

Pulmonary Alveolar Proteinosis

Surfactant clearance failure • Mechanisms • Morphology • Clinical correlation

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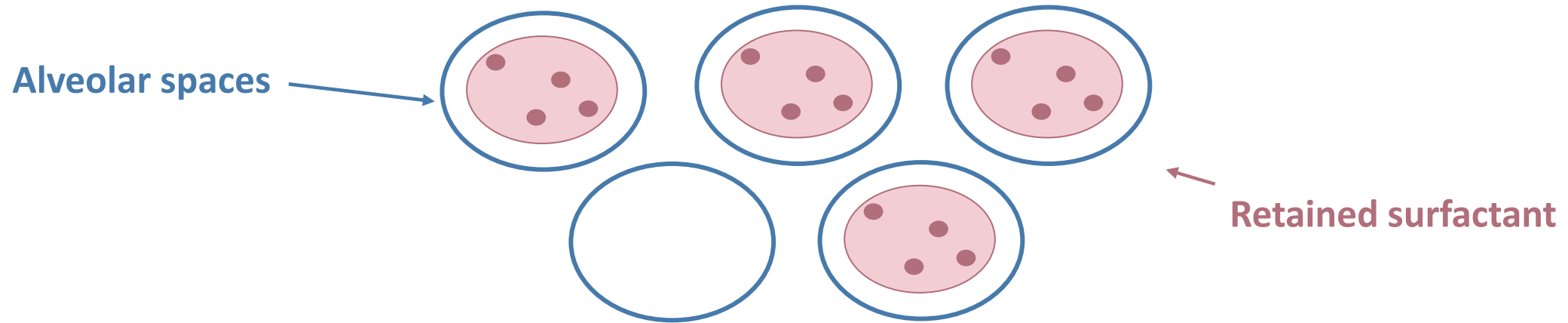
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Learning outcomes

- Explain normal surfactant clearance and the function of GM-CSF signalling.
- Distinguish autoimmune, secondary and hereditary forms of PAP.
- Recognise characteristic alveolar morphology and clinical consequences.
- Integrate a contemporary diagnostic and treatment approach.

What the term PAP describes

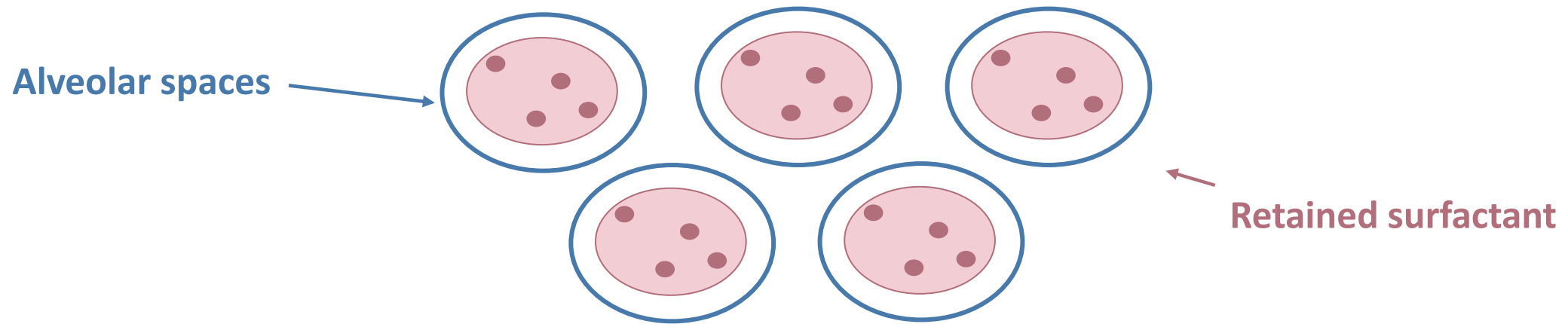
- A rare pulmonary syndrome of abnormal surfactant accumulation.
- Material collects in alveolar and bronchiolar airspaces.
- Deficient alveolar macrophage clearance is the central mechanism.
- Distinct aetiologies converge on similar microscopic findings.



Schematic — not a clinical or histologic specimen

The disease is primarily an airspace-filling process

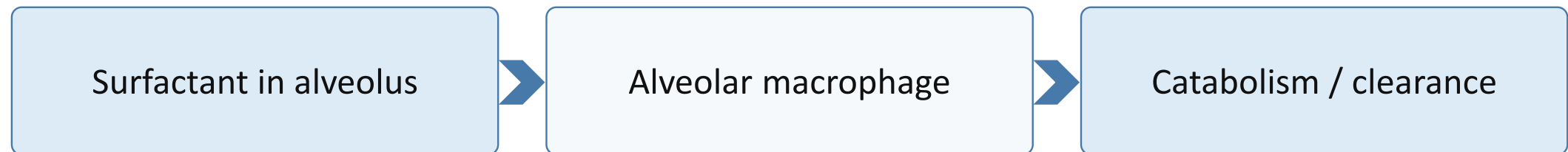
- The hallmark material lies inside alveoli, not predominantly within septa.
- Alveolar walls may remain relatively intact.
- Extensive material can produce confluent areas of consolidation.



Schematic — not a clinical or histologic specimen

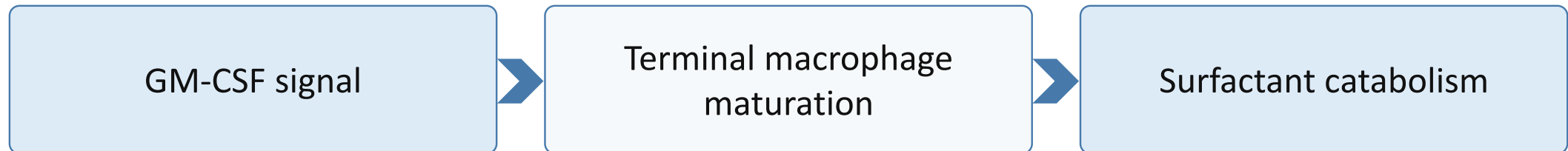
Surfactant clearance: The homeostatic requirement

- Surfactant normally resides along the alveolar air–liquid interface.
- Continuous turnover requires removal and catabolism of material.
- Alveolar macrophages are essential to surfactant catabolism.



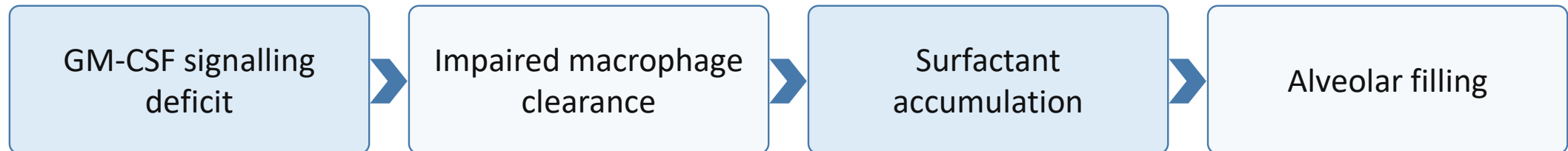
GM-CSF supports alveolar macrophage maturation

- Granulocyte–macrophage colony-stimulating factor (GM-CSF) is a regulatory cytokine.
- GM-CSF signalling permits terminal alveolar macrophage differentiation.
- This specialised macrophage state is required for efficient surfactant disposal.



The central failure in PAP

- Deficient GM-CSF signalling compromises macrophage function.
- Inefficient degradation allows surfactant to accumulate over time.
- Airspace occupancy increases while inflammation can remain minimal.



Why accumulation does not require hypersecretion

- PAP is best understood as impaired clearance of alveolar surfactant.
- Production–clearance imbalance can occur without primary overproduction.
- This distinction explains why therapy may target material removal or macrophage function.

Normal balance

Surfactant turnover

Functional macrophage removal

PAP

Clearance insufficient

Airspace material accumulates

Three groups in the Robbins classification

- Autoimmune PAP: Neutralising anti–GM-CSF autoantibodies.
- Secondary PAP: Acquired conditions associated with impaired macrophage function.
- Congenital/hereditary PAP: Extremely rare signalling defects.

AUTOIMMUNE

Neutralising antibodies

GM-CSF signal blocked

SECONDARY

Associated disorder

Macrophage function impaired

HEREDITARY

Inherited pathway defect

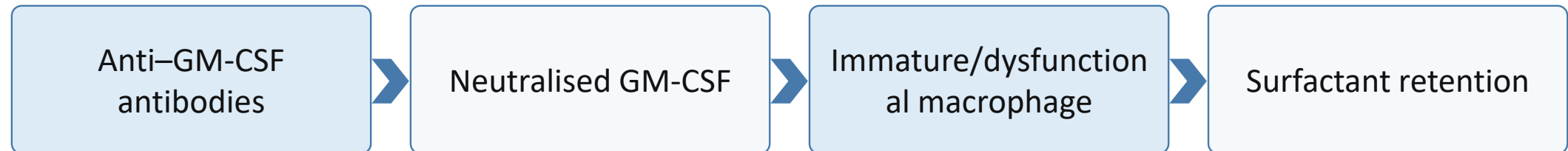
GM-CSF pathway disrupted

Autoimmune PAP is the dominant form

- Autoimmune PAP at 90% of PAP cases.
- The typical onset is during adulthood.
- No familial predisposition is expected in the usual autoimmune form.

Neutralising antibodies interrupt a cytokine signal

- Autoantibodies bind GM-CSF and neutralise its activity.
- The resulting signalling deficiency affects alveolar macrophages.
- Loss of terminal differentiation reduces surfactant clearance.



Evidence supporting GM-CSF dependence

- GM-CSF knockout in mice produces PAP-like disease.
- GM-CSF replacement reverses the phenotype in this experimental model.
- Mechanistic animal findings support the role of signalling loss in PAP.

Secondary PAP has heterogeneous associations

- Secondary cases are uncommon relative to autoimmune PAP.
- A related systemic or inhalational disorder is usually identifiable.
- The mechanism of macrophage impairment can differ across disorders.

Hematopoietic disease and malignancy

- Hematopoietic disorders can be associated with secondary PAP.
- Malignancies are included among described associations.
- The diagnostic search should consider the broader clinical context.

Immunodeficiency as a PAP context

- Immunodeficiency disorders can coexist with PAP.
- Dysfunctional macrophage maturation or activity is proposed.
- Infections can also complicate the PAP course, requiring careful attribution.

Inhalational diseases associated with PAP

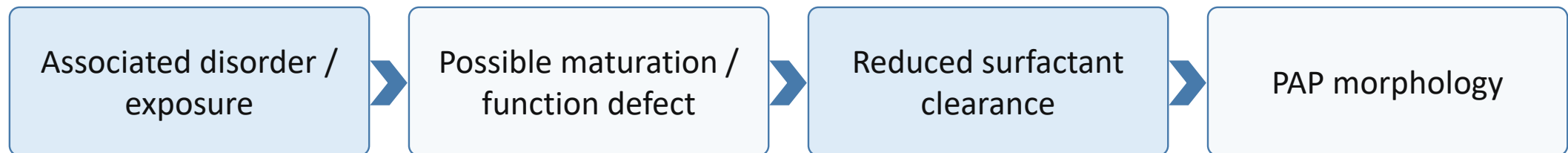
- Acute silicosis and other inhalational syndromes are associated with secondary PAP.
- An exposure history can reveal an otherwise hidden cause.
- The precise downstream defect may not be established.

Lysinuric protein intolerance is another association

- This inherited amino-acid metabolic disorder among secondary-PAP associations.
- The clinical association broadens the differential beyond autoimmune disease.
- Its presence does not imply autoantibody-mediated GM-CSF neutralisation.

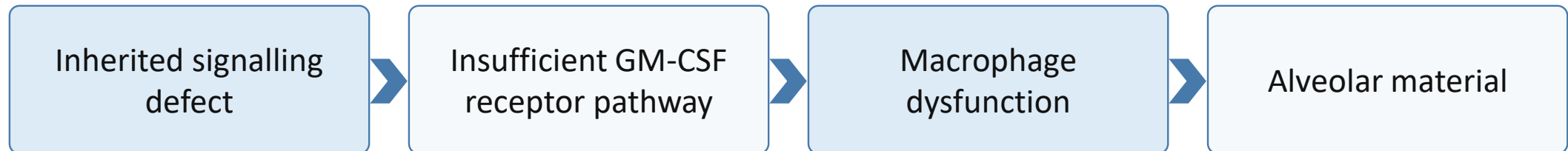
Mechanism in secondary PAP: A cautious model

- GM-CSF-dependent differentiation or downstream macrophage function may be affected.
- The precise link is not known for all associated disorders.
- Robbins characterises some of these proposed connections as speculative.



Hereditary GM-CSF signalling deficiency

- An extremely rare form presents in early life.
- Loss-of-function variants may affect GM-CSF or receptor genes.
- The pathway failure produces abnormal surfactant clearance.



The three groups converge on one phenotype

- Different proximal causes share reduced effective alveolar macrophage activity.
- Histologic deposits can look essentially the same.
- Aetiologic classification therefore requires evidence beyond morphology.

AUTOIMMUNE

Neutralising antibodies

GM-CSF signal blocked

SECONDARY

Associated disorder

Macrophage function impaired

HEREDITARY

Inherited pathway defect

GM-CSF pathway disrupted

Modern nomenclature distinguishes additional entities

- The 2024 ERS scheme separates hereditary GM-CSF-receptor PAP from congenital surfactant dysfunction.
- The supplied Robbins section uses a broader “congenital” label for rare signalling-associated PAP.
- These should not be treated as synonymous molecular diagnoses.

Hereditary PAP

GM-CSF signalling defect

CSF2RA / CSF2RB in ERS algorithm

Congenital surfactant disorders

Surfactant protein/trafficking defect

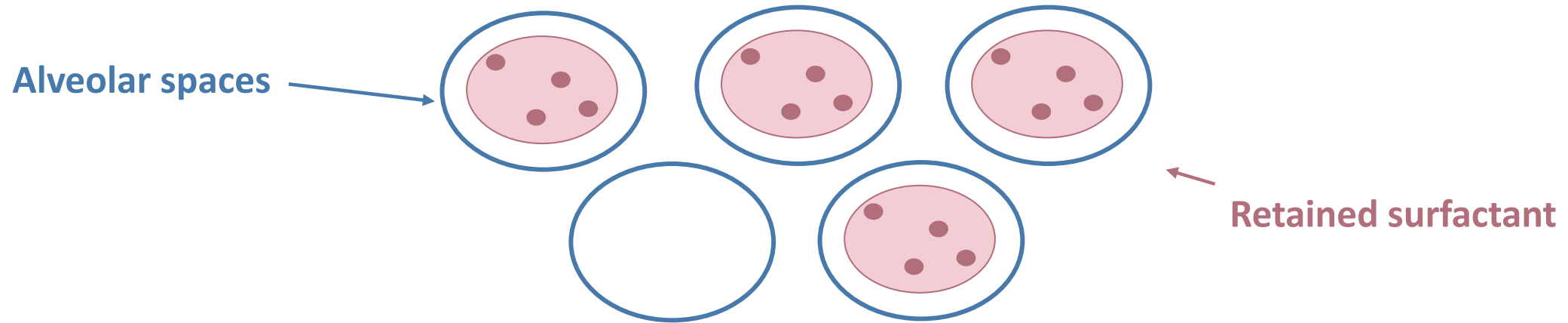
Separate molecular work-up

Gross lung changes

- Deposits can cause focal-to-confluent lung consolidation.
- The lungs may become markedly enlarged and heavy.
- The change reflects accumulation of material in many airspaces.

Low-power architecture: Packed alveoli

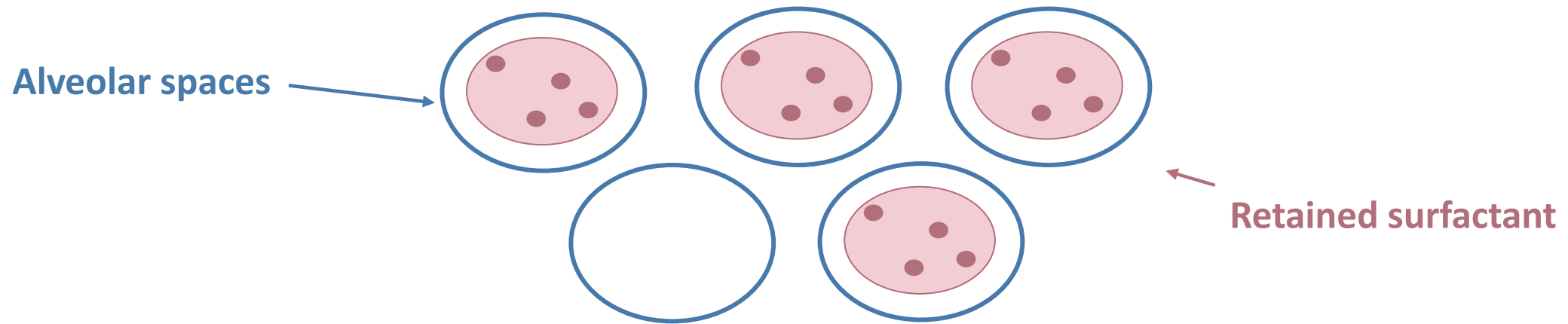
- Widespread alveolar lumina contain extracellular material.
- Accumulation may involve contiguous fields of lung.
- The architectural framework can remain preserved despite filling.



Schematic — not a clinical or histologic specimen

High-power morphology: Eosinophilic precipitate

- Intra-alveolar deposits are pink and relatively homogeneous on H&E.
- The material may appear dense, amorphous or granular.
- Surfactant proteins and lipids account for its composition.



Schematic — not a clinical or histologic specimen

Periodic acid–Schiff positivity

- The alveolar precipitate is periodic acid–Schiff (PAS) positive.
- This is a useful tissue clue for surfactant-rich material.
- PAS positivity is interpreted together with the location and morphology.

H&E morphology

Pink homogeneous material

In alveolar airspaces

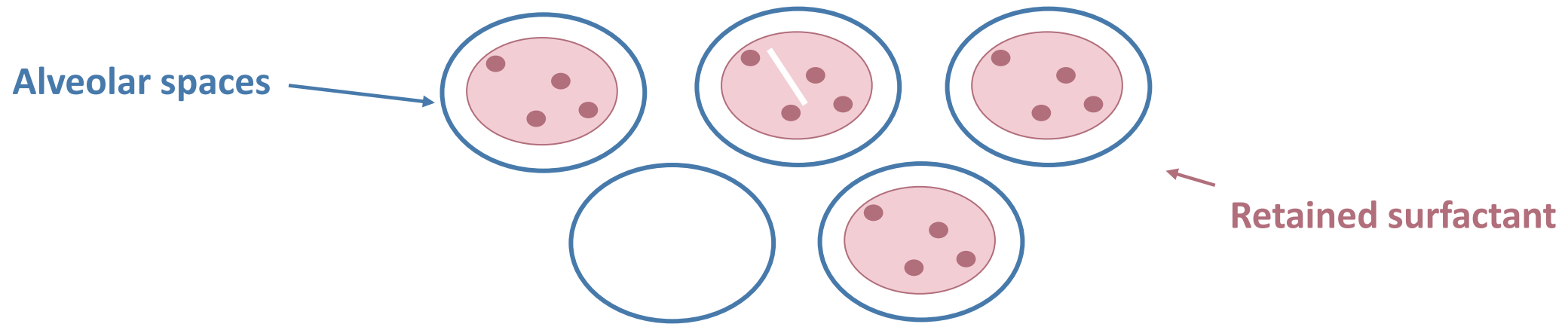
PAS reaction

Positive precipitate

Supports PAP pattern

Cholesterol clefts may be present

- Cholesterol clefts within the precipitated material.
- These reflect the lipid-rich composition of retained surfactant.
- They are supportive but not by themselves a specific PAP test.



Schematic — not a clinical or histologic specimen

Surfactant protein immunostains

- Surfactant proteins are demonstrable within intra-alveolar deposits by immunohistochemistry.
- Their presence supports the biochemical identity of the precipitate.
- A positive stain must be read alongside the tissue pattern.

Minimal inflammatory response

- The classic precipitate causes relatively little inflammation.
- Septa may appear largely normal despite conspicuous luminal filling.
- Marked inflammation should prompt assessment of infection or another process.

Alveolar spaces

Abundant precipitate

Confluent filling

Interalveolar septa

Often largely preserved

Minimal inflammation

Ultrastructure in PAP

- Type II pneumocyte surfactant lamellae are usually normal in classic PAP.
- The primary problem is extracellular accumulation due to reduced catabolism.
- This differs from intrinsic surfactant organelle abnormalities.

PAP versus surfactant dysfunction

- PAP: Impaired macrophage-mediated surfactant clearance is central.
- Surfactant dysfunction: Variants impair surfactant trafficking, processing or secretion.
- The adjacent Robbins topic describes abnormal lamellar bodies in some genetic disorders.

PAP

Macrophage clearance defect

Usually normal type II lamellae

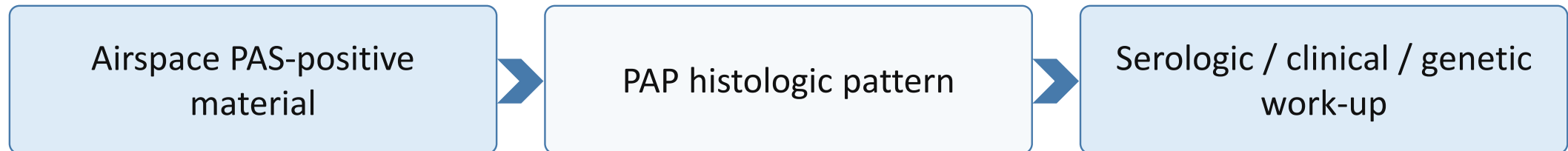
Surfactant dysfunction

Epithelial surfactant defect

Lamellar body abnormalities may occur

What the histology establishes

- The biopsy pattern supports a PAP syndrome.
- Microscopy alone generally cannot distinguish autoimmune from secondary PAP.
- Etiologic classification requires serology, genetics and clinical context.



Anatomic differential: Where is the lesion?

- Airspace-filling diseases primarily occupy alveolar lumina.
- Interstitial lung diseases may primarily thicken or destroy septa.
- This distinction is often more useful than deposit colour alone.

PAP pattern

Intra-alveolar precipitate

Septa relatively preserved

Fibrosing interstitial process

Thickened / scarred septa

Architectural distortion may dominate

PAP versus pulmonary oedema

- Both conditions can produce abundant intra-alveolar material.
- PAP has characteristic surfactant-rich, PAS-positive precipitate.
- The final diagnosis requires integration of imaging, clinical context and laboratory findings.

PAP

Surfactant-rich precipitate

GM-CSF context often decisive

Pulmonary oedema

Protein-poor or proteinaceous oedema fluid

Haemodynamic context relevant

PAP versus Pneumocystis pneumonia

- Both may produce intra-alveolar eosinophilic material.
- Infection requires organism-directed assessment where clinically suspected.
- PAP itself may coexist with secondary opportunistic infection.

PAP

Surfactant accumulation

Evaluate GM-CSF pathway

Pneumocystis pneumonia

Infectious alveolar material

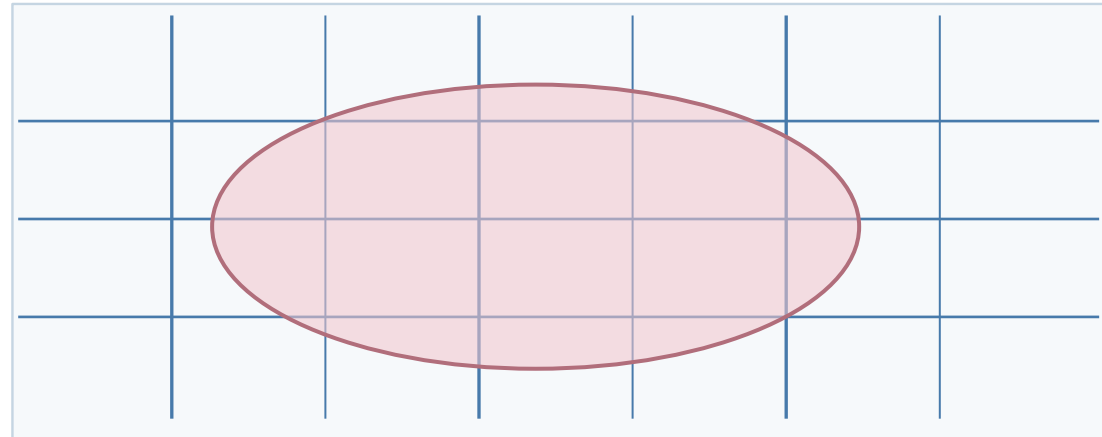
Look for organisms with appropriate stains

Radiologic presentation

- Bilateral pulmonary opacification is typical.
- The distribution may be patchy and asymmetric.
- The imaging pattern is not exclusive to PAP.

CT finding: The crazy-paving pattern

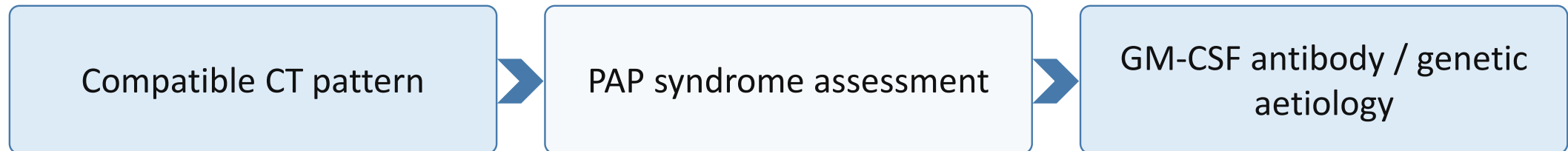
- Ground-glass opacity accompanied by septal or intralobular lines may create “crazy paving”.
- This pattern can support suspicion of PAP.
- Crazy paving is nonspecific and must be interpreted in context.



Ground-glass opacity + intersecting lines

A pattern is not a molecular diagnosis

- Imaging suggests airspace disease but does not define its cause.
- Bronchoalveolar lavage or histology helps establish the PAP syndrome.
- Anti-GM-CSF testing and selected genetic studies refine aetiology.

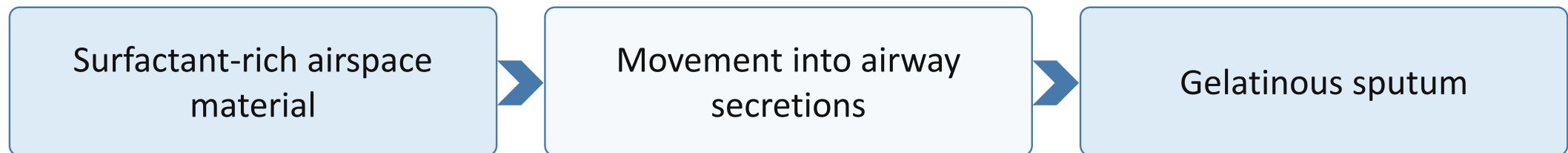


Adult presentation: Cough

- Cough may be a presenting symptom in adult PAP.
- Patients can have substantial expectoration.
- The sputum may contain conspicuous gelatinous fragments.

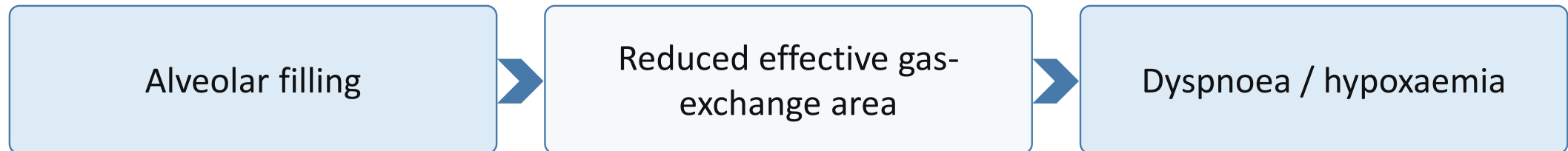
Why sputum can be gelatinous

- Retained intra-alveolar material contains surfactant proteins and lipids.
- Airway transport may move this accumulated material into expectorated sputum.
- The macroscopic appearance reflects the composition of the deposits.



Dyspnoea and impaired gas exchange

- Airspace filling reduces effective ventilated alveolar volume.
- Progressive disease can cause dyspnoea and hypoxaemia.
- Severe cases may progress to cyanosis or respiratory insufficiency.



Secondary pulmonary infection

- Intermittent febrile illness from pulmonary infections.
- Impaired alveolar macrophage function plausibly weakens host defence.
- Fever should not automatically be attributed to sterile surfactant deposits.

Clinical course varies

- Some patients have symptoms that persist for years.
- Progression to respiratory insufficiency is possible.
- Others have a benign course with eventual resolution of lesions.

Progressive course

Worsening dyspnoea

Hypoxaemia / respiratory failure

Improving course

Lesions may resolve

Severity is not uniform

Diagnosis begins with clinicoradiologic suspicion

- Consider PAP with compatible respiratory symptoms and patchy bilateral abnormalities.
- Assess systemic disease, immune status and inhalational exposures.
- Avoid treating the radiologic pattern as pathognomonic.

Bronchoalveolar lavage contributes to diagnosis

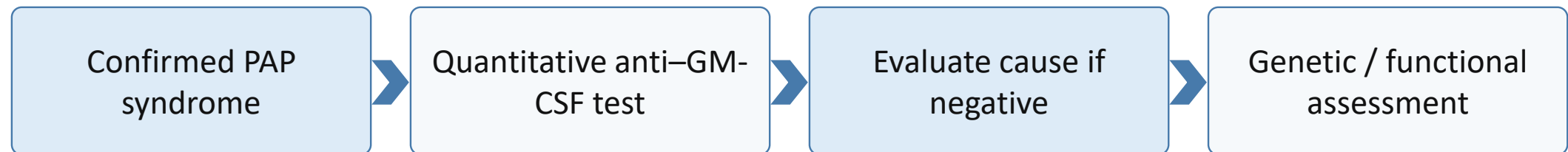
- ERS guidance includes BAL in the work-up of suspected PAP.
- Lavage may yield opaque, milky material containing surfactant-rich deposits.
- Cytology and special stains should be interpreted in context.

Quantitative GM-CSF autoantibody testing

- ERS recommends anti–GM-CSF antibody testing for suspected or confirmed PAP.
- Quantitative results from an experienced laboratory help identify autoimmune PAP.
- The laboratory reference threshold and assay method must be considered.

An updated etiologic decision tree

- Positive anti–GM-CSF testing supports autoimmune PAP.
- Negative testing plus a recognised underlying disorder raises secondary PAP.
- Unexplained cases may require GM-CSF signalling assessment and genetic testing.



Why most patients do not need a lung biopsy

- BAL, serology and selected genetic tests often establish the necessary diagnosis.
- ERS generally advises against routine lung biopsy.
- Biopsy can be considered for unresolved cases in expert consultation.

Interpretation of a pathology report

- Describe alveolar luminal PAS-positive, proteinaceous material.
- Comment on alveolar septa, inflammation and any suspected infection.
- Use “consistent with PAP” without assigning an autoimmune cause from histology alone.

Therapy addresses two different problems

- Whole-lung lavage physically removes accumulated alveolar material.
- GM-CSF augmentation targets deficient macrophage signalling in autoimmune PAP.
- Management of an associated disorder may be necessary in secondary PAP.

Remove deposits

Whole-lung lavage

Treat the airspace burden

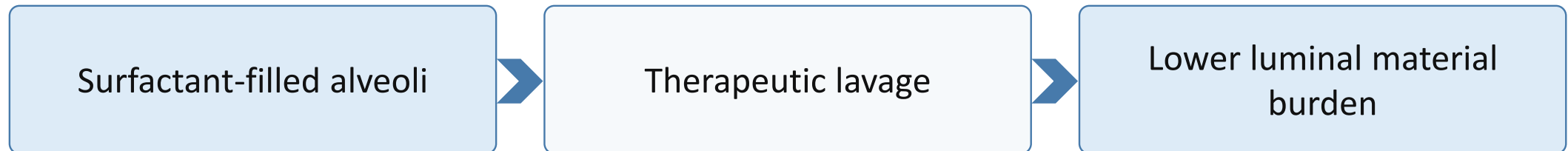
Restore function

GM-CSF replacement

Address macrophage dysfunction

Whole-lung lavage: The treatment principle

- Fluid is instilled and removed to clear accumulated surfactant material.
- Whole-lung lavage as a standard therapeutic approach.
- Modern ERS recommendations specify the clinical setting for autoimmune PAP.



ERS: When to perform whole-lung lavage

- In autoimmune PAP with impaired gas exchange and symptoms or functional impairment.
- This carries a strong recommendation, with very-low-certainty evidence.
- For other PAP types, ERS does not make an equivalent general recommendation.

Inhaled GM-CSF for symptomatic autoimmune PAP

- ERS recommends inhaled GM-CSF in symptomatic confirmed autoimmune PAP.
- Its target is the pathophysiologic deficit in GM-CSF activity.
- It is not automatically applicable to every genetic or secondary form.

Options for refractory autoimmune disease

- ERS conditionally suggests rituximab in selected oxygen-requiring cases despite first-line therapy.
- Plasmapheresis is considered for particularly refractory disease.
- Lung transplantation may be considered for progressive end-stage disease.

Secondary PAP requires aetiologic treatment

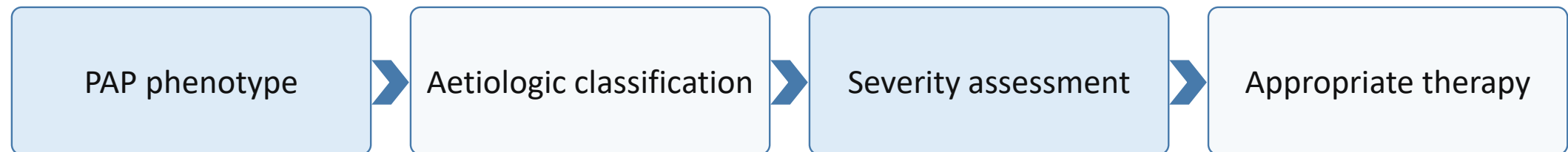
- Identify and address the associated disease or exposure when possible.
- The contribution of lavage may differ by underlying cause.
- Avoid assuming that anti-GM-CSF antibody-directed therapy applies to secondary PAP.

Inherited signalling defects: Therapeutic nuance

- Hereditary GM-CSF pathway defects require specialised phenotyping and genetics.
- Robbins mentions replacement and haematopoietic stem-cell approaches for selected primary inherited disease.
- Management must be individualised rather than extrapolated from autoimmune PAP.

Treatment should follow the mechanism

- Establish the syndrome before selecting targeted therapy.
- Identify autoimmune, secondary or inherited pathogenesis.
- Match the treatment to the dominant biological problem and severity.



Case 1 — chronic cough and bilateral opacities

- Constructed teaching vignette: An adult has cough, gelatinous sputum and patchy bilateral opacities.
- Biopsy, if obtained, shows PAS-positive alveolar material with intact septa.
- Question: What is the likely syndrome, and which test best identifies autoimmune aetiology?

What would an elevated anti-GM-CSF result establish?

Case 1 — reasoning

- A surfactant-rich alveolar precipitate supports a PAP syndrome.
- Quantitative serum anti-GM-CSF autoantibodies assess autoimmune PAP.
- The biopsy pattern alone does not prove the autoimmune subtype.

Case 2 — PAP in a patient with haematologic disease

- Constructed vignette: A patient with a haematologic disorder develops PAP-pattern morphology.
- The anti-GM-CSF test is not elevated.
- Question: Which etiologic group is most relevant, and what additional action is essential?

How would the underlying haematologic disorder affect classification?

Case 2 — reasoning

- The associated haematologic disorder makes secondary PAP plausible.
- Evaluate disease- and therapy-related macrophage dysfunction.
- Address the associated disorder in addition to the pulmonary manifestations.

Case 3 — neonatal disease with GM-CSF defect

- Constructed vignette: A neonate has pulmonary alveolar material and a suspected receptor-signalling defect.
- The clinical presentation raises a hereditary form of PAP.
- Question: Why is anti-GM-CSF neutralisation not the assumed cause?

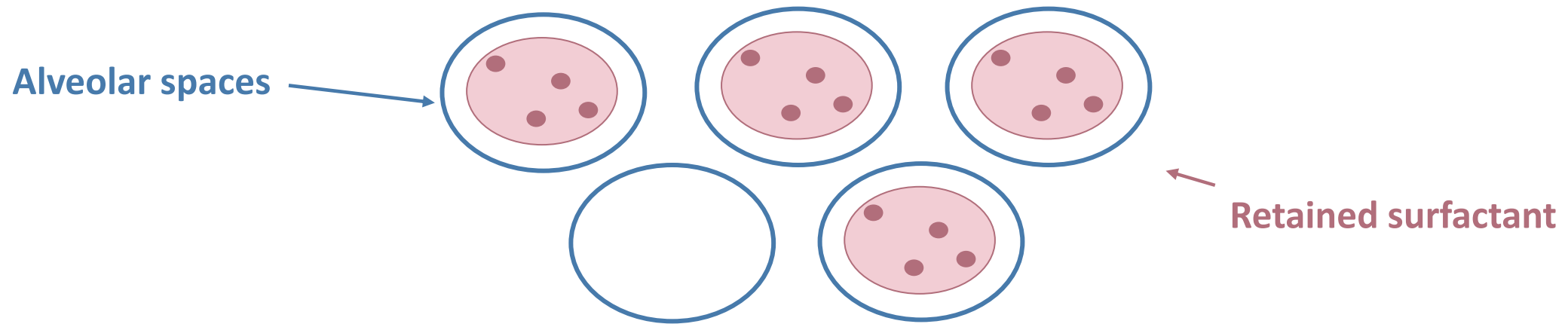
Which tests identify a hereditary signalling defect?

Case 3 — reasoning

- The failure may arise from loss-of-function in the cytokine or receptor pathway.
- Genetic and functional studies—not just routine H&E—identify the cause.
- Distinguish hereditary signalling defects from surfactant trafficking disorders.

Histology challenge — identify the compartment

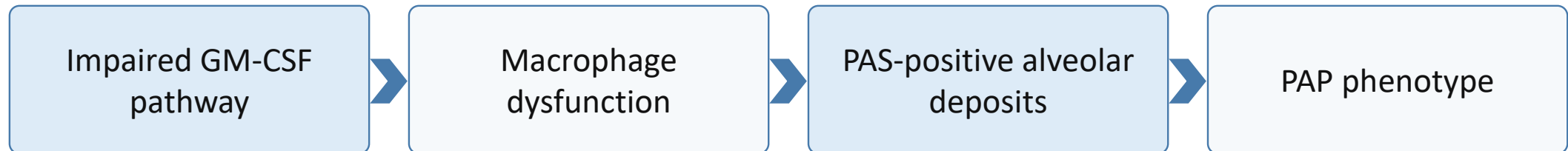
- An alveolar biopsy has homogeneously pink PAS-positive material within lumina.
- Septa remain thin, and conspicuous fibrosis is absent.
- Interpretation: The abnormal process is predominantly intra-alveolar.



Schematic — not a clinical or histologic specimen

High-yield diagnostic synthesis

- PAP is an airspace-filling disease due to failed surfactant clearance.
- GM-CSF signalling is central to alveolar macrophage maturation.
- PAS-positive protein–lipid material with preserved septa supports the pattern.
- Autoantibody testing and clinical/genetic work-up assign cause.



References and reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. The Lung, pp 637–638.
- McCarthy C, et al. ERS guidelines on pulmonary alveolar proteinosis. Eur Respir J. 2024;64:2400725.
- ERS summary for clinicians, Breathe. 2025; PMID: PMC12070199.
- Original Robbins Fig 15.22 is not reproduced; diagrams here are editable schematics.