

Pneumonia in the Immunocompromised Host

Pathologic mechanisms, major pathogens, morphology, and diagnostic reasoning

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Learning objectives

Recognize the clinical significance of a new infiltrate in an immunocompromised host.

Connect the immune defect with likely infectious agents and tissue responses.

Differentiate characteristic pulmonary patterns and morphologies.

Distinguish opportunistic infection from conventional pneumonia and noninfectious mimics.

Why pulmonary infiltrates demand attention

New infiltrates are among the common, serious complications of immune suppression.

Fever and other typical signs of infection may be absent.

The differential is broader than in immunocompetent hosts.

Opportunistic infections carry substantial mortality.

Clinical settings associated with immune suppression

Underlying disease

Immune dysfunction arising from illness, including HIV or hematologic disease.

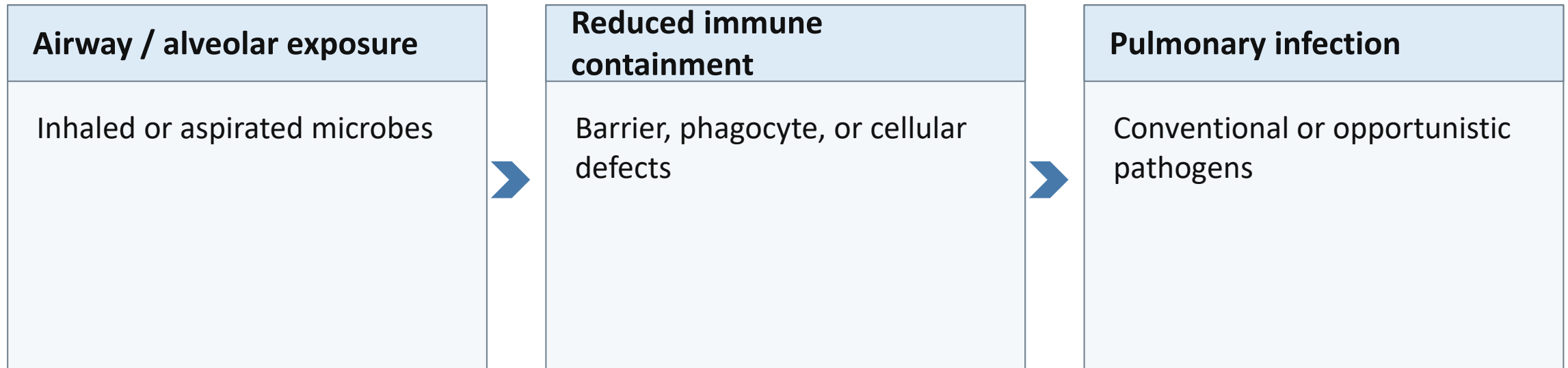
Therapeutic suppression

Immunosuppressive drugs given after organ or stem-cell transplantation.

Cancer therapy

Cytotoxic chemotherapy or irradiation that impairs host defenses.

Host defense failure changes the organism spectrum



Three defenses relevant to pulmonary infection

Airway clearance

Limits deposition and persistence of inhaled microbes.

Phagocyte defense

Macrophages and neutrophils contain bacteria and mold spores.

Cell-mediated immunity

T-cell responses limit intracellular pathogens and many opportunists.

The same infiltrate may have different causes

Infectious

Conventional bacterial pneumonia

Opportunistic fungal disease

Viral infection or reactivation

More than one pathogen

Noninfectious

Drug-related pulmonary injury

Pulmonary involvement by malignancy

Other treatment-associated lung injury

Opportunistic infection is not synonymous with pneumonia

Many opportunists rarely cause disease in normal hosts.

In a compromised host, these microbes may cause severe pulmonary infection.

However, ordinary respiratory pathogens remain relevant.

An opportunist in a sample must be interpreted in clinical and tissue context.

Conventional organisms remain important

Gram-positive bacteria

Streptococcus pneumoniae and Staphylococcus aureus.

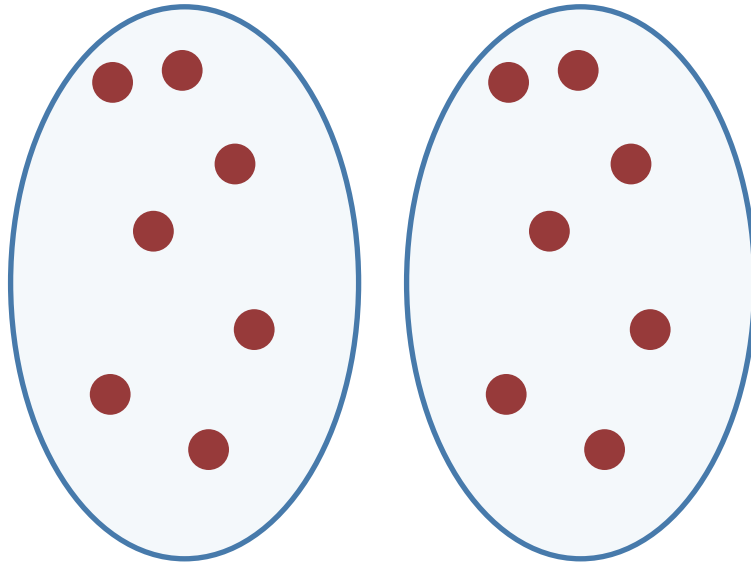
Respiratory gram-negative bacteria

Haemophilus influenzae and other gram-negative rods.

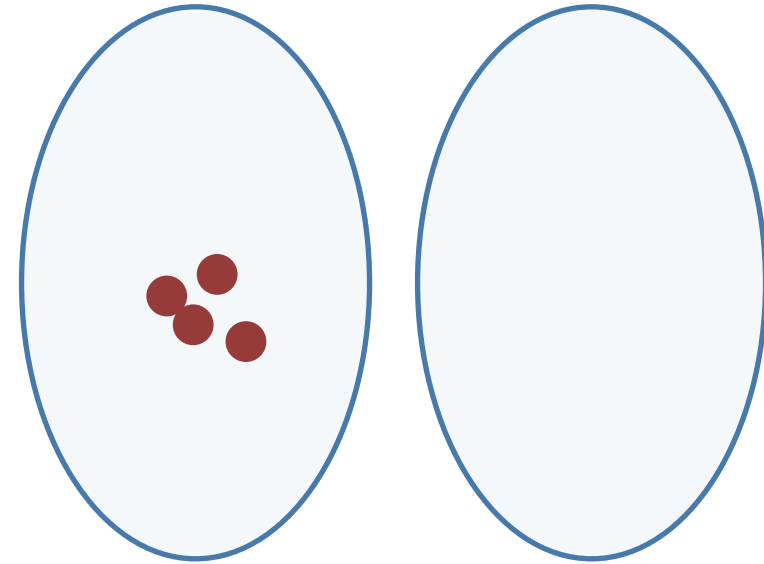
Hospital-associated organisms

Pseudomonas aeruginosa and resistant bacterial pathogens.

Distribution helps organize—but not settle—the differential



Distributed abnormalities



Localized abnormalities

A pattern suggests a differential—not a specific diagnosis.

Pulmonary infiltrates: Common pattern associations

Predominantly diffuse	Predominantly focal
Cytomegalovirus	Gram-negative bacterial infection
Pneumocystis jirovecii	Staphylococcus aureus
Drug reaction	Aspergillus or Candida
Other infectious / neoplastic causes	Malignancy or other focal processes

Patterns overlap; Distribution alone cannot identify the pathogen.

Co-infection is a defining diagnostic difficulty

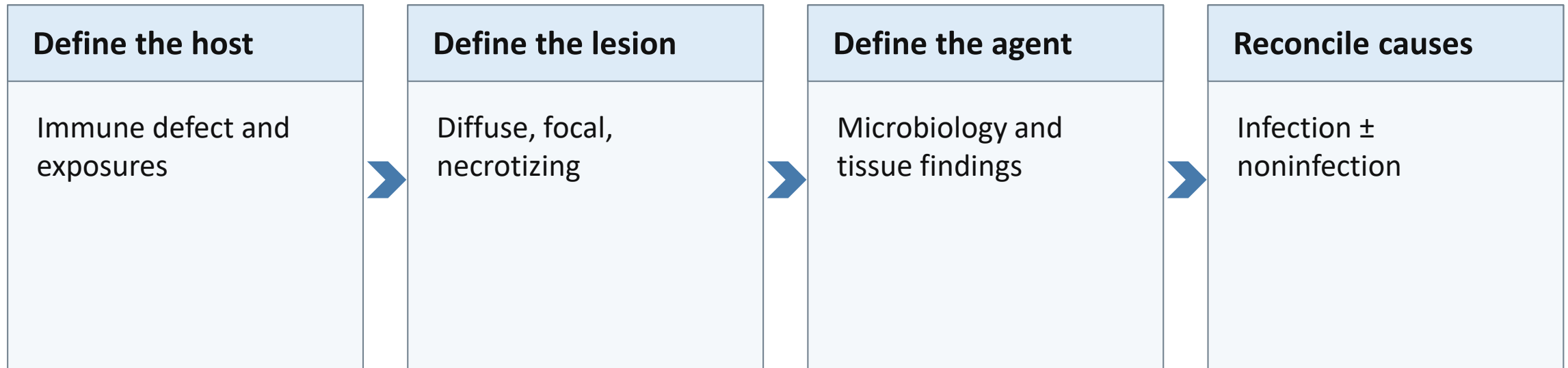
More than one microbial cause may coexist in a single patient.

An identified organism need not account for every lung lesion.

Different patterns can reflect simultaneous infection and noninfectious injury.

Interpret microbiologic results alongside distribution and host history.

A disciplined approach to a new infiltrate



Host-response patterns vary with immune competence

Relatively preserved defenses

Neutrophilic exudates can be conspicuous

Granulomas may form against intracellular agents

Tissue reaction may make infection more apparent

Marked immune failure

Organisms can be numerous with little inflammation

Necrosis and vascular invasion can dominate

Granulomatous response may be attenuated

Why a negative inflammatory response is not reassuring

The immune system generates much of the visible cellular response.

Severe immune defects can reduce the histologic reaction to an organism.

Organism burden and tissue inflammation need not correlate.

Special stains and organism-directed methods remain important.

HIV changes—but does not replace—the differential

Pulmonary disease is a major cause of hospitalization in HIV infection.

Antiretroviral therapy and chemoprophylaxis have altered outcomes.

Conventional bacterial disease and opportunistic disease both remain relevant.

Noninfectious lesions must also be excluded.

CD4-positive T-cell depletion changes pathogen probability

Relatively preserved CD4 counts	Below 200 cells/mm ³	Below 50 cells/mm ³
Usual bacterial pneumonia Tuberculosis	Pneumocystis pneumonia becomes prominent	CMV, MAC, and some fungal infections

These are source-described associations in HIV, not universal diagnostic thresholds.

At higher CD4 counts, do not overlook common infections

Usual bacterial pneumonia

S. Pneumoniae, *S. Aureus*, *H. Influenzae*, gram-negative rods.

Tuberculous disease

May occur with relatively preserved CD4 T-cell numbers.

Clinical significance

Bacterial infection in HIV may be more severe and bacteremic.

Pneumocystis emerges with advanced cellular immune failure

Pneumocystis pneumonia is particularly associated with CD4 counts below 200 cells/mm³ in HIV infection.

The dominant lesion involves alveolar exudate and interstitial thickening.

Opportunistic pathogens can be missed if only conventional bacteria are considered.

Very advanced HIV broadens the pathogen spectrum

Cytomegalovirus

Important viral infection/reactivation in marked immunodeficiency.

Mycobacterium avium complex

Intracellular organisms may become abundant within macrophages.

Invasive fungal disease

Risk increases as cellular defenses become profoundly impaired.

Pulmonary infiltrates in HIV: Infection versus tumor

Infectious examples

Ordinary bacterial pneumonia

Pneumocystis pneumonia

Mycobacterial / fungal disease

CMV and other viral disease

Neoplastic examples

Kaposi sarcoma

Non-Hodgkin lymphoma

Primary lung carcinoma

Why extensive investigation may be justified in HIV

Atypical presentations can occur even with common pathogens.

Two or more etiologies may coexist.

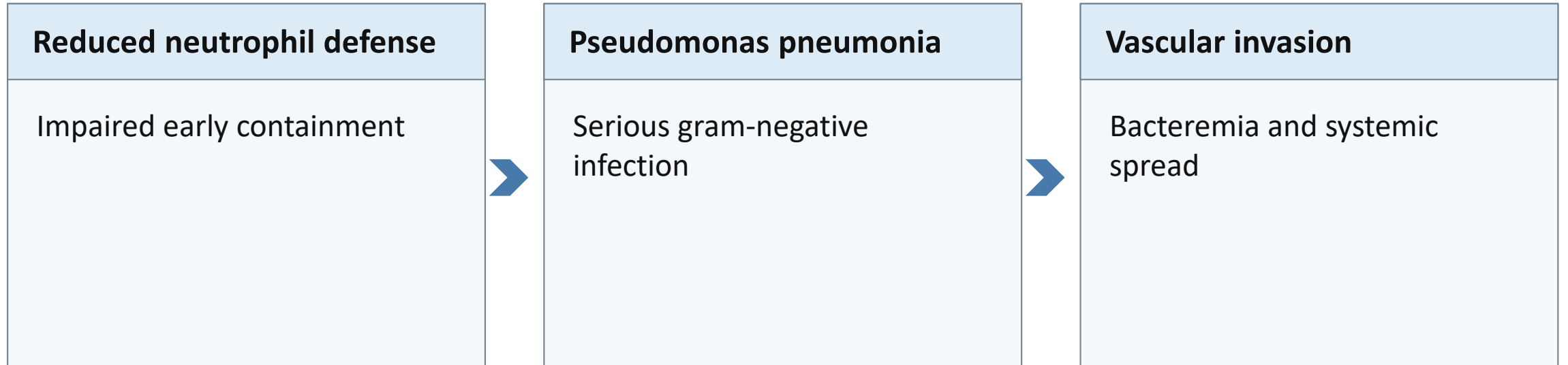
Opportunistic and noninfectious lesions have overlapping appearances.

Diagnosis requires synthesis rather than a single imaging pattern.

Bacterial causes emphasized in immunocompromised hosts

Organism	Reason for emphasis
<i>Pseudomonas aeruginosa</i>	Neutropenia, hospital acquisition, vascular invasion
<i>Legionella pneumophila</i>	Transplant / systemic immune compromise
<i>Mycobacterium</i> species	Intracellular survival; Granulomas may fail to form
<i>Listeria monocytogenes</i>	Recognized opportunistic bacterial pathogen
Conventional respiratory bacteria	Remain causes of serious pulmonary infection

Pseudomonas: Neutropenia and vascular invasion



Legionella in susceptible hosts

Organisms grow in artificial water environments.

Aerosol inhalation or aspiration can introduce infection.

Organ-transplant recipients are particularly susceptible.

Pulmonary infection can be severe; Molecular testing, antigen detection, and culture are diagnostic approaches.

Nocardia: An additional opportunistic pulmonary differential

Organism

Aerobic, branching, gram-positive bacterium; Not a fungus.

Predisposition

Corticosteroid exposure, HIV infection, or diabetes.

Clinical pattern

Indolent lung infection; May mimic tuberculosis or malignancy and disseminate to CNS.

Mycobacterium avium complex: A distinctive tissue response

Marked immunodeficiency permits proliferation within macrophages.

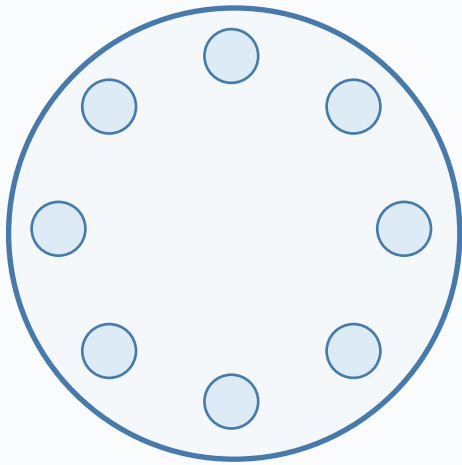
Macrophages may contain abundant acid-fast bacilli.

Granulomas, lymphocytes, and tissue destruction can be surprisingly sparse.

Infection may be pulmonary or disseminated through mononuclear phagocyte tissues.

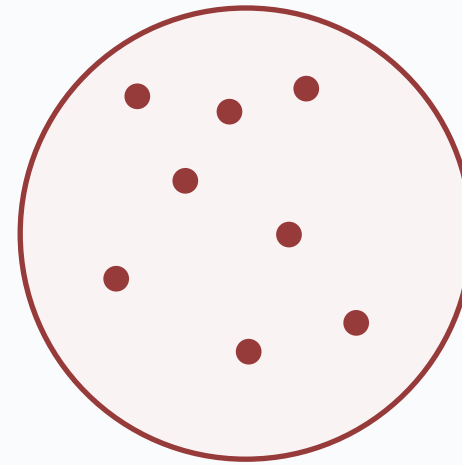
Why profound immune failure can erase a granulomatous pattern

More effective cellular response



Organized macrophage response

Profound immune failure



Numerous bacilli; Poor granuloma

Viral pulmonary pathogens in immune compromise

Cytomegalovirus

Latent herpesvirus capable of reactivation when cellular immunity falls.

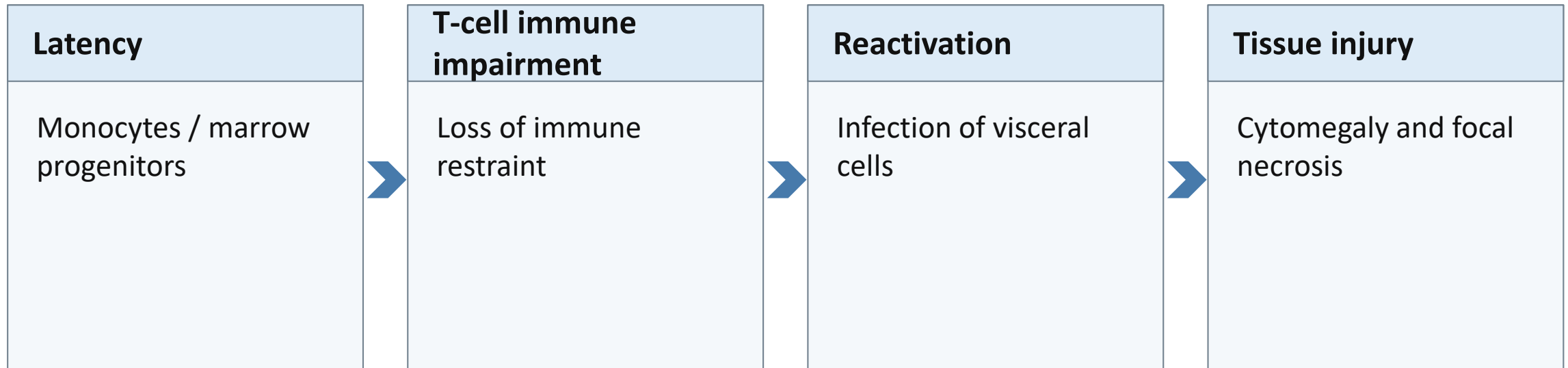
Herpesviruses

Herpes simplex and varicella-zoster viruses can cause visceral / pulmonary disease.

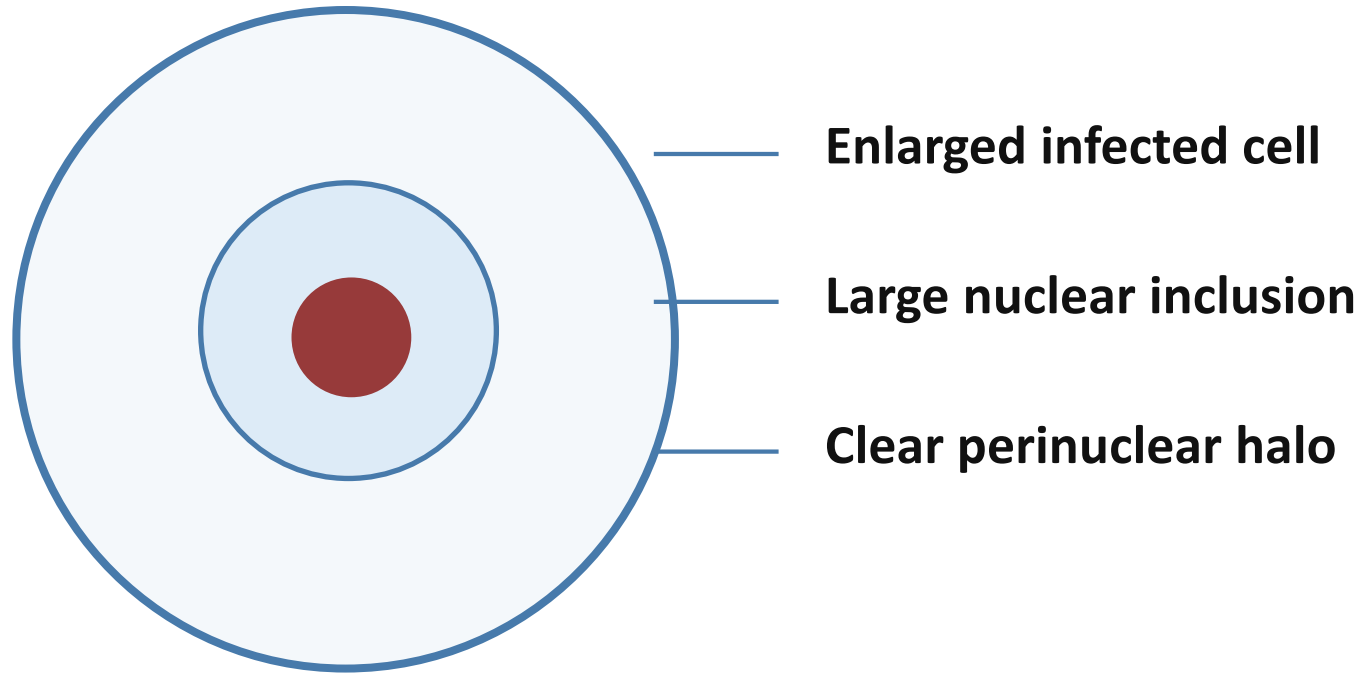
Interpretation

Specific evidence of tissue infection matters when assessing clinical significance.

CMV: Latency, reactivation, tissue injury



CMV cytopathic change: An inclusion pattern



Schematic of cytopathic features — not a photomicrograph

CMV in lung: Which cells are affected?

Pulmonary epithelial cells can be infected.

Alveolar macrophages and endothelial cells may contain the virus.

Characteristic enlarged cells show intranuclear inclusions with a surrounding halo.

Focal necrosis may accompany a relatively limited inflammatory reaction.

Varicella-zoster and other herpesvirus pneumonitis

Varicella-zoster virus can produce interstitial pneumonia in immunosuppressed people.

Herpesviruses belong in the viral differential beyond CMV.

A specific viral tissue effect is more informative than a nonspecific infiltrate pattern.

Pneumocystis jirovecii: Organism and host setting

Organism

Yeast-like fungus with pulmonary tropism.

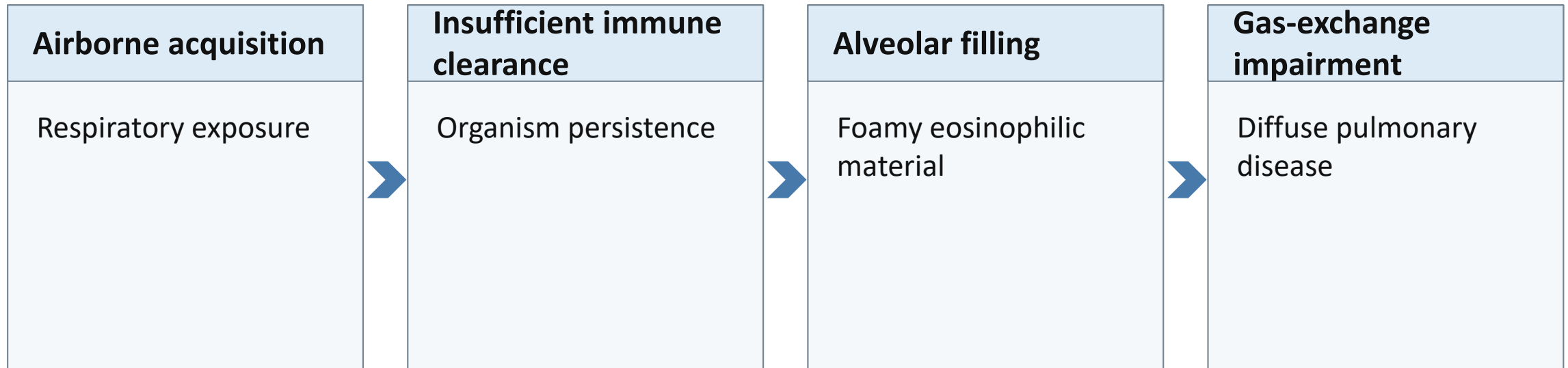
Predisposition

Impaired cellular immunity;
Historically prominent in AIDS.

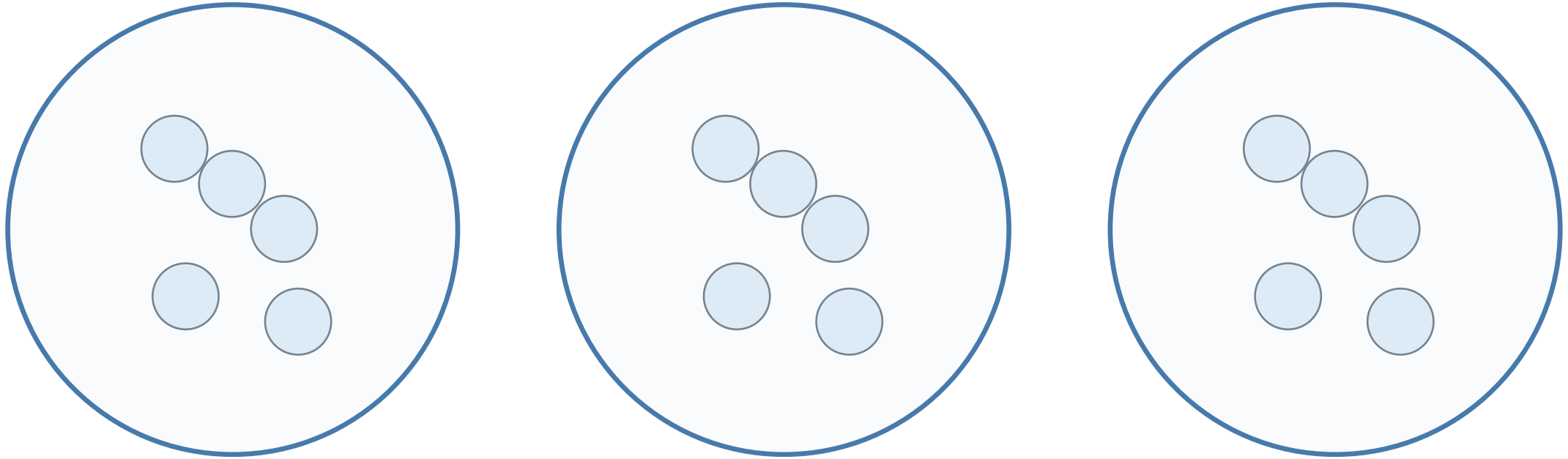
Pulmonary syndrome

Potentially rapidly progressive bilateral pneumonia.

Pneumocystis: How alveolar disease develops



Pneumocystis alveolitis: Tissue-level schematic



Foamy eosinophilic intra-alveolar material

Thickened / inflamed septa

Pneumocystis: What routine tissue morphology shows

Alveolar spaces contain eosinophilic, foamy or honeycomb-like exudate.

Alveolar septa may show interstitial thickening.

Pneumocystis structures can be inconspicuous on routine staining.

The pattern should prompt targeted organism detection.

Pneumocystis: Organism forms versus stain visibility

Cell-wall forms

Cyst / ascus forms are highlighted by methenamine silver stains.

Cyst appearance may be cup-like or crushed-ball shaped.

Other forms / testing

Trophic forms are not highlighted by a fungal cell-wall silver stain.

Immunofluorescent assays and PCR can identify infection.

Pneumocystis diagnostic methods: Interpretive roles

Method	Contribution	Limitation
Methenamine silver	Shows cyst / ascus walls	Does not visualize trophic forms well
Immunofluorescence	Identifies organisms	Requires appropriate specimen
PCR	Detects organism nucleic acid	Clinical context still essential
β -D-glucan	Supports fungal infection	Not specific for Pneumocystis

Pneumocystis outside the lung is uncommon

The primary target is lung parenchyma.

Extrapulmonary infection may involve lymph nodes, spleen, marrow, or liver.

The pulmonary presentation remains central to diagnosis and teaching.

Aspergillus causes biologically different lung diseases

Allergic response

Airway-associated hypersensitivity in susceptible hosts.

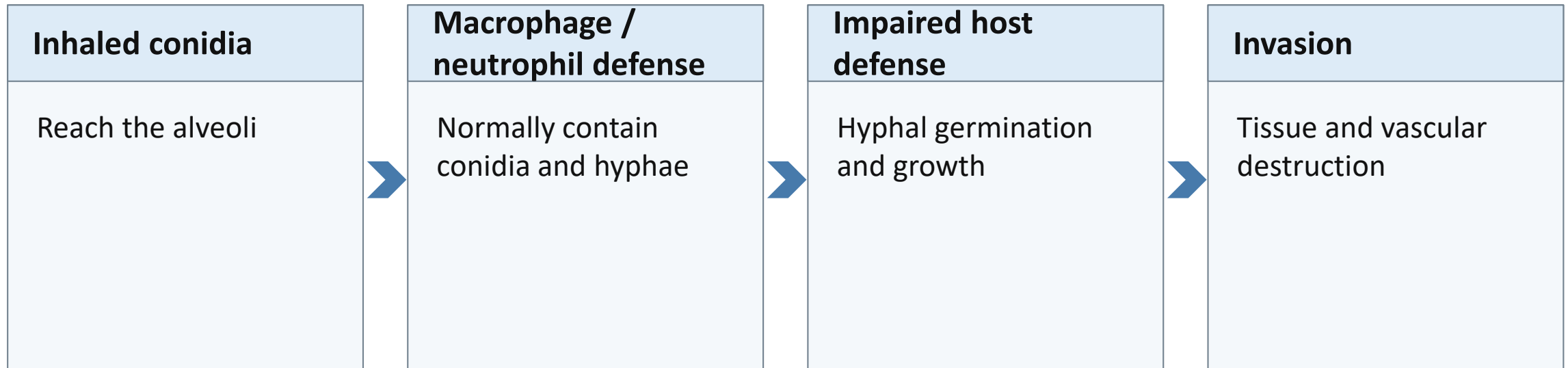
Colonization

Aspergilloma within a previously formed pulmonary cavity.

Invasion

Hyphae invade parenchyma and vessels in immunosuppressed hosts.

From inhaled Aspergillus conidium to tissue invasion



Why neutropenia predicts invasive aspergillosis

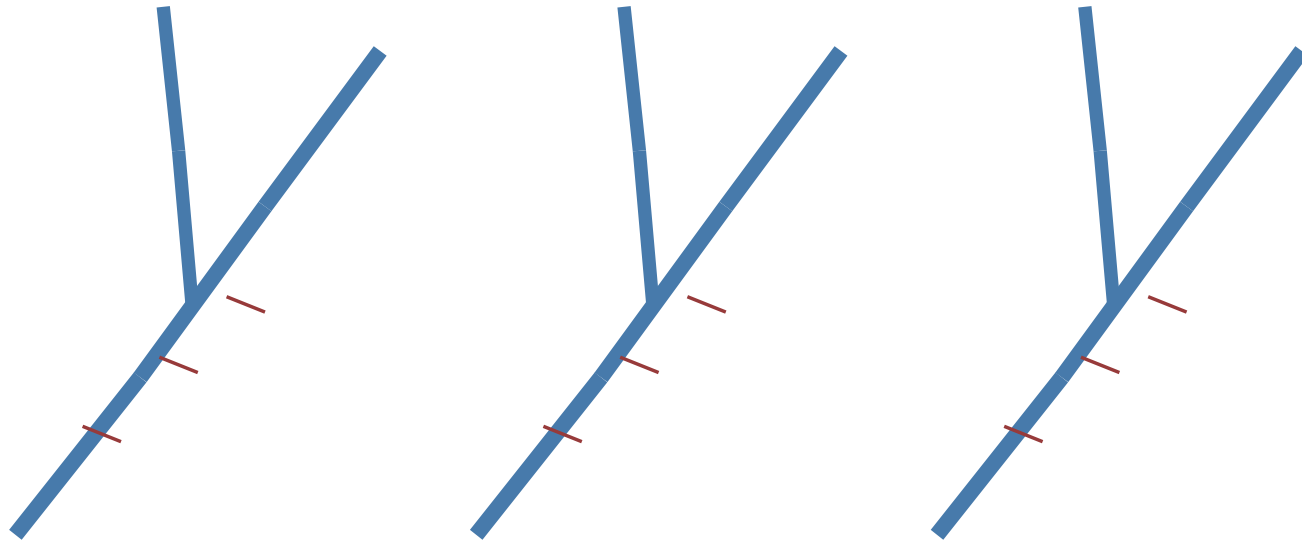
Macrophages ingest and kill inhaled conidia.

Neutrophils are crucial for killing hyphal forms.

Corticosteroids or neutropenia weaken fungal containment.

Once germinated, hyphae may breach tissue and blood vessels.

Septate fungal hyphae with acute-angle branching



Septate hyphae with characteristic acute-angle branching

Invasive aspergillosis: The major pulmonary lesion

A necrotizing pneumonia may form rounded, sharply delimited lesions.

Hemorrhagic borders result from vascular injury.

Intravascular hyphae can cause thrombosis and infarction.

Hematogenous dissemination may involve brain, eyes, skin, liver, and kidneys.

Aspergilloma is not invasive aspergillosis

Aspergilloma (colonization)

Hyphal fungus ball occupies an existing cavity.

Minimal tissue invasion is characteristic.

Hemoptysis can occur.

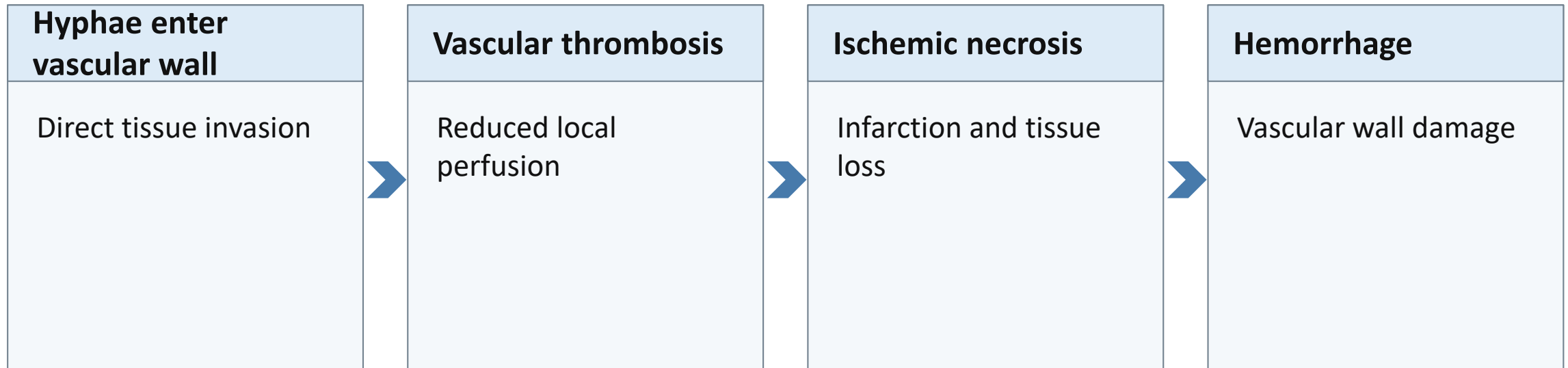
Invasive pulmonary aspergillosis

Invasive hyphae infiltrate parenchyma and vessels.

Necrosis, hemorrhage, and infarction develop.

Occurs with significant immune impairment.

Angioinvasion explains the hemorrhagic lesion



Morphology has limits for species identification

Aspergillus often produces septate, acute-angle branching hyphae in tissue.

Fusarium and Scedosporium / Pseudallescheria can appear similar.

Fungal morphology narrows the differential but may not establish species.

Additional microbiologic correlation is required.

Mucormycosis: Why particular hosts are susceptible

Defective phagocytes

Neutropenia or substantial immunosuppression.

Metabolic vulnerability

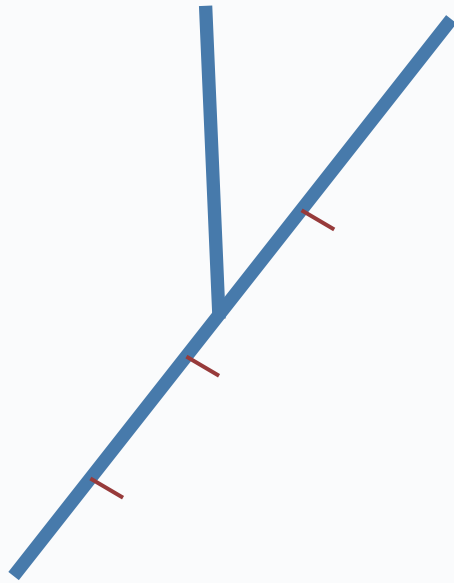
Diabetes mellitus, particularly with ketoacidosis.

Other predispositions

Corticosteroids and increased bioavailable iron.

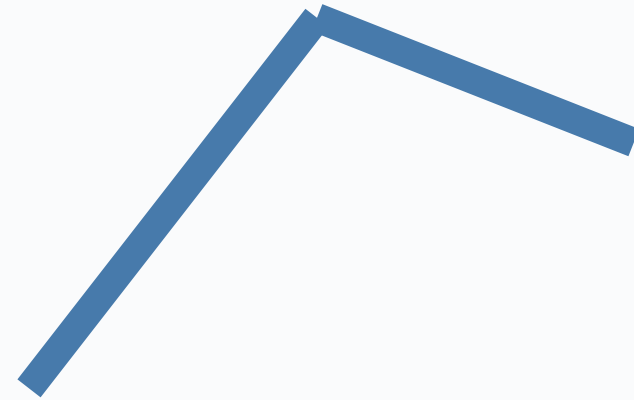
Hyphal morphology: Aspergillus versus Mucorales

Aspergillus-type



Narrow; Frequent septa; Acute angles

Mucorales-type



Broad, irregular; Few septa; Wider angles

Pulmonary mucormycosis is a vascular disease

Mucorales can enter the lung after inhalation of airborne spores.

Broad, irregular, sparsely septate hyphae invade tissues.

Invasion of vessel walls creates thrombosis and ischemic necrosis.

Hemorrhagic pneumonia and pulmonary infarctions may coexist.

Aspergillus and Mucorales: Shared behavior, different hyphae

Aspergillus

Septate hyphae, often acute-angle branching.

Invasive disease: Necrotizing hemorrhagic lung lesions.

Neutropenia and corticosteroids are major risks.

Mucorales

Broader, irregular, pauci-/nonseptate hyphae;
Often near-right-angle branches.

Thrombosis and hemorrhagic infarction.

Diabetes / iron and neutrophil defects add susceptibility.

Candida: Opportunist, tissue forms, and host defenses

Predisposition

Neutropenia, chemotherapy, invasive devices, or severe illness.

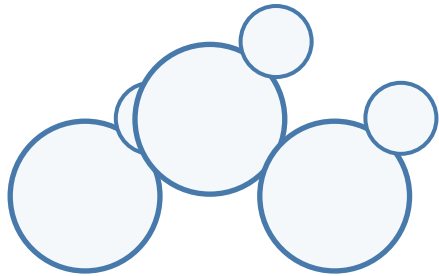
Tissue forms

Budding yeasts, pseudohyphae, occasionally true hyphae.

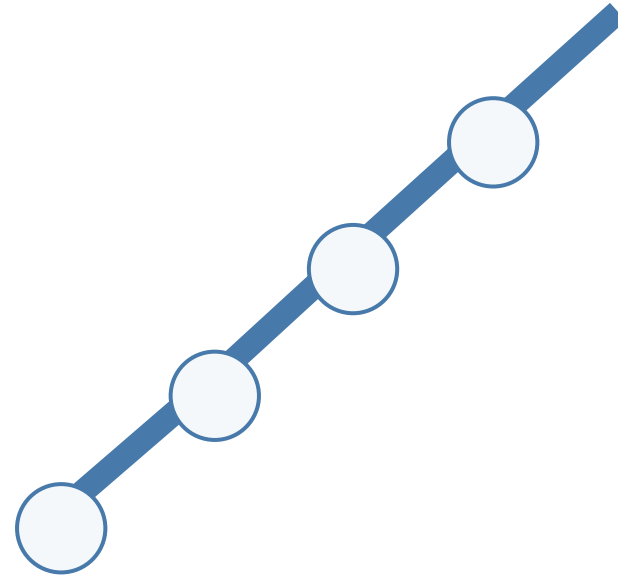
Dissemination

Bloodborne spread can produce microabscesses in distant organs.

Candida budding yeast and pseudohyphae



Budding yeast



Pseudohyphae: Elongated buds joined at constrictions

Invasive candidiasis: Context determines significance

Candida may be part of normal human microbiota.

Disease potential increases with immune defects and barrier disruption.

Invasive disease may provoke suppuration, scant reaction, or granulomas.

Finding fungi at a respiratory site requires evidence-based interpretation of invasion.

Cryptococcus neoformans: Capsule-mediated immune evasion

Route

Usually acquired by inhalation from environmental sources.

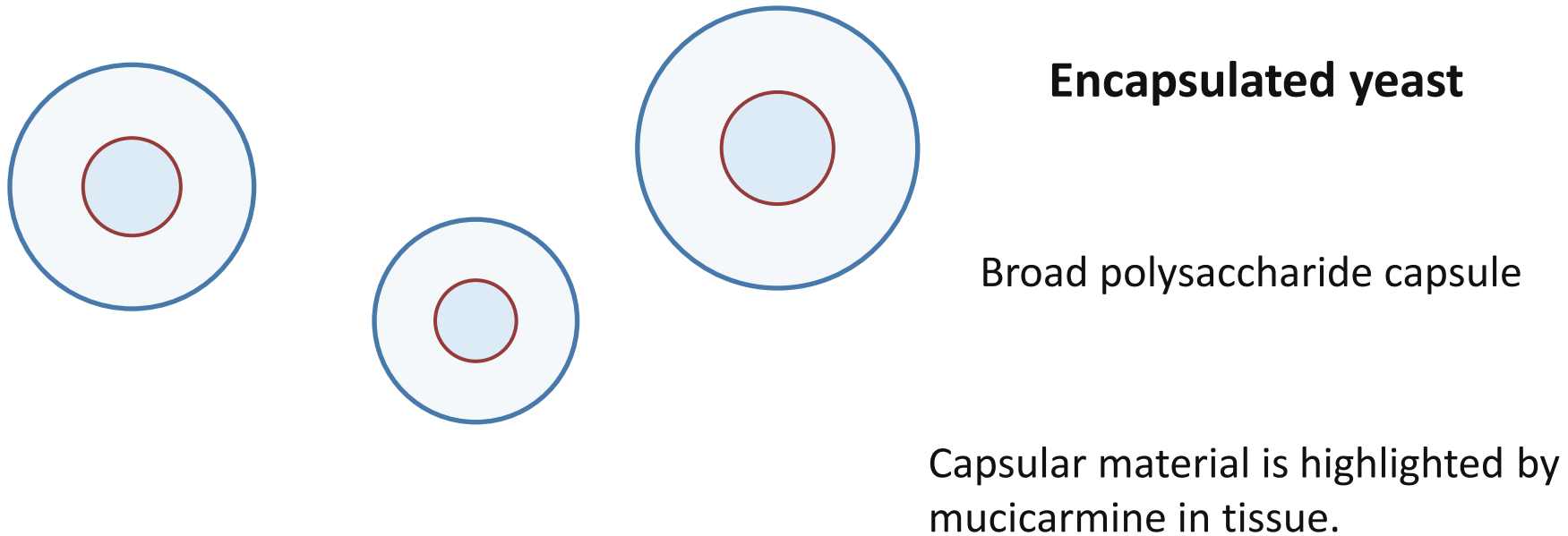
Major virulence factor

Thick polysaccharide capsule inhibits phagocytosis and immune recruitment.

Pulmonary role

Lung is a primary portal; Infection may be clinically mild before dissemination.

Cryptococcus: The capsule is a diagnostic clue



Cryptococcal disease links lung and central nervous system

Pulmonary disease can be mild even when extrapulmonary spread occurs.

Encapsulated yeasts are demonstrable in tissue with mucicarmine and other stains.

Severe immunosuppression can permit organism proliferation with little inflammation.

Granulomatous responses may occur when host defenses are relatively preserved.

Histoplasma: Host response determines morphology

More effective cellular immunity

Granulomatous reaction in the lung.

Lesions may necrose and ultimately fibrose or calcify.

Intracellular small yeasts require identification.

Severe immune deficiency

Disseminated infection with macrophages laden with yeasts.

Granuloma formation may be poor or absent.

Histology differs despite the same organism.

Morphology-oriented comparison of major pathogens

Agent	Characteristic tissue clue	Key pitfall
Pneumocystis	Foamy alveolar exudate; Silver-positive cysts	Silver stain misses trophic forms
CMV	Enlarged cells; “owl-eye” inclusions	Infiltrate pattern alone nonspecific
Aspergillus	Septate, acute-angle branching hyphae	Other hyaline molds can mimic
Mucorales	Broad, variable, pauci-septate hyphae	Tissue damage may obscure architecture
Cryptococcus	Encapsulated budding yeasts	Weak host response can mask disease

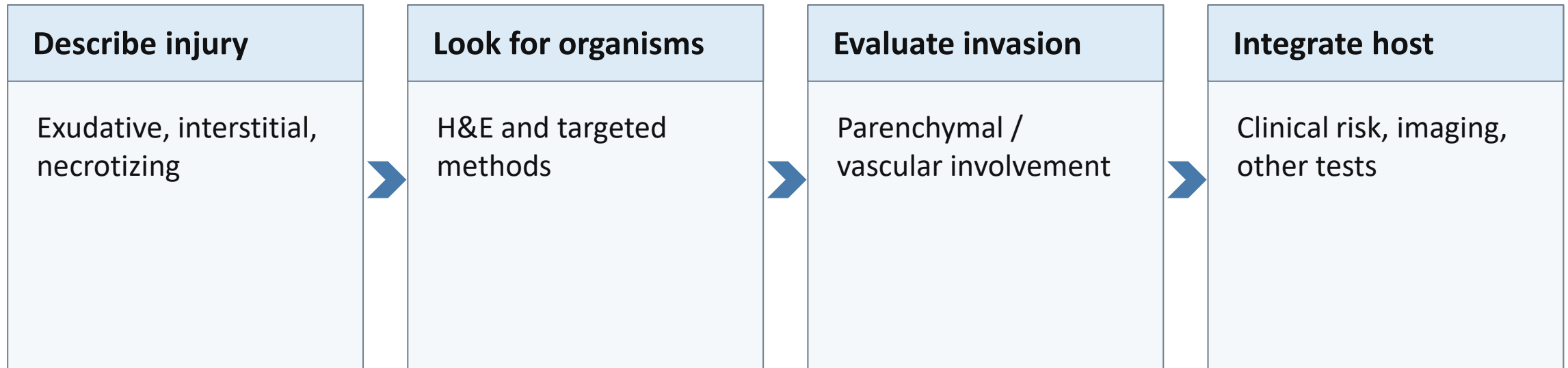
Immune defect influences pathogen and tissue reaction

Immune defect	Pathogen tendency	Tissue response
T-cell depletion	Pneumocystis / CMV / MAC	Foamy exudate; Inclusions; Macrophage-rich disease
Neutrophil dysfunction	Aspergillus / Mucorales / Pseudomonas	Necrosis, suppuration, or vascular invasion
Variable host reserve	Conventional bacteria and other agents	Response may be attenuated or mixed

Diagnostic stains and tests: Organism-oriented overview

Suspected agent	Useful evidence from the source
Pneumocystis	Methenamine silver; Immunofluorescence; PCR; β -D-glucan adjunct
CMV	Characteristic cytomegalic inclusions in infected tissue
MAC	Numerous acid-fast bacilli within macrophages
Candida / Aspergillus / Mucorales	Tissue fungal forms; GMS/PAS where appropriate
Cryptococcus	Encapsulated yeast; Mucicarmine and PAS in tissue
Legionella	PCR, urinary antigen, and culture

Interpretation of a lung specimen in immune compromise



Pulmonary infiltrate: Infection versus noninfectious injury

Evidence supporting infection

Demonstrable organism with relevant lesion

Microbiology compatible with host / pathology

Fungal or viral tissue invasion where applicable

Alternative / coexisting disease

Drug toxicity

Kaposi sarcoma or lymphoma

Other pulmonary neoplasm

Coexisting infectious and noninfectious lesions

Differential by tissue-response pattern

Observed tissue pattern	Illustrative considerations
Alveolar foamy exudate	Pneumocystis pneumonia
Cytomegalic cells / inclusions	CMV disease
Necrotizing hemorrhagic angioinvasion	Aspergillus or Mucorales
Macrophages packed with AFB	Disseminated / pulmonary MAC
Granulomas with yeasts	Cryptococcus or Histoplasma; Response may be absent in profound immunodeficiency
Suppurative consolidation	Usual bacterial pathogens

Clinical application: Neutropenia with focal lung lesions

CLINICAL STEM

A patient receiving chemotherapy develops new rounded pulmonary lesions. A biopsy shows necrosis, hemorrhage, and infiltrating fungal hyphae.

Which pathologic mechanism best explains the hemorrhagic lesions?

Case interpretation: Vascular invasion by mold

The leading mechanism is hyphal penetration of vessel walls.

Thrombosis and ischemic infarction combine with hemorrhagic tissue destruction.

Septation and branching pattern help distinguish *Aspergillus* from Mucorales, but are not species-definitive.

Clinical application: Advanced HIV with diffuse disease

CLINICAL STEM

A person with advanced HIV presents with bilateral pulmonary infiltrates. Tissue shows thickened alveolar walls and foamy luminal material.

Which organism and targeted stain or assay should be considered?

Case interpretation: Pneumocystis alveolitis

Pneumocystis jirovecii produces foamy intra-alveolar material and interstitial inflammation.

Methenamine silver can reveal the cyst / ascus walls.

Immunofluorescence and PCR provide other diagnostic approaches; β -D-glucan is supportive, not specific.

Clinical application: Transplant recipient with viral injury

CLINICAL STEM

A transplant recipient develops pulmonary infiltrates. Enlarged lung cells contain large intranuclear inclusions surrounded by a clear halo.

Which viral infection is suggested by this cytopathic morphology?

Case interpretation: Cytomegalic inclusion disease

Cytomegalovirus reactivation is favored in a patient with suppressed cellular immunity.

Cytomegaly and prominent intranuclear inclusions are the tissue clues.

Correlate the inclusions with the clinical syndrome and other infectious possibilities.

Core clinicopathologic distinctions

Always consider both

Conventional and opportunistic pathogens can coexist.

Read the host

Type and depth of immune defect strongly influence probability.

Read the tissue

Cytopathic effect, foamy exudate, angioinvasion, and intracellular organisms guide the differential.

Final synthesis

Pulmonary infiltrates in immunocompromised patients require an expanded infectious and noninfectious differential.

The immune defect affects both susceptibility and the intensity of tissue inflammation.

Morphology and distribution help prioritize organisms but do not replace confirmatory evidence.

Multiple causes are possible; Reconcile each finding with the complete clinical context.

Source references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition. Chapter 15: The Lung — Pulmonary Infections.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition. Chapter 8: Infectious Diseases — organism-specific pathology.