

Fungal Meningoencephalitis

Organisms • routes of entry • patterns of tissue injury • morphology

Pathology teaching lecture

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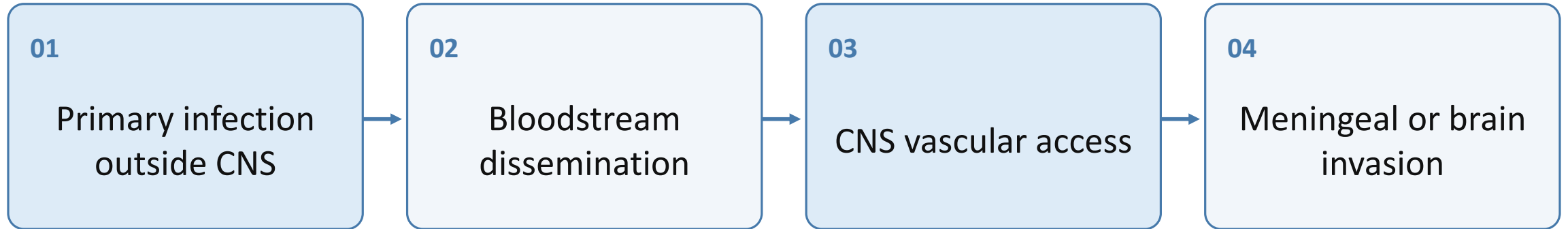
Learning objectives

- Recognize routes of fungal invasion and the three characteristic patterns of CNS injury.
- Differentiate Candida, Cryptococcus, Aspergillus, and mucormycetes by disease pattern and morphology.
- Integrate host immune status, organism morphology, vascular effects, and diagnostic evidence.

CNS fungal infection: Clinical setting

- CNS fungal infections occur predominantly in immunocompromised individuals.
- The brain is usually involved after disseminated hematogenous fungal infection.
- The immune state profoundly affects both tissue response and pattern of involvement.

Two principal routes to the CNS



A distinct route is local extension, notably from the sinuses into the orbit and brain in rhinocerebral mucormycosis.

Frequent agents in CNS mycoses

- *Candida albicans*: Commonly linked to disseminated candidiasis and brain microabscesses.
- *Cryptococcus neoformans*: Encapsulated yeast with meningitis and perivascular accumulation.
- *Aspergillus fumigatus* and mucormycetes: Strongly associated with angioinvasive injury.

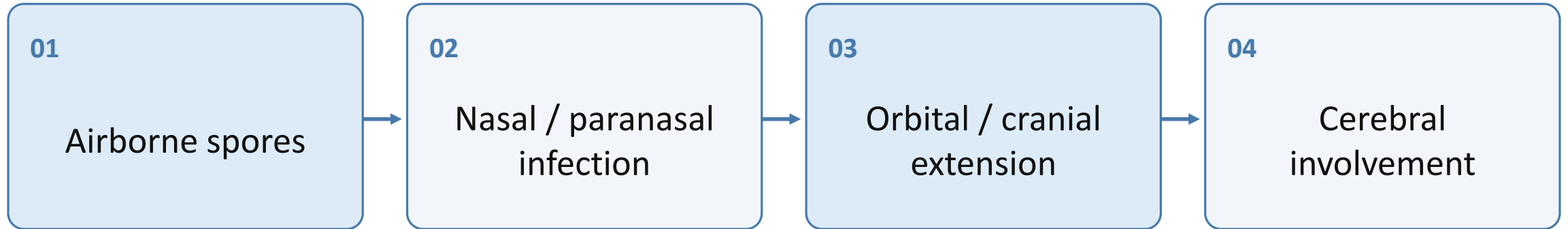
Major fungi and characteristic CNS patterns

Agent	Predominant clue	Typical CNS pathology
Candida	Disseminated invasive candidiasis	Multiple microabscesses ± granulomas
Cryptococcus	Encapsulated budding yeast	Chronic meningitis; perivascular aggregates
Aspergillus	Septate acute-angle hyphae	Angioinvasive necrosis; infarction
Mucormycetes	Broad, sparsely septate hyphae	Rhinocerebral spread; arterial invasion

Geographically endemic fungi can involve the CNS

- Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitidis are recognized causes.
- CNS involvement may follow a primary pulmonary or cutaneous infection.
- Immunosuppression increases the probability of dissemination.

Direct spread: Sinonasal origin



Diabetes mellitus, especially with ketoacidosis, is an important host context for rhinocerebral mucormycosis.

The three CNS injury compartments

MENINGES: Chronic meningitis

VESSELS: Necrotizing vasculitis, thrombosis, hemorrhagic infarction

PARENCHYMA: Microabscesses, granulomas, or yeast aggregates

An infection may involve more than one compartment simultaneously.

Three principal patterns of fungal injury

Chronic meningitis

Persistent fungal involvement of meninges; Especially characteristic of cryptococcal disease.

Vasculitis

Angioinvasion damages vessels; Thrombosis and infarction may follow.

Parenchymal invasion

Organisms form abscesses, granulomas, or perivascular collections in the brain.

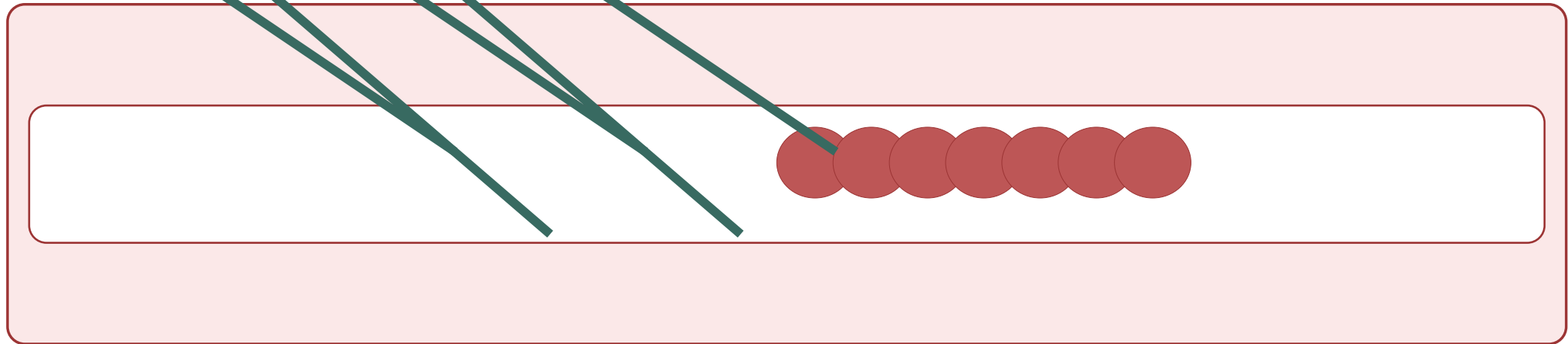
More than one pattern may be present in the same patient.

Chronic fungal meningitis

- The leptomeninges are a major target in cryptococcal disease.
- Inflammation can be surprisingly sparse in severely immunosuppressed hosts.
- Chronic granulomatous reactions are more likely when host cell-mediated defenses are relatively preserved.

Angioinvasion → thrombosis → infarction

Fungal penetration of vessel wall



Intraluminal thrombosis

Downstream hemorrhagic infarction

Schematic: Vascular invasion

Why vascular invasion is especially destructive

- Aspergillus and mucormycetes penetrate vessel walls.
- Necrotizing vasculitis promotes intravascular thrombosis.
- Loss of perfusion causes infarction that may be strikingly hemorrhagic.

Parenchymal infection: Two broad responses

Suppuration

- Fungal microabscesses
- Prominent neutrophil-rich injury can occur
- Candida often produces multiple brain microabscesses

Granulomatous reaction

- Macrophage-rich chronic response
- Can accompany Candida or Cryptococcus
- Magnitude depends on the host immune response

Host–organism–tissue interaction

Organism

Morphologic phenotype

Host defenses

Level and type of
inflammation

Tissue

Meningitis / vasculitis /
invasion

The same fungus may produce markedly different tissue reactions in different hosts.

Immune status changes morphology

- Severe immunosuppression may permit extensive organisms with little inflammation.
- More effective cell-mediated immunity may support macrophage-rich granulomas.
- Interpret the inflammatory response together with fungal burden and clinical context.

Tissue patterns: A diagnostic orientation

Pattern	Key process	Fungi prominently associated
Meningitis	Meningeal fungal persistence	Cryptococcus; endemic fungi
Microabscess	Parenchymal suppurative foci	Candida
Angioinvasion	Vessel injury and thrombosis	Aspergillus; mucormycetes
Perivascular yeast	Expanded Virchow–Robin spaces	Cryptococcus

Cryptococcal meningoencephalitis

- *Cryptococcus neoformans* and *C. Gattii* grow as encapsulated yeasts in human tissue.
- The CNS is a major site of disease following an often subtle pulmonary infection.
- Disease may affect meninges, cortical gray matter, and basal nuclei.

Two clinically important *Cryptococcus* species

C. Neoformans

- Frequent opportunist in AIDS or other immunosuppression
- Often causes meningeal disease
- Can occasionally infect otherwise healthy people

C. Gattii

- May cause disease in apparently immunocompetent hosts
- Associated with localized mass lesions
- Potential immune predisposition still warrants evaluation

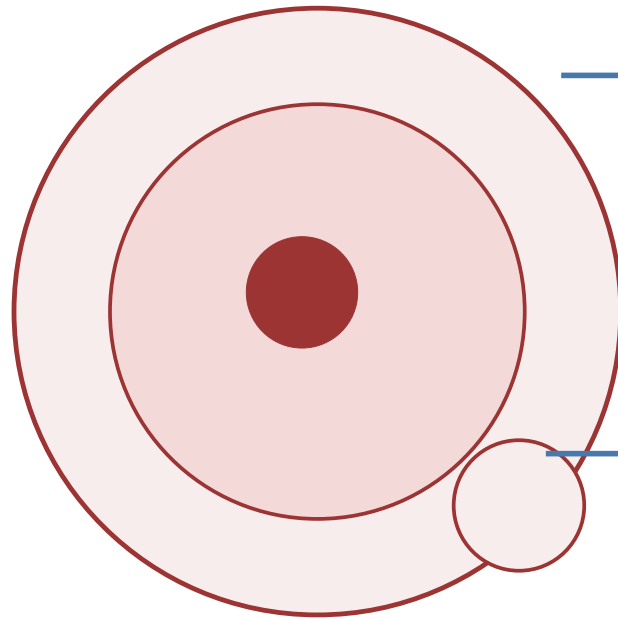
Cryptococcus: Exposure and entry

- Environmental yeasts are acquired principally by inhalation.
- *C. Neoformans* occurs in soil, notably soil containing pigeon guano.
- *C. Gattii* occurs in soils and trees, including eucalypts.
- Pulmonary infection can precede CNS dissemination without prominent pulmonary symptoms.

Risk contexts for C. Neoformans

- HIV-associated immunosuppression / AIDS.
- Leukemia, lymphoma, or immunosuppressive treatment after transplantation.
- Systemic lupus erythematosus and other disorders affecting host defense.
- High-dose corticosteroid exposure is a major recognized risk factor.

Cryptococcus: Capsule and budding yeast



Polysaccharide capsule

Impedes phagocytosis and recruitment of inflammatory cells

Budding yeast

Capsule stains with mucicarmine and PAS

Schematic — not a photomicrograph

The cryptococcal capsule subverts host defense

- The polysaccharide capsule impedes alveolar macrophage phagocytosis.
- It limits leukocyte migration and recruitment of inflammatory cells.
- It can reduce dendritic-cell antigen presentation and cytokine production.

Cryptococcal melanin and virulence

- Laccase catalyzes melanin synthesis.
- Melanin supplies antioxidant protection and interferes with antibody-mediated phagocytosis.
- The source also describes effects on antifungal susceptibility, iron binding, and cell-wall integrity.

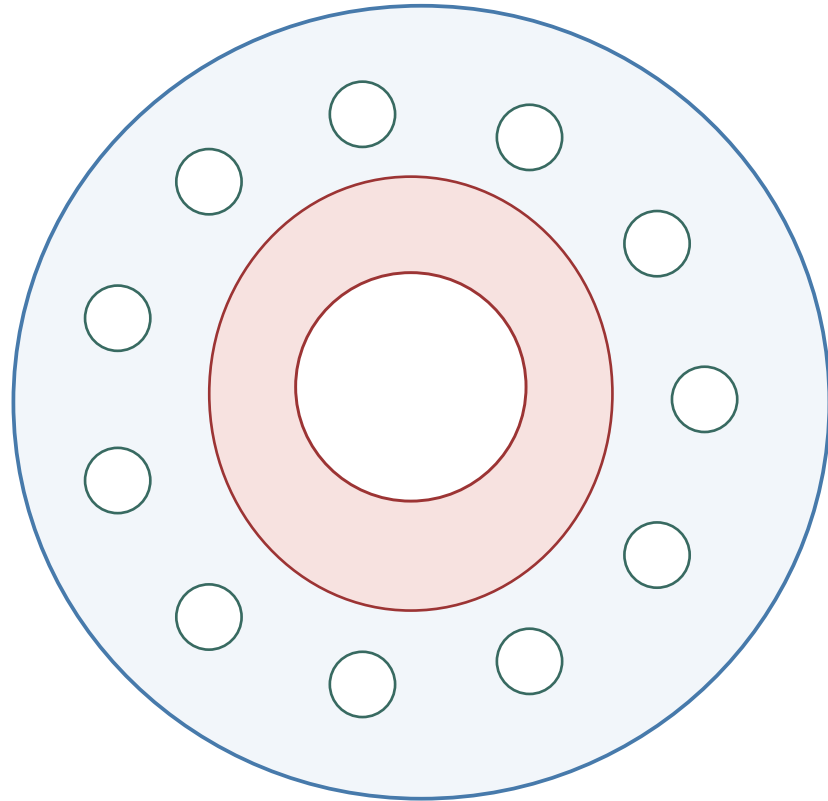
Other cryptococcal virulence attributes

- Phospholipases may facilitate invasion.
- Urease helps counter conditions inside phagocytic cells.
- Chitin is necessary for structural stability of the yeast cell wall.
- Titan cells and small microcells illustrate variable fungal cell size.

Cryptococcus: Tissue morphology

- Round budding yeast without hyphae or pseudohyphae in human tissue.
- An abundant gelatinous polysaccharide capsule surrounds the yeast.
- The capsule is highlighted by mucicarmine and periodic acid–Schiff stains.

Perivascular cryptococcal “soap-bubble” spaces



Expanded perivascular space

Collections of encapsulated cryptococcal yeasts can accumulate with minimal inflammatory response.

“Soap-bubble” appearance

Schematic — not histology

Why cryptococcal lesions may appear minimally inflamed

- Encapsulated organisms can expand perivascular spaces with little reaction.
- Severe cellular immune impairment limits effective inflammatory recruitment.
- Marked organism burden does not necessarily imply marked tissue inflammation.

Cryptococcal host response: Contrasting extremes

Severe immunosuppression

- Abundant yeasts
- Scant inflammation or gliosis
- Gelatinous meningeal and perivascular collections

More preserved immunity

- Chronic macrophage-rich granulomas
- Lymphocytes and giant cells
- Suppuration or granulomatous arteritis may occur

Cryptococcal meningitis: Time course

- Clinical evolution can be very rapid, including fulminant fatal disease.
- Other cases evolve indolently over months or years.
- Course should be interpreted alongside host immune status and fungal burden.

Cryptococcal CSF and antigen evidence

- CSF may contain relatively few inflammatory cells.
- Protein concentration is usually elevated.
- Yeast may be demonstrated with appropriate stains; Cryptococcal antigen assays provide indirect organism evidence.

Cryptococcoma: A space-occupying pattern

- C. Gattii may form relatively large localized CNS fungal masses.
- Mass effect can produce symptoms of increased CNS pressure.
- Imaging may mimic a neoplasm; Morphology and organism-directed studies remain necessary.

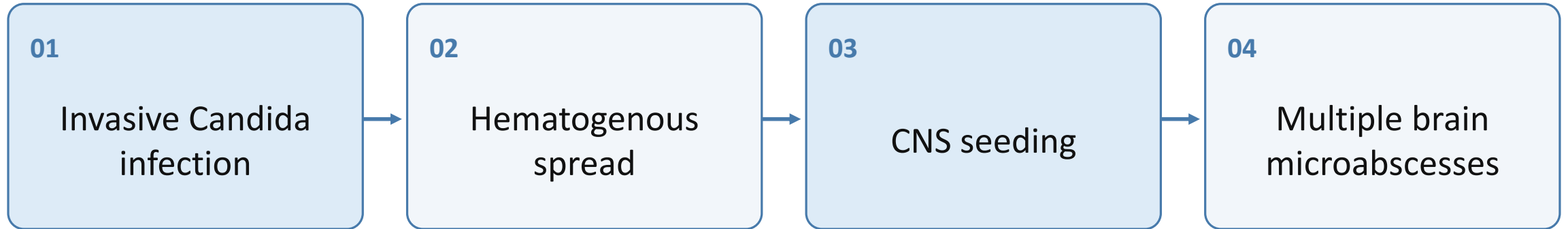
Cryptococcus: Organism, host, lesion

Dimension	Dominant clue	Pathology significance
Organism	Encapsulated budding yeast	Mucicarmine / PAS-positive capsule
Host	Impaired cell-mediated immunity	Fungi with scant reaction
Location	Meninges and perivascular spaces	Chronic meningitis; soap bubbles
Variant pattern	C. gattii mass lesion	Cryptococcoma / mass effect

Cerebral candidiasis

- Candida reaches the CNS during invasive disseminated disease.
- Brain involvement commonly produces multiple microabscesses.
- Granulomatous reactions can coexist with suppurative lesions.

Candida: Disseminated infection to microabscess



Inflammation may be sparse, suppurative, or granulomatous depending on the degree of host immune competence.

Candida: Morphology and staining

- Candida may show budding yeast and pseudohyphal forms in tissue.
- Gömöri methenamine silver and PAS stains help demonstrate fungal elements.
- Morphologic recognition must be integrated with invasive disease and host status.

Candida: The immune-response spectrum

- Profound neutropenia predisposes to invasive systemic candidiasis.
- Infected tissue can contain little inflammation, an acute suppurative response, or granulomas.
- Lesion morphology is shaped by both fungus and host defenses.

Mucormycosis: Organisms and disease

- Opportunistic infection caused by molds such as Mucor and Rhizopus.
- Additional genera named include Rhizomucor and Cunninghamella.
- CNS involvement may follow direct spread or disseminated disease.

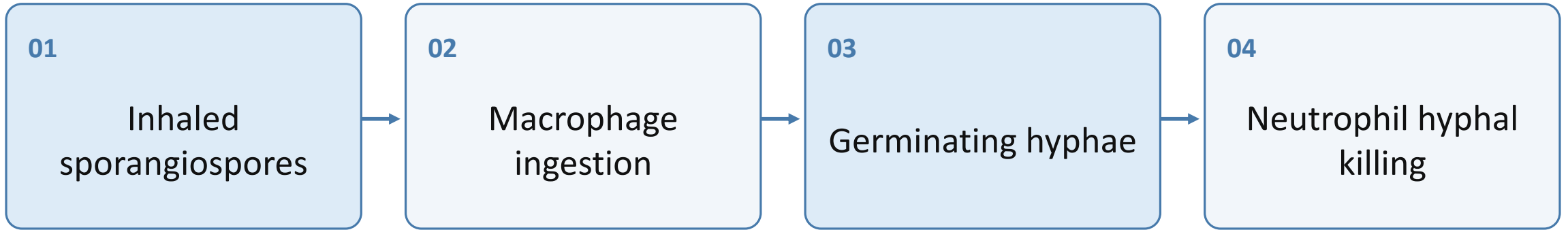
Major host factors in mucormycosis

- Diabetes mellitus, including diabetic ketoacidosis.
- Neutropenia and systemic corticosteroid treatment.
- Iron overload and disruption of protective tissue barriers.

Mucormycetes: Iron and susceptibility

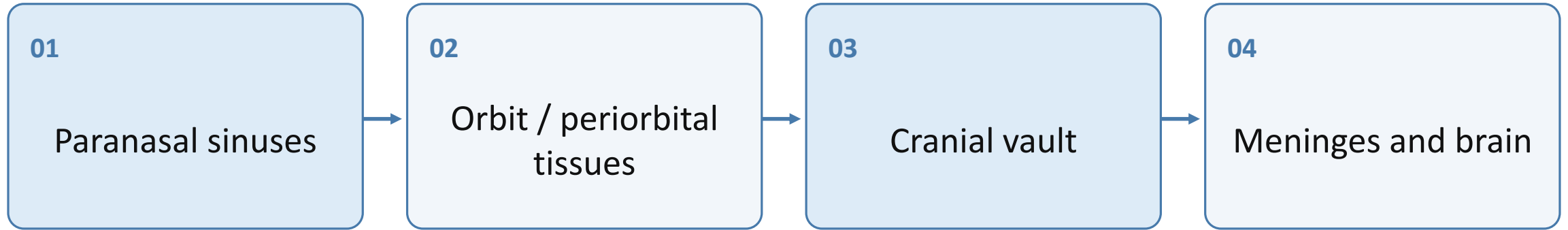
- Fungal growth is enhanced by accessible free iron.
- Diabetic ketoacidosis can increase available free iron.
- Deferoxamine can act as a siderophore for the organism.

Mucor defense: Spores to tissue invasion



Macrophage or neutrophil dysfunction permits the fungus to establish invasive infection.

Rhinocerebral mucormycosis sequence



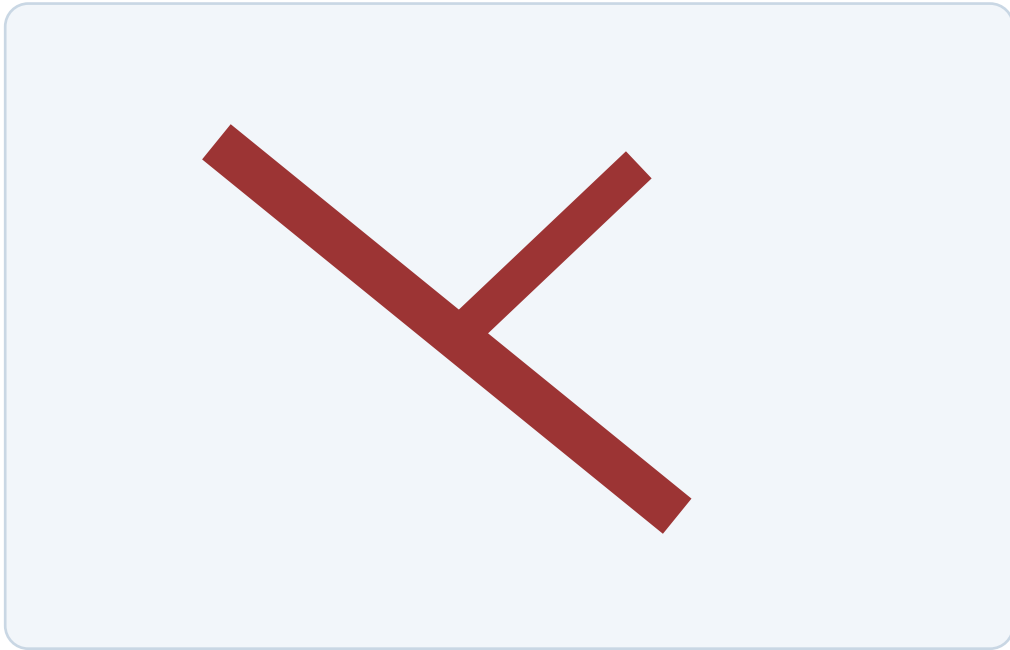
Local necrosis and arterial invasion can culminate in meningoencephalitis and cerebral infarction.

Rhinocerebral mucormycosis: Tissue damage

- Fungi invade nasal or sinus tissues and spread into neighboring compartments.
- Invasion of arteries produces thrombosis and ischemic injury.
- Infarction may complicate fungal meningoencephalitis.

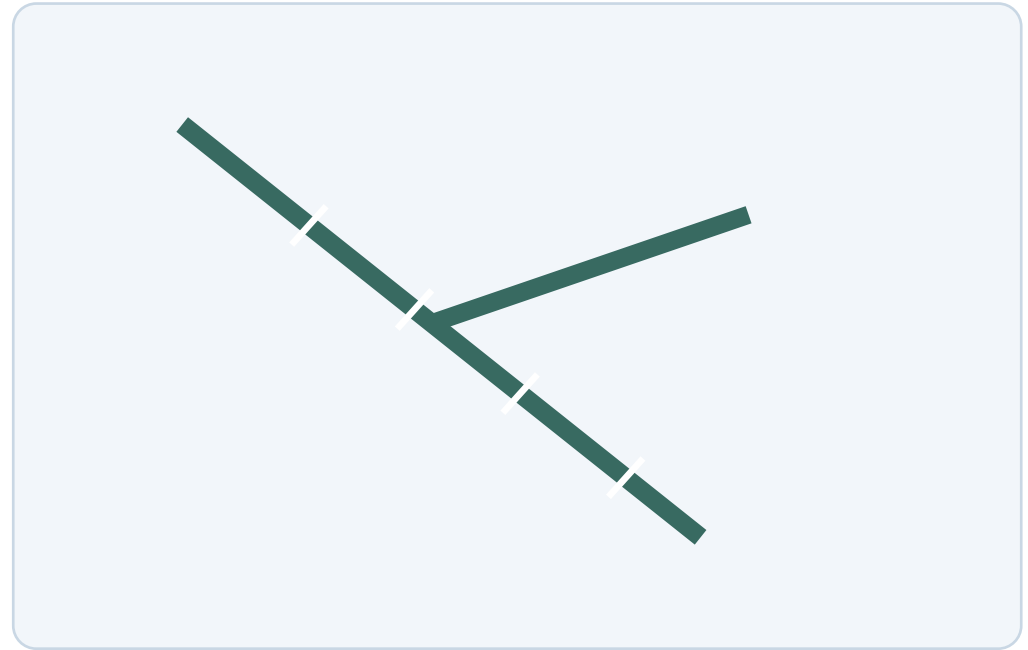
Angioinvasive molds: Basic tissue morphology

Mucormycetes



Broad, irregular; Few or absent septa; Near right-angle branching

Aspergillus



Narrower, septate; Acute-angle branching

Illustrative morphology — not a tissue section

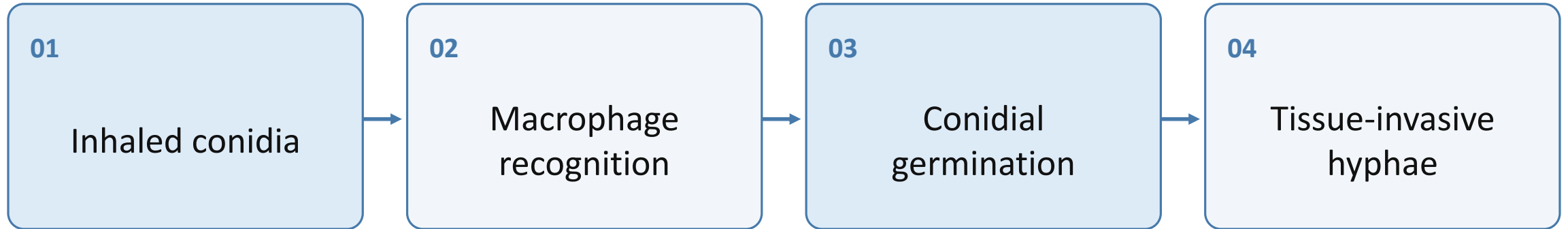
Mucormycetes: Microscopic recognition

- Hyphae tend to be broad, irregular in width, and nonseptate or sparsely septate.
- Branching frequently approaches a right angle.
- H&E and special fungal stains may reveal organisms invading arterial walls.

Aspergillus: Setting and entry

- A. Fumigatus is the most common pathogenic Aspergillus species named.
- Airborne conidia primarily enter via the respiratory tract.
- Neutropenia and corticosteroid exposure favor invasive infection.

Aspergillus: Initial defense versus invasion



Dectin-1 and TLR2 are involved in recognition; Neutrophils are essential in killing hyphae.

Aspergillus: Why neutropenia matters

- Alveolar macrophages ingest and kill inhaled conidia.
- Neutrophils produce reactive oxygen intermediates that damage fungal hyphae.
- Impaired neutrophil defenses strongly favor invasive aspergillosis.

Aspergillus: Microscopic morphology

- Tissue hyphae are typically septate.
- Acute-angle branching is characteristic.
- Similar-appearing hyphae may be caused by other filamentous fungi; Morphologic appearance alone is not always species-specific.

Aspergillus: Vascular invasion and CNS injury

- Pulmonary invasive disease may disseminate hematogenously to brain.
- Angioinvasion is a prominent pathologic feature.
- Hemorrhage and infarction accompany necrotizing inflammation.

Aspergillus versus mucormycetes

Feature	Aspergillus	Mucormycetes
Hyphae	Narrower, septate	Broad, irregular; often aseptate
Branching	Acute angle	Frequent near right angles
Risk context	Neutropenia; corticosteroids	Diabetes; neutropenia; steroids; iron
Major CNS clue	Disseminated angioinvasion	Rhinocerebral extension; angioinvasion

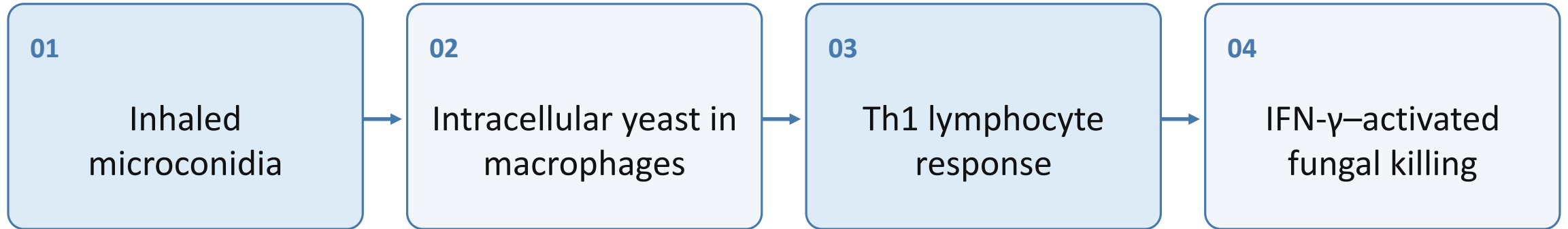
Important pitfall: Hyphal morphology is not unique

- Aspergillus-like septate acute-angle hyphae may occur with other molds.
- Overlap with *Pseudallescheria boydii* and *Fusarium*.
- Species assignment should not be made solely from an undifferentiated tissue fragment.

Histoplasma: CNS risk arises from dissemination

- Primary infection typically begins after inhalation of environmental microconidia.
- Intracellular yeast survives in macrophages until effective T-cell immunity develops.
- Dissemination may include meninges, especially with impaired cell-mediated immunity.

Histoplasma and macrophage activation



Disseminated infection is more likely when this cell-mediated pathway is impaired.

Coccidioides: Meningeal dissemination

- *Coccidioides immitis* and *C. Posadasii* are endemic dimorphic fungi.
- Most primary infections are clinically limited; A minority disseminate.
- Disseminated infection may involve the meninges; Depressed T-cell immunity is a risk factor.

Coccidioides: Distinctive tissue form

- Tissue form is a thick-walled spherule with many internal endospores.
- Rupture releases endospores and may provoke a pyogenic reaction.
- Inflammation may be granulomatous, suppurative, or mixed at involved sites.

Blastomyces: Disseminated disease

- Blastomyces dermatitidis commonly enters as a pulmonary infection.
- Disseminated disease is a recognized clinical pattern.
- The brain may be involved after dissemination, as noted in the CNS fungal overview.

Blastomyces: Recognizable tissue yeast

- Round yeast with a thick, double-contoured cell wall.
- Broad-based budding is a characteristic morphologic clue.
- Inflammatory lesions may be suppurative granulomas.

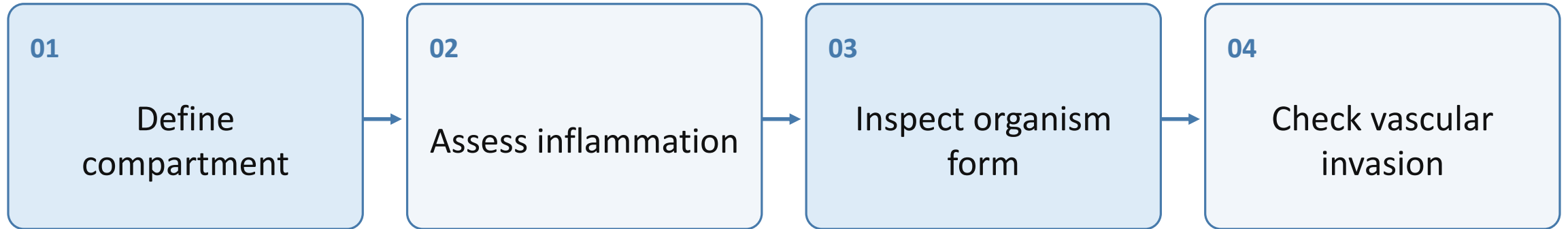
Endemic fungi: Microscopy and CNS relevance

Organism	Tissue form	Relevant route or disease
Histoplasma	Small yeasts in macrophages	Hematogenous spread; meninges
Coccidioides	Spherules with endospores	Dissemination to meninges
Blastomyces	Thick-walled, broad-budding yeast	Disseminated disease can affect CNS

Morphology-focused differentiation of fungi

Tissue observation	Prioritize	Important caution
Encapsulated budding yeasts	Cryptococcus	Host reaction may be nearly absent
Multiple suppurative microabscesses	Candida	Use special stains for organism demonstration
Septate acute-angle hyphae	Aspergillus-like molds	Other hyaline molds can look similar
Broad nonseptate hyphae	Mucormycetes	Look for vessel wall invasion

Pathology interpretation: Start with pattern



Integrate the observed pattern with exposure and immunosuppression; Do not equate morphology with definitive species identification.

Low inflammation does not exclude severe CNS mycosis

Potential false reassurance

- Relatively few CSF inflammatory cells
- Minimal meningeal gliosis or infiltrate
- Organism-rich perivascular spaces

More informative evidence

- Recognize host immune suppression
- Identify fungal structures with appropriate stains
- Use cryptococcal antigen assays when indicated

Case: Progressive meningitis in advanced HIV

CLINICOPATHOLOGIC VIGNETTE

A person with advanced HIV has subacute neurologic illness. CSF contains few inflammatory cells but raised protein. An encapsulated budding yeast is suspected.

Which fungus and lesion pattern best fit the findings?

Case interpretation: Cryptococcal meningitis

Cryptococcus neoformans — opportunistic meningeal infection

- Limited CSF pleocytosis is compatible with cryptococcal meningitis.
- Mucicarmine/PAS can highlight the capsule; Cryptococcal antigen assays support detection.
- Perivascular yeast aggregates may show minimal inflammatory reaction.

Case: Diabetic patient with sinus-to-brain extension

CLINICOPATHOLOGIC VIGNETTE

A patient with diabetic ketoacidosis develops an invasive paranasal sinus infection extending toward the orbit and cranial vault. Necrotic tissue contains broad, irregular fungal hyphae.

Identify the most likely category and main mechanism of brain injury.

Case interpretation: Rhinocerebral mucormycosis

Mucormycetes — direct extension and arterial invasion

- Fungi can spread from sinuses into the orbit and brain.
- Arterial wall invasion causes thrombosis and cerebral infarction.
- Broad often nonseptate hyphae with near right-angle branching favor this group.

Case: Neutropenia with hemorrhagic cerebral injury

CLINICOPATHOLOGIC VIGNETTE

A profoundly neutropenic person with invasive pulmonary fungal disease develops cerebral lesions with hemorrhagic infarction. Tissue shows septate hyphae branching at acute angles.

What process explains the hemorrhage, and which mold is suggested?

Case interpretation: Invasive aspergillosis

Angioinvasion with thrombosis — Aspergillus-like mold

- Tissue-invasive hyphae damage vessel walls.
- Vascular thrombosis and subsequent hemorrhagic infarction explain CNS injury.
- Septate acute-angle hyphae suggest Aspergillus but are not species-specific.

Final synthesis: Three lesions to recognize

Meningitis

Often cryptococcal; Chronic or fulminant disease may occur even with sparse CSF cells.

Vasculitis

Angioinvasive molds can cause thrombosis and hemorrhagic infarction.

Brain invasion

Candida microabscesses;
Cryptococcal perivascular yeast;
Fungal granulomas.

Match lesion pattern and fungus to the host context.

Selected source references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Primary CNS section: fungal meningoencephalitis and adjacent infectious diseases of the nervous system.
- Supporting infectious disease sections: candidiasis, cryptococcosis, invasive aspergillosis, mucormycosis, and dimorphic fungi.
- All illustrations in this deck are editable educational schematics, not real specimens.