

Diffuse pulmonary hemorrhage syndromes

Pulmonary microvascular injury, morphology, and clinicopathologic distinction

Core morphologic patterns • anti-GBM injury • immune vasculitis

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Pulmonary hemorrhage is a lesion, not an etiologic diagnosis

- Intra-alveolar bleeding may accompany several mechanistically different lung disorders.
- The diagnostic question is which process injured the alveolar microvasculature.
- Morphology establishes hemorrhage; Systemic clues and immune pathology identify its cause.

Learning goals

- Recognize alveolar hemorrhage and the evolution of hemosiderin-laden macrophages.
- Explain anti-GBM disease, idiopathic pulmonary hemosiderosis and vasculitis-related hemorrhage.
- Use renal findings, tissue immunofluorescence and clinical context to separate major etiologies.

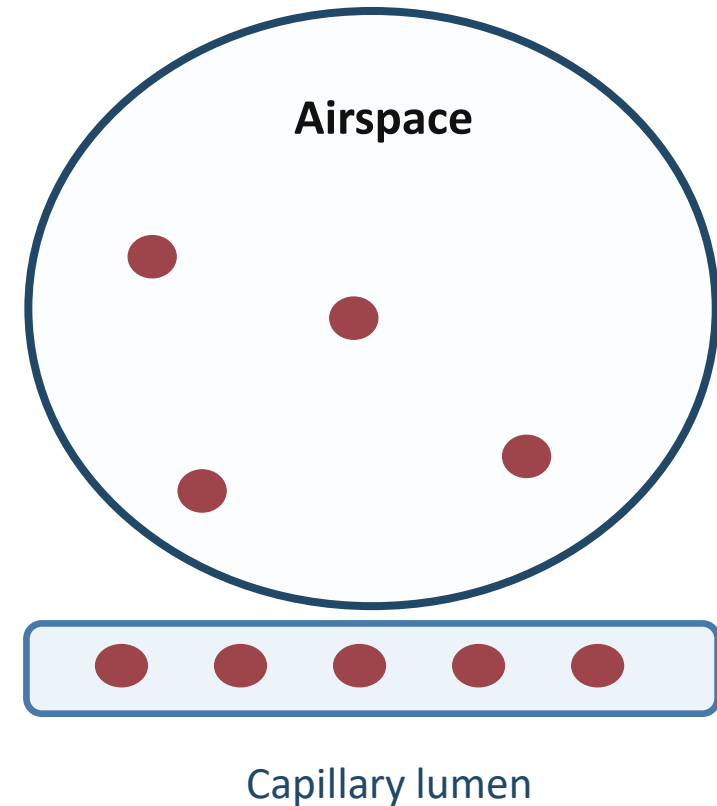
The alveolar–capillary interface is the injured compartment

Pathologic interpretation

Capillary wall damage allows erythrocytes to enter airspaces.

- Alveolar septa separate circulating erythrocytes from alveolar air.
- Disruption of the microvascular barrier produces intra-alveolar blood.

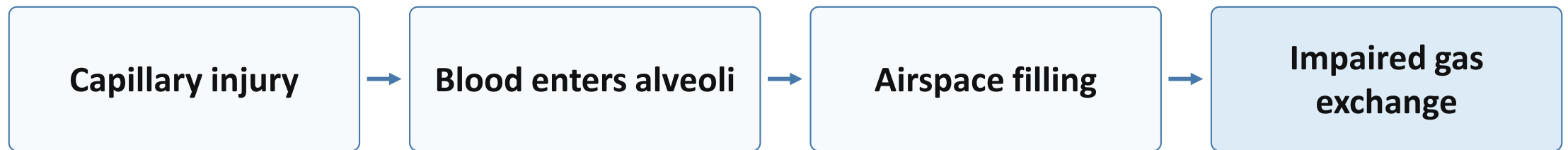
Simplified alveolar–capillary schematic



Schematic — not a photomicrograph

Why bleeding impairs gas exchange

- Blood occupying normally aerated alveoli interferes with effective ventilation.
- Extensive hemorrhage can accompany acute respiratory compromise.



Mechanistic schematic

Robbins groups hemorrhage syndromes into three etiologies

Anti-basement membrane

Goodpasture syndrome

Autoantibodies bind a shared lung–kidney antigen.

Unexplained recurrent bleeding

Idiopathic pulmonary hemosiderosis

Intermittent diffuse hemorrhage without known cause.

Inflammatory vascular injury

Vasculitis-associated hemorrhage

Small-vessel inflammation, often with systemic disease.

Three mechanisms can converge on one lesion

- Autoantibody-mediated basement membrane injury
- Unexplained pulmonary capillary damage
- Neutrophil-rich or immune-complex vascular inflammation



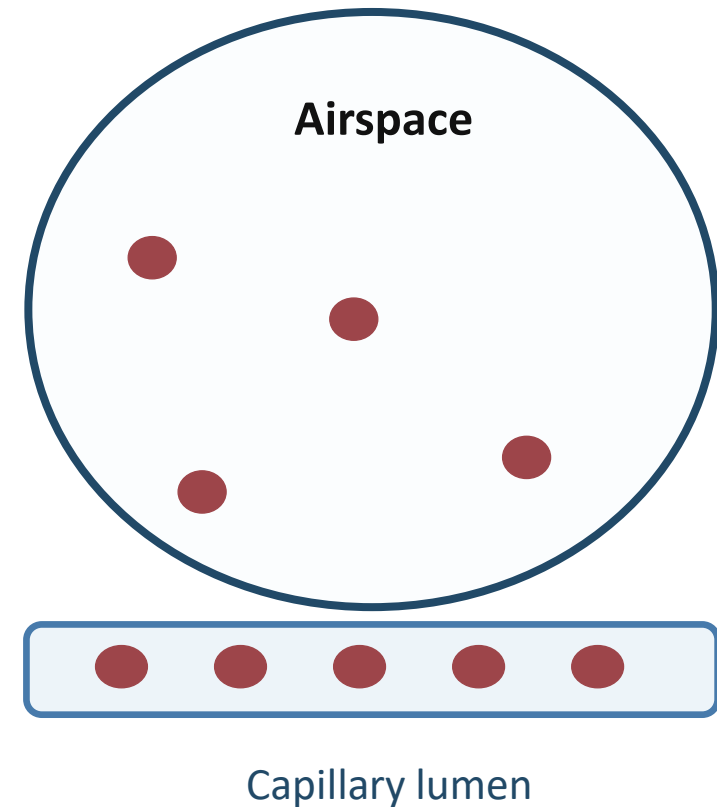
The shared histologic endpoint is intra-alveolar blood

Pathologic interpretation

A diagnosis of hemorrhage requires seeing erythrocytes or sequelae in airspaces.

- Recent bleeding leaves erythrocytes within alveoli.
- Prior bleeding often leaves macrophages carrying hemoglobin-derived pigment.

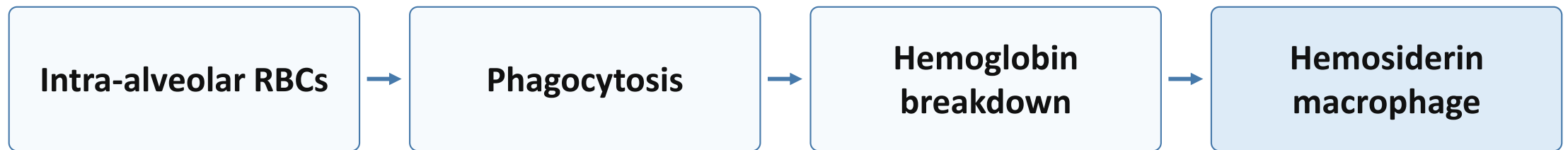
Simplified alveolar–capillary schematic



Schematic — not a photomicrograph

Macrophages retain a record of previous bleeding

- Macrophages ingest extravasated erythrocytes.
- Hemoglobin degradation leaves iron-rich hemosiderin within their cytoplasm.



Mechanistic schematic

Prussian blue demonstrates iron rather than fresh blood

H&E morphology

Erythrocytes in alveolar spaces

Brown granular pigment may occur in macrophages

Prussian blue

Highlights hemoglobin-derived iron

Iron-positive macrophages support earlier hemorrhage

Fresh hemorrhage and older hemorrhage leave different clues

Recent bleeding	Recurrent or older bleeding
Free alveolar erythrocytes	Hemosiderin-laden macrophages
Airspace blood predominates	Macrophage pigment persists
Can coexist with wall necrosis	Can coexist with septal fibrosis / organization

The pathology specimen answers two different questions

Presence of bleeding

Intra-alveolar erythrocytes

Hemosiderin-laden macrophages

Prussian-blue iron

Cause of bleeding

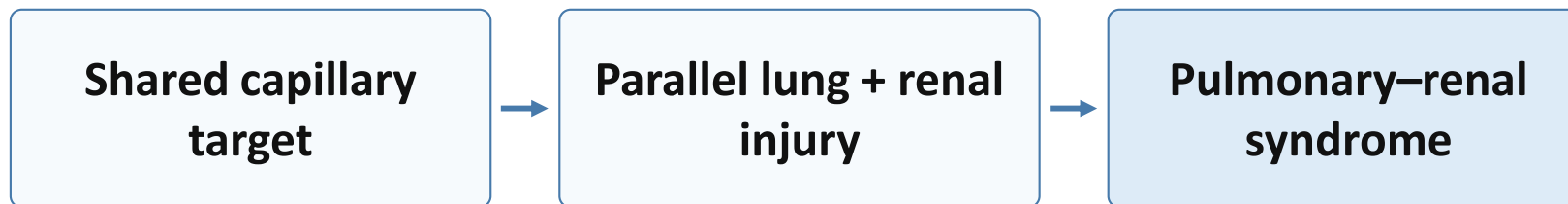
Necrotizing capillaritis?

Linear immune deposits?

Granulomas or systemic features?

Severe pulmonary–renal disease suggests shared capillary injury

- Alveolar and glomerular basement membranes can be targets of the same disease.
- Hemoptysis accompanied by glomerulonephritis requires a systemic explanation.



Mechanistic schematic

Pulmonary–renal syndromes are mechanistically heterogeneous

Mechanism	Characteristic immune pattern	Example
Anti-GBM antibody	Linear glomerular IgG	Goodpasture syndrome
ANCA-associated inflammation	Pauci-immune	GPA / microscopic polyangiitis
Immune complexes	Granular immune deposits	Lupus-associated nephritis

Goodpasture syndrome: Lung plus kidney involvement

Kidney

Autoimmune glomerular injury

Proliferative to crescentic GN

Rapid renal deterioration may follow

Lung

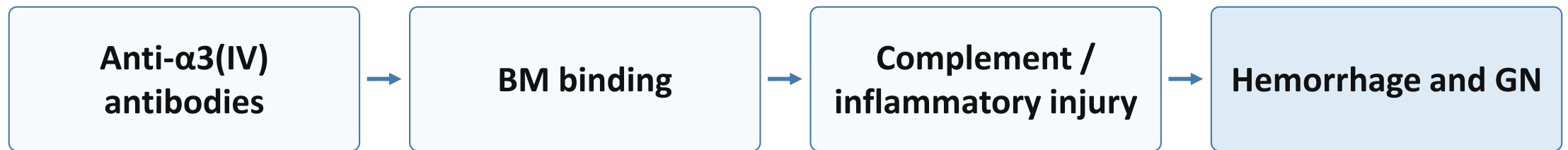
Alveolar basement membrane injury

Necrotizing hemorrhagic pneumonitis

Hemoptysis is characteristic

The target is the $\alpha 3$ chain of type IV collagen

- Circulating autoantibodies recognize a noncollagenous domain on collagen IV $\alpha 3$.
- The target antigen is present in the relevant basement membranes of lung and kidney.



Mechanistic schematic

One antigen links two anatomically separate organs

Pulmonary alveolar BM

Binding injures alveolar capillary interface

Blood crosses into alveoli

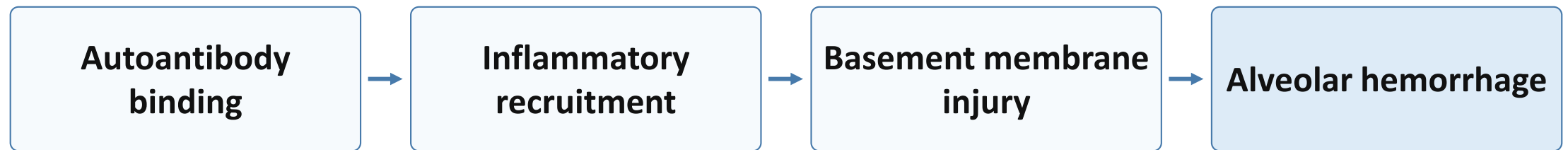
Glomerular BM

Binding damages capillary tuft

Nephritic injury with crescents may follow

The humoral attack leads to destructive inflammation

- Anti-basement membrane antibodies initiate injury at bound sites.
- Inflammation disrupts capillary structures and produces bleeding.



Mechanistic schematic

T-cell contribution is plausible, but evidence is qualified

Established in source

Circulating autoantibodies are central to injury.

Antibodies target type IV collagen $\alpha 3$ NC region.

Experimental inference

Autoreactive T cells may enhance B-cell responses.

T cells may contribute to glomerular damage.

Genetic predisposition is not the same as a known trigger

Association

HLA-DRB1*1501 and *1502 are linked with susceptibility.

Observed HLA association supports immune predisposition.

Unresolved

Trigger for antibody production remains unknown.

Association cannot establish individual causality.

Who develops Goodpasture syndrome?

- Most textbook cases occur in patients in their teens or twenties, but any age is possible.
- A male preponderance is described.
- Many affected patients are active smokers; This is an association, not an identified initiating cause.

Lung gross morphology: Red-brown consolidation

- Lungs are often heavy.
- Red-brown consolidated areas reflect intra-alveolar hemorrhage and its sequelae.
- Gross discoloration does not identify the immunologic cause by itself.

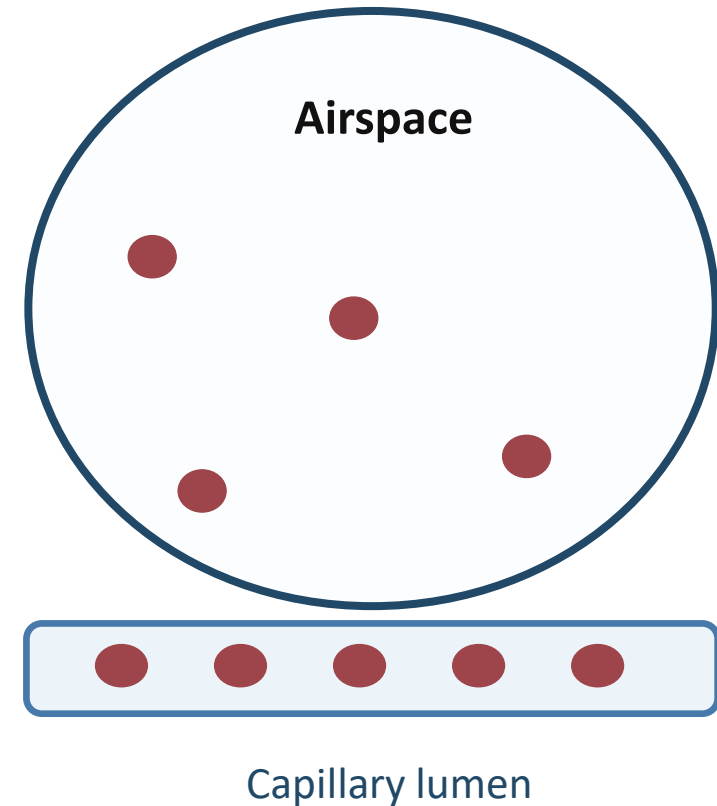
Acute pulmonary morphology in anti-GBM disease

Pathologic interpretation

The source describes focal necrosis of alveolar walls with intra-alveolar hemorrhage.

- Wall necrosis implicates destructive microvascular injury.
- Hemosiderin macrophages are often intermingled with alveolar blood.

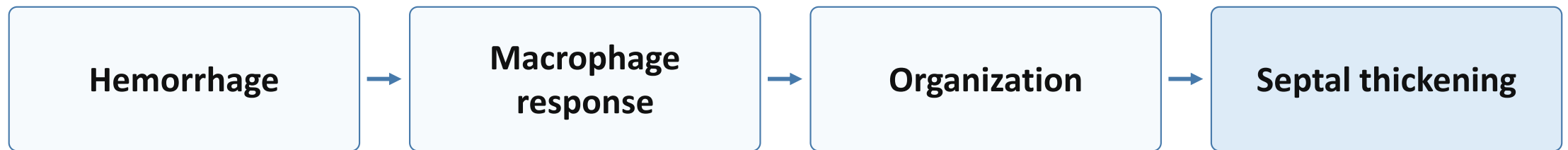
Simplified alveolar–capillary schematic



Schematic — not a photomicrograph

Chronic and healing pulmonary injury

- Septal fibrosis can develop after repeated or persistent injury.
- Type II pneumocyte hyperplasia and organization of intra-alveolar blood may appear.



Mechanistic schematic

Linear immune deposits are a mechanistic clue

Schematic immunofluorescence distributions

LINEAR

Anti-GBM



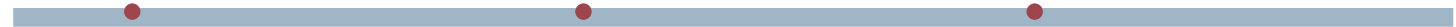
GRANULAR

Immune complexes



PAUCI-IMMUNE

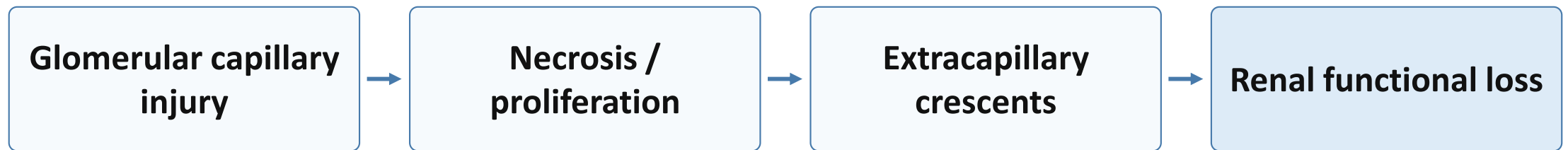
ANCA-associated



Anti-GBM antibodies bind in a continuous pattern along basement membranes. Linear immunofluorescence supports a basement-membrane-directed process.

Renal evolution: Proliferative to crescentic glomerulonephritis

- Early renal lesions may show focal proliferative glomerulonephritis.
- Severe rapidly progressive disease is characterized by crescents.



Mechanistic schematic

Why crescent formation matters

Morphologic event

Capillary tuft injury permits inflammatory constituents into urinary space.

Parietal epithelial cells and mononuclear cells proliferate.

Clinicopathologic consequence

Crescents occupy Bowman space.

Severe injury can rapidly impair glomerular filtration.

Renal immunofluorescence may clinch the mechanism

Schematic immunofluorescence distributions

LINEAR

Anti-GBM



GRANULAR

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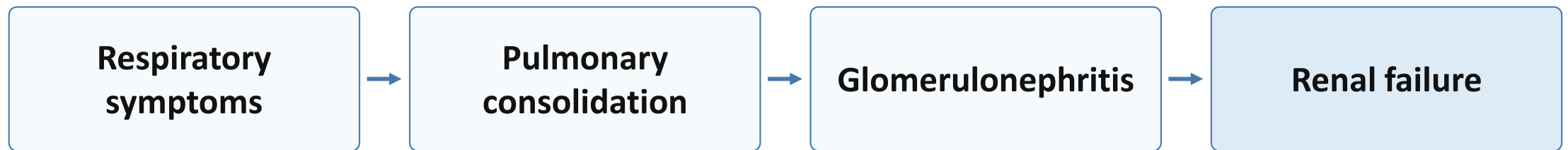
ANCA-associated



Characteristic glomerular pattern is linear IgG, frequently with C3. Immune pattern can be demonstrable even when pulmonary manifestations dominate.

Goodpasture often begins as respiratory disease

- Hemoptysis and radiographic pulmonary consolidations may appear first.
- Glomerulonephritis then emerges and can progress rapidly.



Mechanistic schematic

Goodpasture and renal-limited anti-GBM disease

Feature	Goodpasture syndrome	Renal-limited anti-GBM
Autoantibody	Anti-GBM	Anti-GBM
Kidney involvement	Present	Present
Pulmonary hemorrhage	Present	Absent
Naming point	Lung + renal phenotype	Kidney-restricted phenotype

Serologic and tissue findings answer complementary questions

Serum

Anti-GBM antibody testing assesses circulating pathogenic antibody.

Also assess relevant ANCA / ANA in the differential.

Tissue

Linear glomerular IgG + complement supports anti-GBM GN.

Pulmonary histology may show necrotizing hemorrhage.

Why removal and suppression are paired treatments

- Plasma exchange removes circulating anti-basement membrane antibodies.
- Concurrent immunosuppression reduces production of new pathogenic antibodies.



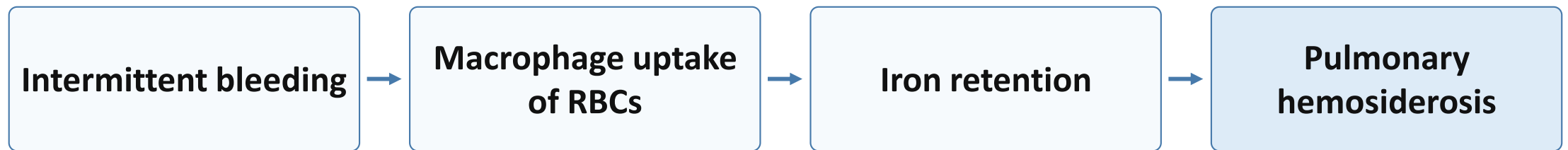
Mechanistic schematic

Goodpasture: Integrated diagnostic pattern

Domain	Expected finding
Lung	Intra-alveolar blood; Necrotizing injury; Hemosiderin macrophages
Kidney	Proliferative or crescentic glomerulonephritis
Immune studies	Anti-GBM antibodies; Linear BM IgG
Presentation	Hemoptysis, pulmonary consolidation, then renal dysfunction

Idiopathic hemosiderosis causes recurrent alveolar hemorrhage

- A rare disorder with recurrent diffuse alveolar hemorrhage.
- Cause and pathogenesis remain unknown.



Mechanistic schematic

Idiopathic pulmonary hemosiderosis: Clinical cluster

- Often begins insidiously.
- Productive cough, hemoptysis and anemia accompany diffuse pulmonary infiltrates.
- Repeated bleeding provides a morphologic explanation for iron-loaded macrophages.

Age distribution supports suspicion, not proof

More typical

Most reported cases occur in young children.

Recurrent respiratory symptoms and anemia deserve evaluation.

Still possible

Adults can also be affected.

Age alone does not establish or exclude the diagnosis.

Absent anti-GBM antibodies is a key distinction

Idiopathic hemosiderosis

Anti-basement membrane antibodies are undetectable in the described disorder.

Underlying cause is not defined.

Goodpasture

Circulating anti-GBM antibodies cause injury.

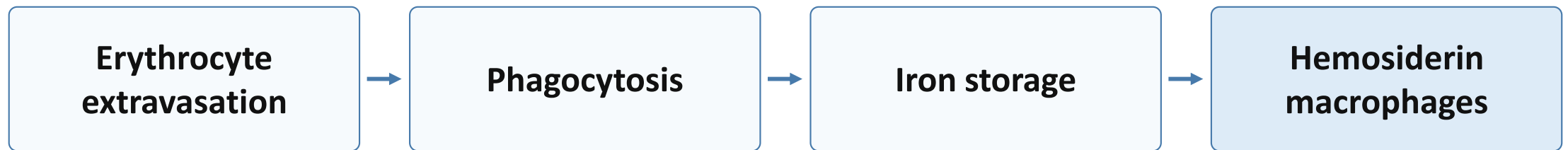
Renal glomerulonephritis is central to the syndrome.

Immune involvement in idiopathic hemosiderosis remains a hypothesis

- The source reports favorable responses to prolonged prednisone and/or azathioprine.
- Some patients subsequently develop other immune disorders.
- These observations suggest, but do not establish, immune-mediated capillary damage.

Repeated hemorrhage explains pulmonary iron accumulation

- Iron-laden macrophages are a consequence of intra-alveolar red-cell breakdown.
- Hemosiderosis describes retained iron; It does not identify why hemorrhage began.



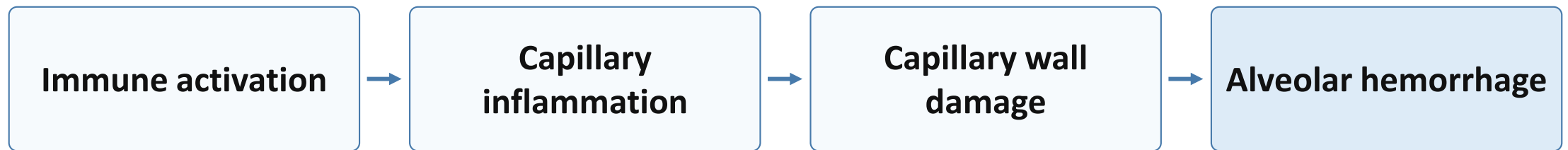
Mechanistic schematic

Goodpasture versus idiopathic hemosiderosis

Feature	Goodpasture	Idiopathic hemosiderosis
Mechanism	Anti-GBM autoimmunity	Unknown
Typical clinical context	Lung + glomerular disease	Intermittent lung bleeding / anemia
Anti-GBM antibodies	Present	Undetectable
Age tendency	Often teens / twenties	Often young children

Vasculitis-associated hemorrhage: Vessel wall inflammation

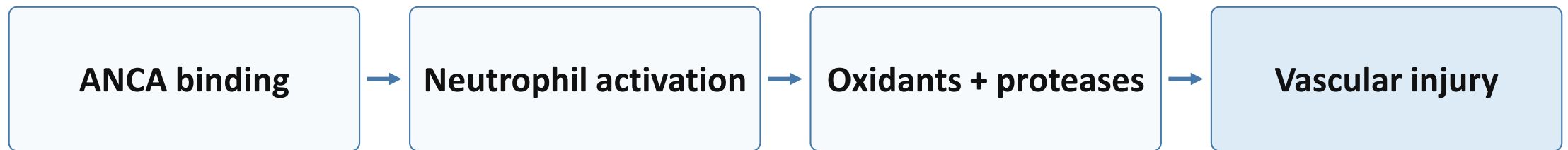
- Inflammatory destruction of small vascular walls may allow alveolar bleeding.
- Pulmonary hemorrhage can be part of multisystem vasculitis.



Mechanistic schematic

ANCA-associated disease targets activated leukocytes

- PR3-ANCA and MPO-ANCA recognize neutrophil constituents.
- ANCAs can activate neutrophils and promote oxidant/protease-mediated endothelial damage.



Mechanistic schematic

Pauci-immune describes tissue deposits, not absence of inflammation

Immune mechanism

Circulating ANCA's participate in neutrophil activation.

Injury can be florid and necrotizing.

Immunofluorescence

Little or no vessel-wall immune-reactant deposition.

Contrasts with linear or granular deposit patterns.

Granulomatosis with polyangiitis is an airway–lung–kidney disorder

Upper airway

Necrotizing granulomas; Sinus or nasal involvement

Anatomic disease clue

Lung

Necrotizing vasculitis, nodules or hemorrhage

Pulmonary capillaritis possible

Kidney

Focal necrotizing $\pm$ crescentic GN

Pulmonary–renal syndrome

GPA produces both granulomatous and vascular lesions

Granulomatous pattern

Upper and lower airway lesions

Nodular or cavitary parenchymal disease

Vascular pattern

Necrotizing inflammation of small/medium vessels

Capillaritis can accompany alveolar hemorrhage

Capillaritis can be the only diagnostic clue in small biopsies

- Transbronchial samples may be too small to capture necrosis or a well-developed vasculitic lesion.
- Scattered poorly formed granulomas and capillaritis remain important findings.
- Absence of conspicuous classic granulomas in a tiny specimen does not exclude GPA.

GPA granulomas are not sarcoid-type granulomas

GPA in limited lung samples

Scattered, poorly formed granulomas

Capillaritis and necrotizing injury may be present

Sarcoidosis comparison

Rounded, more well-defined granulomas

Morphologic comparator, not a stand-alone exclusion rule

GPA clinical context can guide tissue interpretation

- Upper respiratory complaints or chronic sinusitis point toward a systemic airway process.
- Nodules, cavitation and pulmonary hemorrhage can coexist.
- Concomitant nephritic kidney injury supports systemic small-vessel disease.

PR3-ANCA is associated with GPA

Supportive serology

PR3-ANCA is frequent in GPA.

It can support clinicopathologic suspicion.

Required interpretation

No single serologic pattern replaces morphology and organ-based evaluation.

The ANCA antigen is not the anti-GBM target.

Microscopic polyangiitis: Capillaritis without granulomas

Microscopic polyangiitis

Small-vessel necrotizing vasculitis

Pulmonary capillaritis and GN common

Usually MPO-ANCA-associated

Granulomatosis with polyangiitis

Necrotizing vasculitis plus granulomatous respiratory inflammation

Often PR3-ANCA-associated

Nodules/cavities may occur

Small-vessel vasculitis need not leave immune deposits

Schematic immunofluorescence distributions

LINEAR

Anti-GBM



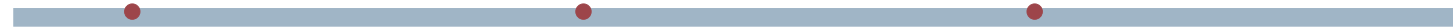
GRANULAR

Immune complexes



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ANCA-associated



ANCA-associated GN may be immunofluorescence pauci-immune. Strong inflammatory pathology does not predict strong Ig staining.

SLE provides an immune-complex alternative

Immune-complex pathway

Lupus autoantibody complexes can deposit in small vessels.

Inflammatory vascular injury may cause hemorrhage.

Renal comparison

Immune-complex crescentic GN exhibits granular immune deposits.

Different from the linear anti-GBM pattern.

Immunofluorescence patterns distinguish mechanisms

Schematic immunofluorescence distributions

LINEAR

Anti-GBM



GRANULAR

Immune complexes



PAUCI-IMMUNE

ANCA-associated



Linear: Anti-GBM antibody binding to basement membrane. Granular: Deposited immune complexes (e.g., lupus nephritis). Pauci-immune: ANCA-associated necrotizing vasculitis.

Vasculitis-associated hemorrhage: Practical distinctions

Disease	Pulmonary pathology	Systemic / immune clue
GPA	Capillaritis; Granulomas; Nodules	Upper airway disease; PR3-ANCA
MPA	Capillaritis; No granulomas	Necrotizing GN; Often MPO-ANCA
SLE-associated	Small-vessel immune injury	Immune-complex deposits; Lupus context

A hematologic finding is not a specific etiology

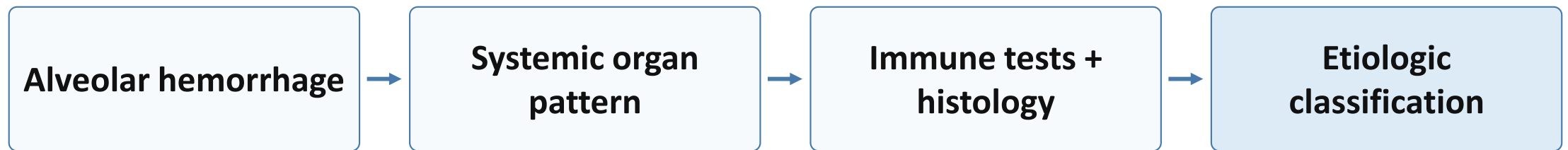
- Hemosiderin-laden macrophages confirm previous bleeding, not a unique disease.
- Intra-alveolar blood occurs in anti-GBM injury, vasculitides and idiopathic hemorrhage.
- The interpretation requires tissue pattern and systemic findings.

Distinguish diffuse hemorrhage from hemorrhagic infarction

Feature	Diffuse alveolar hemorrhage	Embolic hemorrhagic infarct
Distribution	Often multiple/diffuse airspaces	Typically peripheral wedge
Primary process	Diffuse capillary / immune injury	Vascular occlusion with ischemia
Histology	Alveolar blood $\pm$ capillaritis	Necrosis of alveolar walls, bronchioles, vessels

Pathology-focused diagnostic sequence

- Establish bleeding in pulmonary airspaces.
- Assess kidney/upper airway/systemic involvement.
- Integrate anti-GBM, ANCA, ANA and appropriate tissue immune patterns.



Mechanistic schematic

Case A: Hemorrhage with rapidly progressive renal injury

CLINICAL–PATHOLOGY VIGNETTE

A young adult develops hemoptysis, pulmonary consolidation and rapidly worsening kidney function. Glomerular immunofluorescence is linear for IgG.

QUESTION

Which pathophysiologic mechanism best explains the organ combination?

Interpretation: Antibodies targeting type IV collagen α 3 in glomerular and alveolar basement membranes → Goodpasture syndrome.

Case B: Recurrent bleeding without anti-GBM antibodies

CLINICAL–PATHOLOGY VIGNETTE

A child has recurrent cough, hemoptysis, anemia and diffuse pulmonary infiltrates; Anti-GBM antibodies are not detected.

QUESTION

Which textbook syndrome is the strongest match?

Interpretation: Idiopathic pulmonary hemosiderosis; Its initiating mechanism remains uncertain.

Case C: Upper airway disease, capillaritis and granulomas

CLINICAL–PATHOLOGY VIGNETTE

A patient has chronic sinus symptoms, pulmonary hemorrhage and capillaritis with scattered poorly formed granulomas on a small lung biopsy.

QUESTION

Which vascular syndrome is suggested?

Interpretation: Granulomatosis with polyangiitis; The absence of a large formed granuloma in a small biopsy is not exclusionary.

Three immune-pattern traps to avoid

Linear ≠ granular

Anti-GBM patterns track along BM

Do not confuse with immune-complex GN.

Pauci-immune ≠ mild

ANCA lesions may be necrotizing

Minimal staining does not imply minimal disease.

Iron ≠ etiology

Hemosiderin proves prior bleeding

A cause still must be established.

Major take-home messages

- Diffuse alveolar hemorrhage is a shared morphologic endpoint with several causes.
- Macrophage hemosiderin and Prussian-blue positivity record prior intra-alveolar bleeding.
- Goodpasture is anti-GBM-mediated; GPA/MPA are commonly ANCA-associated; Idiopathic hemosiderosis remains unexplained.
- Pulmonary–renal findings and linear, granular or pauci-immune tissue patterns are key discriminators.

Primary references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 15, The Lung: pp. 642–643.
- Same text, Chapter 11, Blood Vessels: sections on small-vessel vasculitis, ANCA, GPA and microscopic polyangiitis.
- Same text, Chapter 20, The Kidney: sections on crescentic glomerulonephritis and immunofluorescence patterns.