

Pulmonary Involvement in Autoimmune Diseases

Morphologic patterns, systemic associations, and clinicopathologic interpretation

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Learning outcomes

- Recognize the pulmonary compartments involved in systemic autoimmune disease.
- Differentiate NSIP, UIP, and organizing pneumonia using morphologic principles.
- Relate rheumatoid arthritis, systemic sclerosis, lupus, and inflammatory myopathies to characteristic pulmonary patterns.
- Explain why both the extent and pattern of disease shape prognosis.

Systemic autoimmunity can involve several lung compartments

Systemic autoimmune disease

Interstitial tissue

Pneumonitis / fibrosis

Pleura

Pleuritis / effusion

Small airways

Bronchiolitis

Pulmonary vessels

Pulmonary hypertension

Parenchymal nodules

Rheumatoid nodules

“Connective tissue disease” is a clinical grouping

- These systemic autoimmune illnesses often include arthritis or other connective-tissue manifestations.
- Lung involvement may emerge at different stages of the systemic disease.
- A single autoimmune diagnosis can produce more than one pulmonary injury pattern.
- Pulmonary findings must be interpreted in the context of the systemic disorder.

Autoimmune disorders emphasized in the pulmonary chapter

Rheumatoid arthritis

Pleura, interstitium, nodules, small airways, pulmonary vessels

Systemic sclerosis

Diffuse interstitial fibrosis; Pleural involvement

Systemic lupus erythematosus

Transient infiltrates, pneumonitis, pleuritis, effusions

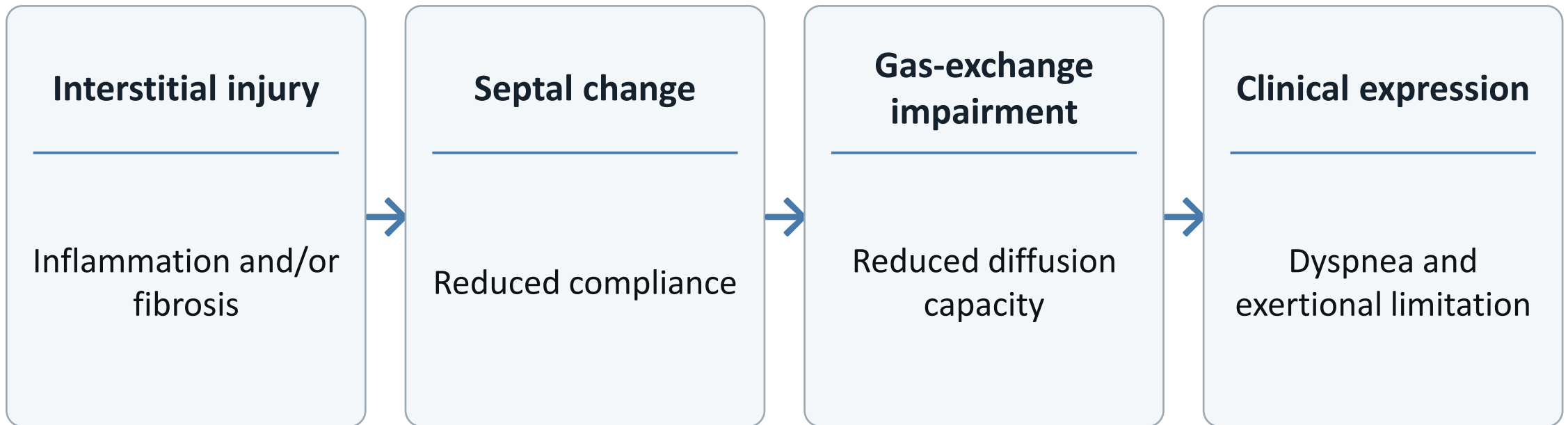
Dermatomyositis / myositis

Interstitial lung disease in relevant subgroups

Connective-tissue disease belongs in the fibrosing ILD group

- Robbins groups CTD-associated disease among major chronic interstitial lung diseases.
- Interstitial inflammation and fibrosis underlie restrictive physiology.
- The histologic pattern is an important classifier; The underlying autoimmune disease provides etiologic context.
- Advanced fibrosis can make initially different processes appear more similar.

How interstitial disease impairs lung function



Typical clinical signals of chronic interstitial disease

- Progressive exertional dyspnea or cough may prompt evaluation.
- End-inspiratory crackles are characteristic of the restrictive interstitial group.
- Restrictive physiology features reduced lung volumes and compliance.
- Reduced diffusion capacity reflects impaired transfer across the alveolar–capillary region.

Four recurring pulmonary tissue patterns

NSIP

Cellular or relatively uniform fibrosing interstitial injury

UIP

Patchy, temporally heterogeneous fibrosis with remodeling

Organizing pneumonia

Fibroblastic plugs in distal air spaces

Bronchiolitis

Small-airway-centered inflammatory injury

Pattern is not the same as etiology

Histologic pattern

NSIP / UIP / organizing pneumonia

Describes distribution and morphology

Can occur in multiple clinical settings

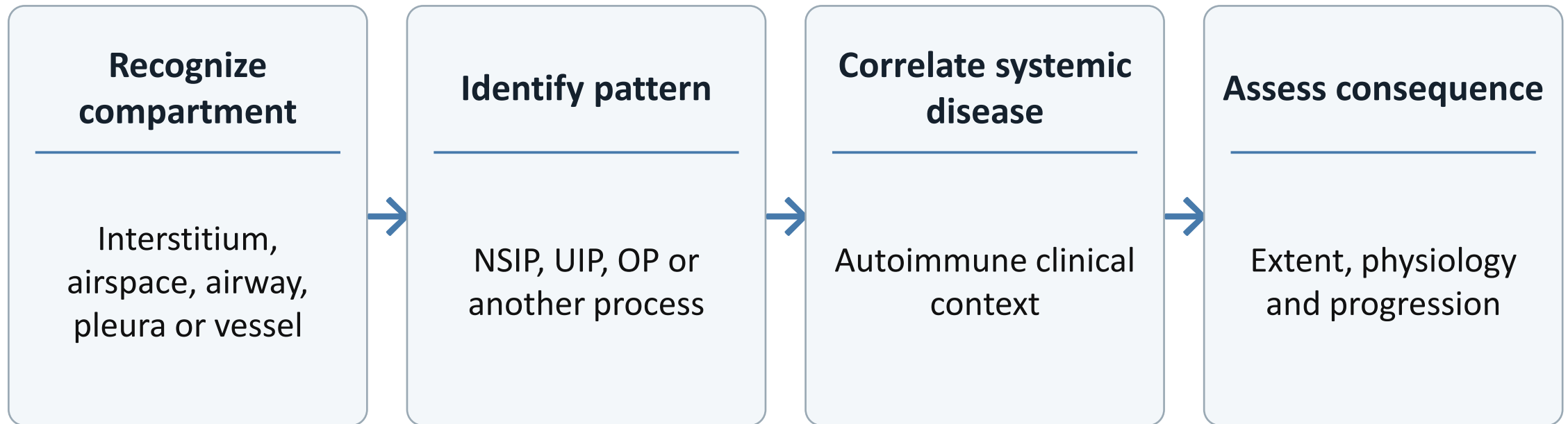
Etiologic diagnosis

Rheumatoid arthritis / sclerosis / lupus

Requires clinical and systemic context

Can manifest in several morphologic patterns

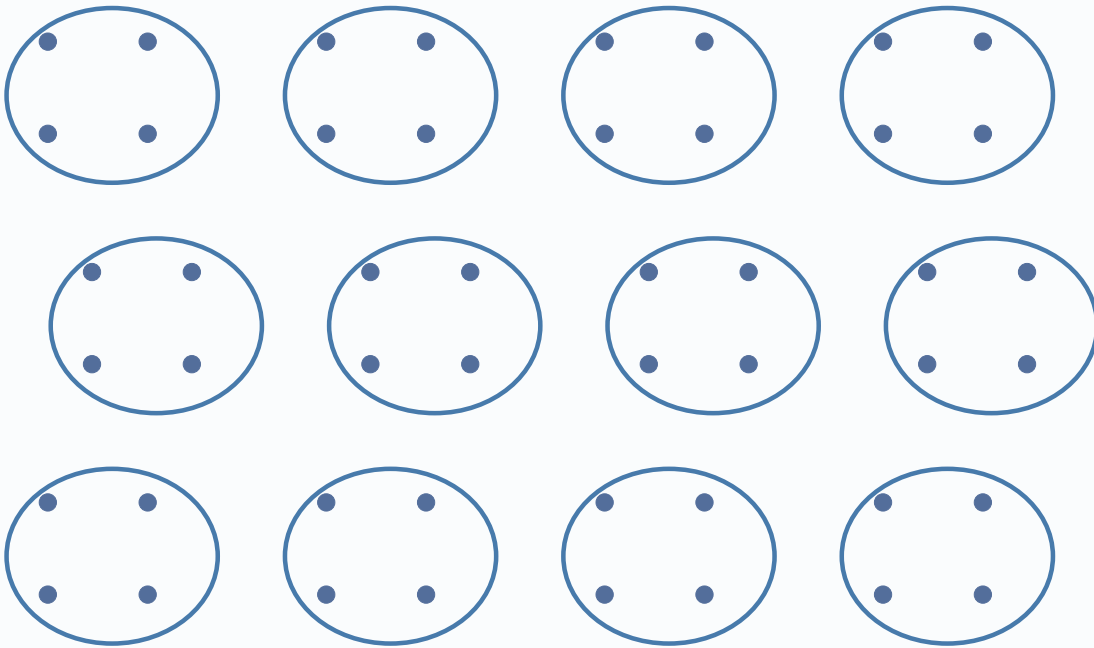
A practical pathology reasoning sequence



NSIP is especially relevant in autoimmune lung disease

- Nonspecific interstitial pneumonia frequently accompanies connective-tissue disease.
- Two major tissue patterns are recognized: Cellular NSIP and fibrosing NSIP.
- The diagnosis describes an injury pattern, not a unique underlying cause.
- Its uniformity contrasts with the heterogeneous scarring typical of UIP.

Cellular NSIP: Inflammatory expansion of septa



Conceptual alveolar-septal schematic — not a histologic specimen

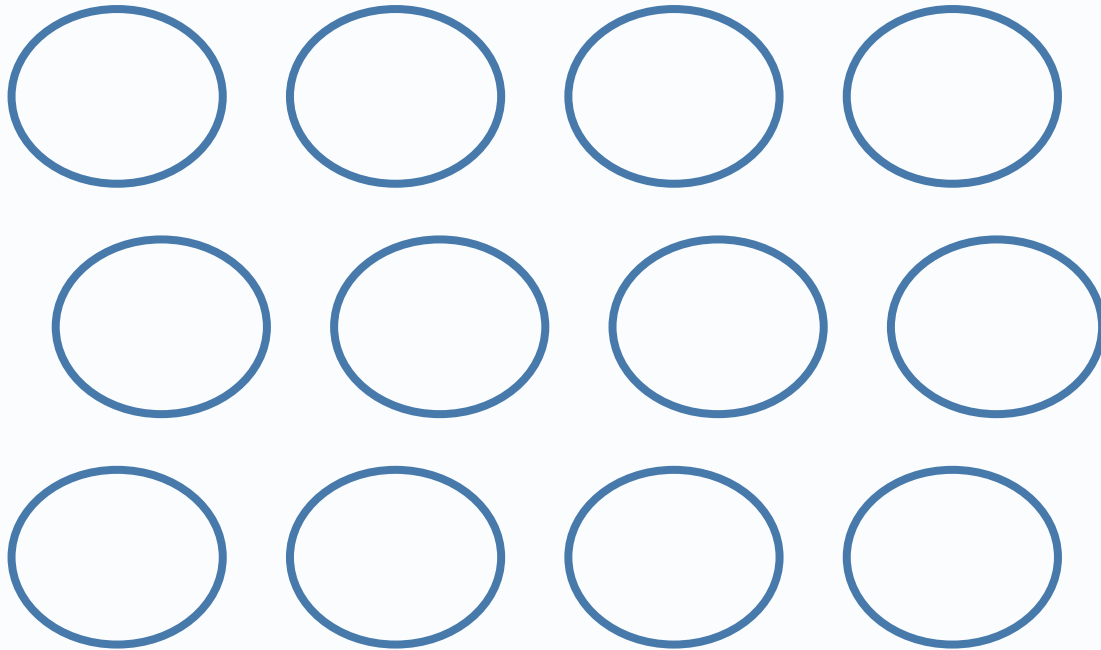
Morphologic meaning

Alveolar septa contain chronic inflammatory cells.

Lymphocytes predominate, with occasional plasma cells.

Inflammatory change may be uniform or patchy.

Fibrosing NSIP: Scarring of similar apparent age



Conceptual schematic — does not reproduce a microscopic section

Morphologic meaning

Interstitium is thickened by fibrosis.

Fibrotic lesions have a roughly similar appearance and age.

This temporal homogeneity distinguishes NSIP from classic UIP.

NSIP has two morphologic components

Cellular pattern

Interstitial lymphocytic inflammation; Limited fibrosis

Fibrosing pattern

More conspicuous fibrosis of relatively uniform age

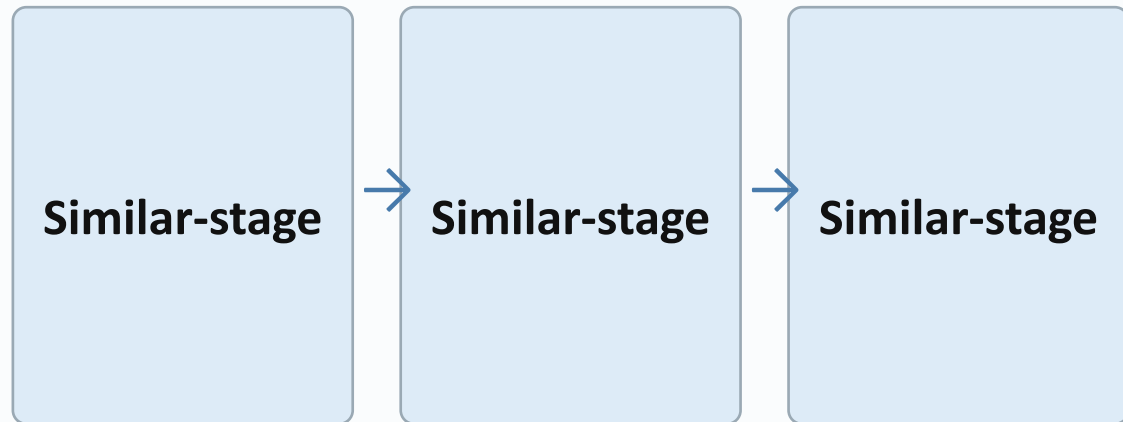
Shared principle

No diagnostic UIP-type temporal heterogeneity

Clinicopathologic link

Cellular NSIP generally has the more favorable course

Temporal homogeneity: What it means



Temporal homogeneity

Schematic representation of relative lesion age

Morphologic meaning

Relatively similar-stage interstitial lesions coexist.

Widespread “old and new” scars are not the defining picture.

Homogeneity is a histologic concept, not a precise disease age.

NSIP: Radiologic and clinical correlations

- Patients commonly have dyspnea and cough over several months.
- Bilateral, relatively symmetric lower-lobe reticular opacities.
- An underlying autoimmune condition must be sought when NSIP is identified.
- Imaging and pathology findings need not specify the exact autoimmune disease.

Cellular versus fibrosing NSIP

Cellular NSIP

Chronic inflammatory septal expansion

Less extensive scarring

Relatively favorable prognosis

Fibrosing NSIP

Collagen-rich interstitial expansion

More conspicuous architectural stiffness

Less favorable than cellular NSIP

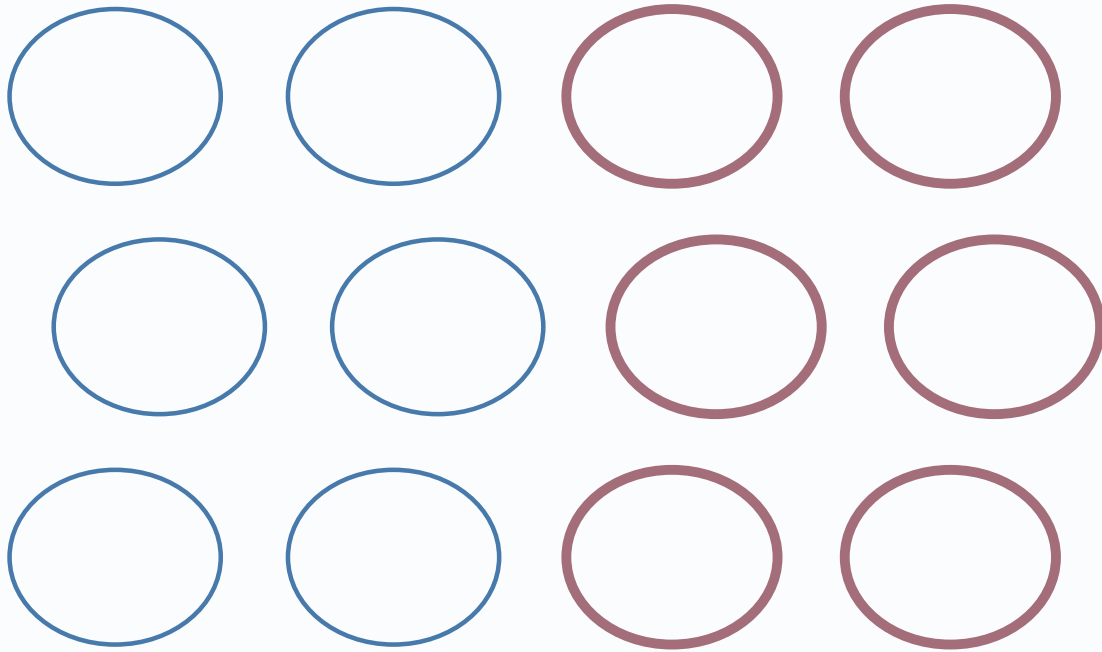
NSIP and therapeutic response: Pathologic relevance

- Some patients with NSIP benefit from immunosuppression.
- This observation supports an immune contribution in at least a subset.
- Response is not universal and should not be inferred from histology alone.
- A CTD-associated NSIP diagnosis should be integrated with clinical severity.

UIP defines a different fibrosing architecture

- Usual interstitial pneumonia shows patchy fibrosis varying by location and maturity.
- Relatively preserved alveoli can lie beside heavily scarred lung.
- Fibroblastic foci and honeycomb remodeling are characteristic.
- UIP is a histologic pattern; Idiopathic pulmonary fibrosis is an etiologic clinical diagnosis.

UIP: Spatial heterogeneity



Conceptual pattern schematic — not a micrograph

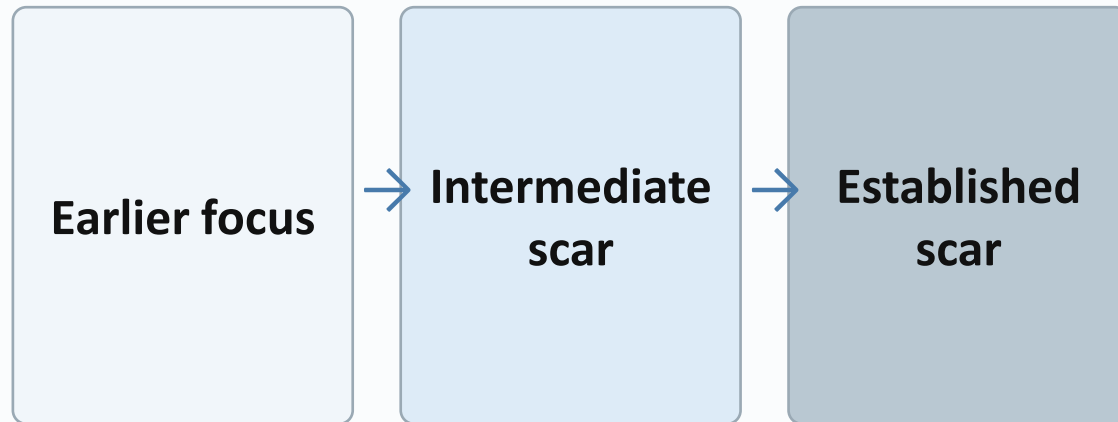
Morphologic meaning

Relatively preserved tissue abuts dense scar.

Fibrosis varies from one region to another.

A small sample can miss important diagnostic regions.

UIP: Temporal heterogeneity



Temporal heterogeneity

Schematic comparison of fibrotic lesion maturity

Morphologic meaning

Early fibroblastic foci and older dense scars coexist.

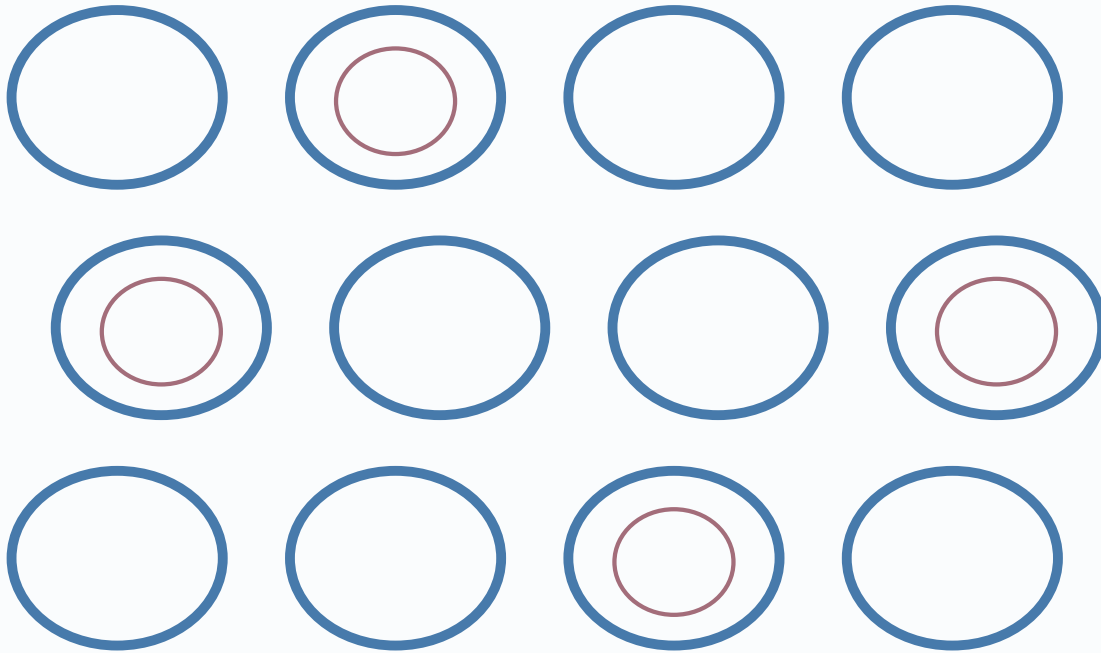
Lesions of different apparent ages are adjacent.

Contrast with uniform-age fibrosis of fibrosing NSIP.

Fibroblastic foci mark active remodeling in UIP

- Discrete fibroblast-rich foci appear at advancing edges of fibrosis.
- They coexist with established, relatively acellular collagenous scar.
- Their presence contributes to temporal heterogeneity.
- They are not equivalent to intraluminal Masson bodies in organizing pneumonia.

Honeycombing represents destroyed alveolar architecture



Native PowerPoint diagram; Not an image of authentic lung tissue

Morphologic meaning

Dense fibrosis replaces normal alveolar units.

Cystic spaces become lined by epithelial cells.

Architectural distortion signals established remodeling.

NSIP versus UIP: Principal discrimination

NSIP

Relatively uniform lesion age

No characteristic fibroblastic foci

No typical honeycomb pattern

Often more favorable course

UIP

Variable lesion age and location

Fibroblastic foci characteristic

Honeycombing may be present

Typically worse prognosis

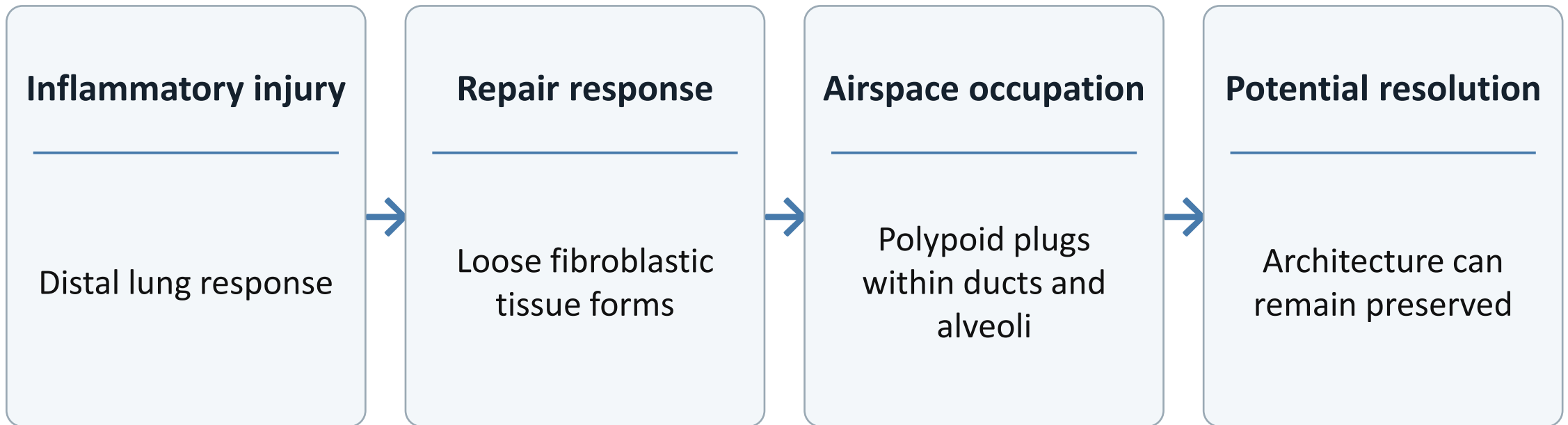
UIP pattern must not be equated automatically with IPF

- Idiopathic pulmonary fibrosis is a distinct disease associated with a UIP pattern.
- UIP-like morphology may also appear in connective-tissue disease.
- Etiologic interpretation requires the systemic history and other data.
- Calling all UIP-pattern fibrosis “idiopathic” would miss secondary disease.

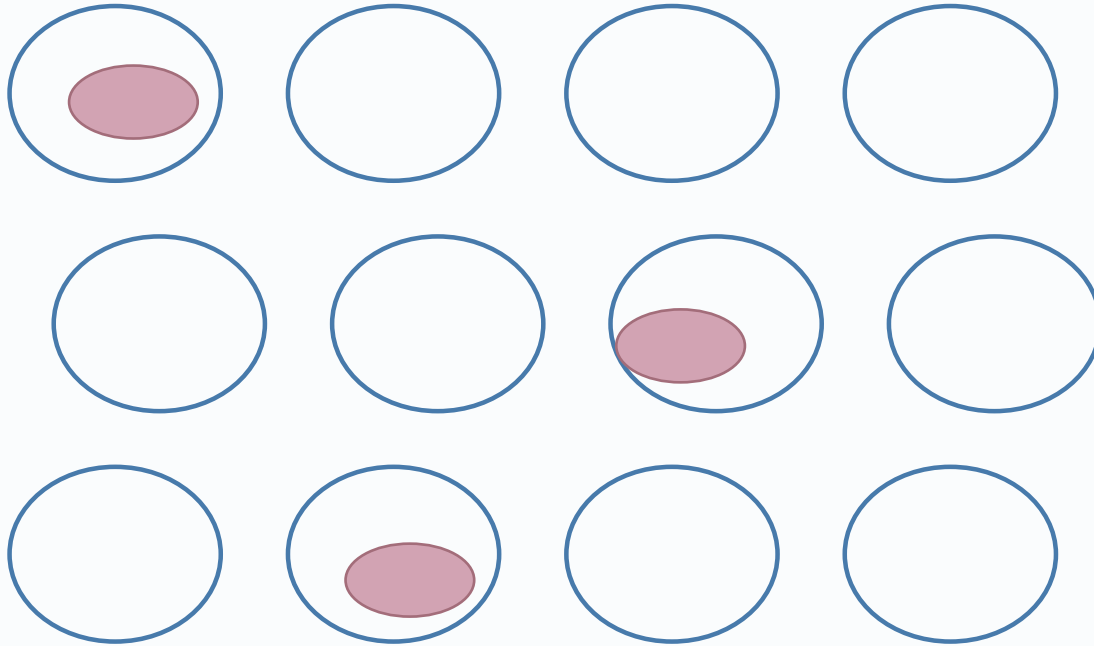
Organizing pneumonia is a response pattern

- Organizing pneumonia often follows pulmonary infection or inflammatory injury.
- It may occur secondary to connective-tissue disease.
- The term “cryptogenic” is appropriate only if an underlying cause is not identified.
- Its defining process lies in distal airspaces rather than diffuse mature interstitial scar.

Organizing pneumonia: Tissue-level sequence



Masson bodies occupy airspaces, not alveolar septa



Schematic of organizing pneumonia — not diagnostic histology

Morphologic meaning

Loose organizing connective-tissue plugs project into airspaces.

They may involve alveoli, ducts and bronchioles.

Underlying lung architecture remains relatively preserved.

Organizing pneumonia versus UIP

Organizing pneumonia

Intraluminal loose fibroblastic plugs

Lesions of similar maturity

Preserved overall architecture

UIP

Interstitial fibroblastic foci plus fibrosis

Temporal and spatial heterogeneity

Distorted architecture / honeycomb change

Organizing pneumonia: Clinical–imaging linkage

- Cough and dyspnea are common presenting complaints.
- Patchy subpleural or peribronchial airspace consolidation may be seen.
- The long-term course depends partly on the underlying disease.
- A CTD association changes the etiologic designation from cryptogenic to secondary.

Three fibrosing and organizing patterns at a glance

Interstitial patterns

NSIP: Often uniform

UIP: Heterogeneous with architectural loss

Think alveolar septa

Airspace organizing pattern

Organizing pneumonia: Masson bodies

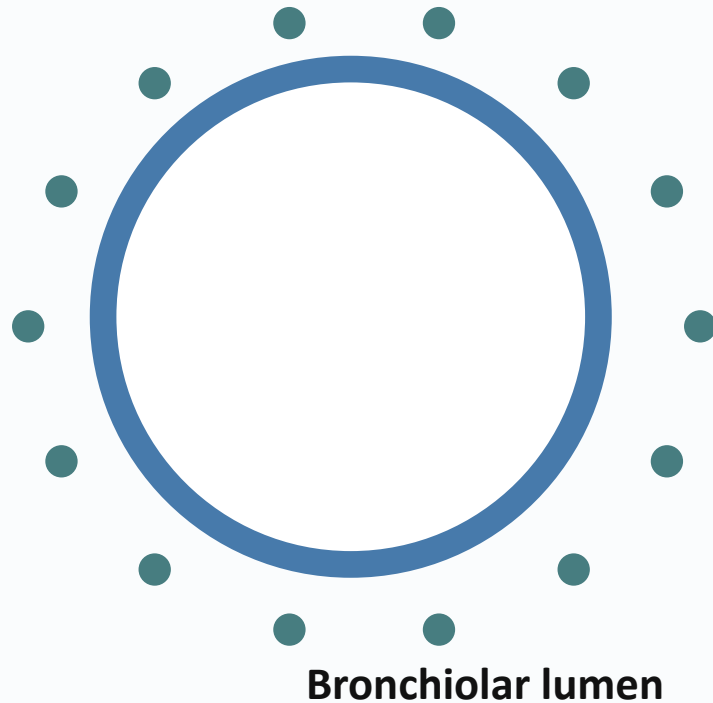
Preserved underlying framework

Think distal airspace plugs

Bronchiolitis localizes injury to small airways

- Bronchiolitis is one of the recurring pulmonary patterns in autoimmune disease.
- An airway-centered process differs conceptually from a primary diffuse interstitial injury.
- Symptoms and physiology may reflect small-airway involvement.
- The exact bronchiolar subtype matters for pathologic interpretation.

Follicular bronchiolitis in rheumatoid disease



Teaching schematic of airway-centered inflammation

Morphologic meaning

Rheumatoid arthritis may be associated with follicular bronchiolitis.

The dominant anatomic compartment is the small airway.

A lymphoid-follicle-centered process should not be mislabeled UIP.

Beyond interstitial disease: Pleura and vasculature

Pleuritis

Inflammation of serosal lining

Pleural effusion

Fluid within pleural cavity

Pulmonary hypertension

Vascular complication listed for rheumatoid disease

Compartment matters

Each produces different clinicopathologic findings

Rheumatoid arthritis can affect lung outside the joints

- Rheumatoid arthritis is systemic, despite joint-dominant clinical manifestations.
- Pulmonary involvement in approximately 30–40% of patients.
- Pleura, interstitium, nodules, bronchioles, and vessels may be involved.
- No single pulmonary pattern is unique to rheumatoid arthritis.

Five pulmonary manifestations of rheumatoid arthritis

1. Chronic pleuritis

With or without effusion

2. Interstitial disease

Pneumonitis and fibrosis

3. Parenchymal nodules

Intrapulmonary rheumatoid nodules

4. Airway injury

Follicular bronchiolitis

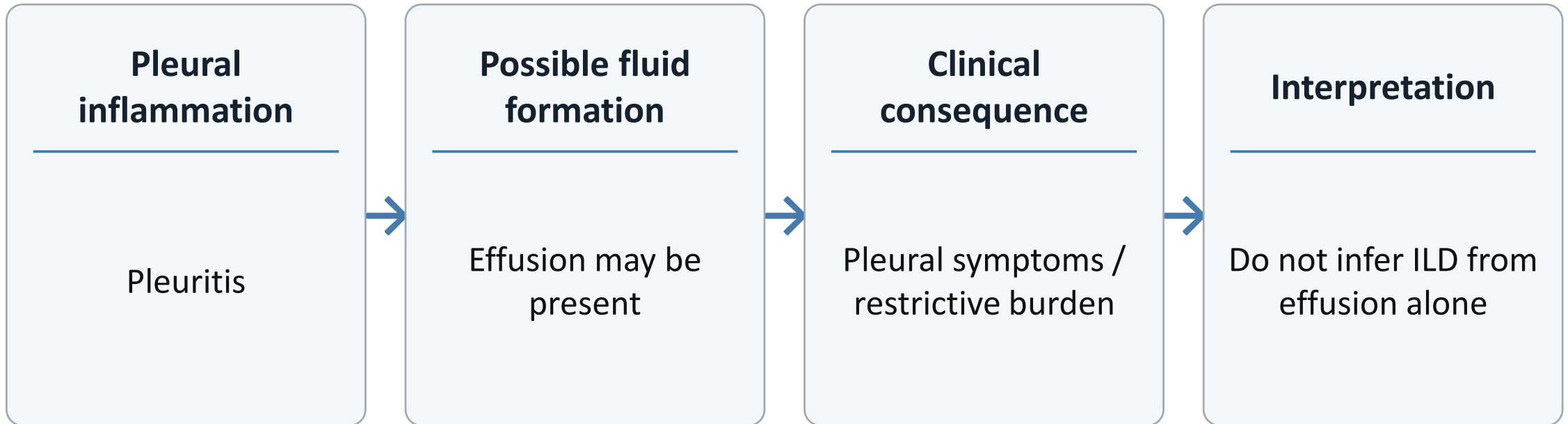
5. Vascular disease

Pulmonary hypertension

Rheumatoid pleuritis is a serosal manifestation

- The pleura is a recognized extraarticular target in rheumatoid disease.
- Chronic pleural inflammation can occur with or without fluid accumulation.
- Pleuritis is anatomically distinct from interstitial pneumonitis.
- A patient may have simultaneous pleural and parenchymal disease.

Why rheumatoid pleural disease requires separate description



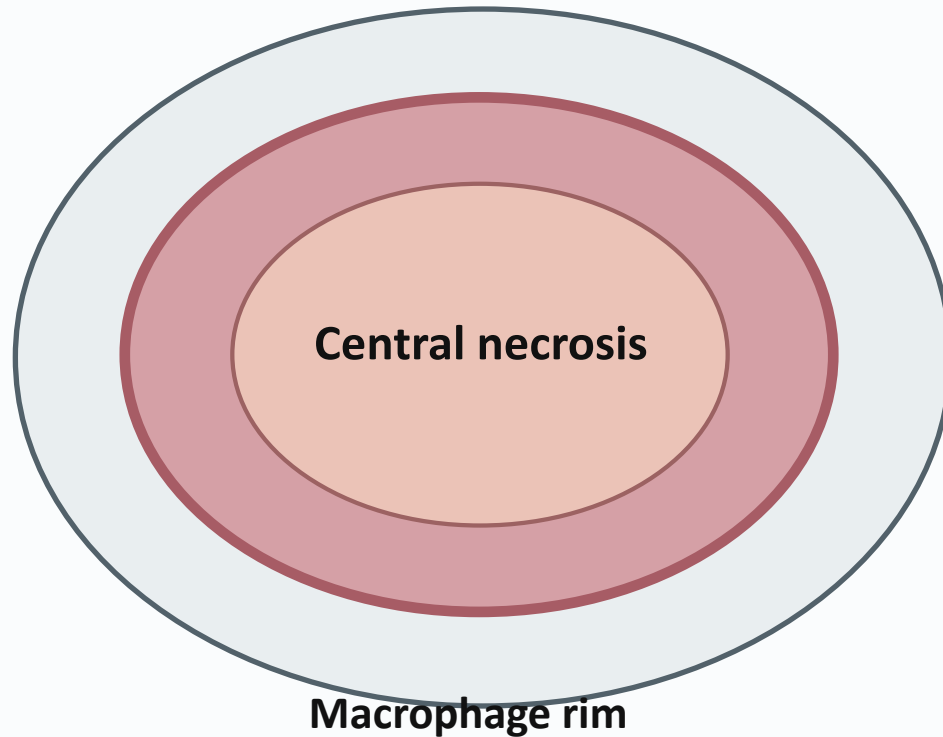
Rheumatoid interstitial pneumonitis may progress to fibrosis

- Rheumatoid arthritis can produce diffuse interstitial pneumonitis.
- Chronic interstitial injury may be accompanied by established fibrosis.
- NSIP and UIP are among autoimmune-associated histologic patterns.
- Underlying rheumatoid arthritis changes the interpretation of the same lung pattern.

Rheumatoid nodules form a focal parenchymal category

- Intrapulmonary rheumatoid nodules are an established manifestation of RA.
- They should be distinguished from diffuse interstitial fibrosis and small-airway disease.
- Tissue examination may be needed when the clinical diagnosis of a nodule is uncertain.
- A nodule alone does not determine the overall burden of interstitial disease.

Rheumatoid nodule: Layered necrobiotic architecture



Conceptual sectional diagram; Robbins morphology from the RA chapter

Morphologic meaning

Typical nodules contain a central zone of fibrinoid necrosis.

Activated macrophages surround the necrotic center.

Lymphocytes and plasma cells form an additional inflammatory component.

Rheumatoid nodule morphology has a source limitation

- The detailed nodule morphology is described principally for extraarticular soft-tissue nodules.
- Pulmonary rheumatoid nodules are listed in the lung chapter.
- Shared nomenclature supports the teaching analogy, but this is not a substitute for a verified lung photomicrograph.
- A specimen must be interpreted by its actual observed features.

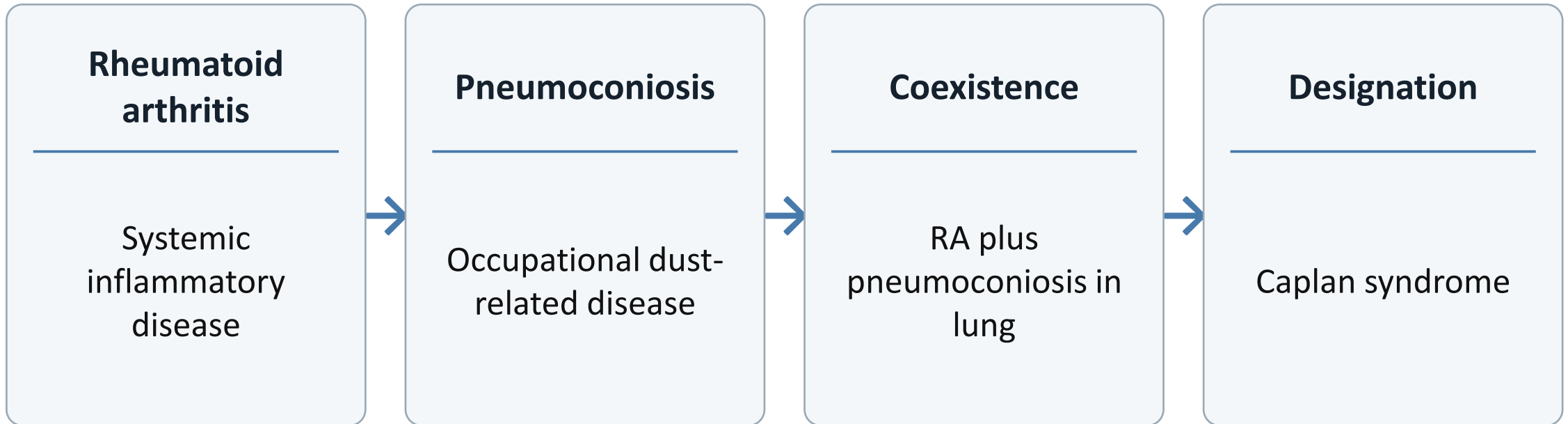
Rheumatoid follicular bronchiolitis targets bronchioles

- Follicular bronchiolitis is explicitly named among RA pulmonary manifestations.
- Its airway-centered location contrasts with diffuse interstitial fibrosis.
- The diagnosis should describe bronchiolar involvement rather than presume every lesion is interstitial.
- Multiple compartments may coexist in the same patient.

Pulmonary hypertension is another rheumatoid complication

- Pulmonary hypertension appears in the Robbins list of RA-associated lung manifestations.
- It concerns pulmonary vascular pressure and remodeling, not an interstitial pattern by itself.
- Vascular disease and parenchymal fibrosis may contribute to pulmonary functional impairment.
- The degree and mechanism require clinical evaluation.

Caplan syndrome links rheumatoid disease and dust exposure



Rheumatoid lung: Compartment-oriented differential

Diffuse process

Interstitial pneumonitis / fibrosis

Small-airway follicular bronchiolitis

Pleural inflammation / effusion

Focal or vascular process

Intrapulmonary rheumatoid nodule

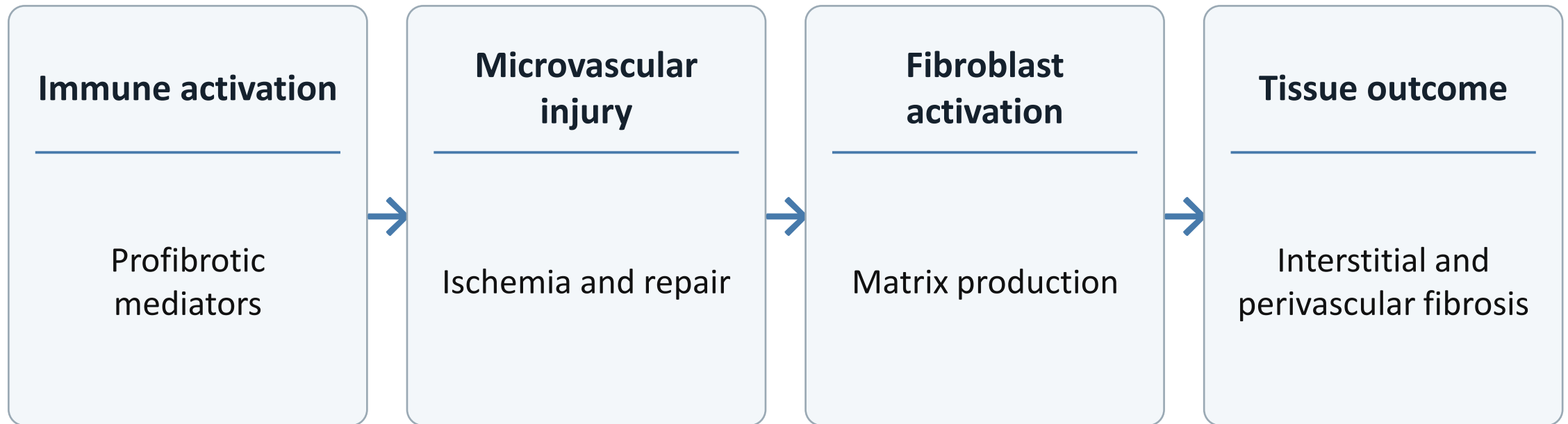
Pulmonary hypertension

Pneumoconiosis overlap (Caplan)

Systemic sclerosis is a fibrosis-predominant systemic disease

- Systemic sclerosis combines chronic autoimmune inflammation, vascular damage, and progressive fibrosis.
- Multiple visceral organs, including the lungs, may be affected.
- Lung fibrosis contributes to pulmonary insufficiency.
- Its pulmonary injury pattern is not identical in every patient.

Systemic sclerosis: Interconnected pathogenic processes



Systemic sclerosis-associated ILD often shows NSIP

- Diffuse interstitial fibrosis as a pulmonary manifestation.
- The NSIP pattern is more common than UIP in systemic sclerosis.
- That predominance does not exclude UIP-pattern lung disease.
- Recognize the difference between disease association and histologic certainty.

NSIP and UIP both occur in systemic sclerosis

More common: NSIP

Fibrosis of relatively uniform stage

Often retains more architecture

Supports CTD-associated interstitial pattern

Less common: UIP

Spatial and temporal heterogeneity

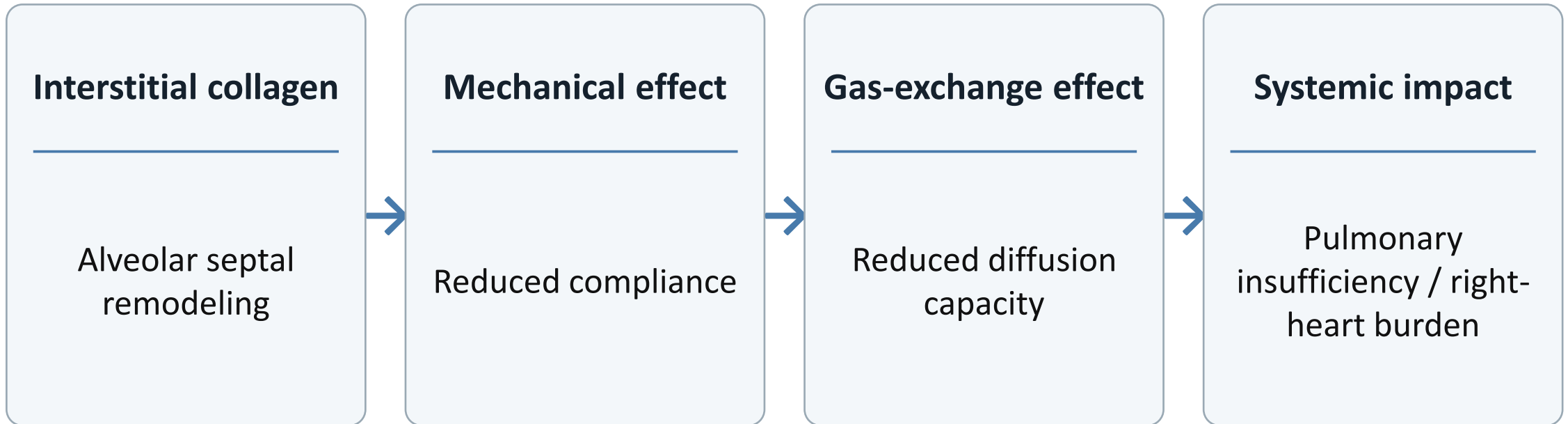
Fibroblastic foci and remodeling

Does not imply idiopathic pulmonary
fibrosis

Systemic sclerosis can also involve the pleura

- Pleural involvement is explicitly listed in the lung chapter.
- It must be assessed independently of the interstitial pattern.
- A multisystem fibrosing disease can have simultaneous pleural and parenchymal manifestations.
- Pathologic classification should specify the compartment affected.

Fibrosis links systemic sclerosis to respiratory limitation



Systemic lupus erythematosus has varied lung expression

- SLE is a systemic autoimmune disease involving immune-complex and antibody-mediated injury.
- The lung chapter describes parenchymal infiltrates, severe pneumonitis, pleuritis, and effusions.
- Pulmonary involvement may be intermittent or severe.
- Its manifestations can span parenchymal and serosal compartments.

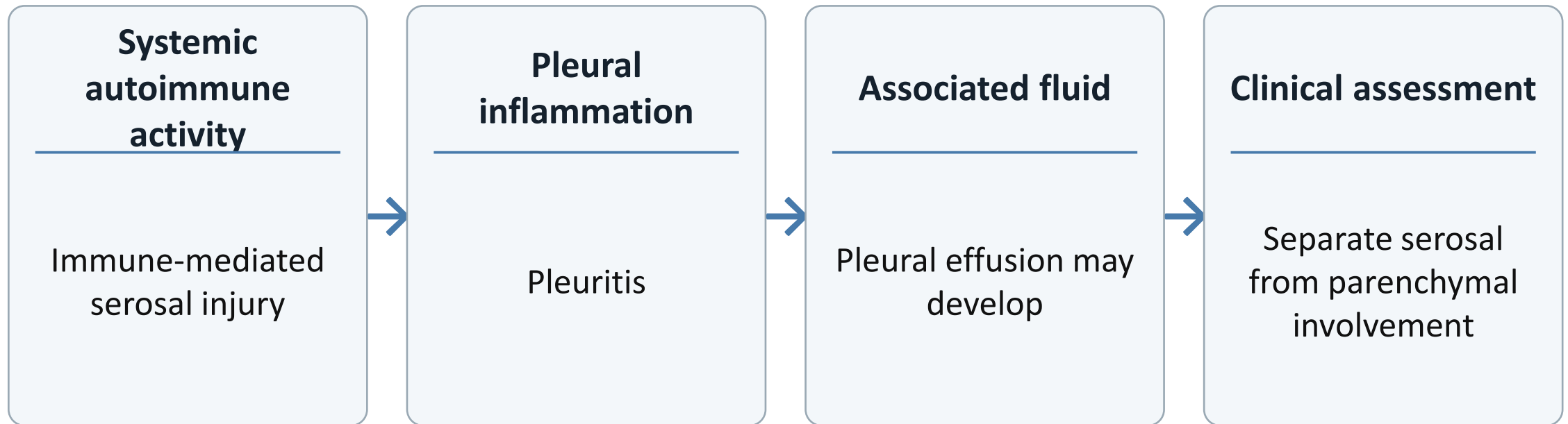
Lupus may cause transient patchy parenchymal infiltrates

- Patchy, transient pulmonary infiltrates in SLE.
- A transient radiologic infiltrate is not equivalent to fixed fibrotic remodeling.
- Activity and distribution help distinguish the clinical process.
- Systemic context matters because a radiologic infiltrate is nonspecific.

Severe lupus pneumonitis is an important exception

- Lupus pneumonitis can occasionally be severe.
- This is a parenchymal inflammatory manifestation rather than isolated pleural disease.
- Severity should not be inferred from the autoimmune diagnosis alone.
- The potential for severe injury justifies active clinicopathologic correlation.

Lupus serositis explains pleuritis and effusions



SLE versus systemic sclerosis: Different emphases

SLE

Patchy / transient infiltrates

Occasionally severe pneumonitis

Pleuritis and effusions

Systemic sclerosis

Diffuse interstitial fibrosis

NSIP more common than UIP

Pleural involvement also possible

The inflammatory-myopathy spectrum also has pulmonary relevance

- The lung chapter includes dermatomyositis–polymyositis among CTD-associated lung diseases.
- The skeletal-muscle chapter recognizes a more granular inflammatory-myopathy classification.
- Lung disease should be considered within the appropriate myositis subtype.
- The older label “polymyositis” should not be assumed to cover all modern subsets.

Anti-MDA5 dermatomyositis identifies an important ILD phenotype

- Some anti-MDA5 dermatomyositis patients develop rapidly progressive ILD.
- This pulmonary phenotype is associated with poor prognosis in that subgroup.
- Other anti-MDA5 subgroups may have different manifestations and outcomes.
- The antibody association is informative but not sufficient to assign the histologic pattern.

Antisynthetase syndrome links muscle, lung, and joints

- Defined by antibodies against aminoacyl–tRNA synthetases.
- A prototypical autoantibody is anti-Jo-1; Other antisynthetase antibodies are described.
- Muscle involvement, interstitial lung disease, and arthritis are a characteristic constellation.
- Recognizing the systemic syndrome can provide the etiologic context for ILD.

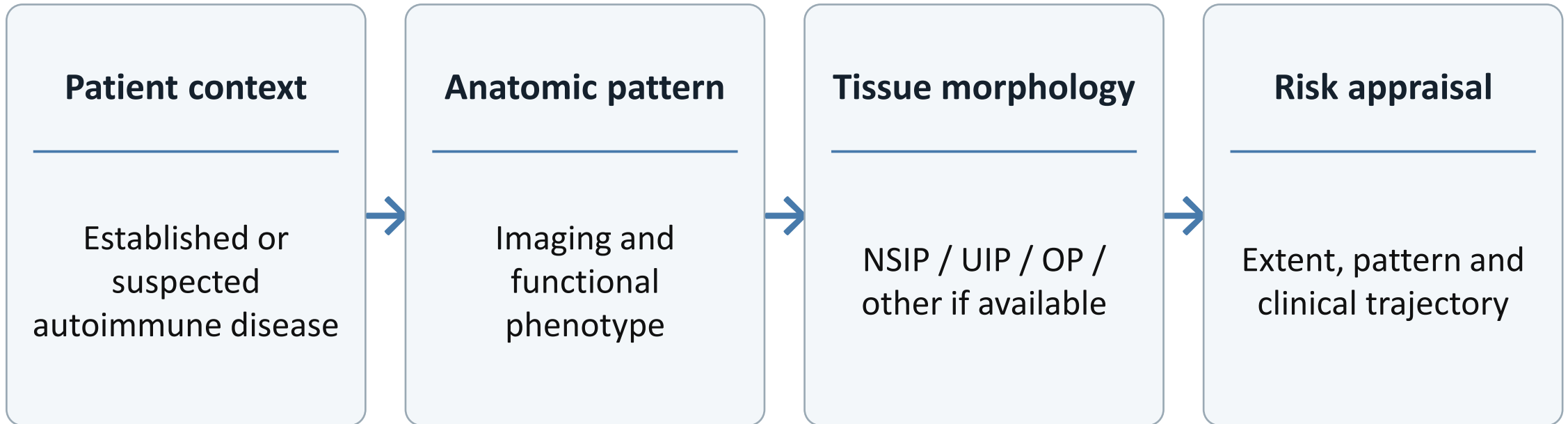
Autoimmune diagnoses and their pulmonary expressions

Disease	Important pulmonary expressions
Rheumatoid arthritis	Pleuritis ± effusion; Interstitial pneumonitis/fibrosis; Nodules; Follicular bronchiolitis; Pulmonary hypertension
Systemic sclerosis	Interstitial fibrosis (NSIP > UIP); Pleural involvement
SLE	Transient infiltrates; Severe pneumonitis; Pleuritis; Pleural effusion
Inflammatory myopathy	ILD in defined subsets (including anti-MDA5 DM and antisynthetase syndrome)

Classifying by compartment prevents diagnostic shortcuts

Compartment	Descriptive finding	Avoid assuming
Interstitialium	NSIP or UIP pattern	Specific autoimmune disease from morphology alone
Distal airspace	Organizing pneumonia	Cryptogenic etiology when CTD present
Bronchiole	Follicular bronchiolitis	Diffuse interstitial fibrosis
Pleura	Pleuritis / effusion	Parenchymal injury is necessarily present
Vessels	Pulmonary hypertension	Primary pulmonary fibrosis

Integrated assessment of autoimmune-associated ILD



Disease extent is a major prognostic determinant

- Robbins explicitly links prognosis to the extent of pulmonary involvement.
- Extent reflects how much lung is functionally compromised.
- A localized pleural or nodular finding is not equivalent to diffuse advanced fibrosis.
- Clinical assessment must quantify physiologic and structural impact.

Histologic pattern also shapes prognosis

- The source identifies histologic pattern as an independent prognostic consideration.
- NSIP typically has a more favorable prognosis than UIP.
- Cellular NSIP generally fares better than fibrosing NSIP.
- Advanced architectural destruction can limit reversibility.

Case discussion: Rheumatoid disease with mixed findings

Case stem

A patient with established rheumatoid arthritis has a pleural effusion and separate diffuse parenchymal abnormalities.

Interpretation

Describe the pleural lesion and parenchymal process separately.

Consider more than one rheumatoid-associated pulmonary phenotype.

Do not diagnose UIP from the clinical label alone.

Case discussion: Systemic sclerosis and uniform fibrosis

Case stem

A patient with systemic sclerosis has a restrictive pattern. Lung tissue shows interstitial fibrosis of roughly similar age without honeycombing.

Interpretation

The described morphologic pattern favors fibrosing NSIP.

NSIP is more common than UIP in systemic sclerosis.

Link interpretation to disease extent and physiology.

Case discussion: Lupus with changing infiltrates

Case stem

A patient with SLE develops patchy pulmonary infiltrates that subsequently resolve; Another has pleuritic symptoms and pleural fluid.

Interpretation

Transient parenchymal infiltrates are a recognized lupus finding.

Pleural inflammation/effusion is a separate manifestation.

Clinical severity varies across pulmonary phenotypes.

Diagnostic challenge: Masson body or fibroblastic focus?

Case stem

A lung lesion contains loose fibroblastic tissue. The critical question is whether it is in an alveolar lumen or within a heterogeneous fibrotic interstitium.

Interpretation

Intraluminal plugs favor organizing pneumonia.

Interstitial fibroblastic foci with heterogeneous scar support UIP.

Location and background architecture are decisive.

Synthesis: Four principles to retain

- Autoimmune diseases can involve interstitium, pleura, airways, nodules and pulmonary vessels.
- NSIP, UIP and organizing pneumonia name morphologic patterns, not etiologies.
- Rheumatoid arthritis, systemic sclerosis, lupus and myositis have overlapping but distinguishable pulmonary profiles.
- Prognosis depends on both the extent and histologic pattern of lung involvement.

Primary textbook and adjacent context

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 15, The Lung: pulmonary involvement in autoimmune diseases, pp. 629–630.

Chapter 15: chronic diffuse interstitial diseases; NSIP, UIP and organizing pneumonia, pp. 627–629.

Chapter 6: systemic lupus erythematosus and systemic sclerosis.

Chapter 26: rheumatoid arthritis and rheumatoid nodules.

Chapter 27: dermatomyositis, antisynthetase syndrome and inflammatory myopathies.