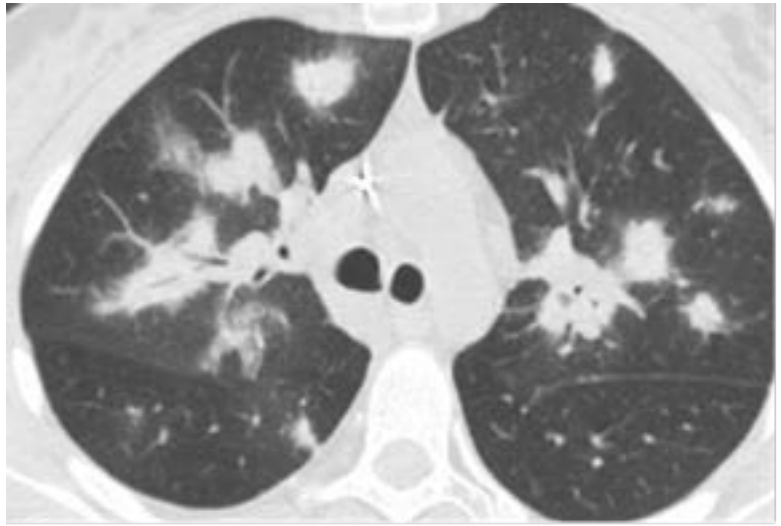


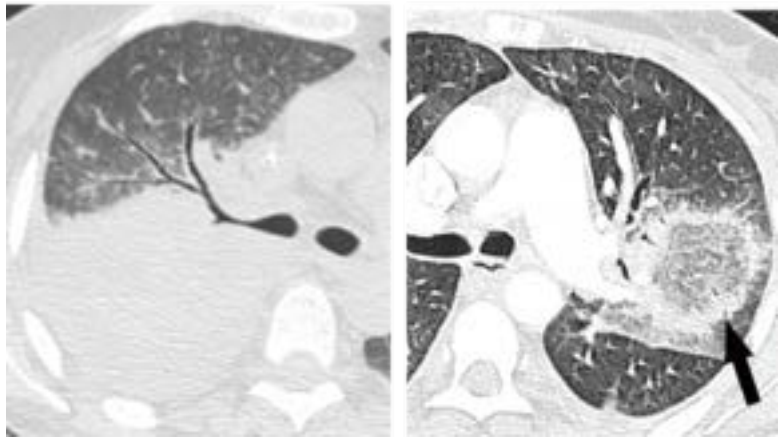
MRI





Pan sinusitis with multiple bilateral nodular infiltrated in lung

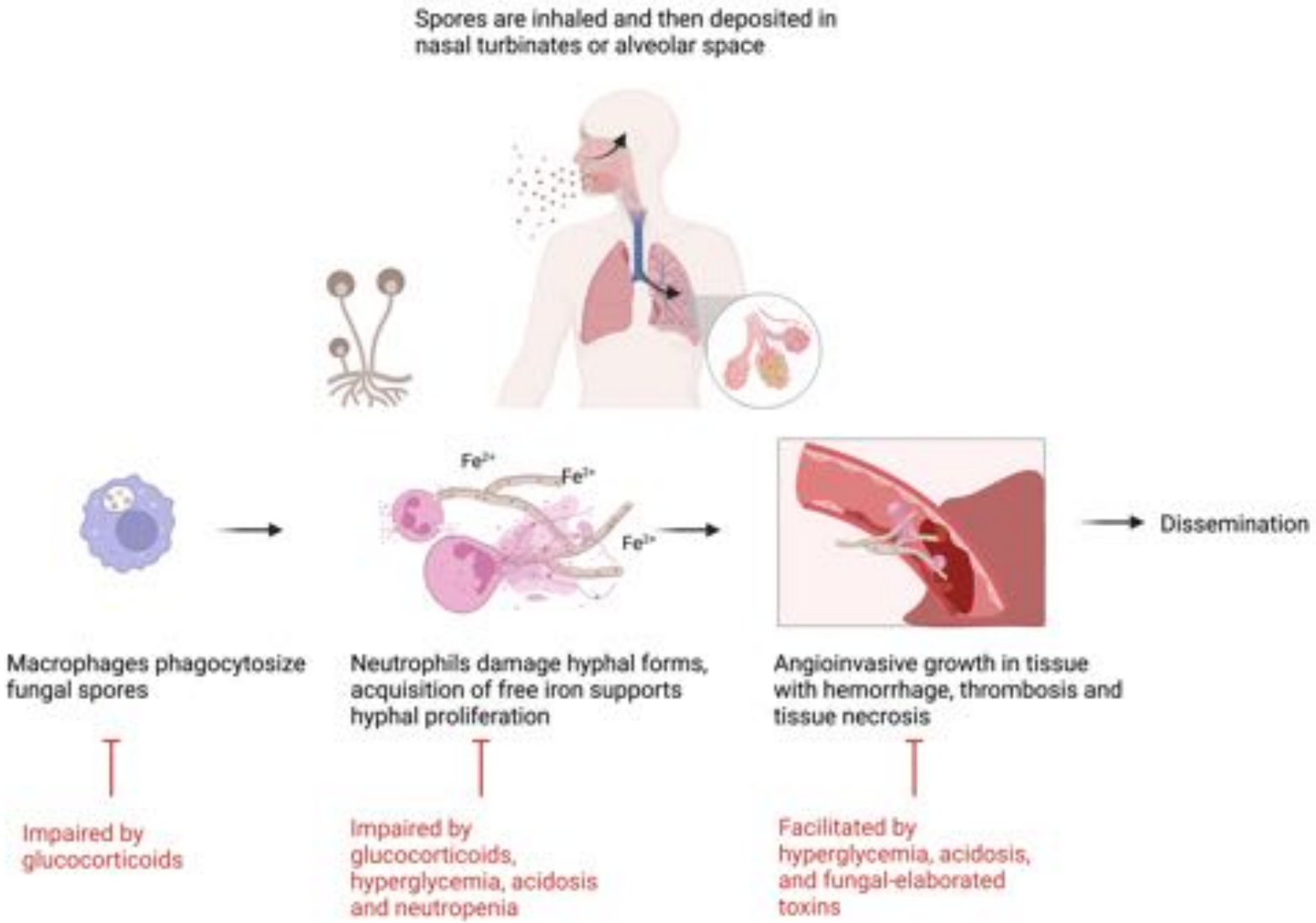




large pleural effusions

reverse halo sign

Pathogenesis of invasive mucormycosis



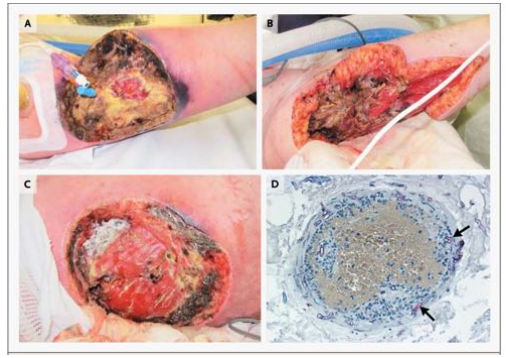
Combat and trauma-related mucormycosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Necrotizing Cutaneous Mucormycosis after a Tornado in Joplin, Missouri, in 2011

Robyn Neblett Fanfair, M.D., M.P.H., Kaitlin Benedict, M.P.H., John Bos, M.P.H., Sarah D. Bennett, M.D., M.P.H., Yi-Chun Lo, M.D., Tolu Adebanjo, M.D., M.P.H., Kizee Etienne, M.P.H., Eszter Deak, Ph.D., M.P.H., Gordana Derado, Ph.D., Wun-Ju Shieh, M.D., Ph.D., M.P.H., Clifton Drew, D.V.M., Ph.D., Sherif Zaki, M.D., Ph.D., David Sugerman, M.D., M.P.H., Lalitha Gade, M.Pharm., Elizabeth H. Thompson, B.S., Deanna A. Sutton, Ph.D., David M. Engelthaler, M.S., James M. Schupp, M.B.A., Mary E. Brandt, Ph.D., Julie R. Harris, Ph.D., M.P.H., Shawn R. Lockhart, Ph.D., George Turabelidze, M.D., and Benjamin J. Park, M.D.



Invasive Mold Infections Following Combat-related Injuries

Tyler Warkentien,[1] Carlos Rodriguez,[1] Bradley Lloyd,[2] Justin Wells,[1] Amy Weintrob,[1,3] James R. Dunne,[1] Anuradha Ganesan,[1,3] Ping Li,[3] William Bradley,[3] Lakisha J. Gaskins,[3] Françoise Seillier-Moiseiwitsch,[3] Clinton K. Murray,[4] Eugene V. Millar,[3] Bryan Keenan,[1] Kristopher Paolino,[1] Mark Fleming,[1] Duane R. Hospenthal,[4] Glenn W. Wortmann,[1] Michael L. Landrum,[3,4] Mark G. Kortepeter,[3] and David R. Tribble[3]; for the Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study Group

[1]Walter Reed National Military Medical Center, Bethesda, Maryland; [2]Landstuhl Regional Medical Center, Germany; [3]Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, and [4]San Antonio Military Medical Center, Texas

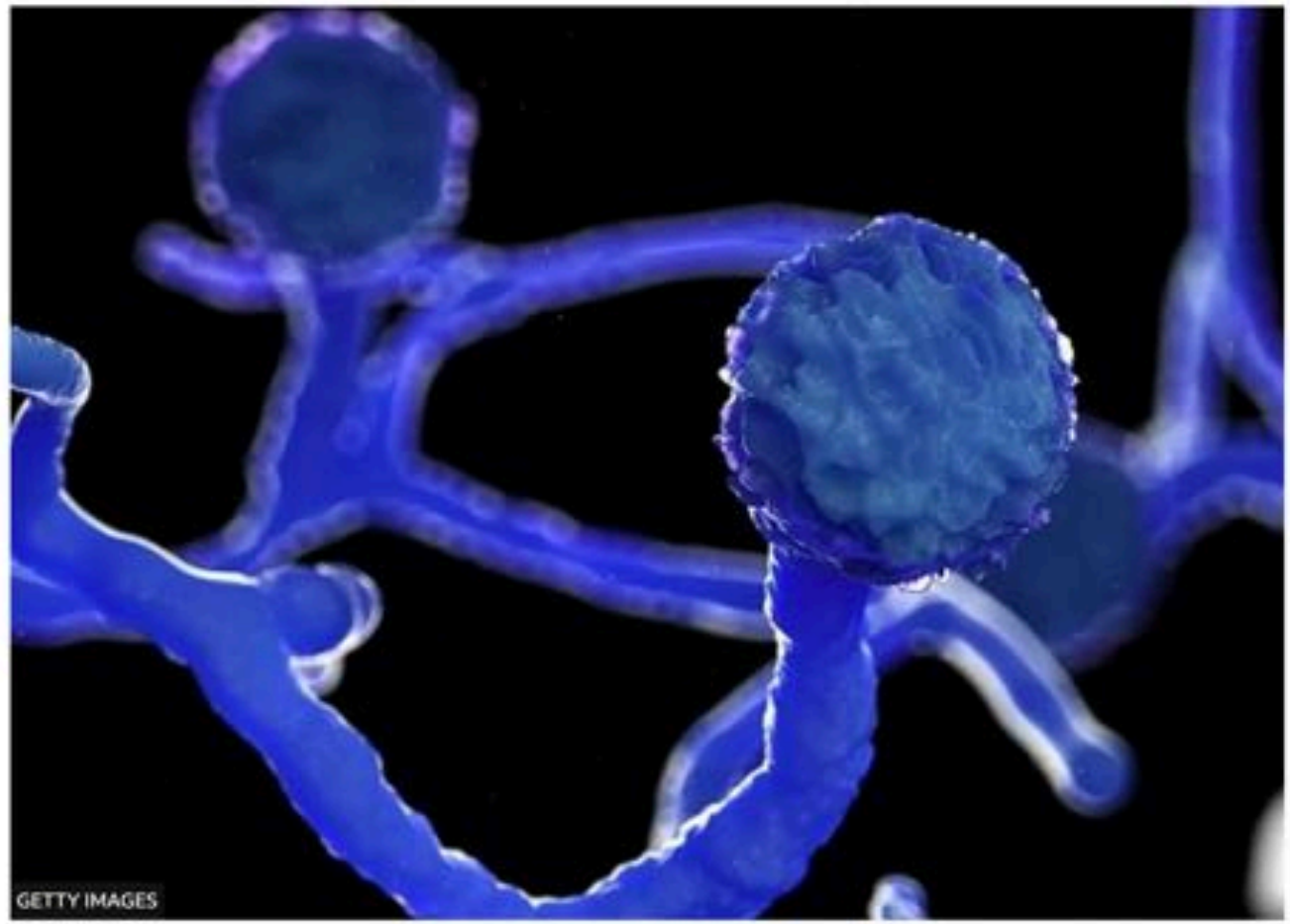
Background. Major advances in combat casualty care have led to increased survival of patients with complex

Car accidents, trauma, burns…

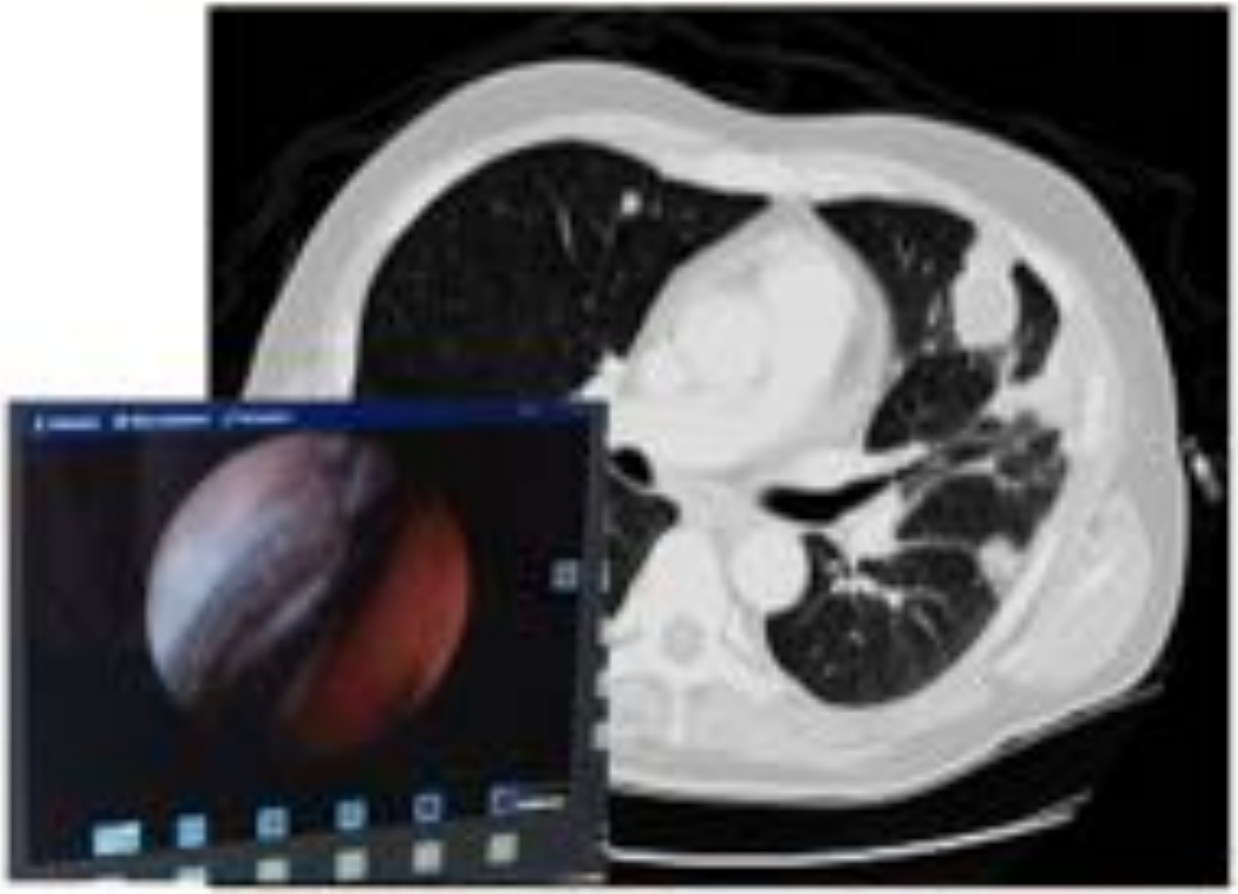
Mucormycosis: The 'black fungus' maiming Covid patients in India

9 May 2021

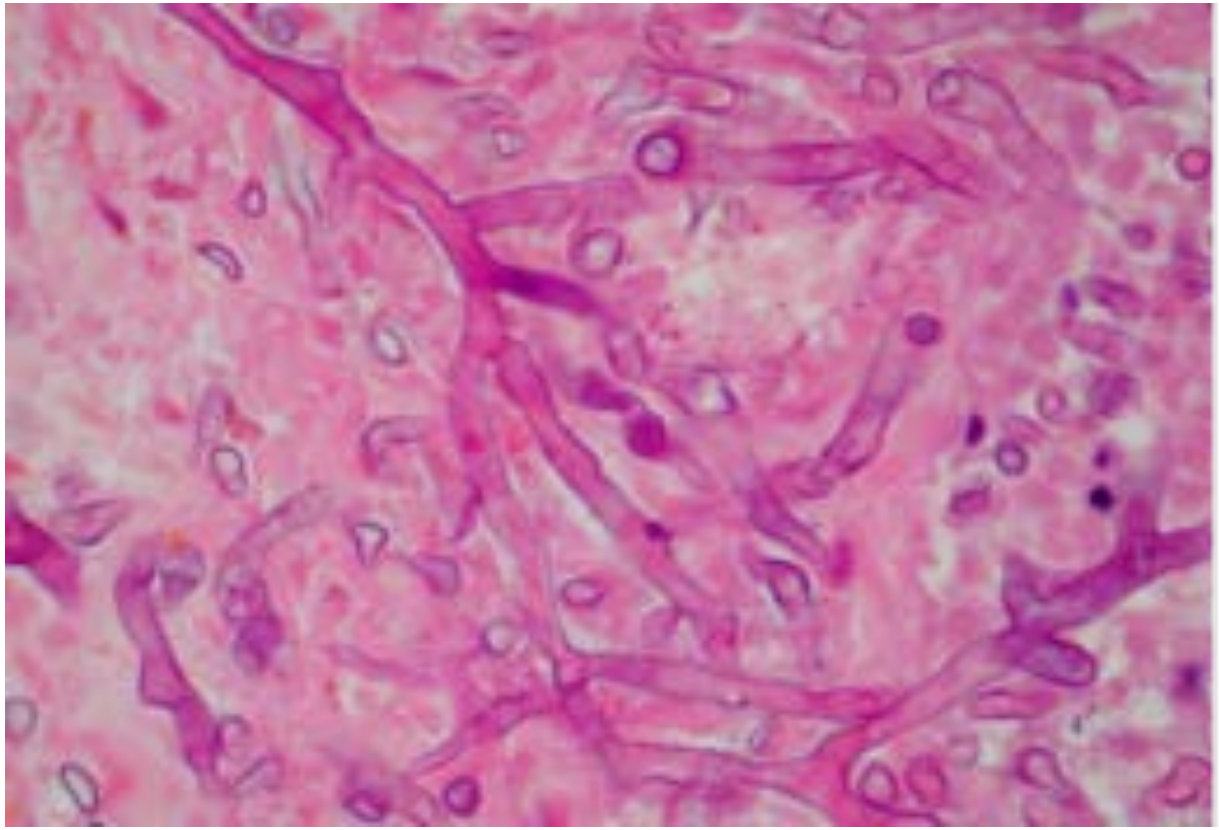
India coronavirus lockdown

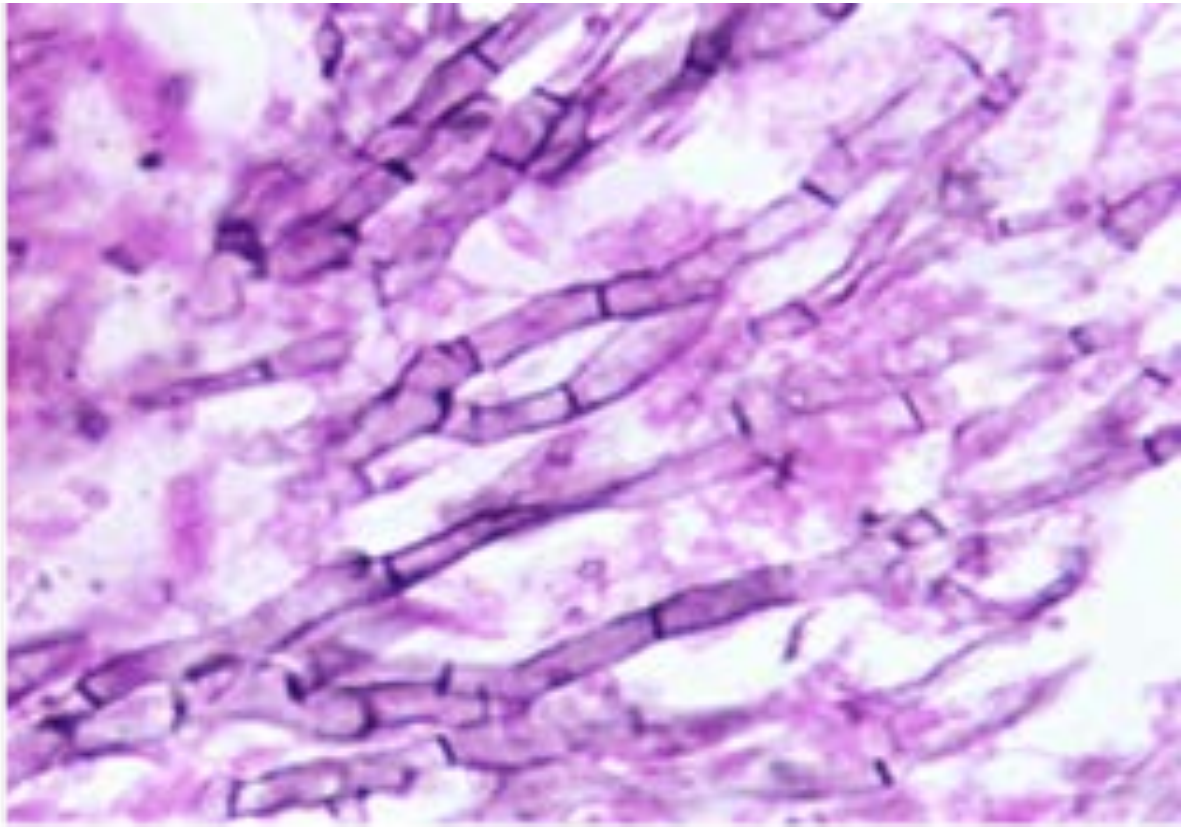


Mucor mould is found in soil, plants, manure and decaying fruits



Diagnosis of mucormycosis

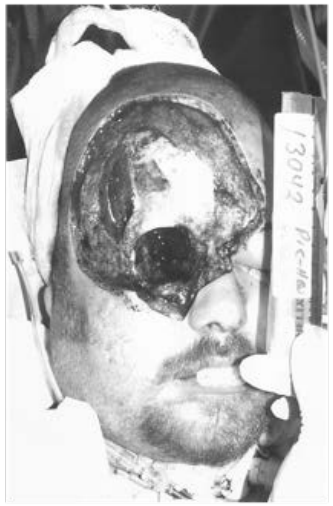


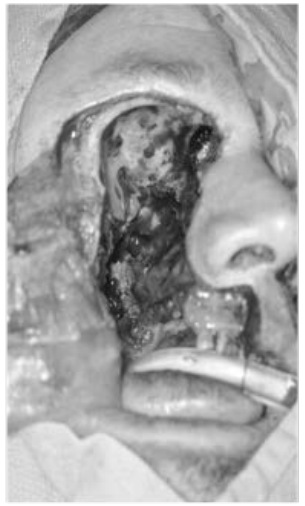


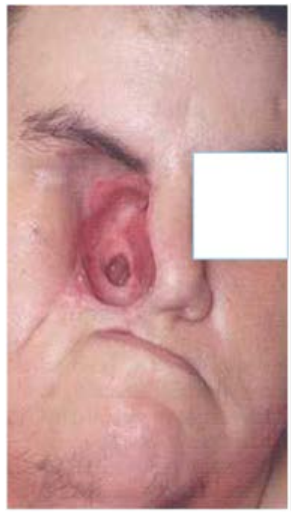
- Identification of organisms in tissue by histopathology with culture confirmation
- Serum β-D glucan and galactomannan **DO NOT** detect Mucorales
- PCR-based techniques with sequencing and MALDI-TOF used in some larger centers

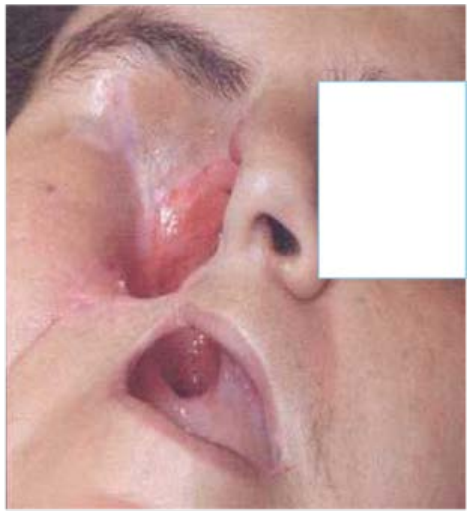
Treatment of mucormycosis

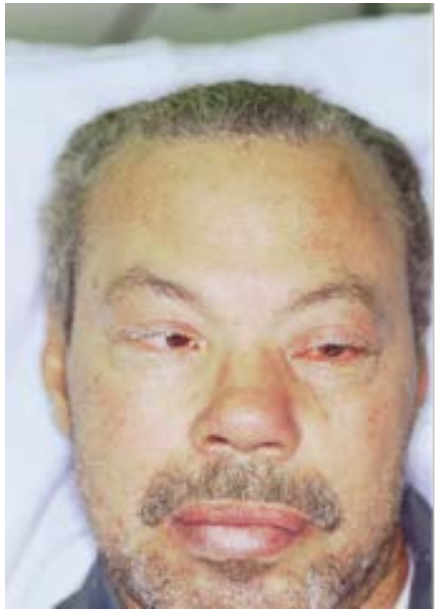
- **Surgical debridement and antifungal therapy**
- **Reversal of underlying predisposing conditions, if possible**
  - **I.e. acidosis, glucose control**
- **Initial treatment:**
  - Liposomal AMB 5-10 mg/kg/day
- **Step-down therapy:**
  - Posaconazole or isavuconazole
- **Patient who do not respond to L-AMB or develop toxicity**
  - Posaconazole or isavuconazole

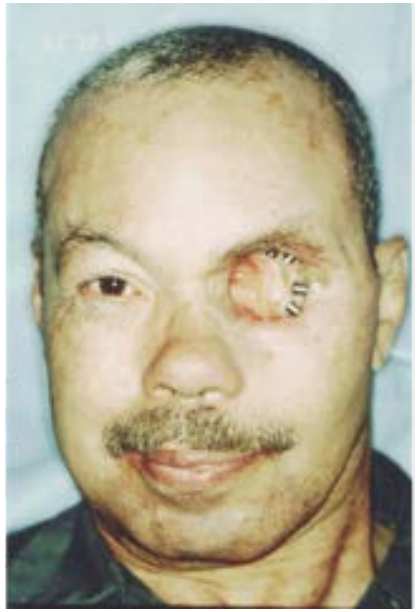


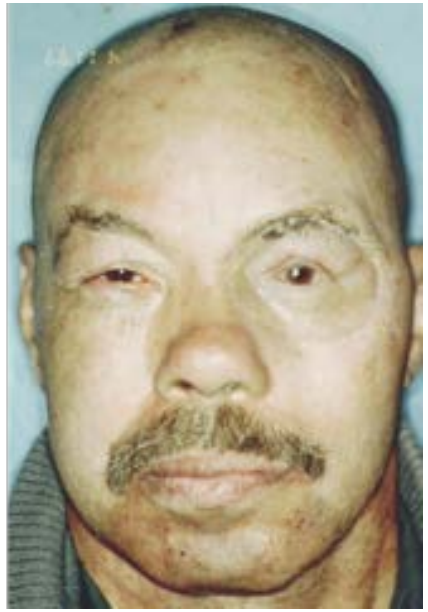


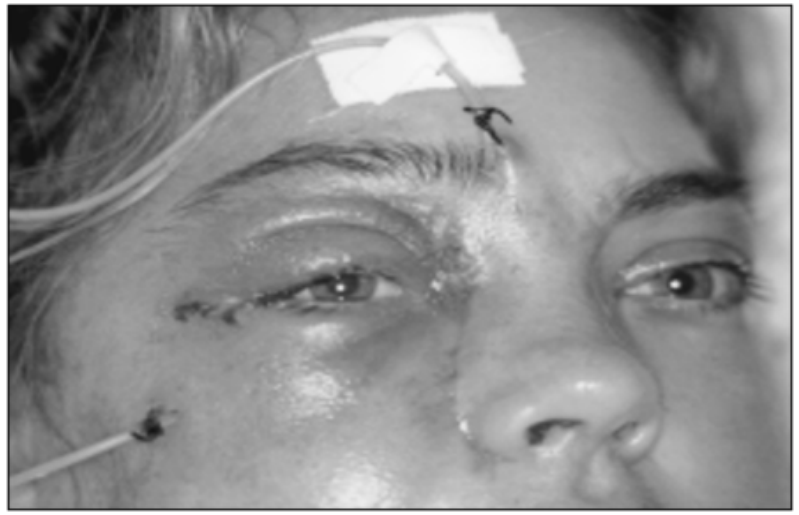












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@ABsteward

I'm curious : as a person specialized or interested in Infectious Diseases or as a health care professional, which one scares you the most? #IDtwitter #medtwitter #TwitteRx
Others 🙏 comment

Candida auris	18%
Staph aureus	24%
Coronavirus /SARS-COV-2	14%
Mucor spp/Mucormycosis ✓	**44%**

1,885 votes · Final results

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