

Noninfectious vasculitis

Immune mechanisms, vessel patterns and clinicopathologic interpretation

Large vessels

Medium vessels

Small vessels

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Learning objectives

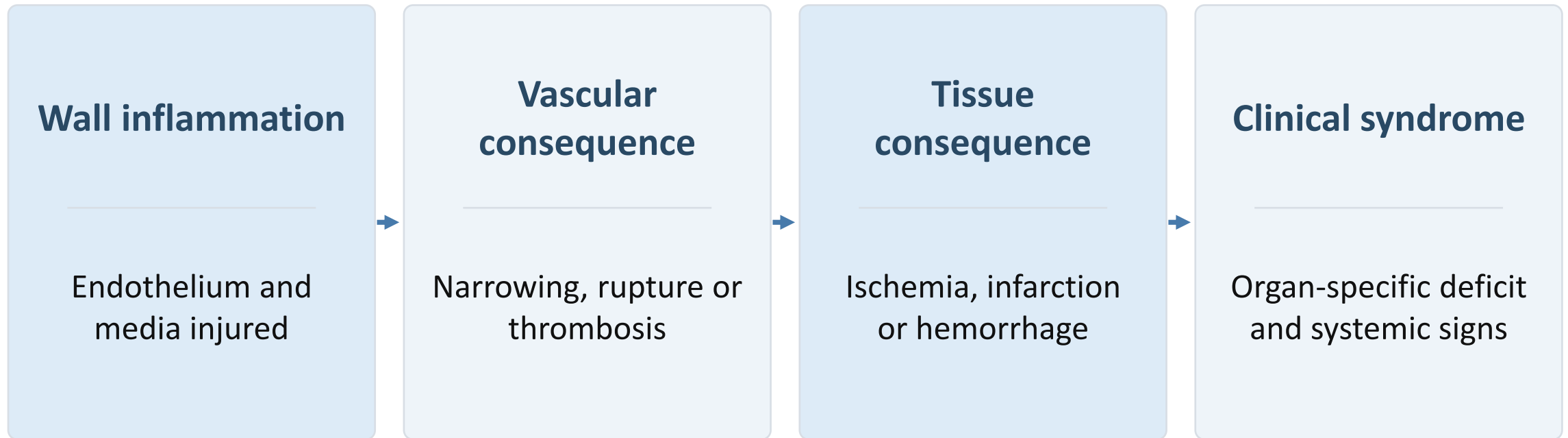
- Classify noninfectious vasculitides by vessel caliber, distribution and immune-deposit pattern.
- Explain how immune complexes, ANCA, endothelial-directed antibodies and T cells damage vessels.
- Connect vascular injury with ischemia, hemorrhage, thrombosis and aneurysmal change.
- Distinguish major vasculitic patterns using morphology, tissue distribution and laboratory clues.

Vasculitis is inflammation of the vessel wall

Inflammatory injury centered on vascular walls can compromise perfusion or disrupt vascular integrity.

- Vascular beds of many organs can be involved.
- Clinical manifestations depend on the caliber and location of affected vessels.
- Systemic inflammation may coexist with local ischemic injury.

The injured vascular bed determines the phenotype



Systemic and organ-limited patterns

Systemic distribution

- Multiple vascular territories become inflamed.
- Fever, malaise, myalgia and arthralgia may accompany organ injury.
- Manifestations may evolve as additional beds are involved.

Initially limited disease

- One tissue or organ may dominate the presentation.
- Local injury can precede recognition of a wider syndrome.
- A limited presentation does not define a unique mechanism.

Infectious versus noninfectious injury

Direct infectious arteritis

- Microorganisms invade or directly damage the vessel wall.
- Can accompany adjacent infection, bacteremia or infected emboli.
- Antimicrobial/source management is a primary concern.

Noninfectious immune-mediated vasculitis

- Immune attack drives wall inflammation without direct microbial invasion.
- Infections may trigger immune complexes or immune cross-reactivity.
- Immunosuppression may be appropriate after an infectious cause is assessed.

Therapeutic implications of the distinction

Is direct microbial invasion plausible?

YES

Investigate infectious source

Avoid assuming primary autoimmunity

NO / ALTERNATE

Correlate immune patterns

Consider immune-mediated differential

An immune trigger after infection is not identical to direct infectious invasion.

Noninfectious vasculitis is not one disease

The textbook recognizes more than 25 primary forms, with overlapping clinical and pathologic features.

- Vessel caliber is a useful starting point, not an absolute boundary.
- Tissue predilection, immunity and demographics add discriminatory information.
- Exceptions and mixed patterns occur across the nomenclature.

Four complementary classification axes

Vessel size

Large, medium or small

Distribution

Aorta, viscera, capillaries or organ-limited

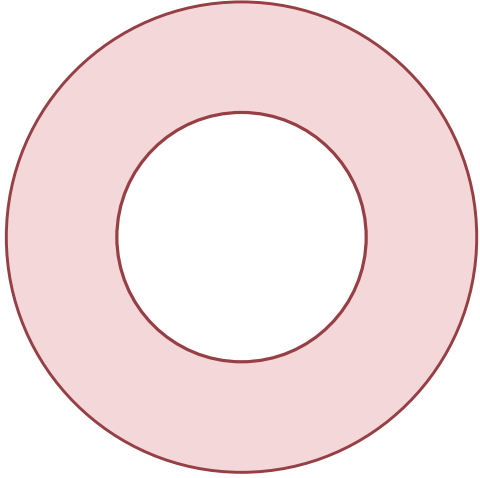
Immune pattern

Deposits, ANCA-associated or cellular

Context

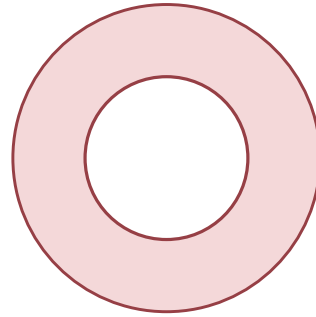
Granulomas, autoantibodies and demographic clues

Vessel caliber provides an anatomical map



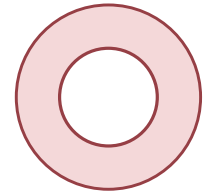
Large

Aorta; Major branches



Medium

Muscular organ arteries



Small

Arterioles; Capillaries;
Venules

Large-vessel category: Aorta and major branches

- The aorta, great arch vessels and large limb arteries are preferentially affected.
- Chronic inflammation often produces mural thickening and stenosis.
- Giant cell arteritis and Takayasu arteritis are the major textbook examples.
- Smaller arteries can also be affected: “large vessel” denotes predominance.

Medium-vessel category: Muscular arteries

- Medium-sized visceral arteries and their branches are the usual targets.
- Wall necrosis may cause microaneurysms, thrombosis and organ ischemia.
- Polyarteritis nodosa, Kawasaki disease and thromboangiitis obliterans illustrate distinct phenotypes.
- An entity may also affect some smaller or larger arteries.

Small-vessel category: Microcirculation

- Small intraparenchymal arteries, arterioles, capillaries and venules predominate.
- Glomerular and pulmonary capillary involvement can be clinically critical.
- The amount and pattern of immunoglobulin deposition distinguish major groups.
- Skin and kidney can provide accessible tissue manifestations.

Classification overview

Predominant caliber	Representative entities	Discriminating emphasis
Large	Giant cell arteritis; Takayasu arteritis	Aorta and major branches; granulomatous patterns
Medium	PAN; Kawasaki; Buerger disease	Muscular artery ischemia or aneurysm
Small, ANCA-associated	MPA; GPA; EGPA	Pauci-immune necrotizing vasculitis
Small, immune deposits	IgA; cryoglobulinemic; anti-GBM patterns	Immunoglobulin/complement in tissues

Classification has overlapping boundaries

Caliber predominance



Site + morphology



Immune mechanism

A diagnosis comes from the intersection, not a single label.

What constitutes noninfectious pathogenesis?

Immune complexes

Antibody–antigen deposits activate inflammation

ANCA

Neutrophil-directed antibodies provoke effector injury

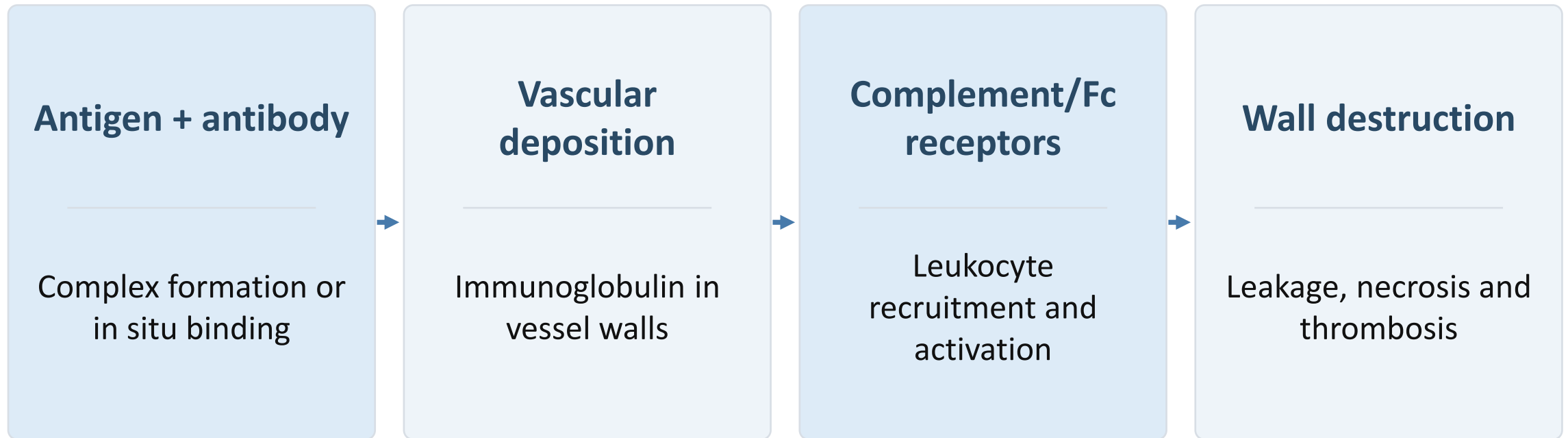
Anti-endothelial antibodies

Antibodies react with endothelial targets

Autoreactive T cells

Cell-mediated vascular inflammation and granulomas

Immune complexes initiate vascular injury



Where can pathogenic immune complexes originate?

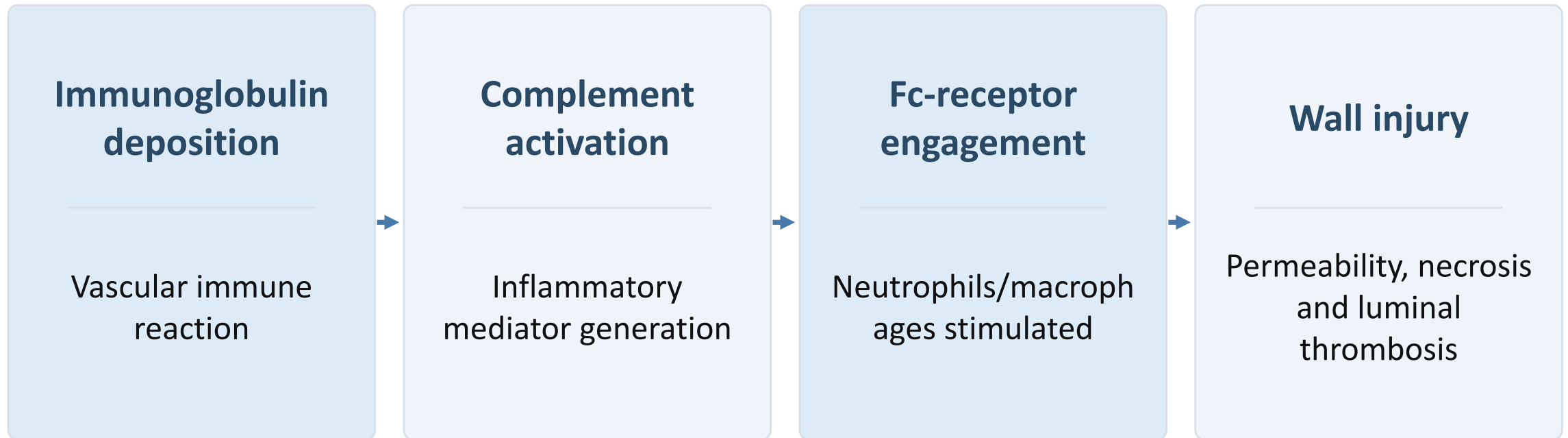
Circulating complexes

- An antigen–antibody complex forms in blood.
- Complexes may lodge in susceptible vascular beds.
- The initiating antigen is often not identified.

Local formation

- Antibody may encounter antigen at the vessel.
- Inflammatory effector mechanisms follow local recognition.
- The two possibilities are often difficult to distinguish.

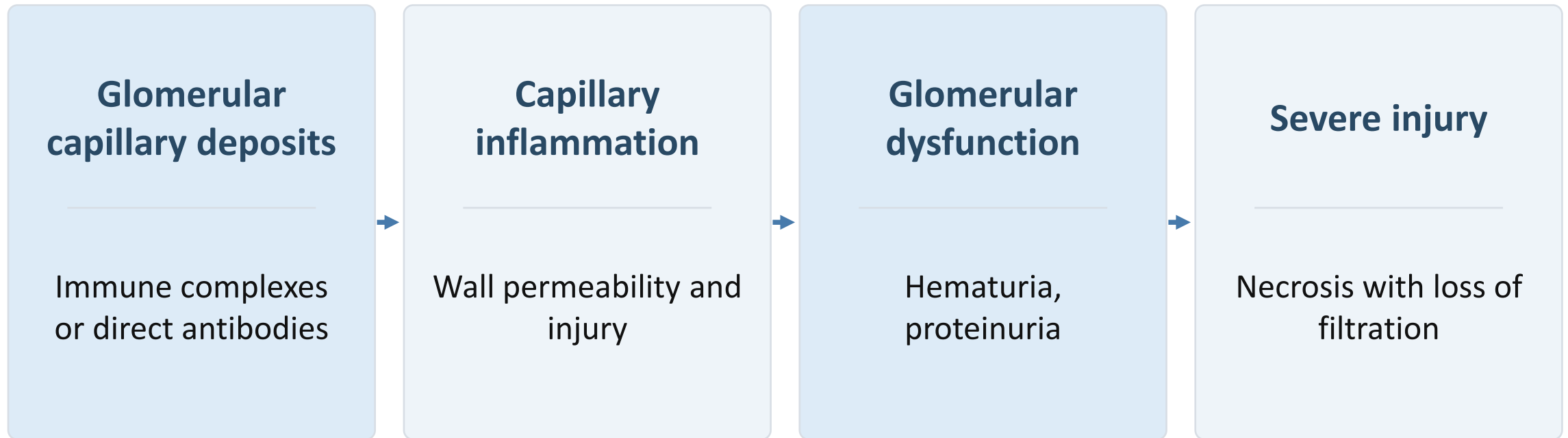
Complement links deposits to neutrophil injury



Immune complex morphology: The diagnostic signature

- Inflamed small vessels may show immunoglobulin and complement deposition.
- Direct immunofluorescence helps demonstrate deposited reactants.
- Necrotizing injury may coexist with neutrophilic fragmentation.
- Distribution and deposit composition must be interpreted with clinical context.

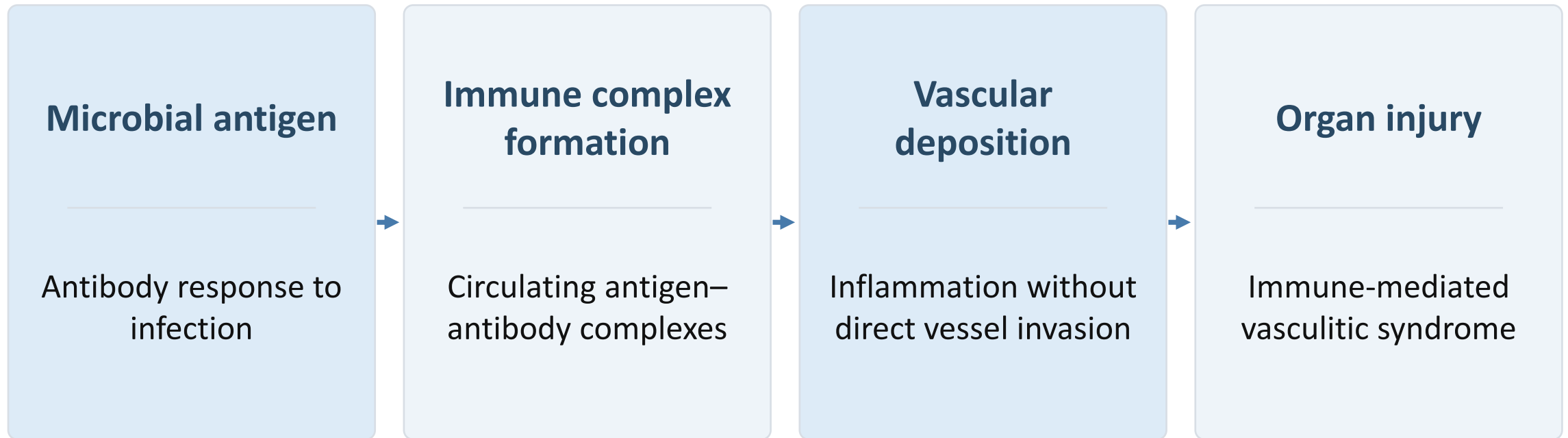
Kidney involvement reflects capillary injury



Drug-associated immune complex vasculitis

- Some drugs act as haptens after binding serum proteins.
- Antibody formation can generate circulating immune complexes.
- Skin manifestations are common, but severity varies.
- A careful drug-exposure history can identify a potentially reversible trigger.

Infection may trigger a noninfectious mechanism



Hepatitis B provides an immune-complex example

In a subset of polyarteritis nodosa, hepatitis B surface antigen–antibody complexes contribute to vascular disease.

- The link is immune-complex-mediated, not simply direct invasion of arterial walls.
- The association does not explain all PAN cases.
- Mechanistic context helps avoid misclassifying every infection-associated vasculitis.

Vasculitis associated with systemic autoimmunity

Systemic lupus erythematosus

- DNA/anti-DNA immune complexes may contribute.
- Vascular lesions can occur in small and medium vessels.
- Other autoantibodies can participate in injury.

Rheumatoid arthritis

- Vasculitis typically occurs with severe long-standing disease.
- Small- or medium-vessel involvement may predominate.
- Immune complexes and cellular mechanisms may both contribute.

IgA and cryoglobulinemic processes

IgA vasculitis

- Abnormally glycosylated IgA participates in immune complexes.
- Small vessels and glomeruli are characteristic sites.
- Deposits provide an immune-pathologic clue.

Cryoglobulinemic vasculitis

- Cryoglobulin immunoglobulins precipitate below body temperature.
- Immunoglobulin deposition damages small vessels.
- Systemic and renal injury may accompany skin disease.

Anti-GBM injury: Binding rather than complexes

Immune-complex pattern

- Preformed or locally assembled antigen–antibody complexes.
- Deposits trigger complement and leukocyte activation.
- Patterns depend on antigen and lesion location.

Anti-GBM pattern

- Autoantibodies directly bind basement-membrane components.
- Glomerular and pulmonary capillaries are major targets.
- Antibody deposition is a direct-binding mechanism.

Why deposit mechanisms cannot be conflated

Immune complexes and direct basement-membrane autoantibodies both recruit inflammation, but antigen recognition differs.

- Mechanism informs the expected tissue deposit pattern.
- Similar clinical pulmonary–renal manifestations can arise by different routes.
- Morphology, immunopathology and serology should be integrated.

ANCA-associated vasculitis is usually pauci-immune

Autoantibodies recognize neutrophil antigens; Extensive antibody deposits in vascular lesions are usually absent.

- Major specificities are proteinase 3 (PR3) and myeloperoxidase (MPO).
- Neutrophil activation produces oxidants, enzymes and endothelial injury.
- Small-vessel necrotizing lesions are typical.

PR3-ANCA and MPO-ANCA

Antibody specificity	Target	Common textbook association
PR3-ANCA	Proteinase 3; neutrophil primary granules	Granulomatosis with polyangiitis
MPO-ANCA	Myeloperoxidase; leukocyte granules	Microscopic polyangiitis; eosinophilic GPA

Antigen specificity supersedes staining shorthand

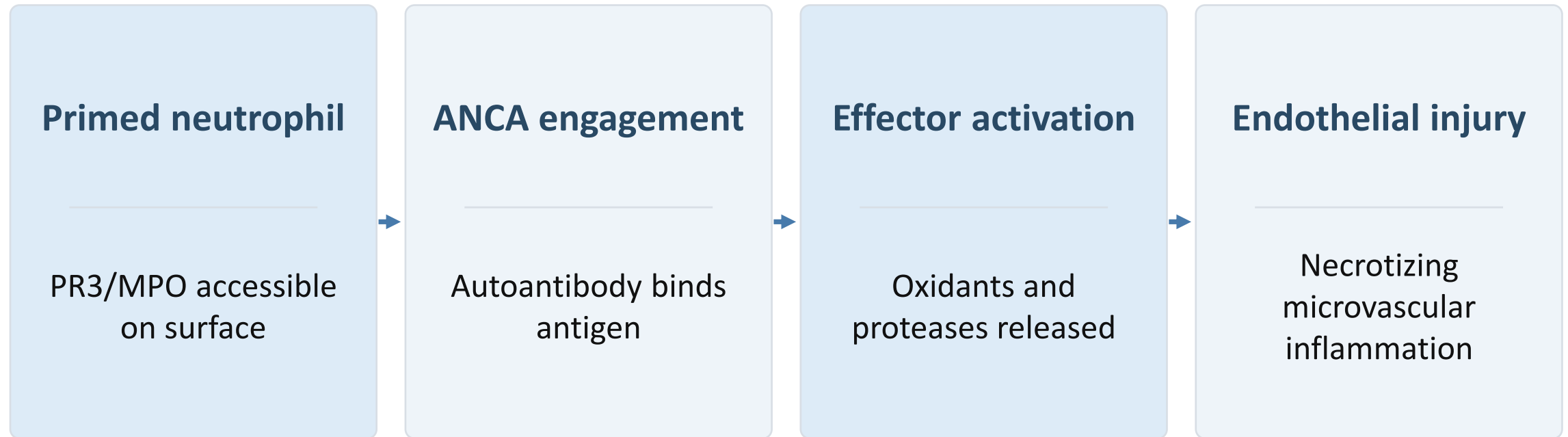
Historical terminology

- C-ANCA: Cytoplasmic staining pattern.
- P-ANCA: Perinuclear staining pattern.
- Pattern names refer to assay appearance.

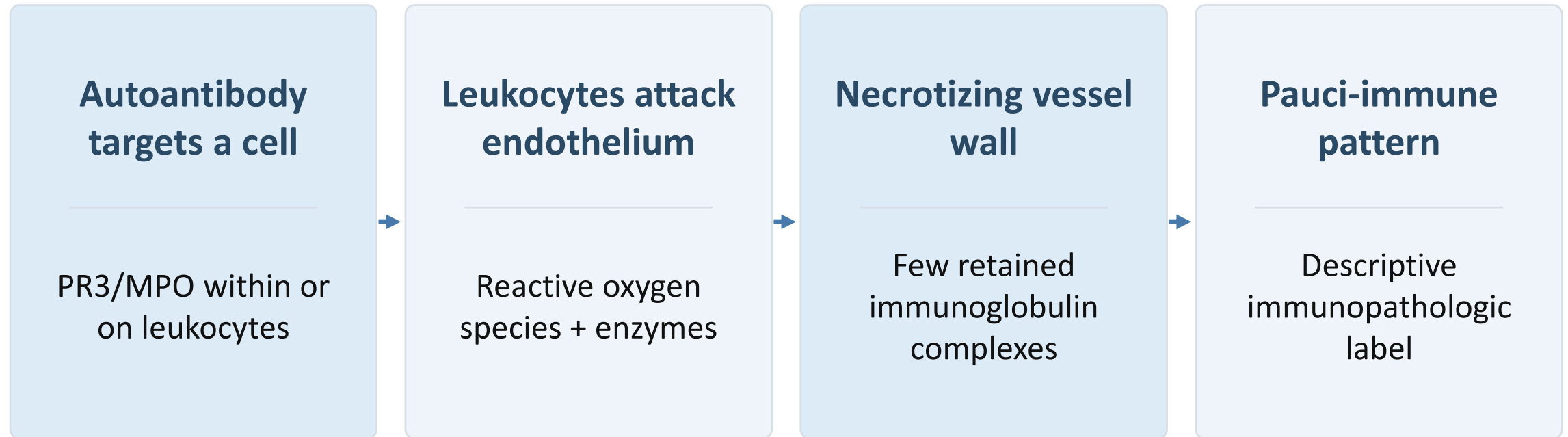
Preferred mechanistic terminology

- PR3-ANCA identifies the antigenic target.
- MPO-ANCA identifies the antigenic target.
- Specificity gives a clearer disease association.

How ANCAs activate neutrophils



Why ANCA lesions contain few immune deposits



ANCA is mechanistic and diagnostically useful

- PR3-ANCA and MPO-ANCA support recognition of characteristic vasculitic syndromes.
- A serologic result does not replace organ distribution or tissue morphology.
- The source associates ANCA titer changes with activity and relapse.
- Interpret the antigen specificity alongside the clinical phenotype.

Microscopic polyangiitis: Small-vessel archetype

- Necrotizing vasculitis affects capillaries, arterioles and venules.
- Glomerulonephritis and pulmonary capillaritis are prominent potential manifestations.
- MPO-ANCA is commonly associated.
- Granulomatous inflammation is absent in the described pattern.

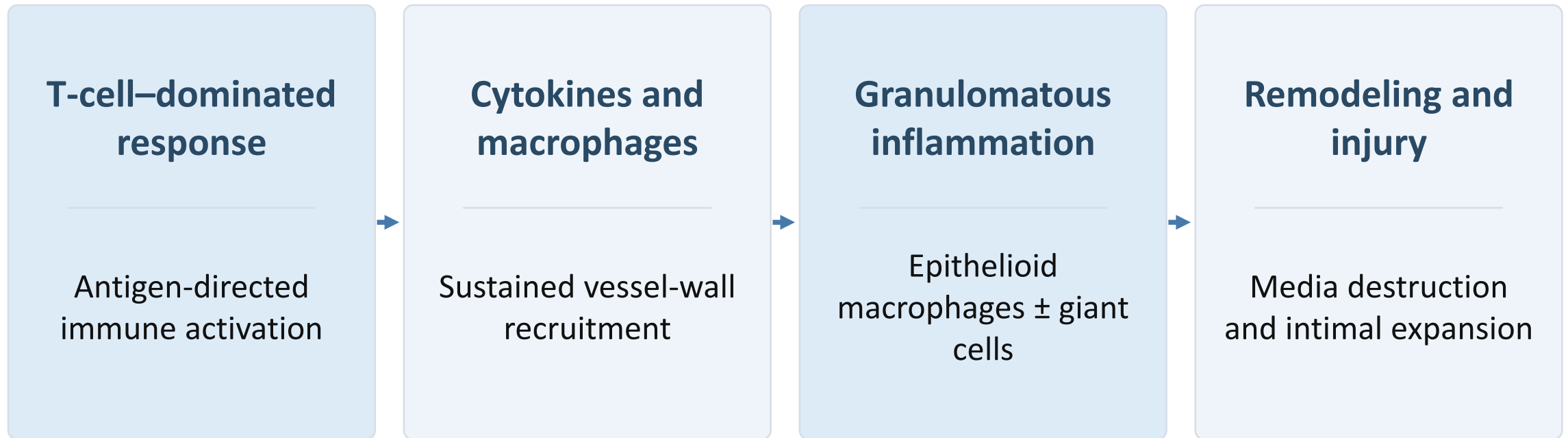
Granulomatosis with polyangiitis

- Necrotizing granulomatous inflammation affects the respiratory tract.
- Necrotizing vasculitis involves small to medium vessels.
- Focal necrotizing glomerulonephritis may occur.
- PR3-ANCA is characteristic in the source description.

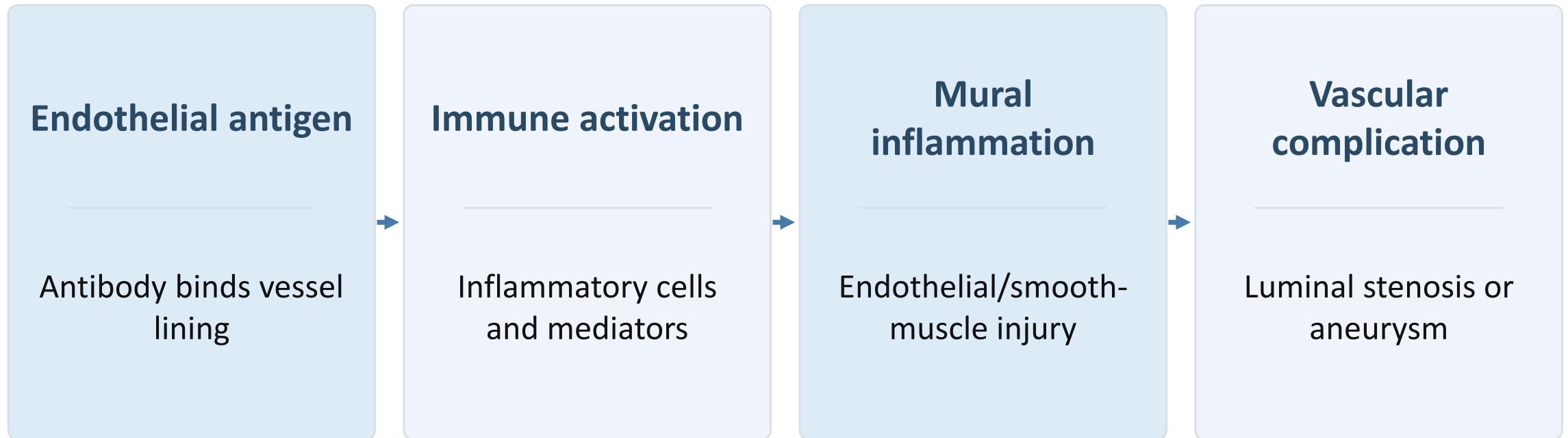
Eosinophilic granulomatosis with polyangiitis

- Asthma, allergic rhinitis and tissue eosinophilia define the broader phenotype.
- Necrotizing vasculitis occurs with eosinophilic and granulomatous inflammation.
- MPO-ANCA occurs in a subset, particularly with renal involvement.
- Cardiac injury can arise from eosinophilic infiltration.

Granulomas imply organized cellular immunity



Anti-endothelial antibody mechanisms



Kawasaki disease illustrates endothelial injury

- A childhood febrile mucocutaneous syndrome can involve coronary arteries.
- Immune activation with antibodies to endothelium and smooth muscle is implicated.
- Arteritis can damage the coronary wall and allow aneurysm formation.
- The cardiac consequence reflects location, not only the degree of inflammation.

T-cell immunity contributes to large-vessel disease

- Giant cell arteritis is associated with a T-cell–mediated wall response.
- IFN- γ and IL-17 are noted among inflammatory mediators.
- Macrophage-rich inflammation can disrupt the internal elastic membrane.
- Healing may produce concentric intimal thickening and ischemia.

No single pathway explains every vasculitis

Autoantibodies



Cellular immunity



Vessel-specific context

The same clinical syndrome may involve more than one effector mechanism.

Wall inflammation produces four major lesions

Stenosis

Intimal thickening or luminal narrowing

Thrombosis

Luminal occlusion on an injured surface

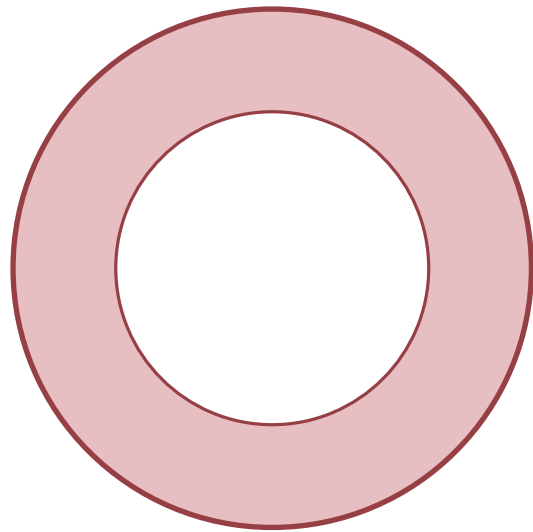
Aneurysm

Loss of mural structural support

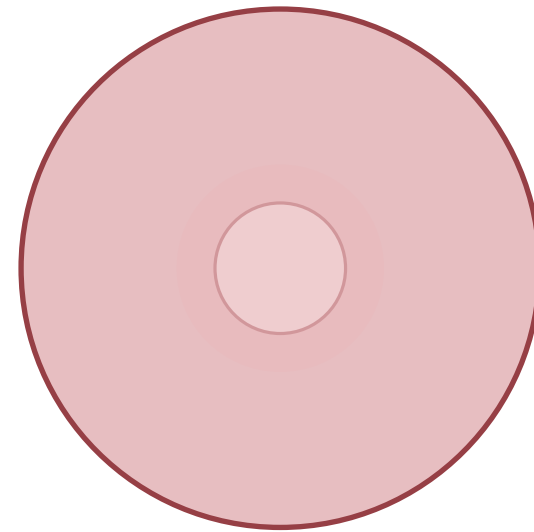
Hemorrhage

Rupture or small-vessel leakage

Vascular cross-section: Normal versus stenotic



Reference architecture

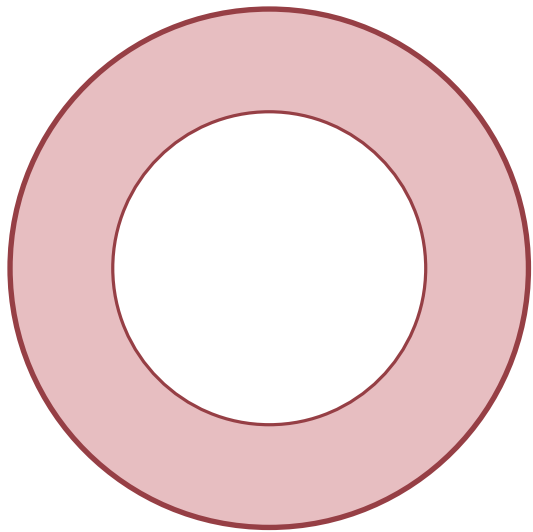


Inflammatory narrowing

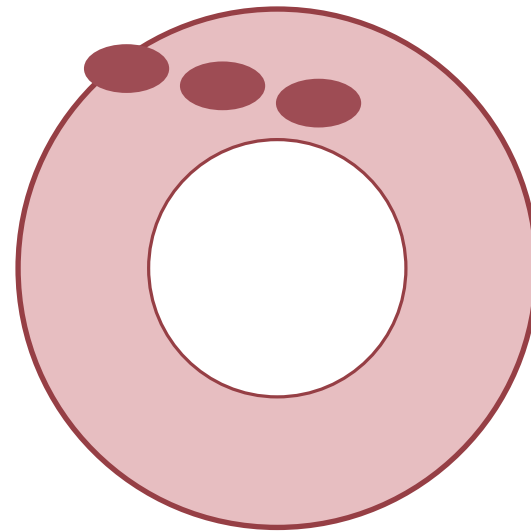
Inflammation + intimal proliferation → reduced luminal flow

Original native PowerPoint schematic — not a histologic specimen.

Necrotizing arteritis compromises the media



Reference architecture

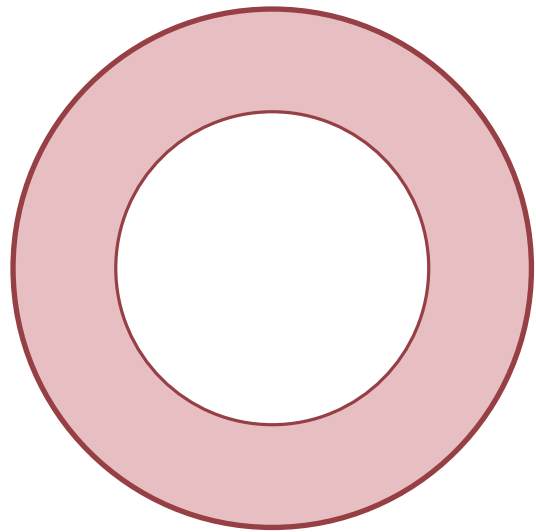


Destructive arteritis

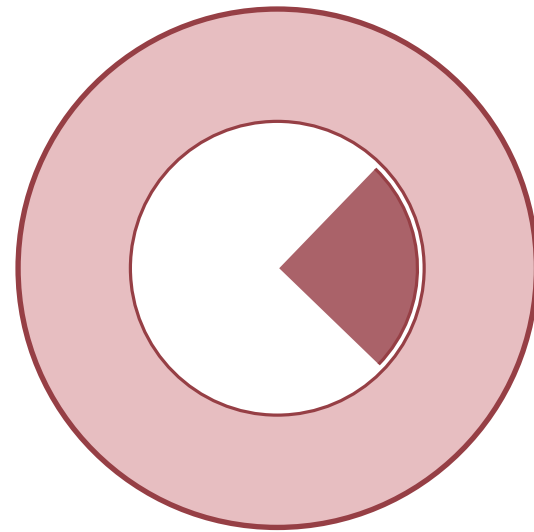
Transmural injury disrupts normal layers of the wall

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An inflamed wall can thrombose



Reference architecture

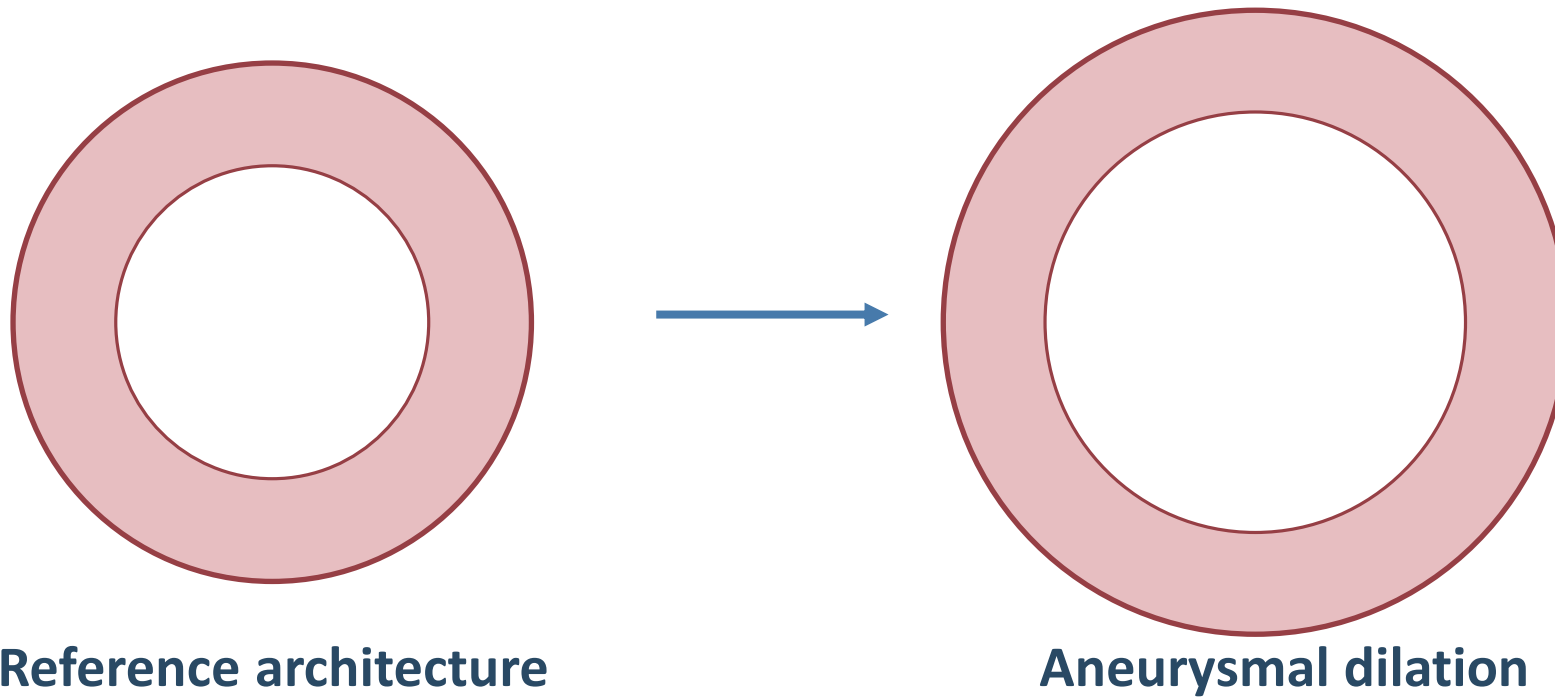


Superimposed thrombus

Endothelial injury promotes flow-limiting thrombus

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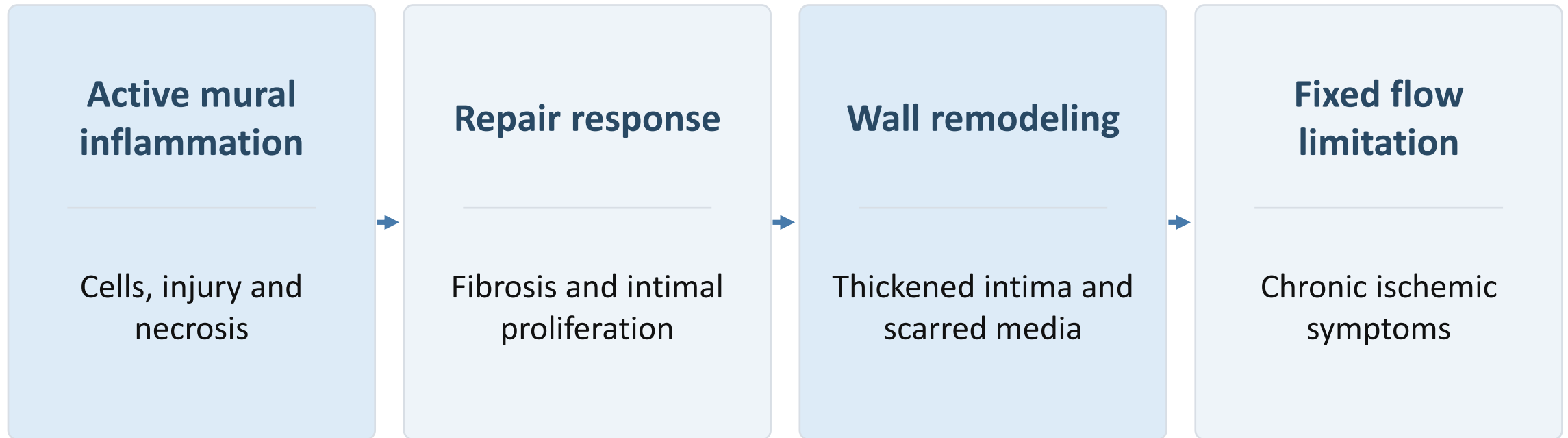
Wall destruction may lead to aneurysm



Loss of wall integrity permits pathological dilation

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Healing can cause persistent luminal loss



Lesions are frequently segmental and patchy

- Active and unaffected segments may alternate along an artery.
- A biopsy can miss pathologic involvement in a clinically affected vessel.
- Older scars and active inflammation can coexist across different arterial segments.
- Sampling must be interpreted in light of the distribution and differential diagnosis.

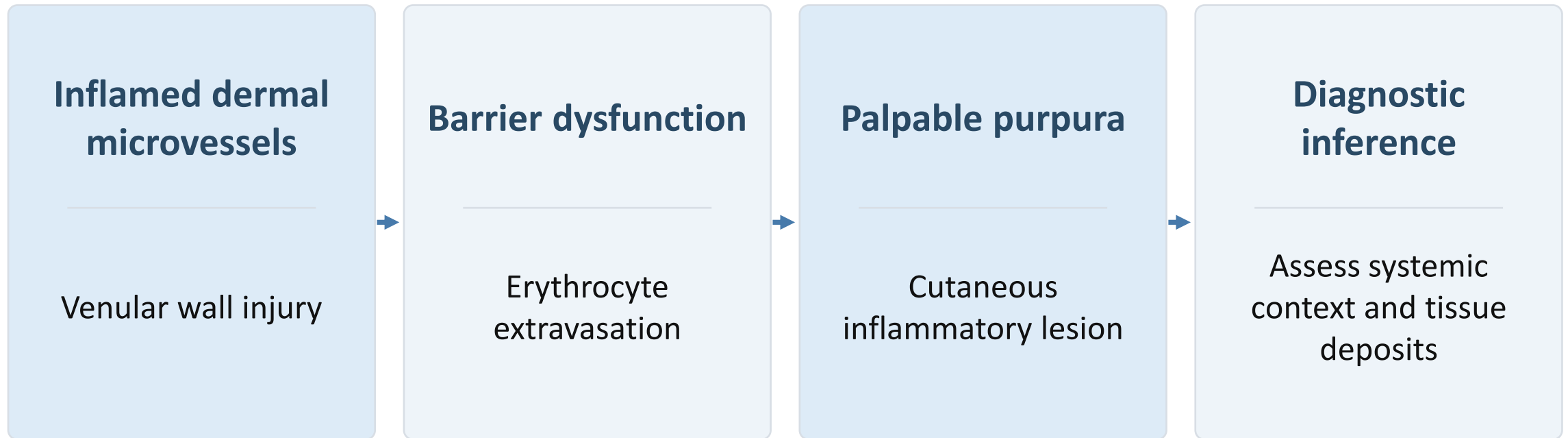
Fibrinoid necrosis indicates severe vascular injury

- Necrotizing arteritis may show intensely eosinophilic wall material on H&E.
- It accompanies destructive inflammation and loss of normal mural architecture.
- Luminal thrombosis and downstream tissue ischemia may accompany the lesion.
- This morphology is not specific to one named vasculitic syndrome.

Leukocytoclasia is a morphologic pattern

- Fragmentation of infiltrating neutrophils produces nuclear debris.
- Postcapillary venules are a common site of leukocytoclastic injury.
- The pattern may occur in both immune-complex and ANCA-associated disease.
- It should not be used as a stand-alone etiologic diagnosis.

Cutaneous purpura reflects microvascular damage



A pulmonary–renal pattern has mechanistic breadth

Pulmonary capillary injury

- Capillaritis may produce alveolar hemorrhage.
- Airway symptoms can reflect inflammatory injury.
- The lung pattern is not unique to ANCA disease.

Glomerular capillary injury

- Necrotizing lesions may yield hematuria and impaired function.
- Crescents can appear after severe capillary injury.
- Deposits versus pauci-immune staining refine the mechanism.

Distribution is a diagnostic clue, not proof

Finding	Plausible vessel context	Interpretive caution
Pulse asymmetry or limb ischemia	Major branch arteries	Consider other causes of arterial stenosis
Visceral ischemia or aneurysms	Muscular medium arteries	Several vasculitides may affect the same site
Purpura + glomerulonephritis	Dermal/renal small vessels	Deposit analysis distinguishes mechanisms
Pulmonary–renal injury	Capillary beds	ANCA and anti-GBM patterns differ

Named syndromes: Large-vessel contrasts

Entity	Characteristic emphasis	Important caveat
Giant cell arteritis	Older patients; head arteries $\pm$ aorta	Granulomas may be patchy or absent
Takayasu arteritis	Aorta and arch branch stenosis	Histology can overlap giant cell arteritis

Named syndromes: Medium-vessel contrasts

Entity	Characteristic emphasis	Vascular consequence
Polyarteritis nodosa	Muscular arterial necrosis; pulmonary arteries spared	Ischemia, infarction, microaneurysms
Kawasaki disease	Febrile childhood syndrome; coronary arteritis	Coronary aneurysm/thrombosis
Buerger disease	Distal thrombosing arteritis; tobacco association	Extremity ischemia and gangrene

Named syndromes: Small-vessel contrasts

Entity	Defining context	Immune pattern
Microscopic polyangiitis	Necrotizing capillaritis; no granulomas	Usually MPO-ANCA; pauci-immune
Granulomatosis with polyangiitis	Respiratory granulomas + renal disease	Often PR3-ANCA; pauci-immune
Eosinophilic GPA	Asthma + eosinophils ± granulomas	MPO-ANCA in a subset
IgA/cryoglobulinemic vasculitis	Deposit-associated microvascular injury	Immunoglobulin/complement deposits

Why organ involvement helps separate categories

Artery size

Pulse loss or visceral ischemia can localize injury to large/medium vessels.

Organ pattern

Skin, kidney and lung disease suggest small-vessel participation.

Immune deposits

Deposits versus pauci-immune lesions further narrows mechanisms.

A mechanism-led diagnostic approach

Does evidence indicate vessel-wall inflammation?

YES

Map vessel size + affected organs
Assess deposits, ANCA and granulomas

NO / ALTERNATE

Evaluate nonvasculitic mimics
Reassess tissue and clinical evidence

Before immune suppression, consider direct infectious arteritis and infection-triggered immune disease.

Tissue evaluation and immunopathology complement each other

Routine morphology

- Locate the lesion within the vessel wall.
- Assess fibrinoid necrosis, granulomas and leukocytoclasia.
- Recognize thrombosis, aneurysm or healed scar.

Immune evaluation

- Ask whether immunoglobulin/complement deposits are present.
- Relate PR3/MPO specificity to the clinical phenotype.
- Consider direct anti-GBM antibody binding.

A negative sample is not always exclusionary

Skip lesions and variable vessel involvement impose an important limitation on biopsy interpretation.

- An adequately sampled artery can still miss a focal lesion.
- Destructive, healed and uninvolved regions may coexist.
- Clinical and tissue findings should be reconciled rather than treated in isolation.

Teaching case: Headache and visual symptoms

An older adult develops new temporal headache, scalp tenderness, constitutional symptoms and abrupt visual disturbance.

Which vessel category and mechanism are most relevant?

Head/ophthalmic arterial
territory

High consequence of ischemia

Possible discontinuous wall
inflammation

Case analysis: Ischemia in large-vessel arteritis

Consider giant cell arteritis, with T-cell/macrophage-mediated arterial inflammation.

- An inflamed arterial wall may thicken and narrow the lumen.
- Ophthalmic arterial involvement can cause permanent visual loss.
- A negative arterial biopsy does not absolutely exclude patchy disease.

Teaching case: Purpura with hematuria

A patient has palpable purpura, microscopic hematuria and a history of a recent medication exposure.

Which vessel compartment and immune pathway merit evaluation?

Dermal postcapillary venules

Renal microvasculature

Possible medication-derived
immune complexes

Case analysis: Deposit-associated small-vessel injury

Assess small-vessel vasculitis and consider an immune-complex mechanism.

- Neutrophilic wall injury can produce purpura.
- Glomerular capillary injury explains hematuria.
- Tissue immunoglobulin/complement deposits help distinguish this from pauci-immune patterns.

Teaching case: Lung and kidney injury

Pulmonary hemorrhage accompanies new glomerular abnormalities and constitutional symptoms.

Which different immune mechanisms can converge on this phenotype?

Pulmonary capillary disruption

Glomerular inflammation

Potentially similar clinical
manifestations

Case analysis: The pulmonary–renal differential

Distinguish ANCA-associated pauci-immune disease from anti-GBM antibody injury and immune-complex disease.

- PR3/MPO testing informs the ANCA-associated pathway.
- Direct anti-GBM antibodies target basement membranes.
- Immunopathology separates mechanisms that share target organs.

Three questions that organize vasculitis

Where?

Which vessel sizes and vascular beds are involved?

How?

Do deposits, ANCA, anti-endothelial antibodies or T cells predominate?

What happens?

Stenosis, thrombosis, aneurysm, hemorrhage or healed fibrosis?

Core concepts to retain

- Noninfectious vasculitides are classified by predominant caliber, anatomy and immune findings.
- Immune complexes, ANCAs, anti-endothelial antibodies and T cells are major mechanisms.
- Overlap and exceptions prevent diagnosis from caliber or one serologic marker alone.
- The vascular lesion determines the resulting ischemic, hemorrhagic or systemic syndrome.

Source and teaching boundaries

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 11, Blood Vessels.

Primary section: “Noninfectious Vasculitis,” printed p. 464; neighboring vasculitis sections, printed pp. 463–470.

Classification derived from the textbook table adapted from the 2012 Chapel Hill Consensus nomenclature.

All vascular and immune illustrations in this presentation are original native PowerPoint schematics; no histologic specimen images are reproduced.