Invasive Fungal Infections

Learning Objectives

Upon completion of this chapter, learners will be able to:

1. Describe the epidemiology and risk factors for invasive candidiasis, cryptococcosis, aspergillosis, and mucormycosis
2. Identify key clinical presentations and diagnostic approaches for each major invasive fungal infection
3. Select appropriate antifungal therapy based on patient factors, fungal species, and infection site
4. Recognize antifungal drug toxicities and their management
5. Apply evidence-based treatment guidelines to clinical scenarios

Introduction to Invasive Fungal Infections

The Global Burden of Fungal Disease

Invasive fungal infections (IFIs) represent a significant and growing threat to global health. While often overlooked compared to bacterial and viral pathogens, fungi cause substantial morbidity and mortality, particularly among immunocompromised populations (Brown et al., 2012).

! Key Statistics

- Over 1 million deaths annually from invasive fungal infections worldwide
- Fungal infections kill more people than malaria and are equivalent to tuberculosis deaths
- The burden is likely underestimated due to diagnostic challenges

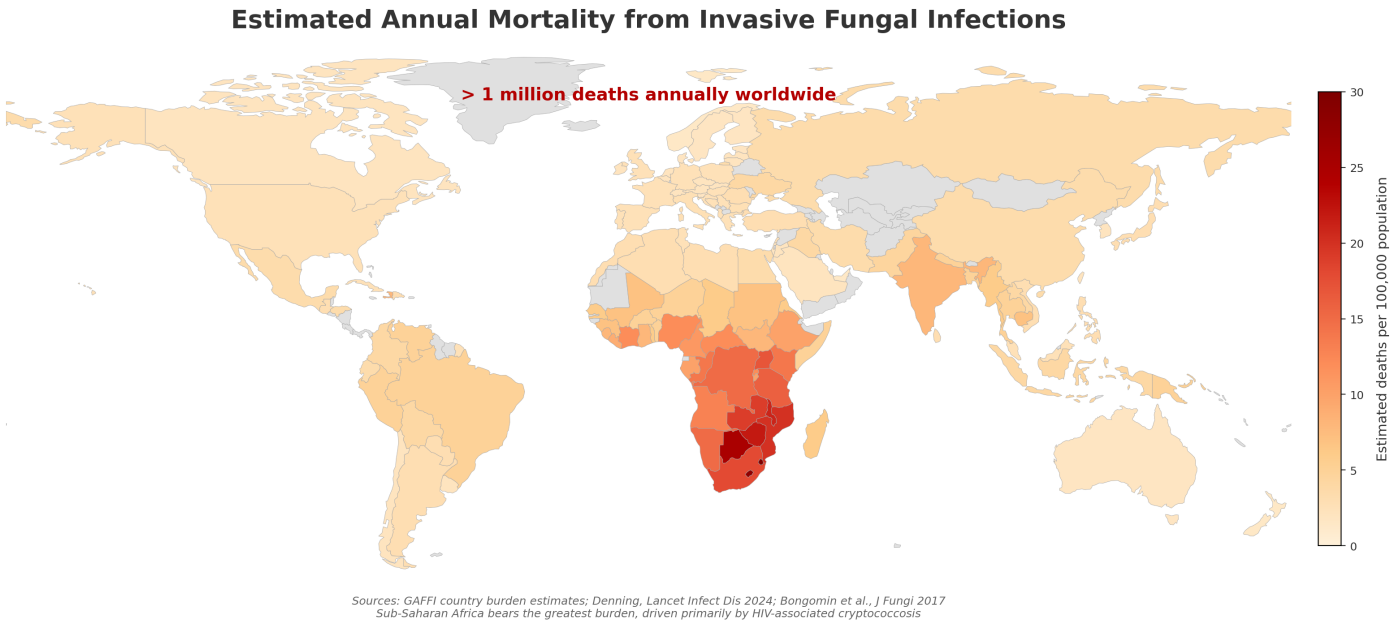


Figure 1: Global distribution of invasive fungal disease mortality. Deaths from major fungal pathogens are dramatically underreported, particularly in resource-limited settings where diagnostic capacity is limited.

Spectrum of Fungal Diseases

Fungal infections can be categorized by their anatomical involvement and host immune status:

Table 1: Classification of Mycoses

Type	Location	Examples	Primary Hosts
Superficial mycoses	Epidermis, hair, nails	Dermatophytosis, pityriasis	Immunocompetent
Subcutaneous mycoses	Dermis, subcutaneous tissue	Sporotrichosis, chromoblastomycosis	Immunocompetent (trauma)
Systemic mycoses from primary pathogens	Deep organs	Histoplasmosis, coccidioidomycosis	Immunocompetent & compromised

Type	Location	Examples	Primary Hosts
Systemic mycoses from opportunistic pathogens	Deep organs	Candidiasis, aspergillosis, cryptococcosis	Immunocompromised

Figure 2: Spectrum of fungal diseases, ranging from superficial infections (skin and nails) to life-threatening systemic mycoses in immunocompromised hosts.

WHO Fungal Priority Pathogens List (2022)

The World Health Organization released its first fungal priority pathogens list in 2022, categorizing fungi by public health importance (World Health Organization, 2022):

WHO Priority Groups

Critical Priority:

- *Cryptococcus neoformans*
- *Candida auris*
- *Aspergillus fumigatus*
- *Candida albicans*

High Priority:

- *Nakaseomyces glabrata* (formerly *Candida glabrata*)
- *Histoplasma* spp.
- Eumycetoma causative agents
- Mucorales
- *Fusarium* spp.

- *Candida tropicalis*
- *Candida parapsilosis*

Medium Priority:

- *Scedosporium* spp.
- *Lomentospora prolificans*
- *Coccidioides* spp.
- *Pichia kudriavzevii* (formerly *Candida krusei*)
- *Cryptococcus gattii*
- *Talaromyces marneffei*
- *Pneumocystis jirovecii*
- *Paracoccidioides* spp.

Antifungal Therapies

Evolution of Antifungal Development

The development of systemic antifungal agents has progressed significantly since the introduction of amphotericin B in 1958:

Table 2: Timeline of Antifungal Development

Era	Year(s)	Agents	Target
Early	1958	Amphotericin B deoxycholate	Ergosterol binding
Azole development	1981-1992	Ketoconazole, fluconazole, itraconazole	Lanosterol 14- -demethylase
Lipid formulations	1990s	L-AMB, ABLC, ABCD	Ergosterol (reduced toxicity)
Expanded-spectrum azoles	2002-2015	Voriconazole, posaconazole, isavuconazole	Lanosterol 14- -demethylase
Echinocandins	2001-2006	Caspofungin, micafungin, anidulafungin	-1,3-glucan synthase
Novel agents	2023+	Ibrexafungerp, rezafungin, olorofim	Various new targets

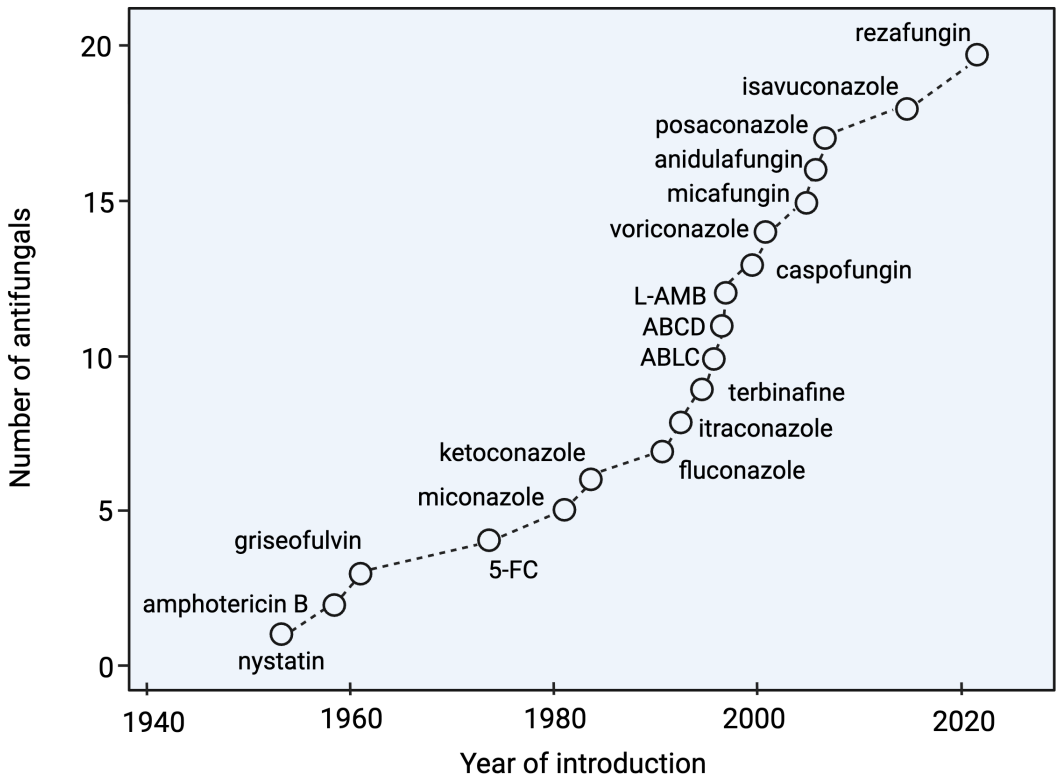


Figure 3: Timeline of systemic antifungal drug development from amphotericin B (1958) through contemporary novel agents.

Mechanisms of Action

Antifungal agents target distinct components of the fungal cell:

Cell Membrane Targets:

- **Polyenes** (amphotericin B): Bind ergosterol, creating pores that lead to cell death
- **Azoles**: Inhibit lanosterol 14- -demethylase (CYP51), disrupting ergosterol synthesis

Cell Wall Targets:

- **Echinocandins**: Inhibit -1,3-glucan synthase, disrupting cell wall integrity

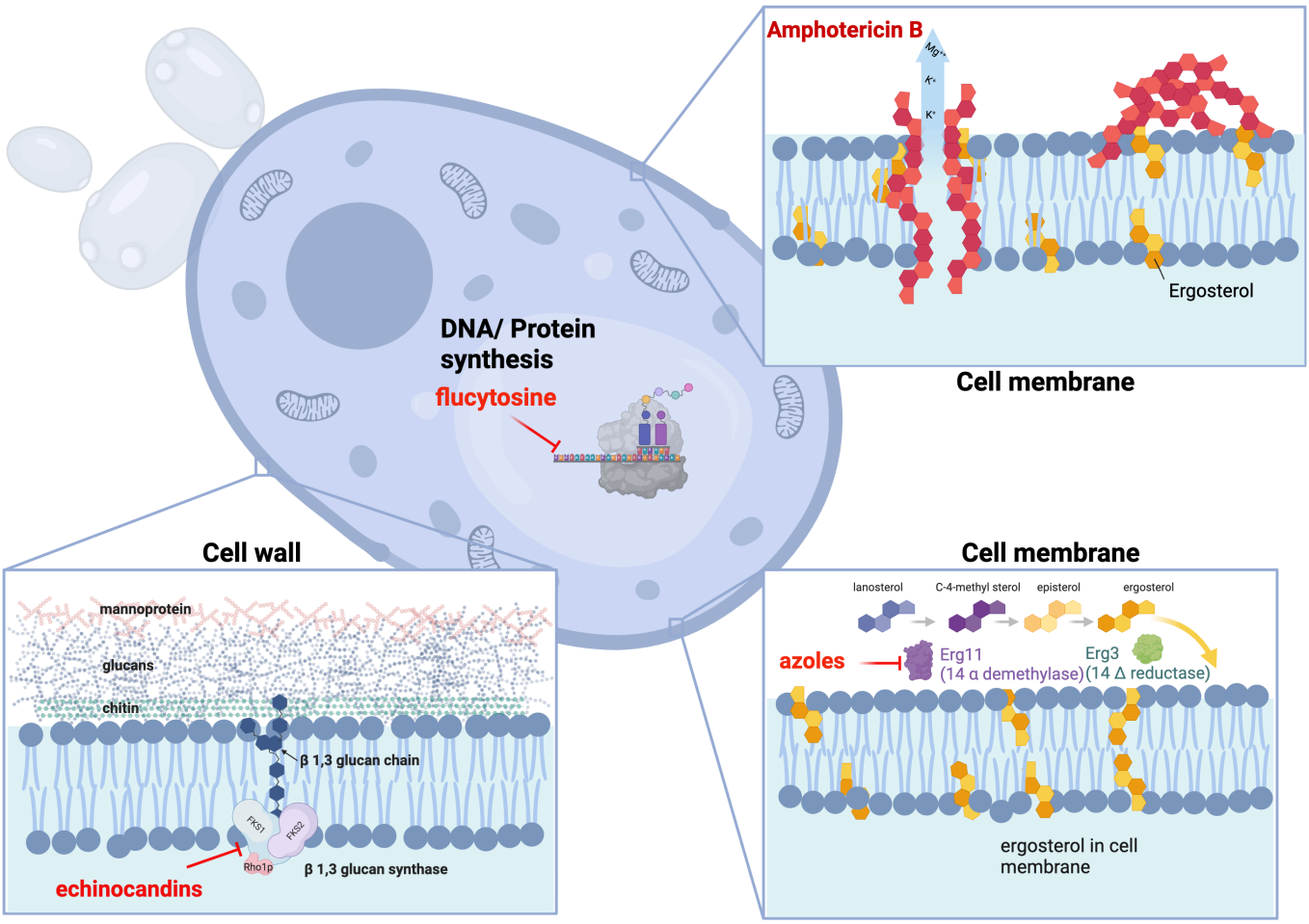


Figure 4: Antifungal mechanisms of action, showing primary targets on the fungal cell membrane (ergosterol) and cell wall (-1,3-glucan).

Antifungal Spectrum of Activity

The spectrum of activity varies significantly across drug classes. Selecting the appropriate agent requires matching the likely or confirmed pathogen against coverage gaps:

Table 3: Antifungal Spectrum of Activity

Agent	*Candida*	*Aspergillus*	*Cryptococcus*	Mucorales
Fluconazole	++	–	++	–
Voriconazole	+++	+++	+	–
Posaconazole	+++	+++	+	++

Agent	*Candida*	*Aspergillus*	*Cryptococcus*	Mucorales
Isavuconazole	+++	+++	+	++
Echinocandins	+++	++	–	–
Amphotericin B	+++	++	+++	+++

Clinical Pearl

The spectrum of antifungal activity varies significantly between drug classes:

- **Fluconazole**: Most *Candida* spp. (not *C. krusei*, reduced activity vs *C. glabrata*); no mold activity
- **Voriconazole/Isavuconazole/Posaconazole**: Broad *Candida* coverage + *Aspergillus*; posaconazole and isavuconazole have Mucorales activity
- **Echinocandins**: *Candida* spp. (including *C. glabrata*) + *Aspergillus*; no *Cryptococcus* or Mucorales activity
- **Amphotericin B**: Broadest spectrum - most yeasts and molds including Mucorales

Antifungal Tissue Distribution

Understanding antifungal tissue penetration is critical for selecting appropriate therapy (Felton et al., 2014):

Table 4: Antifungal Tissue Penetration

Drug	CSF	Eye/Vitreous	Urine	Lung ELF
Fluconazole	+++	+++	+++	++
Voriconazole	++	++	+	+++
Posaconazole	+	+	-	+++
Isavuconazole	+	+	-	+++
Amphotericin B	+/-	+/-	+	++
Echinocandins	-	-	-	+

Important Consideration

Echinocandins have poor CNS, eye, and urine penetration. They should not be used as monotherapy for infections at these sites.

Invasive Candidiasis

Epidemiology

Invasive candidiasis is the most common invasive fungal infection in hospitalized patients. The epidemiology has evolved significantly over recent decades (Pappas et al., 2018):

Species Distribution:

- *Candida albicans*: 40-60% (decreasing)
- *Candida glabrata*: 15-25% (increasing, especially with azole exposure)
- *Candida parapsilosis*: 10-20% (associated with central lines, TPN)
- *Candida tropicalis*: 5-10% (more common in neutropenic patients)
- *Candida krusei*: 2-5% (intrinsically fluconazole-resistant)
- *Candida auris*: Emerging multidrug-resistant threat

Risk Factors

Major Risk Factors for Invasive Candidiasis

Host Factors:

- Neutropenia
- Diabetes mellitus
- Extremes of age
- Recent surgery (especially abdominal)
- Burns

Healthcare Exposures:

- Central venous catheters
- Total parenteral nutrition
- Broad-spectrum antibiotics
- ICU admission >3 days
- Prior colonization with *Candida*

Medications:

- Corticosteroids
- Immunosuppressive agents
- Prior antifungal exposure

Pathogenesis

Candida species are commensal organisms of the human gastrointestinal tract, skin, and mucous membranes. Invasive disease occurs when host defenses are compromised or mucosal barriers are breached.

Key Pathogenic Steps:

1. Colonization of mucosal surfaces
2. Breach of mucosal barrier (surgery, mucositis, catheters)
3. Bloodstream invasion
4. Dissemination to deep organs
5. Biofilm formation (especially on devices)

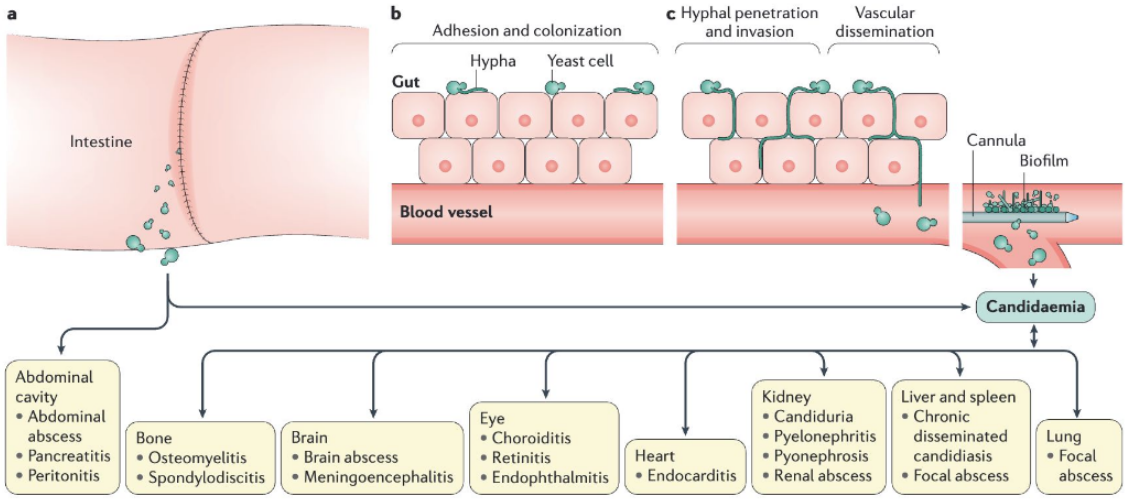


Figure 1 | **Pathogenesis of invasive candidiasis.** *Candida* spp. can be detected on the mucosal surfaces of ~50–70% of healthy humans. **a** | When breaches in the intestinal barriers occur, for example, after gastrointestinal surgery, *Candida* spp. can disseminate to the abdominal cavity directly and invade the bloodstream (candidaemia). **b** | Under normal conditions, the fungus behaves as a commensal organism without causing disease. **c** | Impairment of immune response, among other factors, can promote fungal overgrowth in the gut and candidaemia, which can lead to deep-seated opportunistic infections in various organs (invasive candidiasis).

Figure 5: Pathogenesis of invasive candidiasis. Disruption of mucosal barriers (e.g., by surgery, chemotherapy-induced mucositis, or catheters) allows *Candida* to translocate from commensal sites to the bloodstream and deep organs. Biofilm formation on intravascular devices further complicates treatment.

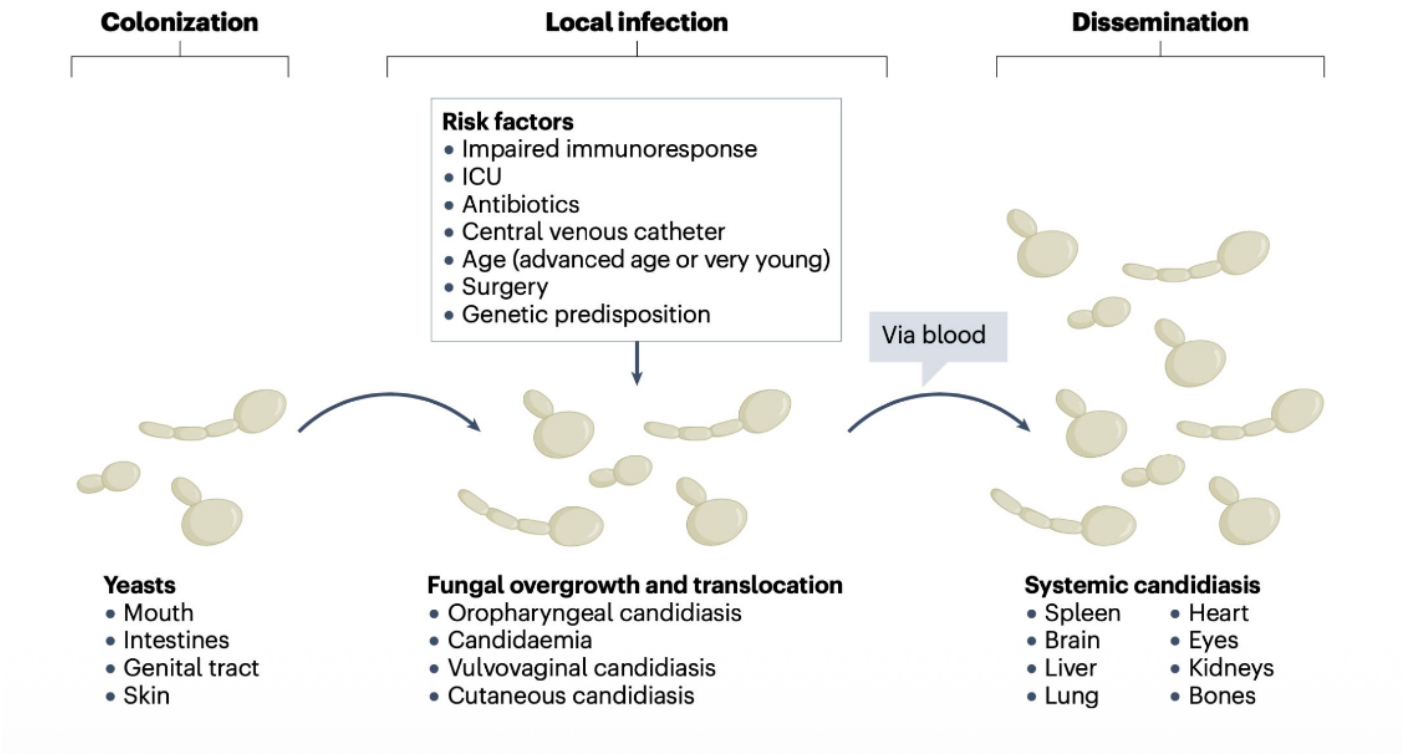


Figure 6: Continuum of invasive candidiasis, from superficial colonization through candidemia to deep-seated organ involvement. (Pappas et al., 2018)

Clinical Presentations

Candidemia:

- Fever unresponsive to antibiotics
- Often no localizing signs
- May have metastatic complications (endophthalmitis, osteomyelitis, endocarditis)

Deep-seated Candidiasis:

- Hepatosplenic candidiasis (chronic disseminated): Fever, elevated alkaline phosphatase, target lesions on imaging
- Candida peritonitis: Abdominal surgery, peritoneal dialysis
- Candida endocarditis: Prosthetic valves, IV drug use

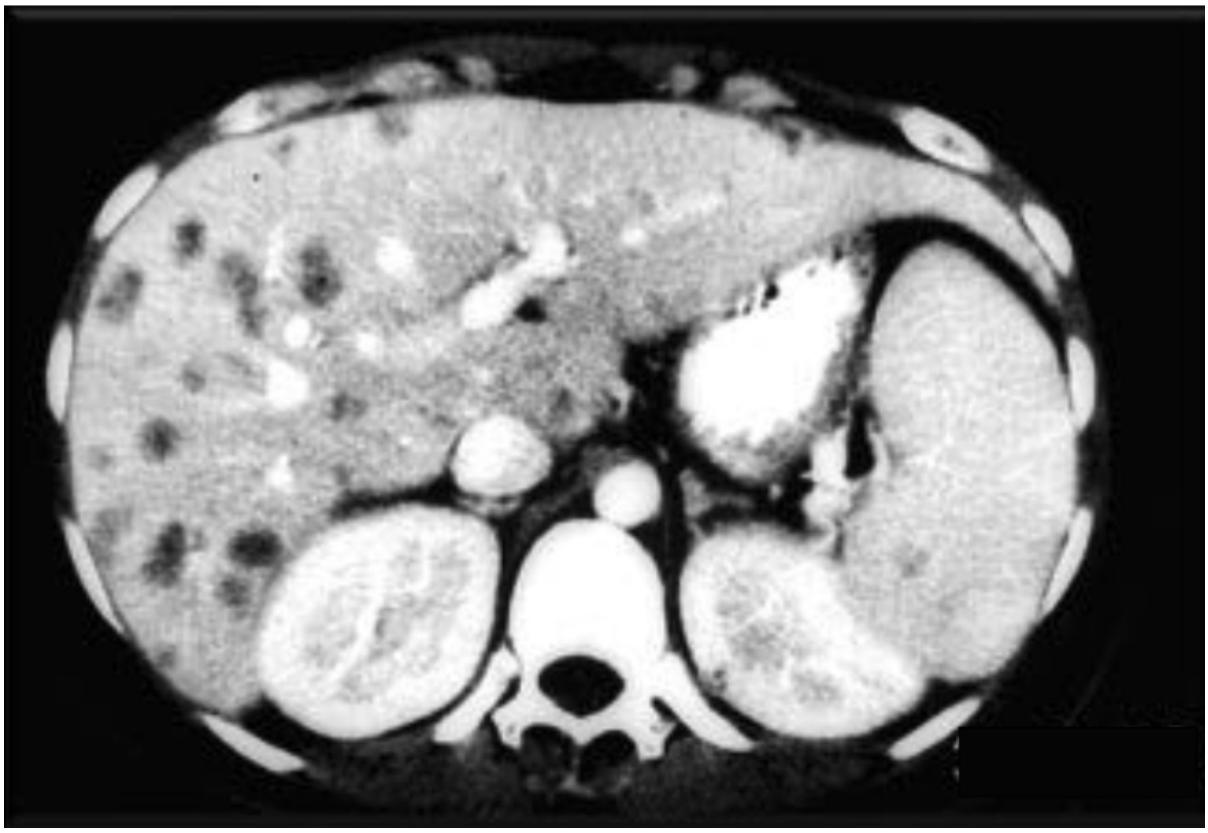


Figure 7: Hepatosplenic (chronic disseminated) candidiasis. Characteristic "bull's eye" target lesions visible on CT/MRI, typically appearing as neutrophil counts recover following chemotherapy-induced neutropenia.

Diagnosis

> **!** The "Missing 50%"
>
> Blood cultures detect only approximately 50% of invasive candidiasis cases, highlighting the need for adjunctive diagnostic methods (Clancy and Nguyen, 2013).

Culture-Based Methods:

- Blood cultures: Gold standard but limited sensitivity
- Tissue cultures: Higher yield but require invasive sampling

Non-Culture Diagnostics:

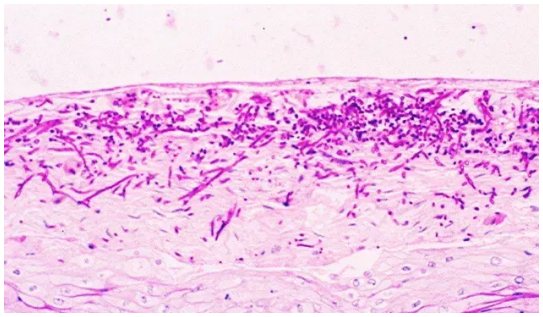
Table 5: Non-Culture Diagnostics for Invasive Candidiasis

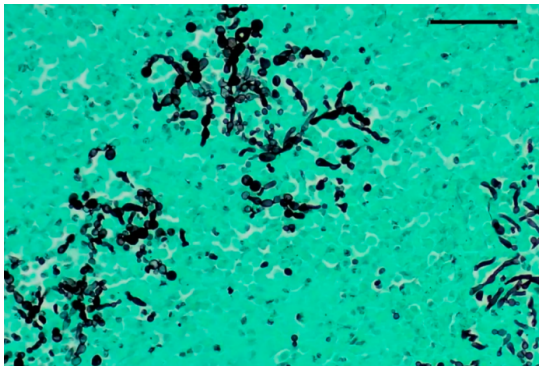
Test	Sensitivity	Specificity	Comments
-D-glucan	75-80%	80%	Pan-fungal; false positives with dialysis, gauze, some antibiotics
T2Candida Panel	91%	99%	Direct from blood; rapid results; detects 5 common species
Candida PCR	85-95%	90-95%	Not widely standardized

Histopathology:

Tissue diagnosis of invasive candidiasis relies on special stains to highlight fungal elements in tissue specimens:

Stain	Appearance
PAS (Periodic Acid–Schiff)	Magenta yeast and pseudohyphae
GMS (Gomori Methenamine Silver)	Black yeast and hyphae against green background

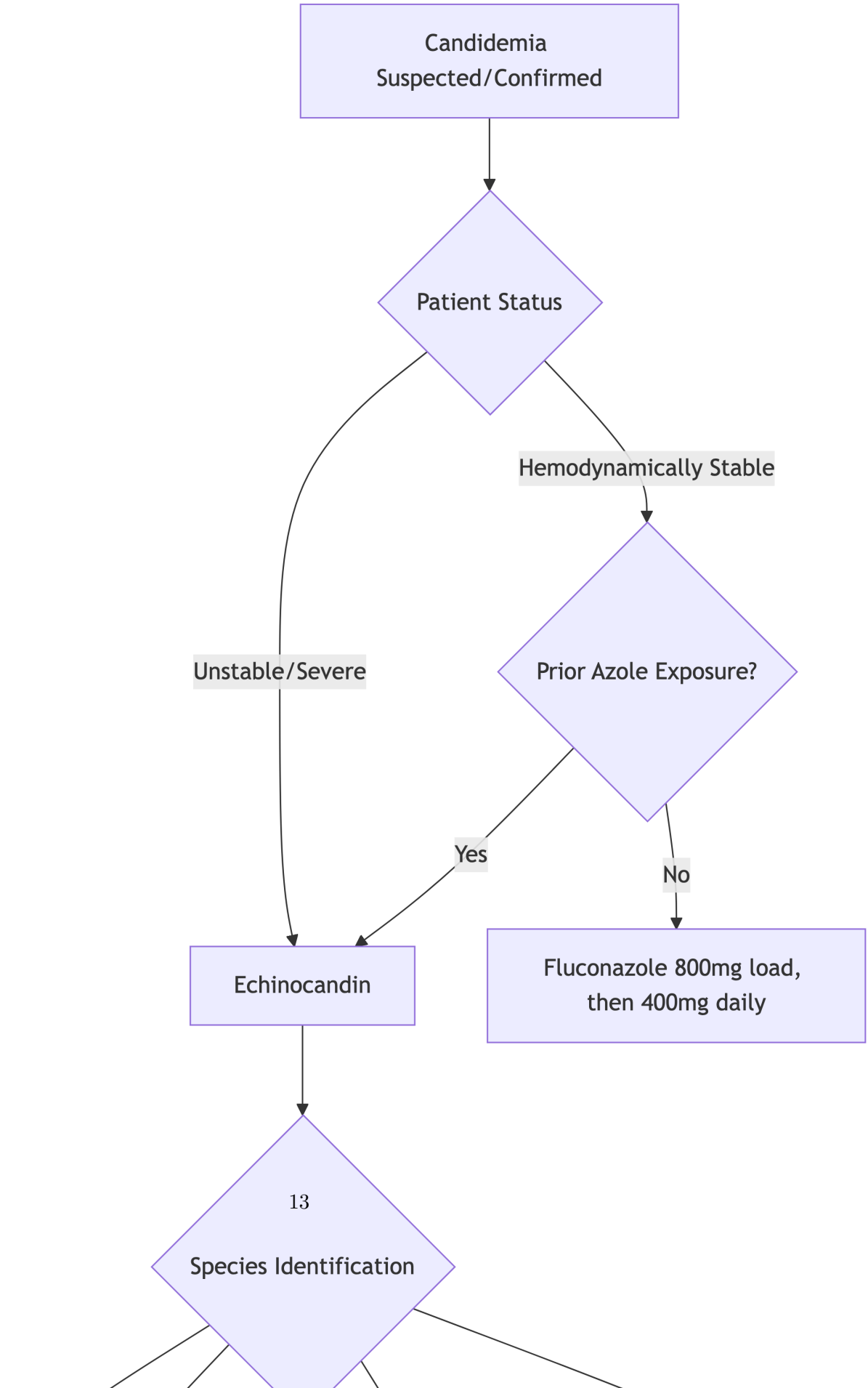




Treatment

Initial Therapy

Treatment selection depends on patient stability, prior azole exposure, and suspected species (Pappas et al., 2016):


Candidemia
Suspected/Confirmed
Patient Status
Hemodynamically Stable
Unstable/Severe
Prior Azole Exposure?
Yes
No
Echinocandin
Fluconazole 800mg load,
then 400mg daily
Species Identification

Source Control

> **Critical Intervention**
>
> Central venous catheter removal is associated with improved outcomes and should be performed whenever feasible in patients with candidemia.

Duration of Therapy

- **Uncomplicated candidemia**: 14 days after first negative blood culture and resolution of symptoms
- **Deep-seated infection**: Extended duration based on site (e.g., endocarditis: 6 weeks post-valve surgery)

Ophthalmologic Examination

All patients with candidemia should receive a dilated funduscopic examination to evaluate for endophthalmitis:

- **Timing**: Within 1 week of diagnosis (after neutrophil recovery in neutropenic patients)
- **Finding**: Chorioretinal lesions with or without vitritis
- **Management**: Extended antifungal therapy; ophthalmology consultation

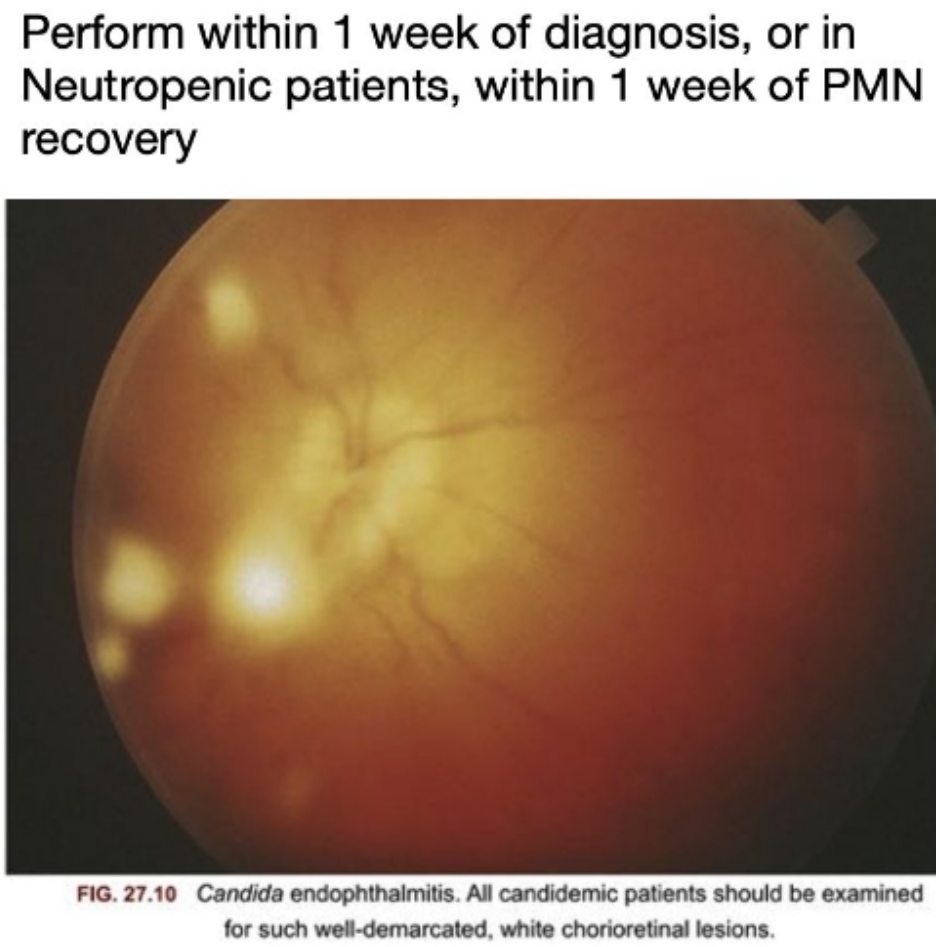


Figure 9: Funduscopic appearance of *Candida* chorioretinitis/endophthalmitis. Cotton-wool exudates and "string of pearls" lesions in the vitreous indicate ocular involvement, which occurs in 10–15% of candidemia cases and requires prompt ophthalmology consultation. Note that echinocandins do not penetrate the vitreous — fluconazole or voriconazole is required for ocular disease.

Antifungal Susceptibility Testing

Susceptibility testing is recommended for all bloodstream isolates. CLSI and EUCAST breakpoints guide interpretation:

Table 6: CLSI Breakpoints for Candida Species (mg/L)

Species	Fluconazole	Echinocandins	Comments
C. albicans	S 2	S 0.25	Usually susceptible
C. glabrata	SDD 32	S 0.12	Dose-dependent; check echinocandin susceptibility
C. krusei	R (intrinsic)	S 0.25	Use echinocandin or amphotericin B
C. parapsilosis	S 2	Higher MICs (S 2)	Fluconazole often preferred
C. auris	Often R	Variable	Requires individualized testing

Cryptococcosis

Epidemiology

Cryptococcosis is caused by encapsulated yeasts of the *Cryptococcus* species complex. It remains a leading cause of mortality in HIV-infected individuals, particularly in resource-limited settings (Park et al., 2009; Tugume et al., 2023).

Global Burden:

- Approximately 220,000 cases of cryptococcal meningitis annually
- 180,000 deaths per year
- Most cases occur in sub-Saharan Africa
- Leading cause of meningitis in adults with HIV in Africa

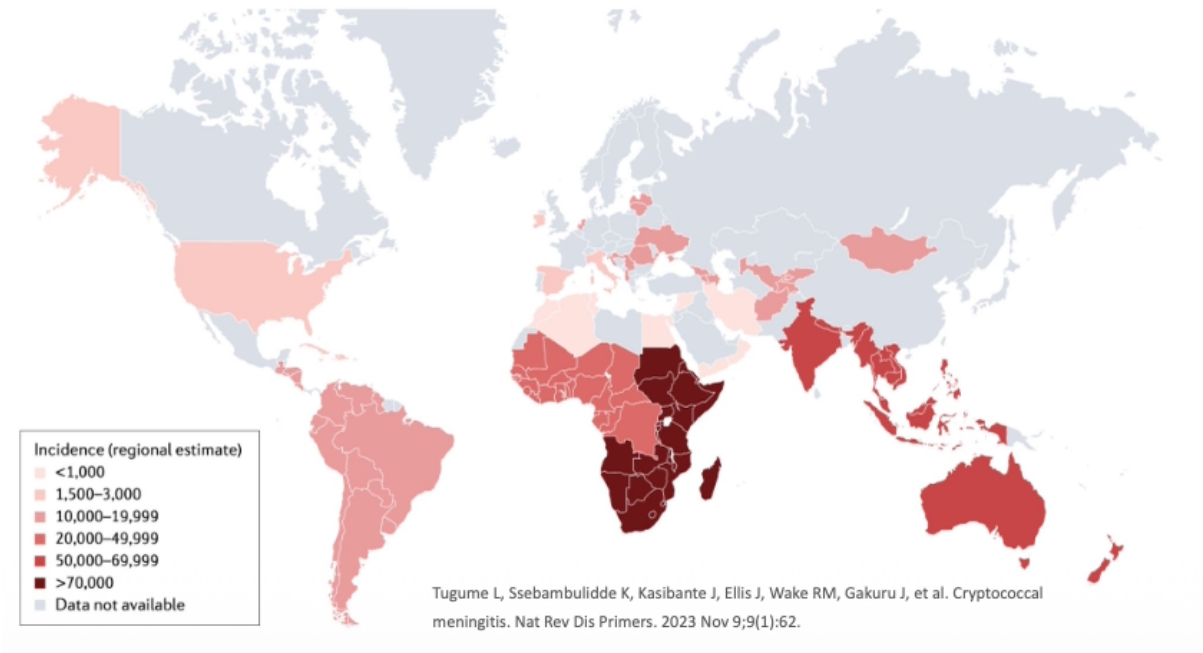


Figure 10: Global distribution of cryptococcal meningitis. Sub-Saharan Africa bears the greatest burden, where *Cryptococcus neoformans* is a leading cause of meningitis-related mortality in HIV-infected individuals. The incidence has declined substantially in settings with widespread antiretroviral therapy access.

Species and Ecology

Table 7: Cryptococcus Species Characteristics

Species	Primary Host	Geographic Distribution	Clinical Association
C. neoformans	Immunocompromised (HIV, transplant)	Worldwide	Soil, bird droppings
C. gattii	Immunocompetent & immunocompromised	Pacific Northwest, Australia, tropics	Eucalyptus trees

Pathogenesis

Cryptococcus has several virulence factors that enable evasion of host defenses:

1. **Polysaccharide capsule**: Antiphagocytic; immunomodulatory
2. **Melanin production**: Antioxidant protection
3. **Ability to survive within macrophages**: Trojan horse mechanism for CNS penetration
4. **Titan cells**: Large cells resistant to phagocytosis

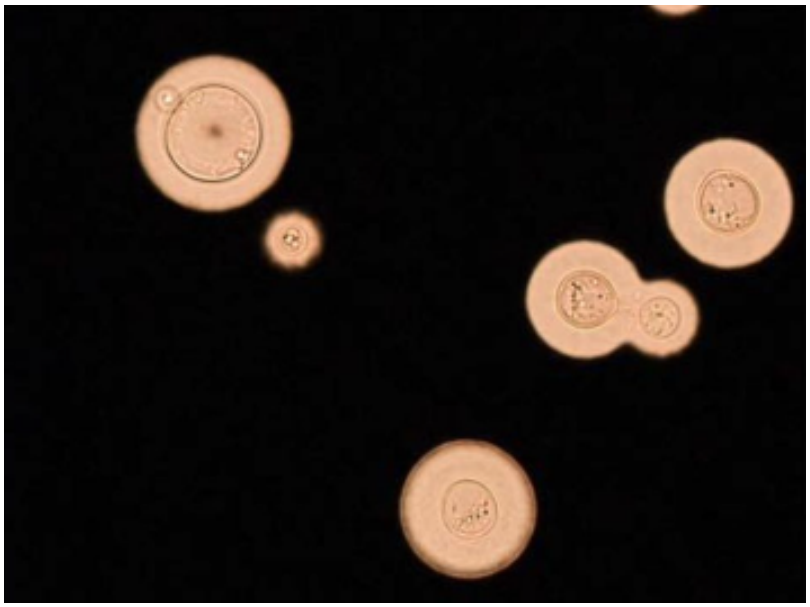


Figure 11: India ink preparation of cerebrospinal fluid showing encapsulated *Cryptococcus* yeast. The prominent polysaccharide capsule (visible as a clear halo surrounding the yeast cell) prevents phagocytosis and is the organism's primary virulence factor.

Clinical Manifestations

Cryptococcal Meningitis:

- Subacute presentation over 1-2 weeks
- Headache (most common)
- Fever
- Altered mental status
- Neck stiffness (less common than bacterial meningitis)
- Cranial nerve palsies
- Visual disturbances

! Elevated Intracranial Pressure

Elevated intracranial pressure (ICP) is a major cause of morbidity and mortality in cryptococcal meningitis. Opening pressure >25 cm H O is associated with poor outcomes.

Pulmonary Cryptococcosis:

- May be asymptomatic (incidental finding)
- Cough, dyspnea, chest pain
- Nodules or infiltrates on imaging

Disseminated Disease:

- Skin lesions (umbilicated papules resembling molluscum)
- Bone involvement
- Prostate (sanctuary site)

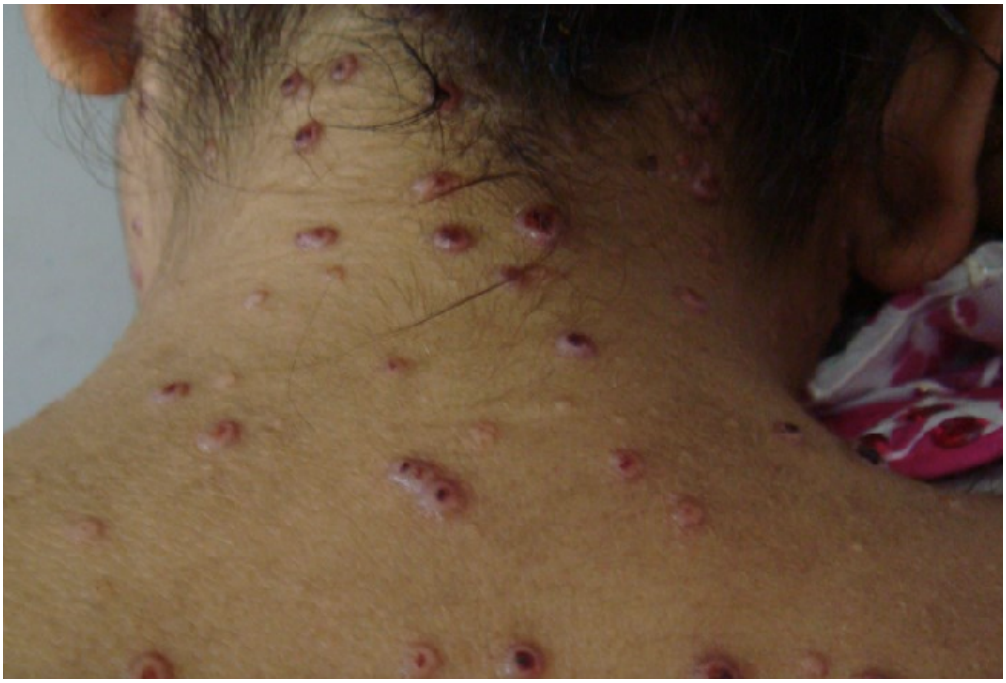


Figure 12: Cryptococcal skin lesions. Papulonodular umbilicated lesions on the neck and upper trunk can mimic molluscum contagiosum. Skin involvement indicates disseminated cryptococcosis and should prompt full evaluation including lumbar puncture.

Diagnosis

Lumbar Puncture Findings:

Table 8: CSF Findings in Cryptococcal Meningitis

Parameter	Typical Finding
Opening pressure	Elevated (often >25 cm H O)
WBC	Elevated (lymphocyte predominant); may be low in severe immunosuppression
Glucose	Low
Protein	Elevated
CrAg (LFA)	Positive
India ink	Positive in ~75–85% of cases

! Elevated Opening Pressure

Opening pressure must always be measured and documented. Severely immunosuppressed patients may have a paradoxically low WBC despite high fungal burden — this portends a worse prognosis. ICP management is often more critical than antifungal drug choice in the first days of treatment.

Diagnostic Tests:

Table 9: Diagnostic Tests for Cryptococcosis

Test	Sensitivity	Specificity	Comments
CSF CrAg (lateral flow)	99%	99%	Rapid, point-of-care
Serum CrAg	99%	99%	Can be positive before symptoms
CSF India ink	75-85%	>95%	Visualizes capsule; less sensitive
CSF culture	95%	100%	Gold standard; takes 3-7 days

Screening Recommendation

Serum cryptococcal antigen (CrAg) screening is recommended for HIV-infected individuals with CD4 <100 cells/ L to identify subclinical disease before symptom onset.

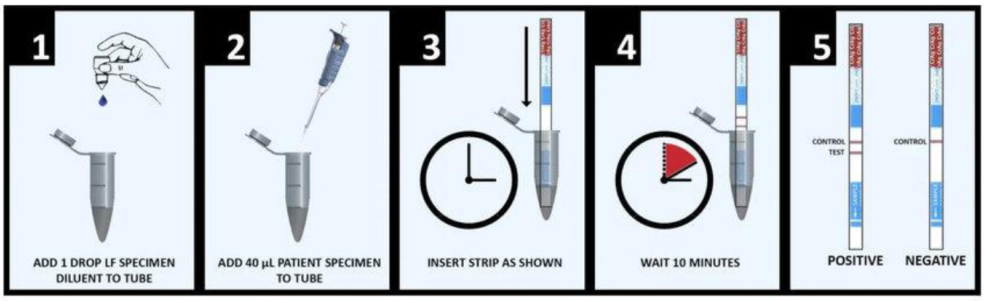


Figure 13: Point-of-care lateral flow assay (LFA) for cryptococcal antigen (CrAg). This rapid, inexpensive, highly accurate test (sensitivity and specificity ~99%) has transformed early diagnosis, particularly in resource-limited settings. A positive serum CrAg can precede clinical symptoms and should prompt lumbar puncture to evaluate for CNS involvement.

Treatment

The AMBITION Trial

The AMBITION trial established single high-dose liposomal amphotericin B as the preferred induction regimen (Jarvis et al., 2022):

Key Findings:

- Single dose L-AMB (10 mg/kg) + 14 days flucytosine + fluconazole was non-inferior to 7-day amphotericin B deoxycholate regimens
- 10-week mortality: 24.8% vs 28.7% (difference -3.9%, 95% CI -10.4 to 2.6)
- Fewer adverse events with single-dose regimen
- Simplified administration

Treatment Regimens

Table 10: Cryptococcal Meningitis Treatment Phases

	Induction (2 weeks)	**Consolidation** (8 weeks)	**Maintenance**
Preferred	L-AMB 10 mg/kg × 1 dose + flucytosine 100 mg/kg/day × 14 days + fluconazole 1200 mg/day × 14 days	Fluconazole 800 mg/day	Fluconazole 200 mg/day

	Induction (2 weeks)	**Consolidation** (8 weeks)	**Maintenance**
Alternative	AmB deoxycholate 1 mg/kg/day × 7 days + flucytosine × 7 days	—	—
Discontinue	—	—	CD4 >100 cells/ L for 3 months on ART

Induction (2 weeks):

1. **Preferred**: Single dose liposomal amphotericin B (10 mg/kg) + flucytosine (100 mg/kg/day) + fluconazole (1200 mg/day)
2. **Alternative**: Amphotericin B deoxycholate (1 mg/kg/day) + flucytosine (100 mg/kg/day) × 7 days

Consolidation (8 weeks):

- Fluconazole 800 mg/day

Maintenance:

- Fluconazole 200 mg/day until immune reconstitution (CD4 >100 for 3 months on ART)

Management of Elevated ICP

> ⚠ Critical Intervention
>
> Aggressive management of elevated intracranial pressure is essential for survival. Therapeutic lumbar punctures should be performed to reduce opening pressure by 50% or to <20 cm H O.

Approach:

1. Daily lumbar punctures initially if opening pressure >25 cm H O
2. Remove sufficient CSF to reduce pressure by 50% or to normal
3. Consider lumbar drain or VP shunt for refractory cases
4. Avoid corticosteroids (associated with worse outcomes)
5. Acetazolamide and mannitol are not effective

Prognosis

Factors associated with poor outcome (Williamson et al., 2017):

- High CSF fungal burden
- Altered mental status at presentation
- Elevated opening pressure
- Low CSF white cell count
- Underlying malignancy
- Inadequate ICP management

Invasive Aspergillosis

Spectrum of Aspergillus Diseases

The clinical manifestations of *Aspergillus* infection depend on host immune status:

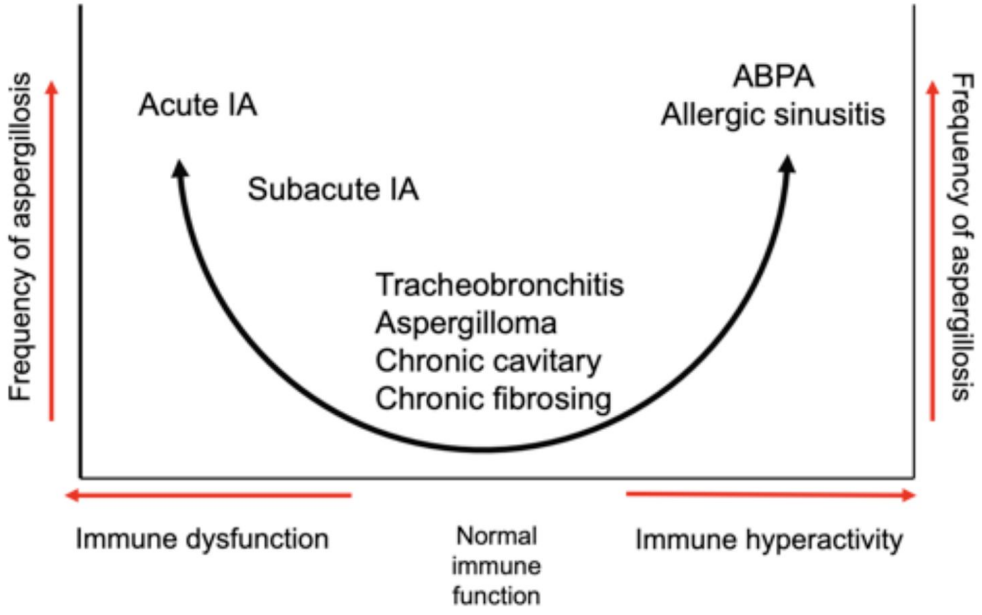


Figure 14: Spectrum of *Aspergillus* disease, illustrating how host immune status determines clinical presentation. Immunocompromised patients develop invasive disease (left), patients with structural lung disease develop aspergillomas (center), and those with immune hyperreactivity develop allergic syndromes (right).

Immunocompromised Hosts (Immune Dysfunction):

- Acute invasive aspergillosis
- Subacute invasive aspergillosis

Normal Immune Function (Middle of Spectrum):

- Tracheobronchitis
- Aspergilloma
- Chronic cavitary aspergillosis
- Chronic fibrosing aspergillosis

Immune Hyperactivity:

- Allergic bronchopulmonary aspergillosis (ABPA)
- Allergic fungal sinusitis

Aspergillus Species

Table 11: Common Aspergillus Species

Species	Frequency	Clinical Significance
A. fumigatus	70-80%	Most common cause of IA
A. flavus	10-15%	More common in sinusitis; produces aflatoxins
A. niger	5-10%	Otomycosis; may produce aspergillomas
A. terreus	2-5%	Intrinsically amphotericin B resistant
A. nidulans	Rare	Associated with chronic granulomatous disease

Mode of Acquisition

Aspergillus conidia (2-3 m) are ubiquitous in the environment and inhaled daily. In immunocompetent hosts, conidia are cleared by:

1. Mucociliary clearance
2. Alveolar macrophage phagocytosis
3. Neutrophil killing of germinating hyphae

Risk Factors

Major Risk Factors for Invasive Aspergillosis

Host Factors:

- Severe and prolonged neutropenia (3 weeks)
- Hematopoietic stem cell transplant (especially allogeneic)
- Solid organ transplant (especially lung)
- Chronic granulomatous disease
- Advanced AIDS

Iatrogenic:

- High-dose corticosteroids (0.5 mg/kg/day prednisone equivalent)
- Ibrutinib and other BTK inhibitors
- T-cell depleting therapies

Emerging Risk Groups:

- COPD with corticosteroid therapy
- ICU patients (especially with influenza or COVID-19)
- Liver cirrhosis

Pathogenesis

Bronchial-Alveolar Phase

Initial invasion occurs through bronchial and alveolar walls:

- Conidia germinate in airways
- Hyphae invade bronchial/alveolar epithelium
- Associated inflammation
- CT findings: Centrilobular nodules, tree-in-bud pattern
- Low fungal burden; serum galactomannan often negative
- BAL galactomannan/culture may be positive

Angioinvasive Phase

In severely immunocompromised patients, disease progresses to angioinvasion:

Progression Timeline:

Table 12: Temporal Progression of Angioinvasive Aspergillosis

Day	Pathology	CT Finding	Biomarkers
0-3	Hyphal tissue invasion	Macronodule ± halo sign	GM may be negative
5-7	Hemorrhage, infarction	Dense consolidation	Serum GM positive
10-12	Extensive necrosis	Hypodense sign	High fungal burden
15-18	Neutrophil recovery, cavitation	Air-crescent sign	May persist

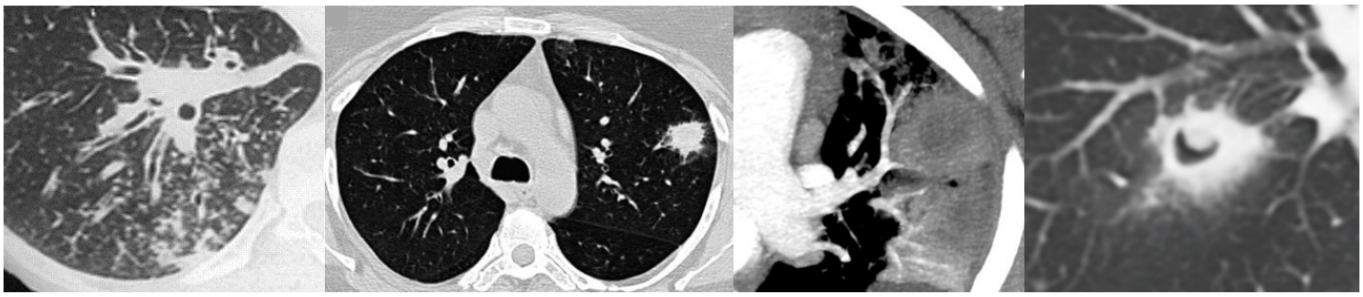


Figure 15: CT evolution of invasive pulmonary aspergillosis in a neutropenic patient. Early lesions show a macronodule with halo sign (hemorrhagic infarction); later findings include dense consolidation and eventual air-crescent sign with neutrophil recovery.

Clinical Presentation

Pulmonary Aspergillosis:

- Fever unresponsive to antibiotics
- Pleuritic chest pain
- Cough, hemoptysis
- Dyspnea

Sinus Aspergillosis:

- Facial pain
- Nasal congestion/discharge
- Periorbital swelling
- Black eschar on nasal examination

Disseminated Aspergillosis:

- CNS involvement (ring-enhancing lesions, abscesses)

- Cutaneous lesions
- Multiple organ involvement

Diagnosis

Imaging

CT Findings Suggestive of IPA:

- Nodules with halo sign (ground-glass surrounding dense core)
- Air-crescent sign (late finding with neutrophil recovery)
- Wedge-shaped infiltrates
- Cavitation

> **Halo Sign**
>
> The halo sign (ground-glass attenuation surrounding a nodule) is relatively specific for angioinvasive mold infection in neutropenic patients, particularly in the first week of infection.

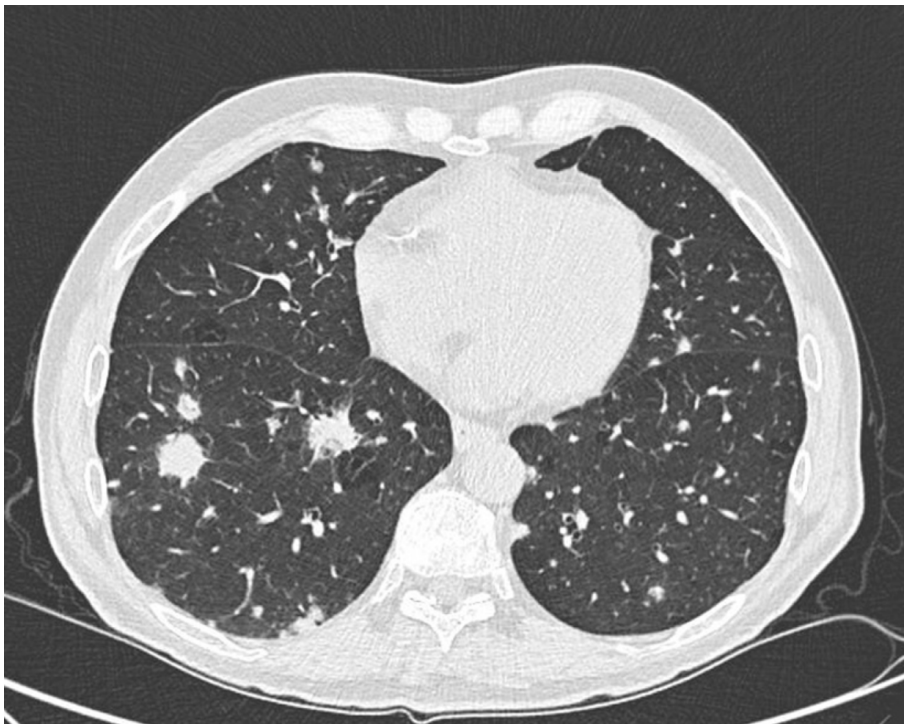


Figure 16: CT halo sign in invasive pulmonary aspergillosis. Ground-glass opacity (hemorrhage) surrounds a dense nodule (fungal infarct), producing the characteristic halo appearance. This sign is most useful in the first 5–7 days and may disappear as disease evolves. Note that it can also occur with mucormycosis and other angioinvasive infections.

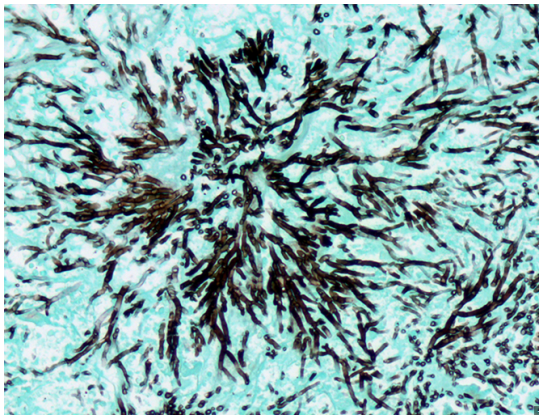
CT Pulmonary Angiography (Vessel Occlusion Sign):

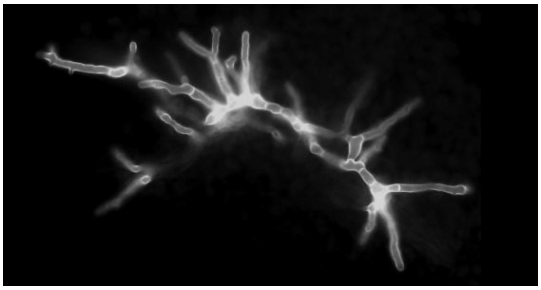
- Can help differentiate IPA from other pulmonary processes
- Positive VOS shows vessel truncation within or adjacent to nodules

Laboratory Diagnosis

Culture and Histopathology:

- BAL culture: Sensitivity 50-60%
- Tissue biopsy: Septate hyphae with acute-angle (45°) branching
- PAS and GMS stains highlight fungal elements





Galactomannan Testing:

Table 13: Galactomannan Testing Performance

Sample	Cutoff	Sensitivity	Specificity	Notes
Serum	0.5 ODI	70-80%	85-90%	Better in neutropenic patients
BAL	1.0 ODI	85-90%	90-95%	Higher sensitivity than serum

⚠ False Positives

Galactomannan false positives can occur with:

- Piperacillin-tazobactam (older formulations)
- Mucositis
- Certain foods
- Cross-reactivity with other fungi (*Fusarium*, *Histoplasma*)

Other Biomarkers:

- **-D-glucan**: Less specific (pan-fungal); may be useful in combination
- **Aspergillus PCR**: High sensitivity; not yet standardized

Treatment

First-Line Therapy

Triazoles with mold activity are preferred for primary therapy (Thompson and Young, 2021):

If NO Prior Mold-Active Prophylaxis:

- Voriconazole (loading: 6 mg/kg IV q12h × 2 doses; maintenance: 4 mg/kg IV q12h or 200-300 mg PO q12h)
- Isavuconazole (loading: 200 mg q8h × 6 doses; maintenance: 200 mg daily)
- Posaconazole (300 mg IV/PO q12h × 2 doses, then 300 mg daily)

If Receiving Posaconazole Prophylaxis:

- Liposomal amphotericin B (3-5 mg/kg/day) initially
- Reassess triazole failure: drug levels, resistance, alternative diagnosis
- Consider switching to alternative triazole if isolate is susceptible and patient stabilizes

Antifungal Resistance

Triazole resistance in *Aspergillus fumigatus* is an emerging concern:

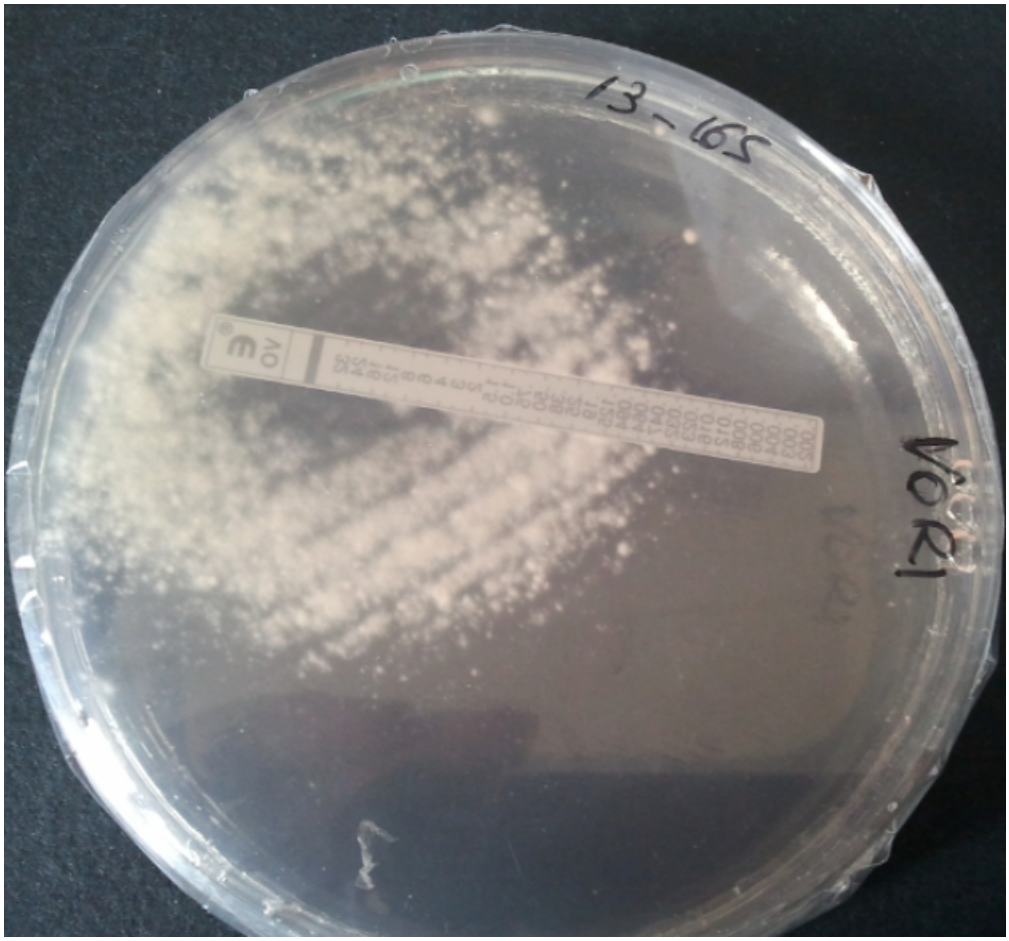


Figure 17: Emerging environmental azole resistance in *Aspergillus fumigatus*. TR34/L98H and TR46/Y121F/T289A mutations arise through agricultural fungicide use and are associated with treatment failure. Resistance prevalence varies markedly by geographic region.

! Azole Resistance

Environmental azole resistance (TR34/L98H and TR46/Y121F/T289A mutations) is increasing globally due to agricultural fungicide use. Rates vary by region:

- Netherlands: 5-15%
- UK: 5-10%
- Germany: 3-5%
- United States: 1-3%
- Some Asian regions: Up to 30%

Consider resistance testing in refractory cases or high-prevalence regions.

Duration

- **Minimum**: 6-12 weeks
- **Continue until**: Resolution of all lesions, reversal of immunosuppression
- **Secondary prophylaxis**: Consider during subsequent immunosuppression

Prognosis

Key prognostic factors:

- Early diagnosis and prompt antifungal therapy
- Recovery from neutropenia/immune suppression
- Underlying disease status
- Site of infection (CNS involvement = worse prognosis)
- Triazole resistance

Other Mold Infections

Fusariosis

Fusarium species are emerging pathogens causing severe infections in neutropenic patients.

Key Features:

- Most common scenario: Persistent neutropenia
- Common species: *F. solani* complex (50%), *F. oxysporum* (14%), *F. verticillioides* (10-11%)
- Characteristic finding: Metastatic skin lesions
- **Positive blood cultures in 30-50% of cases** (unlike other mold infections)
- Macroconidia are classic (banana-shaped)

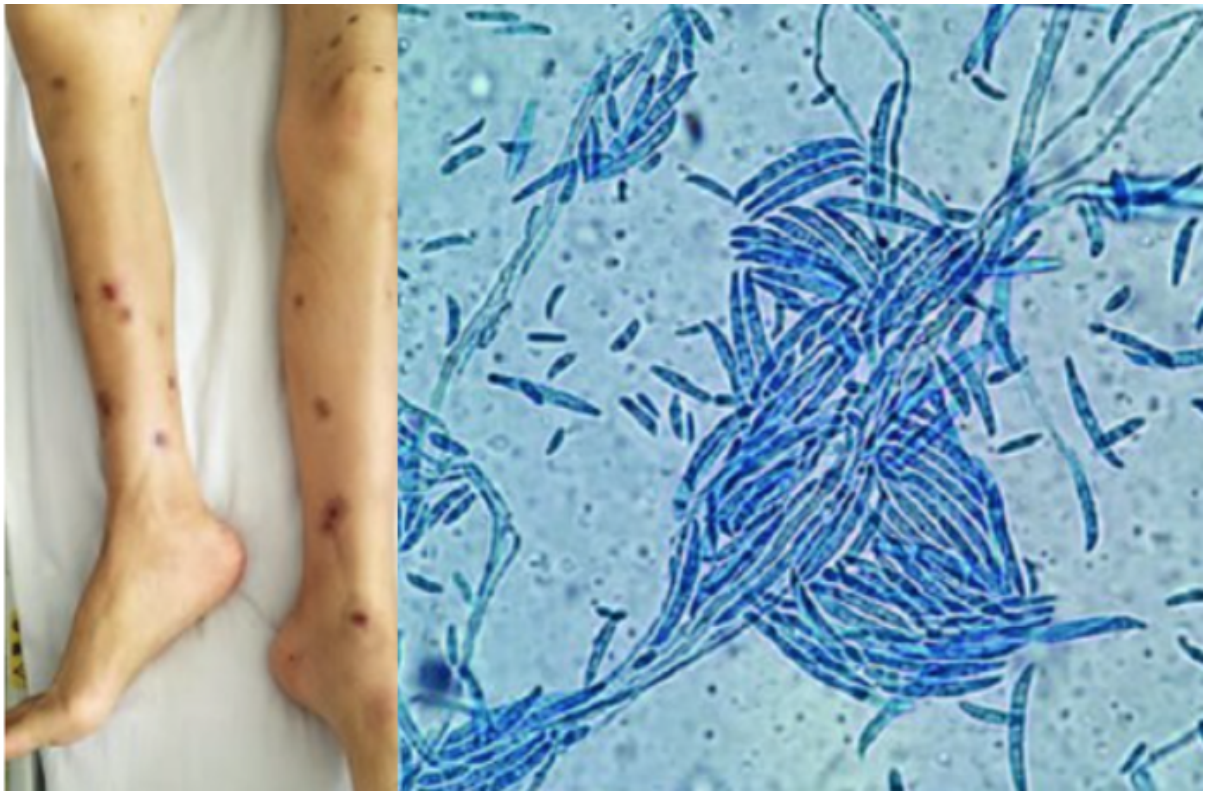


Figure 18: Breakthrough *Fusarium* infection during neutropenia. Unlike most invasive mold infections, *Fusarium* frequently produces positive blood cultures. Characteristic banana-shaped macroconidia are visible on microscopy. Metastatic necrotic skin lesions (ecthyma gangrenosum-like) and ocular involvement are distinctive features not typically seen with aspergillosis.

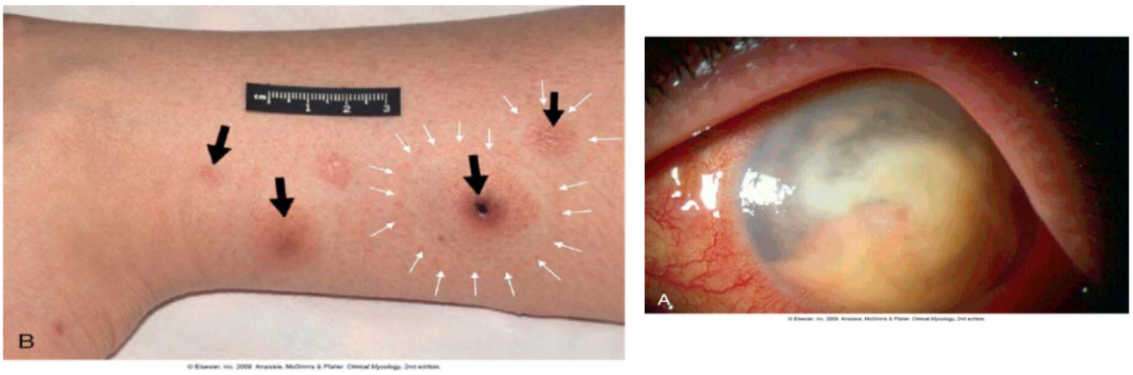


Figure 19: Metastatic skin, ocular, and CNS lesions of disseminated fusariosis. These necrotic cutaneous lesions can mimic ecthyma gangrenosum from *Pseudomonas* infection. CNS involvement carries a particularly poor prognosis, especially in the absence of neutrophil recovery.

Treatment:

- High-dose liposomal amphotericin B ± voriconazole
- Neutrophil recovery is critical
- G-CSF may be beneficial

Fusarium Outbreak

A multinational outbreak (185 exposed, 9 cases) of nosocomial *Fusarium solani* meningitis occurred among immunocompetent patients who underwent surgery with epidural anesthesia in Mexico in 2023 (Strong et al., 2024). The pathogen showed high predilection for the brainstem and vertebrobasilar arterial system, with high mortality from vessel injury.

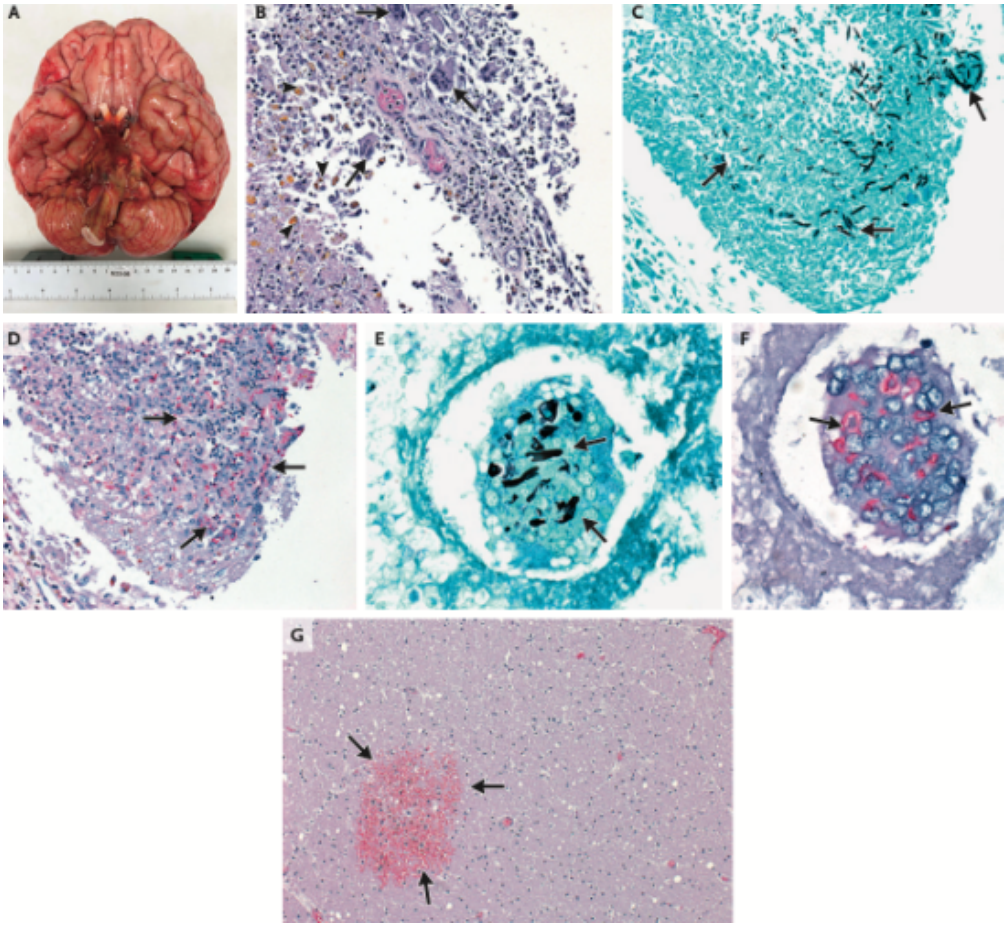


Figure 20: Epidemiological map of the 2023 multinational nosocomial *Fusarium solani* meningitis outbreak, linked to contaminated surgical/anesthesia equipment. This outbreak highlights the risk of invasive fungal infections in immunocompetent patients following breaches in sterile technique. (Strong et al., 2024)

Mucormycosis

Epidemiology and Risk Factors

Mucormycosis is caused by fungi of the order Mucorales, including *Rhizopus*, *Mucor*, *Lichtheimia*, and others.

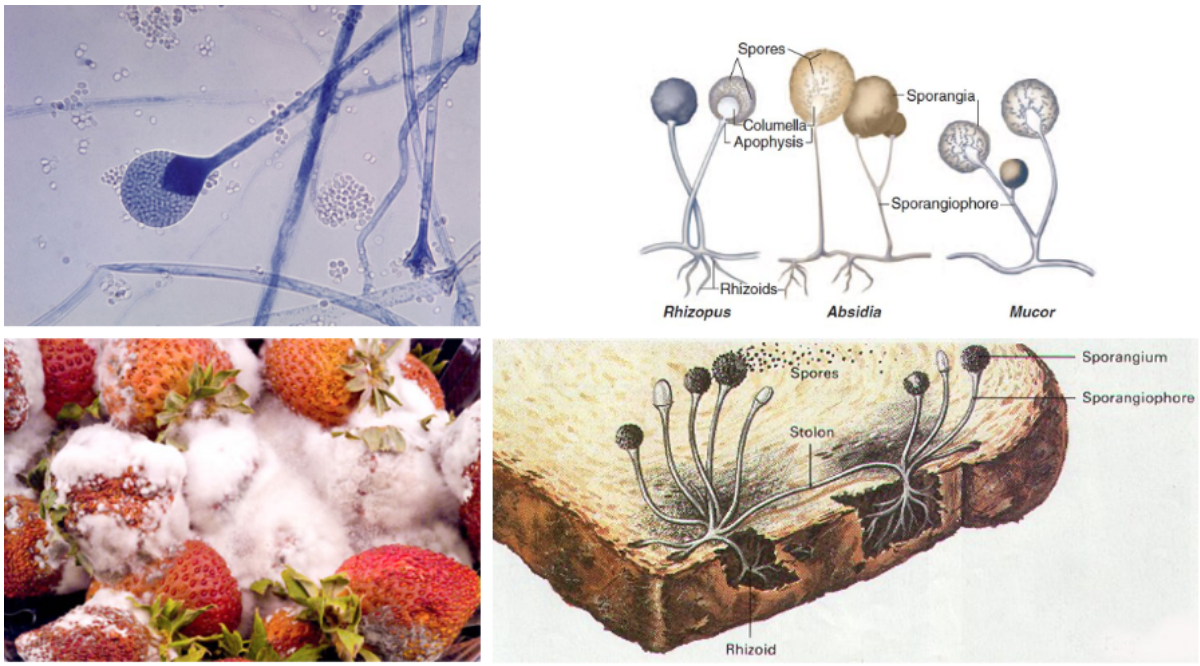


Figure 21: Ecology and morphology of Mucorales. These ubiquitous environmental saprophytes are found in soil and decaying organic matter. Characteristic features include large, ribbon-like, pauciseptate hyphae with right-angle branching — distinguishing them from the septate, acute-angle-branching hyphae of *Aspergillus*.

Risk Factors:

- Uncontrolled diabetes mellitus (especially ketoacidosis)
- Hematologic malignancy with neutropenia
- Hematopoietic stem cell transplant
- Solid organ transplant
- Iron overload states
- Deferoxamine therapy (acts as a siderophore)
- Trauma, burns
- COVID-19 (especially in India, 2021 outbreak)

Common Species

Table 14: Common Mucorales Species

Genus	Clinical Significance
Rhizopus spp.	Most common (especially *R. arrhizus*)

Genus	Clinical Significance
Mucor spp.	Less common but significant
Lichtheimia spp.	Common in immunocompromised
Rhizomucor spp.	More aggressive disease
Cunninghamella spp.	Disseminated disease; very poor prognosis
Apophysomyces spp.	Cutaneous/soft tissue (trauma)

Pathogenesis

Mucorales have a unique relationship with iron:

1. Spores inhaled, deposited in nasal turbinates or alveoli
2. Macrophages attempt phagocytosis (impaired by glucocorticoids)
3. Neutrophils damage hyphal forms; iron acquisition supports proliferation
4. **Angioinvasion** leads to thrombosis, hemorrhage, and tissue necrosis
5. Hyperglycemia, acidosis, and free iron facilitate growth

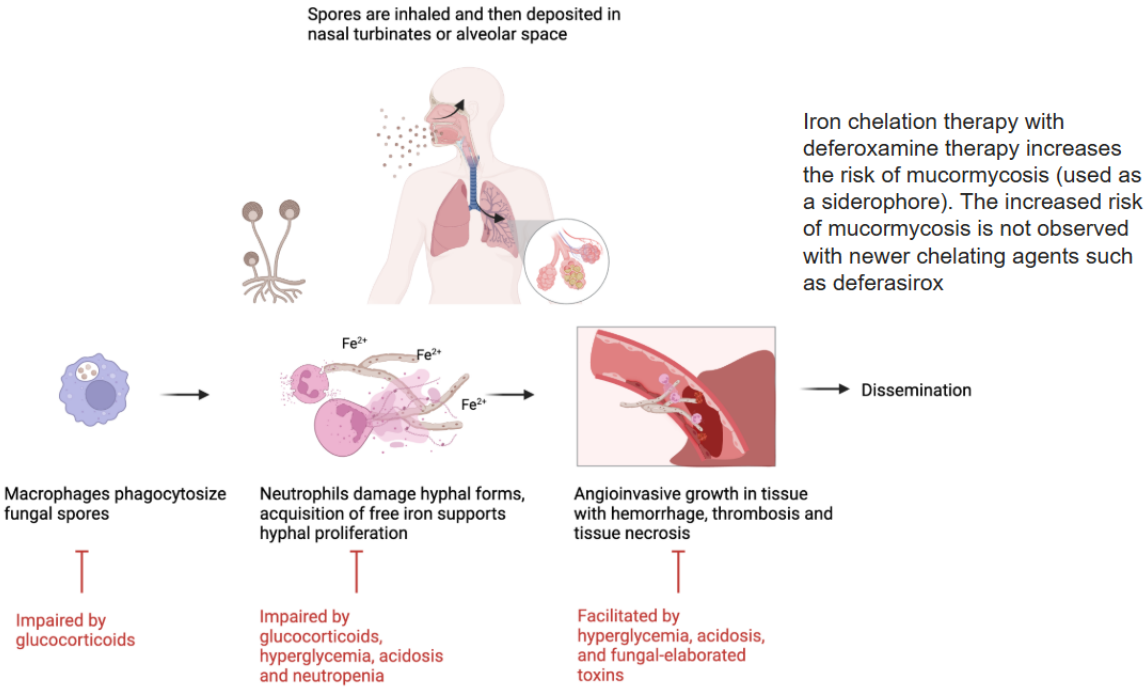


Figure 22: Pathogenesis of mucormycosis. The interplay of metabolic factors (hyperglycemia, acidosis, iron overload) and immune defects (impaired macrophage and neutrophil function) creates the conditions for spore germination, angioinvasion, and rapid tissue destruction.

Deferoxamine Risk

Iron chelation with deferoxamine increases mucormycosis risk (fungus uses it as a xenosiderophore). Newer chelating agents like deferasirox do not carry this risk.

Clinical Manifestations

Rhinocerebral Mucormycosis:

- Most common form in diabetic patients
- Begins with sinusitis, facial pain
- Rapid progression with necrotic eschar (black eschar = late finding)
- Orbital involvement: Proptosis, vision loss
- Cavernous sinus thrombosis
- CNS extension: High mortality

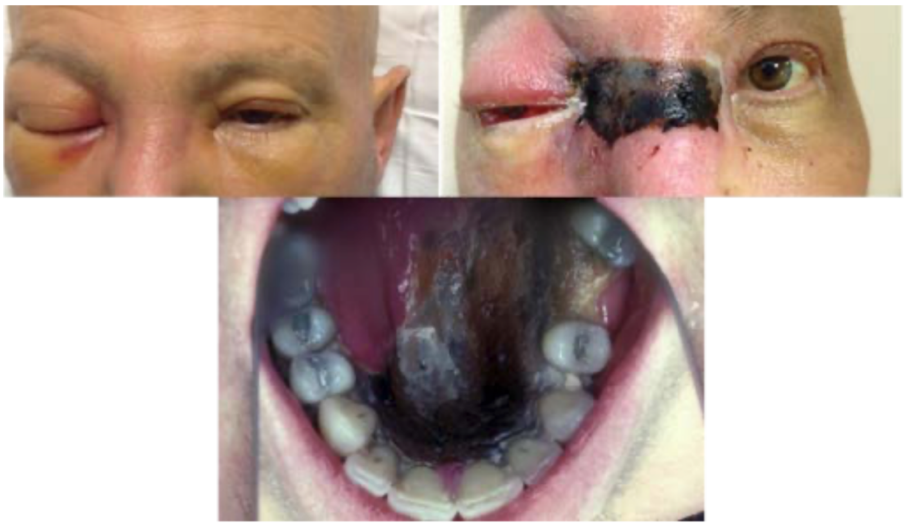


Figure 23: Progression of rhinocerebral mucormycosis. What begins as facial pain and sinusitis can progress rapidly to periorbital edema, black nasal eschar, and orbital/CNS invasion. "Time is tissue" — any diabetic patient with periorbital swelling or facial pain/numbness requires urgent evaluation. Black eschar is a late sign; do not wait for it before acting.

Pulmonary Mucormycosis:

- More common in neutropenic patients
- Nodular infiltrates
- Reverse halo sign

- Pleural effusions
- Rapid progression

Cutaneous Mucormycosis:

- Trauma, burns, surgical wounds
- Natural disasters (e.g., Joplin tornado)
- Combat injuries
- Necrotizing soft tissue infection

Diagnosis

> **!** Diagnostic Limitations
>
> Serum -D-glucan and galactomannan do NOT detect Mucorales. These tests being negative does not exclude mucormycosis.

Diagnostic Approach:

- Histopathology: Wide (6-16 m), ribbon-like, pauciseptate hyphae with right-angle branching
- Culture: Rapid growth ("lid lifter"); confirm species identification
- PCR/sequencing: Available in some centers
- MALDI-TOF: For isolate identification

Imaging:

- MRI: "Black turbinate sign" (devitalized tissue in sinuses)
- CT: Reverse halo sign in pulmonary disease

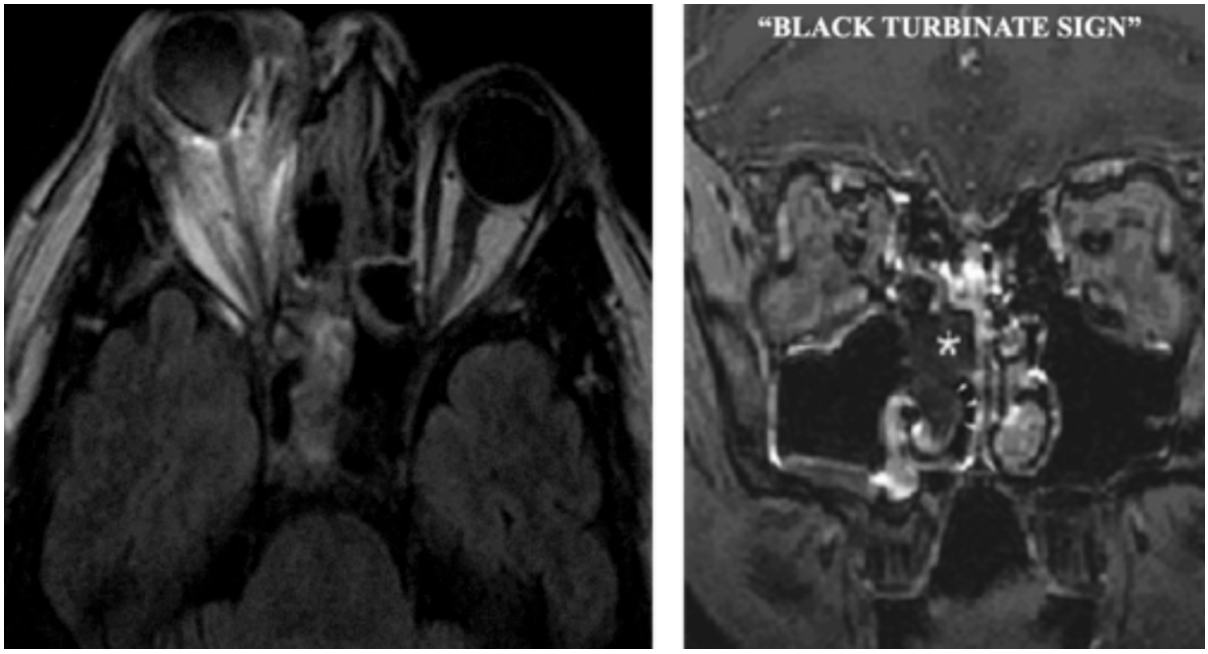


Figure 24: MRI "black turbinate sign" in rhinocerebral mucormycosis. Loss of contrast enhancement of the turbinates indicates devitalized, infarcted tissue — a highly specific finding in the appropriate clinical context. MRI is more sensitive than CT for early tissue invasion; a normal CT should not provide false reassurance in a high-risk patient.

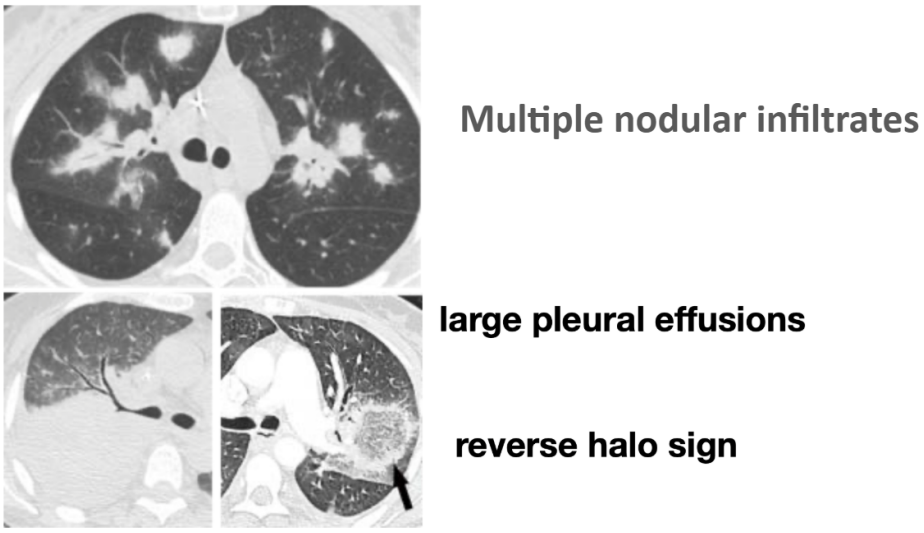


Figure 25: Reverse halo sign on CT in pulmonary mucormycosis. In contrast to the aspergillosis halo sign (dense nodule surrounded by ground-glass), the reverse halo shows ground-glass opacity *surrounded* by a rim of consolidation. This finding is relatively specific for pulmonary mucormycosis in the appropriate clinical setting.

Treatment

Principles:

1. **Surgical debridement**: Essential; often requires multiple operations
2. **Reversal of predisposing conditions**: Glucose control, reduce immunosuppression
3. **Antifungal therapy**: Start immediately

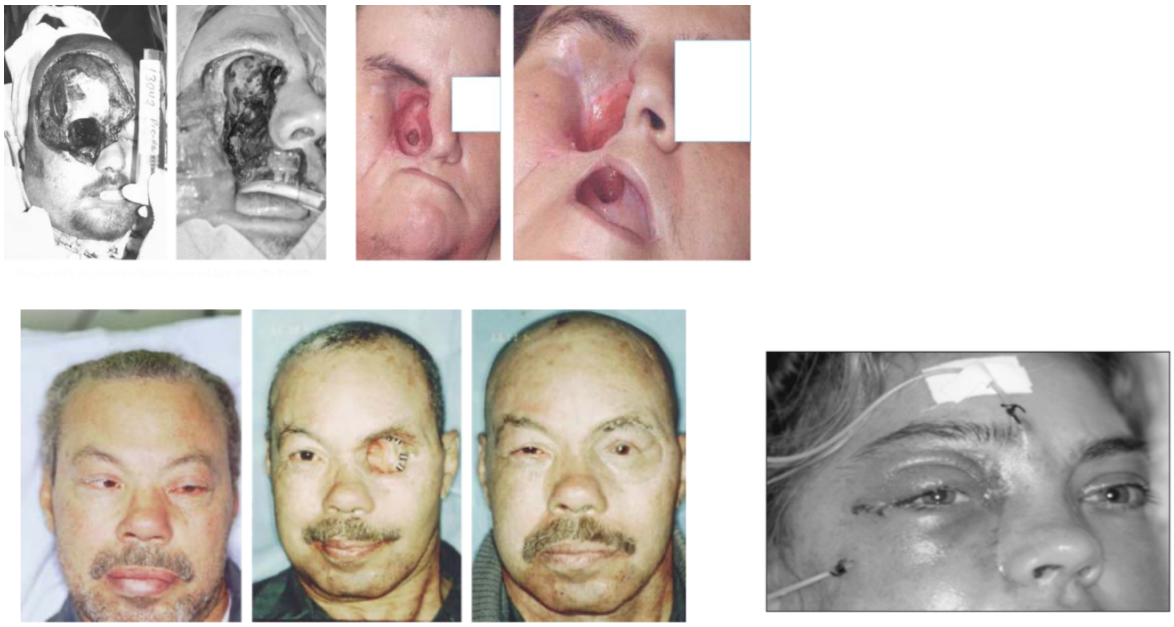


Figure 26: Radical surgical debridement for rhinocerebral mucormycosis. While often disfiguring, aggressive surgery removing all necrotic tissue is associated with significantly improved survival. Facial prosthetics and reconstructive surgery can be pursued after the infection is cured. Do not delay surgery awaiting culture results in high-risk patients.

Antifungal Regimen:

- **Initial**: Liposomal amphotericin B 5-10 mg/kg/day
- **Step-down**: Posaconazole or isavuconazole (for patients responding or with toxicity)
- **Duration**: Prolonged; minimum until clinical/radiographic resolution

Treatment Pearls

- Higher doses of L-AMB (10 mg/kg/day) may be considered for CNS involvement
- Combination therapy (L-AMB + posaconazole/isavuconazole) is sometimes used but not proven superior
- Surgical debridement should not be delayed for imaging; early aggressive surgery improves outcomes

Prognosis

Mucormycosis carries significant morbidity and mortality:

- Overall mortality: 40-80% depending on form and host
- Rhinocerebral with CNS extension: >80% mortality
- Disseminated disease: >90% mortality
- Factors improving survival: Early diagnosis, surgical debridement, immune recovery

Healthcare Professional Survey

In a Twitter poll of 1,885 infectious disease specialists, 44% rated mucormycosis as the "scariest" infectious disease, more than *Candida auris* (18%), *Staphylococcus aureus* (24%), or SARS-CoV-2 (14%).

Antifungal Toxicities

Amphotericin B Toxicities

Nephrotoxicity

Amphotericin B deoxycholate causes significant nephrotoxicity through multiple mechanisms:

1. **Afferent arteriole constriction**: Reduced renal blood flow
2. **Tubuloglomerular feedback**: Further vasoconstriction
3. **Direct tubular toxicity**: LDL-bound AMB accumulates via LDL receptors
4. **Electrolyte wasting**: K , Mg^{2} , Na loss

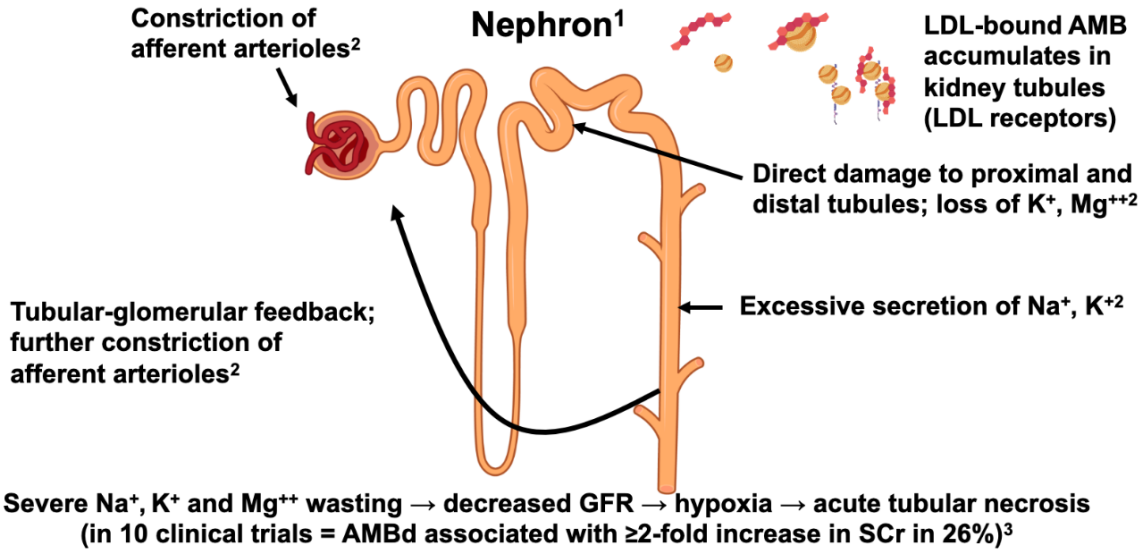


Figure 27: Mechanism of amphotericin B nephrotoxicity. Afferent arteriolar vasoconstriction reduces renal blood flow, while LDL-mediated drug accumulation in tubular cells causes direct damage and electrolyte wasting. Understanding this mechanism helps guide monitoring (creatinine, potassium, magnesium) and underscores the advantage of liposomal formulations.

Clinical Impact:

- 2-fold increase in serum creatinine in 26% of patients receiving AMB deoxycholate
- Severe electrolyte abnormalities common

Liposomal Formulation Advantages

Liposomal amphotericin B reduces nephrotoxicity:

- Liposomes do not undergo glomerular filtration
- Reduced binding to LDL receptors
- 2-fold SCr increase in only 10% of patients
- Allows higher dosing when needed

Infusion-Related Reactions

- Fever, rigors, chills
- Hypotension

- More common with deoxycholate formulation
- Premedication with acetaminophen, diphenhydramine may help

Triazole Toxicities

Table 15: Triazole-Specific Toxicities

Toxicity	Most Commonly Associated Agent(s)
Hepatotoxicity	All azoles (highest with voriconazole)
QTc prolongation	All azoles (less with isavuconazole)
Visual disturbances (photopsia)	Voriconazole
Phototoxicity/skin cancer	Voriconazole (long-term)
CNS effects (hallucinations)	Voriconazole
Peripheral neuropathy	Itraconazole > voriconazole > others
GI intolerance	Itraconazole, posaconazole
Cardiomyopathy	Itraconazole
Periostitis (bone pain)	Voriconazole (fluoride toxicity)
Adrenal suppression	Itraconazole, posaconazole

Monitoring Recommendations

- Liver function tests at baseline and periodically during therapy
- Trough drug levels for voriconazole (target 1-5 g/mL), posaconazole (>1 g/mL), and isavuconazole (if concerns about efficacy/toxicity)
- ECG at baseline if risk factors for QTc prolongation
- Visual symptoms inquiry for voriconazole patients

Summary and Key Points

Take-Home Messages

Invasive Candidiasis:

- Blood cultures miss 50% of cases; use adjunctive diagnostics
- Source control (catheter removal) improves outcomes
- Echinocandins are first-line for unstable patients
- Dilated eye exam for all patients with candidemia

Cryptococcosis:

- CrAg screening for HIV patients with CD4 <100

- Single high-dose L-AMB (AMBITION regimen) is preferred
- Aggressive ICP management is critical
- Avoid corticosteroids

Invasive Aspergillosis:

- Early CT and galactomannan testing in high-risk patients
- Voriconazole, isavuconazole, or posaconazole for primary therapy
- Use L-AMB if breakthrough on azole prophylaxis
- Monitor for azole resistance

Mucormycosis:

- -D-glucan and galactomannan do NOT detect Mucorales
- Surgical debridement is essential
- High-dose liposomal amphotericin B (5-10 mg/kg/day)
- Control underlying conditions (diabetes, immunosuppression)

Appendix: Quick Reference Tables

Antifungal Dosing Reference

Table 16: Antifungal Dosing Quick Reference

Drug	Loading Dose	Maintenance Dose	Notes
Fluconazole	800 mg	400 mg daily	Dose-adjust for renal impairment
Voriconazole	6 mg/kg IV q12h × 2	4 mg/kg IV q12h or 200–300 mg PO q12h	TDM target: 1–5 g/mL; avoid IV in renal impairment (cyclodextrin)
Posaconazole DR	300 mg q12h × 2	300 mg daily	Tablet preferred over suspension (better bioavailability)

Drug	Loading Dose	Maintenance Dose	Notes
Isavuconazole	200 mg q8h × 6 doses	200 mg daily	No dose adjustment for renal/hepatic impairment
Caspofungin	70 mg	50 mg daily	Dose-adjust for hepatic impairment
Micafungin	—	100 mg daily	—
Anidulafungin	200 mg	100 mg daily	—
Liposomal AMB	—	3–5 mg/kg daily (mucormycosis: 5–10 mg/kg)	Monitor renal function and electrolytes

Antifungal Drug Interactions

All triazoles are significant CYP450 inhibitors. Dose reductions and/or level monitoring are essential when co-administering with immunosuppressants and other narrow-therapeutic-index drugs.

Table 17: Key Azole Drug Interactions via CYP450

Azole	CYP Inhibition	Key Interactions
Voriconazole	3A4, 2C19, 2C9	Calcineurin inhibitors (↑↑), sirolimus (↑↑↑; often contraindicated), warfarin, phenytoin
Posaconazole	3A4	Calcineurin inhibitors (↑↑), sirolimus (↑↑↑), statins
Isavuconazole	3A4 (moderate)	Calcineurin inhibitors (↑); fewer interactions than voriconazole
Fluconazole	3A4, 2C9	Warfarin (↑↑), calcineurin inhibitors (↑), sulfonylureas

⚠ Sirolimus and Voriconazole

Voriconazole dramatically increases sirolimus levels (often 10-fold or more). This combination is generally avoided; if unavoidable, reduce sirolimus dose by ~90% and monitor levels closely.

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