

Hypersensitivity

Immunologically Mediated Tissue Injury

Antibody-mediated inflammation

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Learning objectives: Explain antibody-mediated inflammation

- Identify the fixed-tissue targets of type II antibodies.
- Trace complement activation to leukocyte-mediated injury.
- Relate inflammatory effectors to tissue damage and clinical disease.
- Distinguish tissue-bound antibody injury from immune-complex disease.

Antigen location

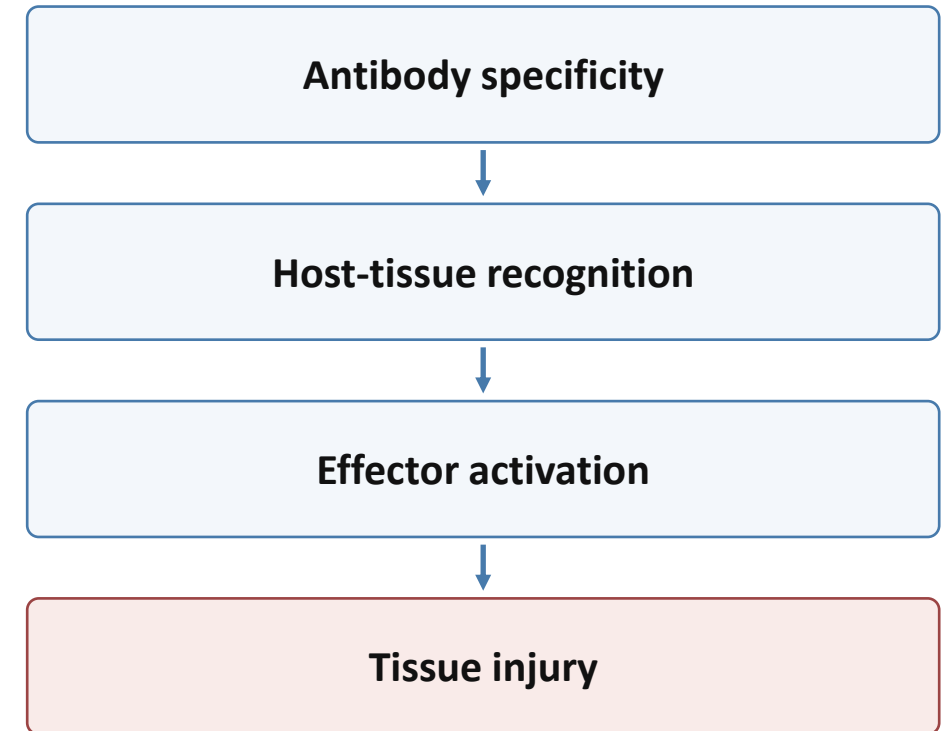
**Complement
products**

Fc receptors

**Clinicopathologic
patterns**

Protective immune mechanisms can damage host tissue

- Antibodies and leukocytes normally eliminate infectious agents.
- The same effectors cause pathology if aimed at self or innocuous antigens.
- Injury depends on antigen location, antibody action, and downstream cells.



Classification depends on the dominant effector mechanism

Hypersensitivity type	Principal injury mechanism
Type I — immediate	Th2/IgE, mast-cell mediators, late-phase leukocytes
Type II — antibody-mediated	IgG/IgM react with cell or fixed-tissue targets
Type III — immune complexes	Antigen–antibody complexes deposit and trigger inflammation
Type IV — T-cell-mediated	Cytokine-mediated inflammation or CTL cytotoxicity

Type II hypersensitivity has three major outcomes

- Antibodies recognize cell-surface or extracellular-matrix antigens.
- Target and effector mechanism determine the clinical lesion.
- Inflammation is one branch—not synonymous with all of type II injury.

**Opsonization and cell
removal**

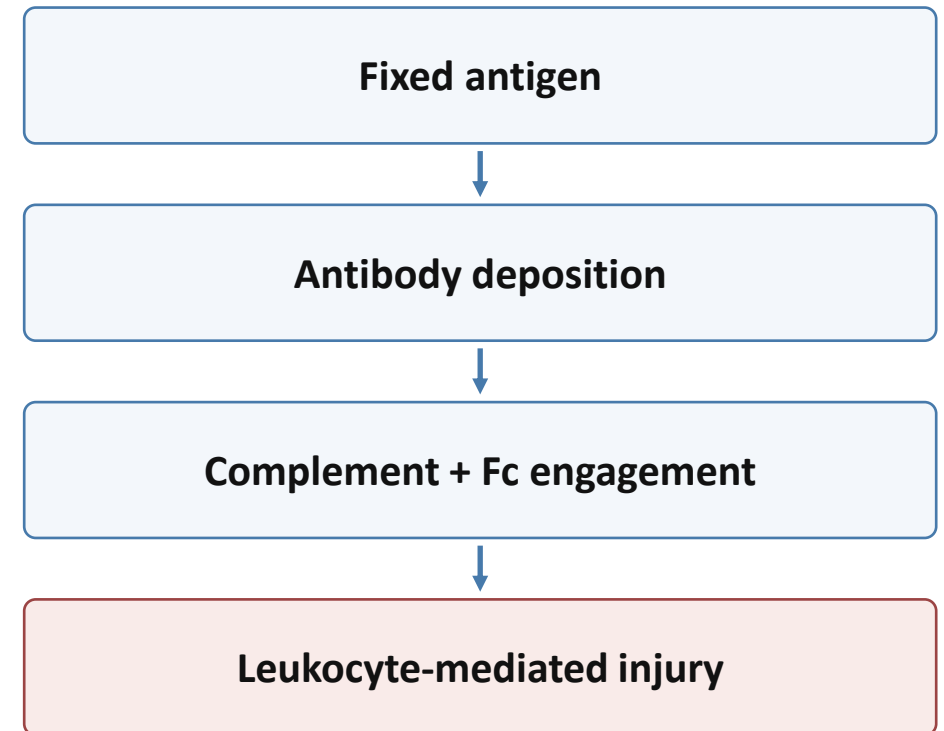
**Complement/Fc-
mediated
inflammation**

**Receptor blockade or
stimulation**

**Mechanisms may
overlap**

Fixed-tissue antibodies initiate local inflammation

- IgG binds antigens anchored to basement membranes or extracellular matrix.
- Bound antibody can activate complement in situ.
- Complement and antibody Fc regions recruit and activate inflammatory cells.



Antigen location directs the site of tissue injury

- Basement membrane is a major fixed-tissue target.
- Extracellular matrix provides additional immobile antigens.
- Antibody binding sites localize inflammation to structurally important compartments.

**Glomerular basement
membrane**

**Alveolar basement
membrane**

Vascular endothelium

**Other extracellular
matrix**

Type II differs from circulating immune-complex deposition

- Both pathways can recruit complement and neutrophils.
- The critical distinction is how antigen is presented at the injury site.
- Type II antibodies bind fixed targets; Type III complexes form and deposit.

Type II

Antibody binds
intrinsic tissue target

Target is structurally
localized

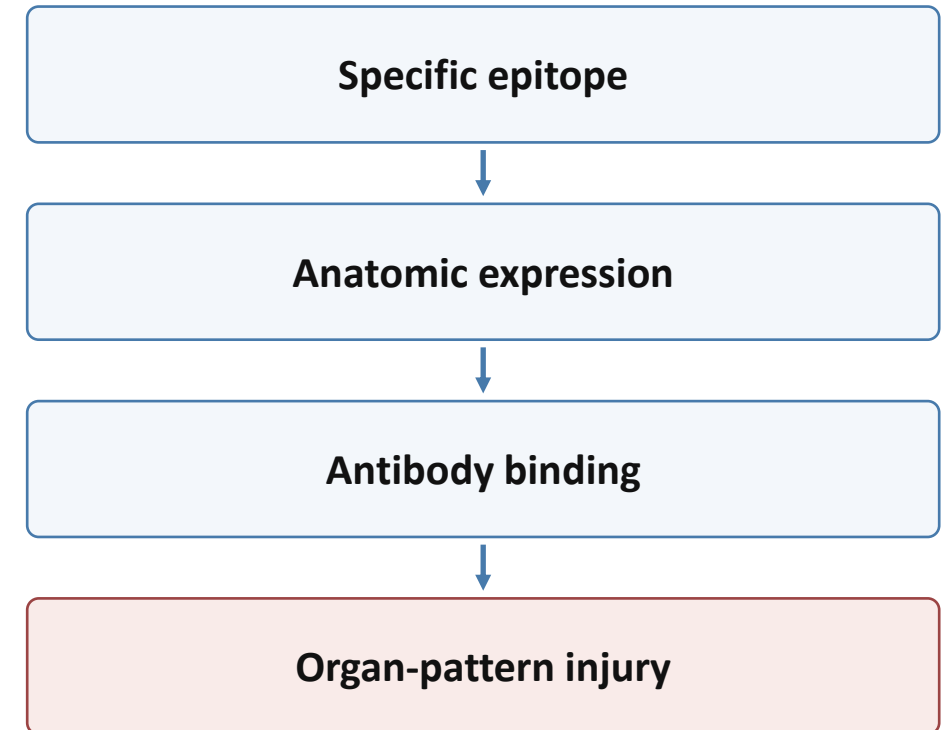
Type III

Antigen–antibody
complexes
accumulate

Deposits may be
circulating or formed
in situ

Autoantibody specificity determines tissue distribution

- Antibodies react with specific host antigenic determinants.
- Expression of the target in more than one organ can explain multi-organ disease.
- Tissue damage remains localized to compartments bearing the target.



IgG is the dominant antibody class in this mechanism

- Type II diseases are commonly mediated by IgG.
- IgG has Fc regions recognized by receptors on leukocytes.
- IgG can activate the classical complement pathway in appropriate settings.

**Fab recognizes
antigen**

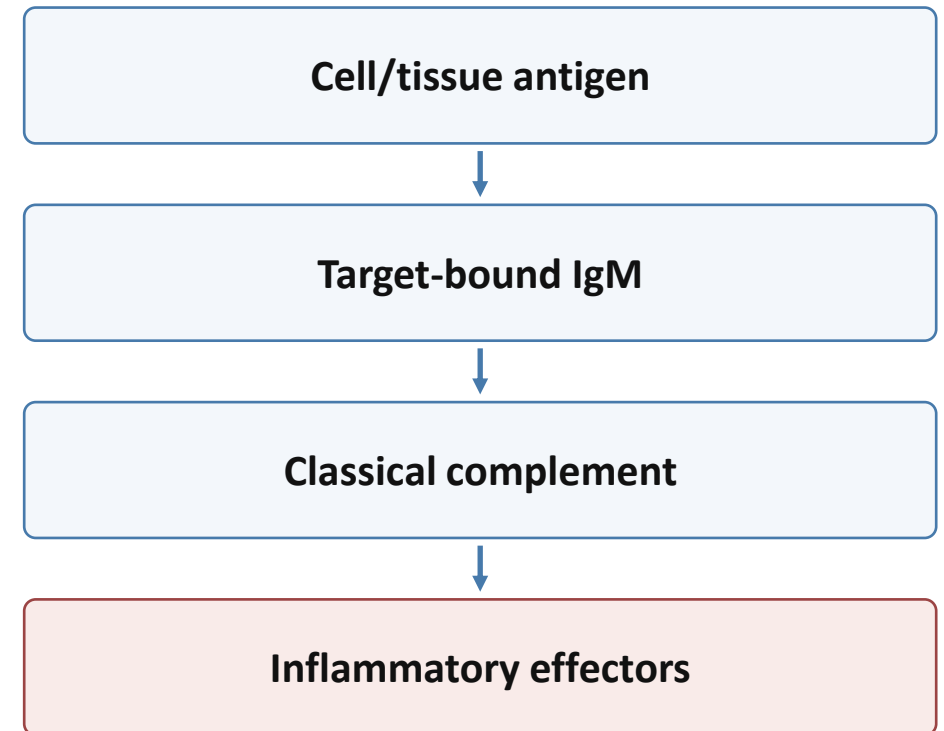
Fc recruits effectors

**Complement
activation**

**Leukocyte
engagement**

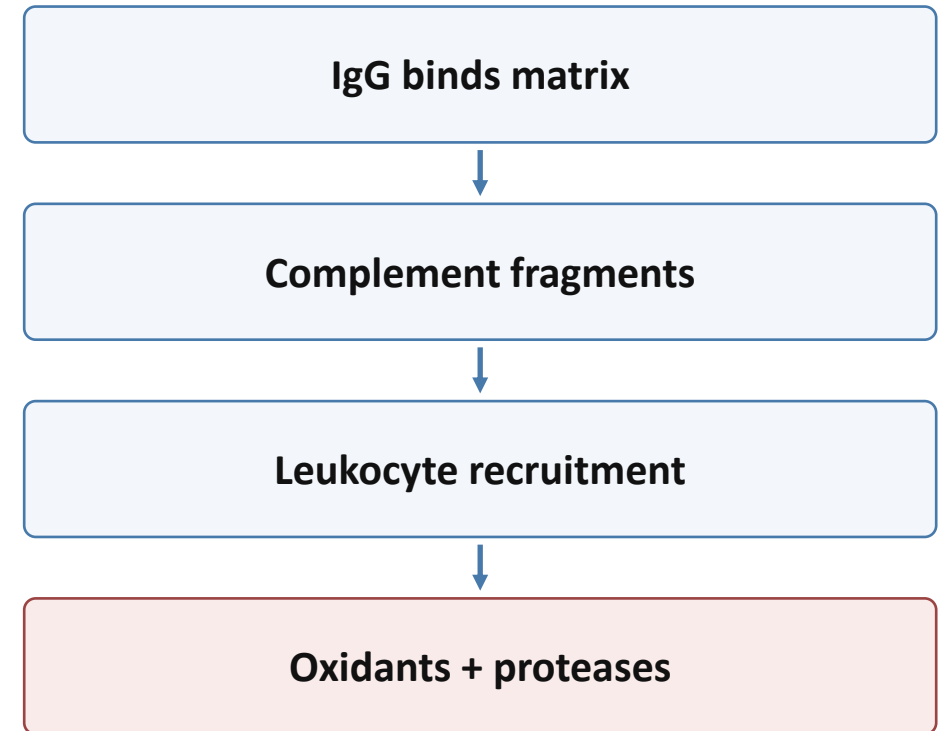
IgM can also initiate complement-dependent injury

- Type II responses may involve IgG or IgM antibodies.
- IgM bound to a suitable target efficiently engages classical complement activation.
- Fc receptor–dependent leukocyte responses are most directly described for IgG.



The inflammatory cascade follows a causal sequence

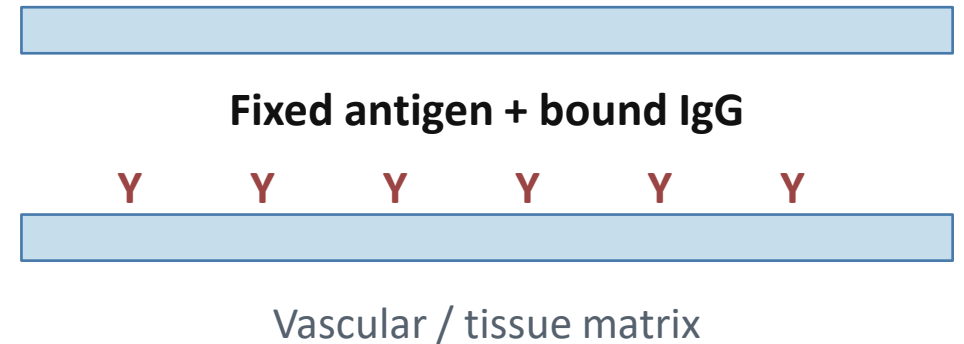
- Antibody first binds a pre-existing antigenic target.
- Complement activation produces chemotactic and permeability mediators.
- Recruited leukocytes release damaging reactive molecules and enzymes.



Complement activation begins at the antibody-bound surface

- Bound antibody activates complement by the classical pathway.
- Effector products are generated near the antigen-bearing tissue.
- Local production couples antigen recognition to inflammation.

Schematic — native PowerPoint shapes



Complement cleavage produces distinct inflammatory signals

- C3a and C5a increase vascular permeability as anaphylatoxins.
- C5a is a major chemoattractant for granulocytes and monocytes.
- C3b deposits on surfaces and is recognized by complement receptors.

C3a → permeability

C5a → chemotaxis

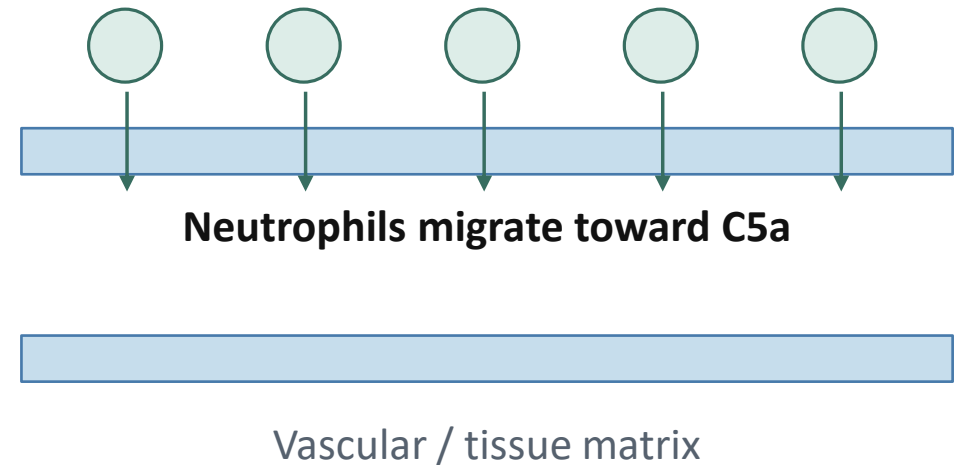
C3b → recognition

**Inflammatory
amplification**

C5a directs granulocytes toward antibody deposits

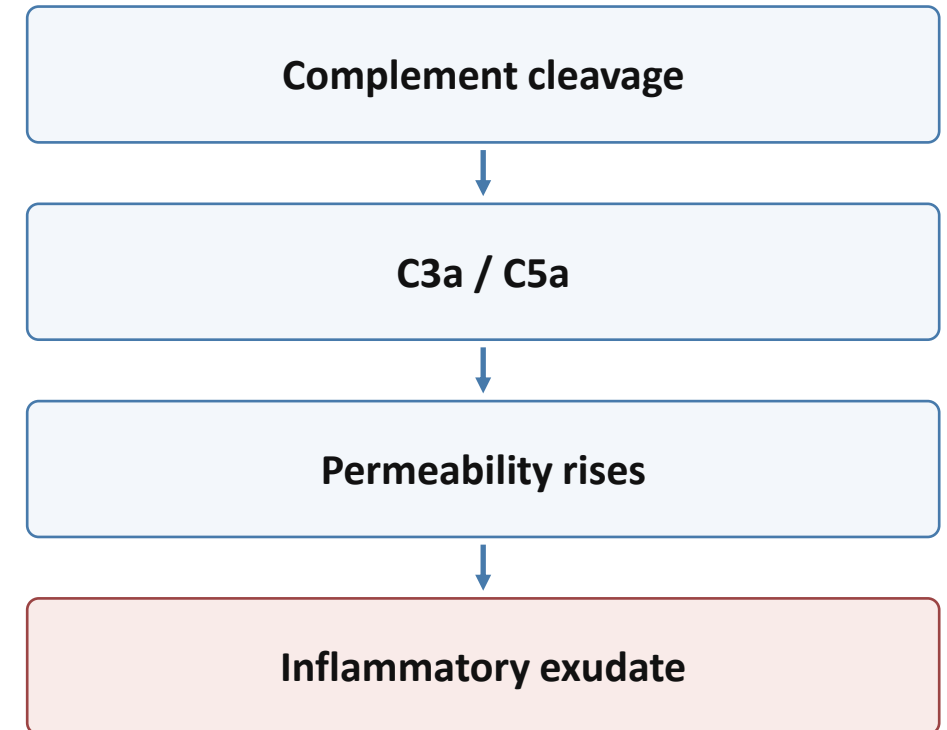
- C5a is the major chemotactic agent highlighted in this pathway.
- Granulocytes and monocytes migrate into affected tissue.
- Recruitment precedes release of leukocyte-derived injurious substances.

Schematic — native PowerPoint shapes



C3a and C5a increase local vascular permeability

- Anaphylatoxins modify the microvascular response.
- Greater permeability facilitates inflammatory exudation.
- Vascular change and chemotaxis cooperate to concentrate leukocytes.



Granulocytes and monocytes are key recruited effectors

- Neutrophils are prominent acute inflammatory granulocytes.
- Monocytes enter tissue and contribute macrophage functions.
- Their tissue-destructive capacity requires local activation.

**Neutrophil
recruitment**

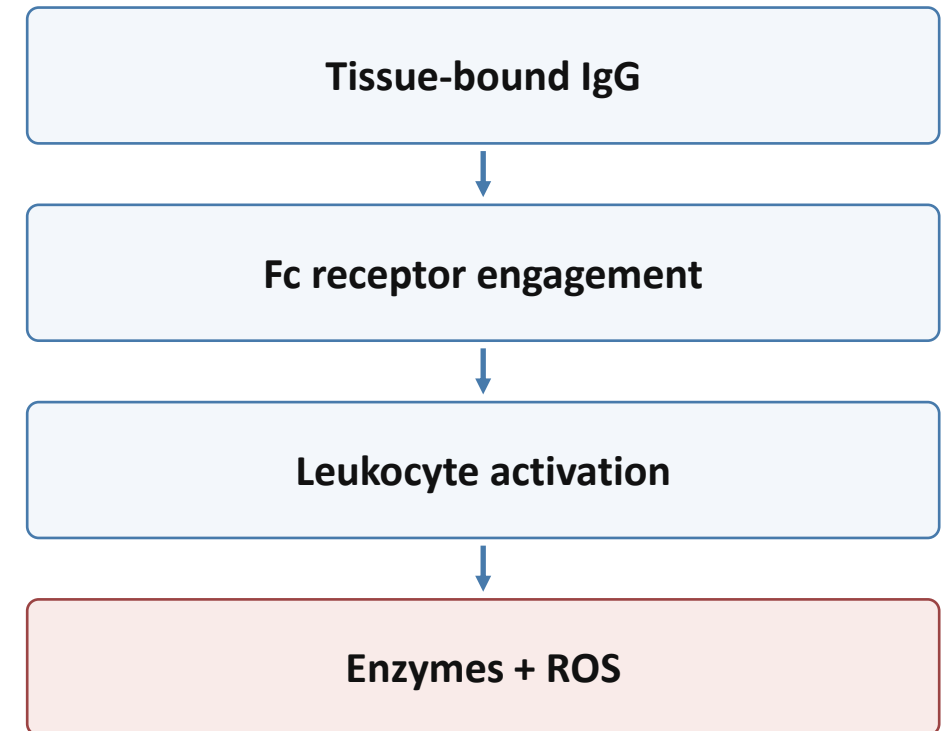
**Monocyte
recruitment**

Receptor engagement

Effector release

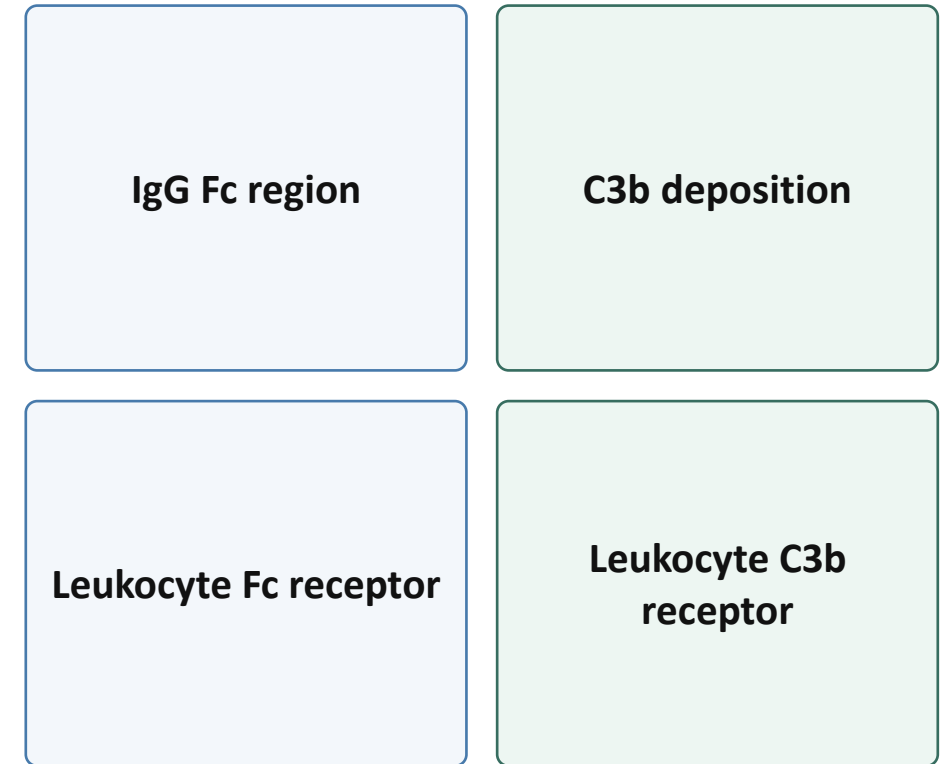
Fc receptors couple bound IgG to leukocyte activation

- Leukocytes recognize the Fc portions of tissue-bound IgG.
- Engagement delivers an activation signal at the antibody-decorated site.
- This recognition contributes directly to inflammatory tissue injury.



Complement receptors cooperate with Fc receptors

- Complement activation generates C3b on local surfaces.
- Leukocyte complement receptors recognize bound complement fragments.
- Engagement of Fc and complement receptors activates leukocyte effector functions.



Recognition and recruitment are distinct steps

- Chemotactic products bring leukocytes to tissue.
- Fc and complement receptors help activate recruited leukocytes.
- Both are required to explain efficient localized inflammation.

Recruitment

C5a directs cell migration

Increased permeability supports entry

Activation

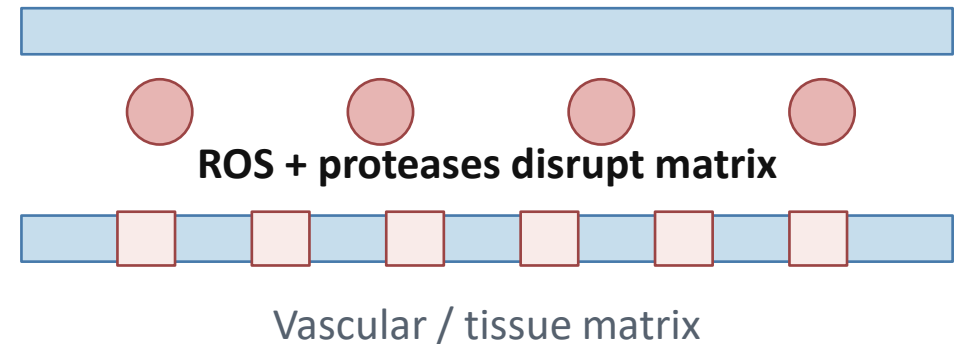
Fc receptors bind tissue IgG

Complement receptors detect C3b

Activated leukocytes damage the extracellular matrix

- Activated granulocytes and monocytes release lysosomal enzymes.
- They generate reactive oxygen species (ROS).
- Extracellular effector release damages tissue surrounding antibody deposits.

Schematic — native PowerPoint shapes



Proteases target basement membrane and connective tissue

- Proteases can digest basement-membrane constituents.
- Collagen and elastin are susceptible extracellular-matrix substrates.
- Cartilage is also vulnerable to proteolytic injury.

Basement membrane

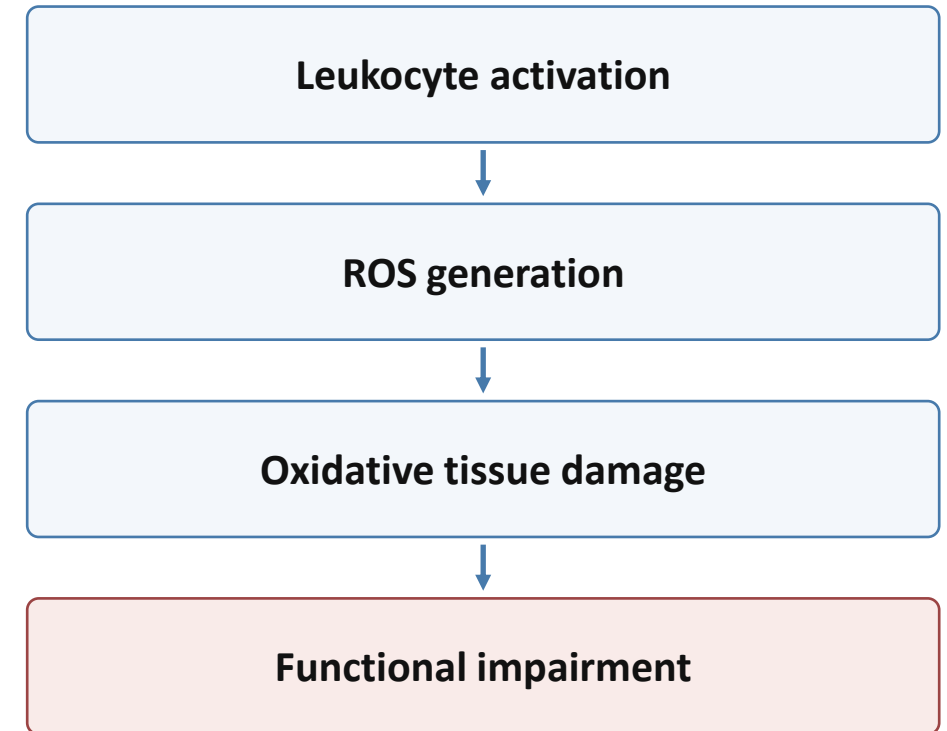
Collagen fibers

Elastin

Cartilage matrix

Reactive oxygen species add a second mode of injury

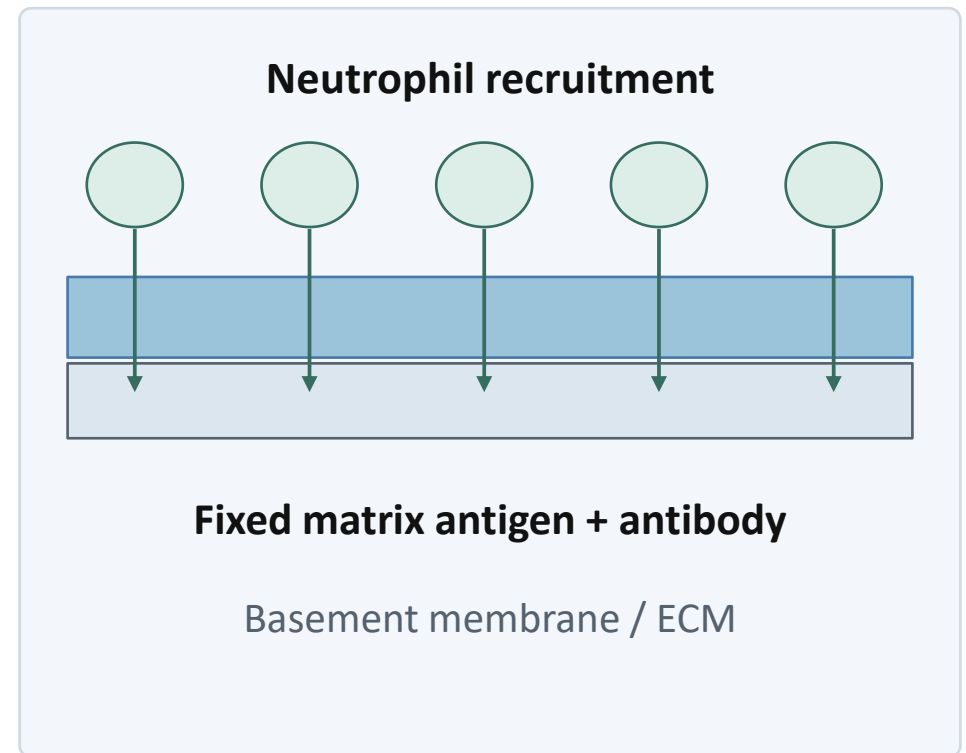
- Activated leukocytes generate oxidant species.
- Oxidants can damage nearby cellular and extracellular structures.
- Protease and oxidant injury may be concurrent.



The antigen need not be the structure ultimately destroyed

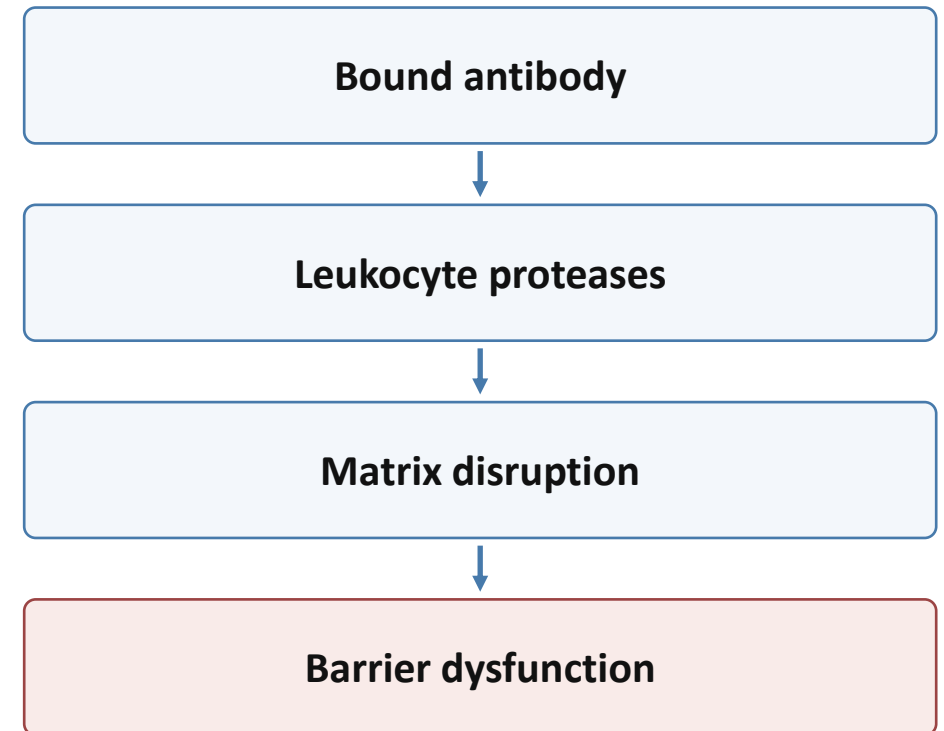
- Antibody binding identifies a target site.
- Released mediators can diffuse into neighboring tissue.
- This explains inflammatory injury beyond the antigen-bearing molecule itself.

Schematic cross-section — not a histology image



Basement-membrane injury compromises tissue barriers

- Basement membranes contribute to structural separation and filtration.
- Leukocyte proteases can digest the matrix scaffold.
- Barrier dysfunction leads to organ-specific clinical consequences.



The local lesion reflects location and inflammatory intensity

- Capillary compartments are vulnerable when target antigens are accessible.
- Leukocyte-rich inflammation can injure adjacent endothelium and matrix.
- The resulting pathology varies with organ structure and severity.

**Capillary
endothelium**

**Subendothelial
matrix**

Leukocyte exudation

Parenchymal injury

Anatomic context shapes the inflammatory phenotype

- The same complement/Fc pathways operate in distinct organs.
- Renal injury impairs the filtration barrier.
- Pulmonary capillary injury may produce alveolar hemorrhage.

Glomerulus

Filtration barrier

Nephritic injury

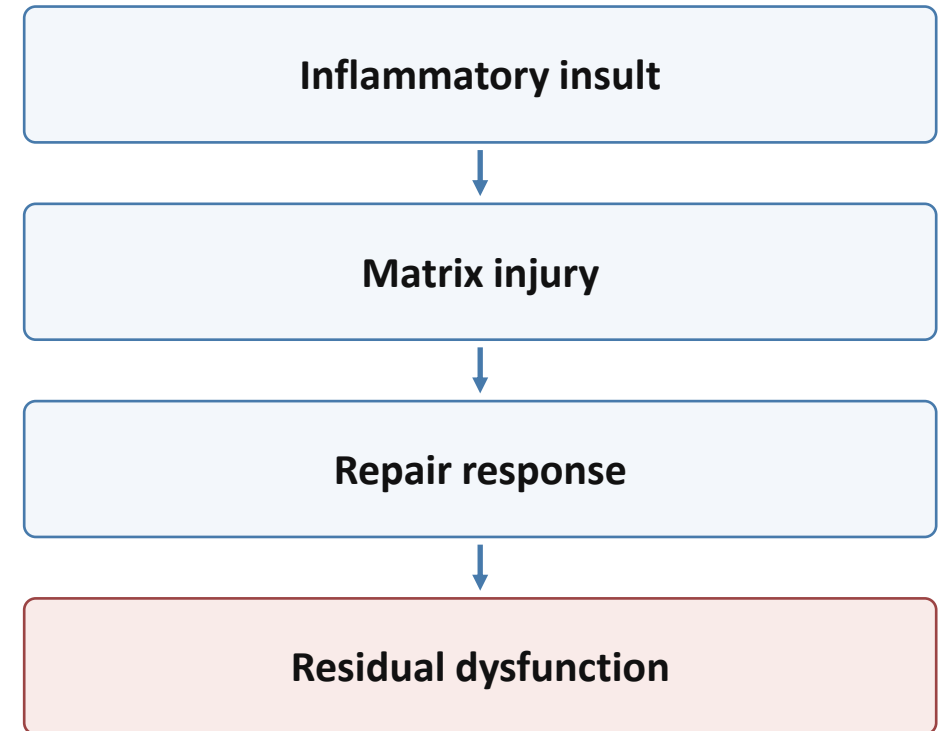
Alveolus

Gas-exchange interface

Hemorrhage

Acute tissue injury may be followed by remodeling

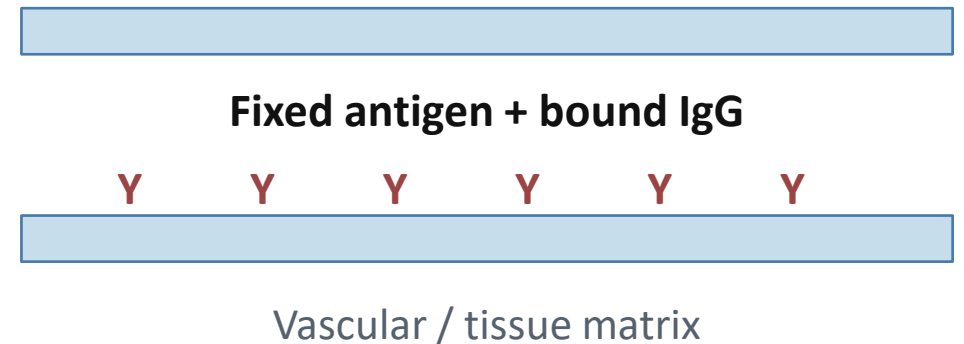
- Continued or severe inflammation can extend tissue destruction.
- Repair and chronic change may follow unresolved injury.
- Clinical outcome depends on severity, duration and the organ involved.



Glomeruli are a key example of fixed-target injury

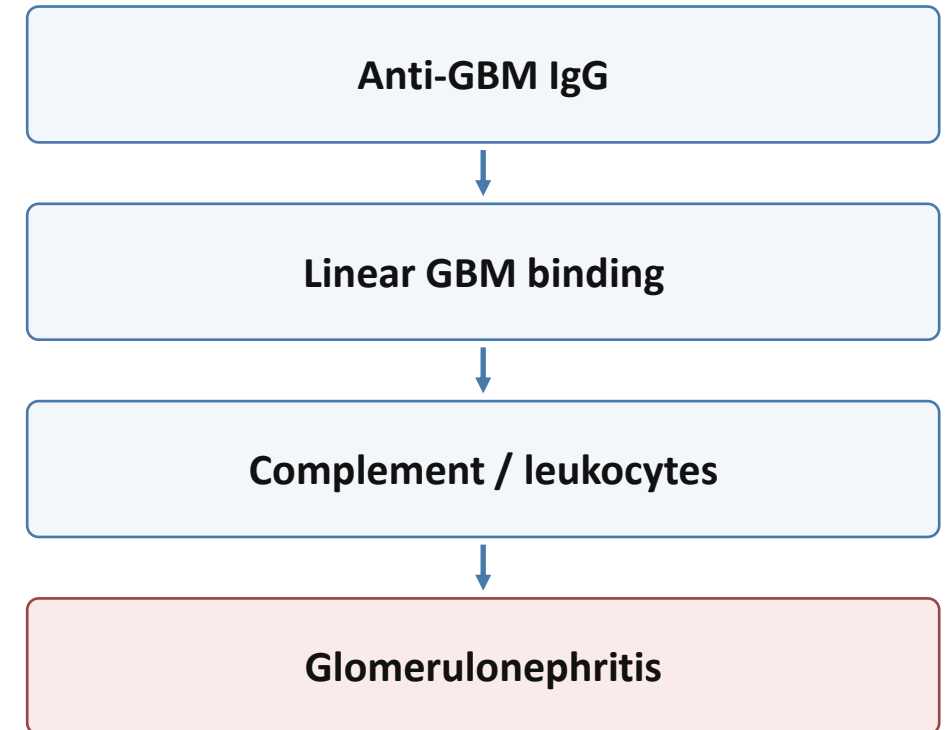
- Intrinsic glomerular basement membrane (GBM) antigens can bind autoantibodies.
- The immune attack occurs along glomerular capillary walls.
- Inflammation damages the filtration apparatus.

Schematic — native PowerPoint shapes



Anti-GBM disease is a prototypical type II lesion

- IgG reacts with an intrinsic component of the GBM.
- Tissue-bound antibody drives inflammatory glomerular injury.
- The deposition pattern follows the distribution of the fixed antigen.



The anti-GBM target is shared by kidney and lung

- The implicated autoantigen lies in the noncollagenous region of the $\alpha 3$ chain of type IV collagen.
- This antigen is expressed in renal and pulmonary basement membranes.
- Shared antigen localization accounts for the pulmonary–renal syndrome in some patients.

**$\alpha 3$ chain of type IV
collagen**

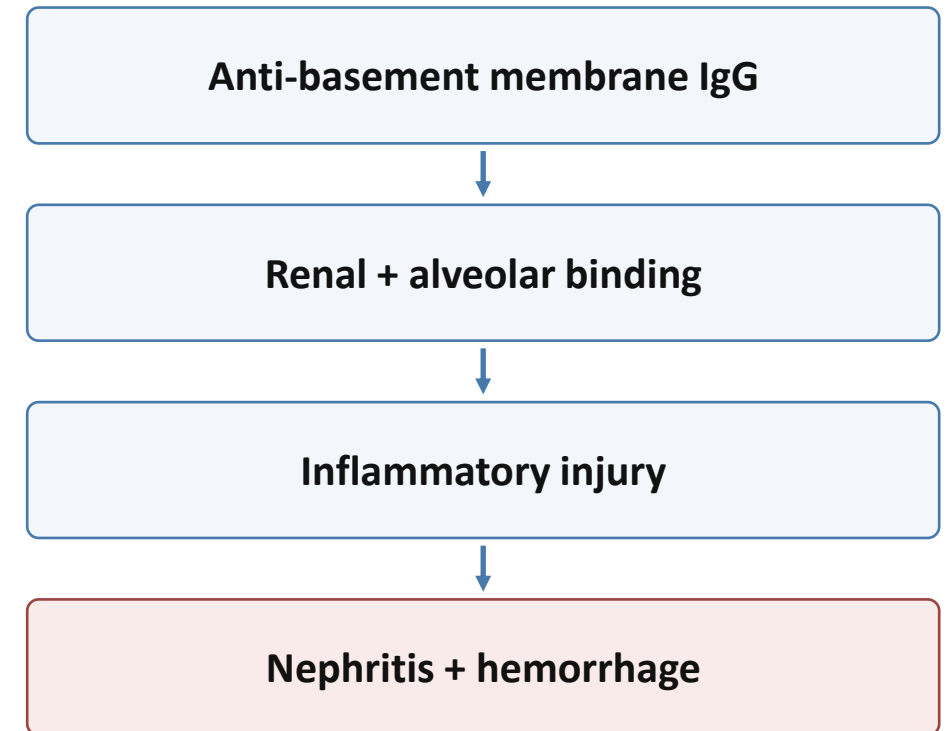
Renal GBM

**Alveolar basement
membrane**

Shared autoantibody

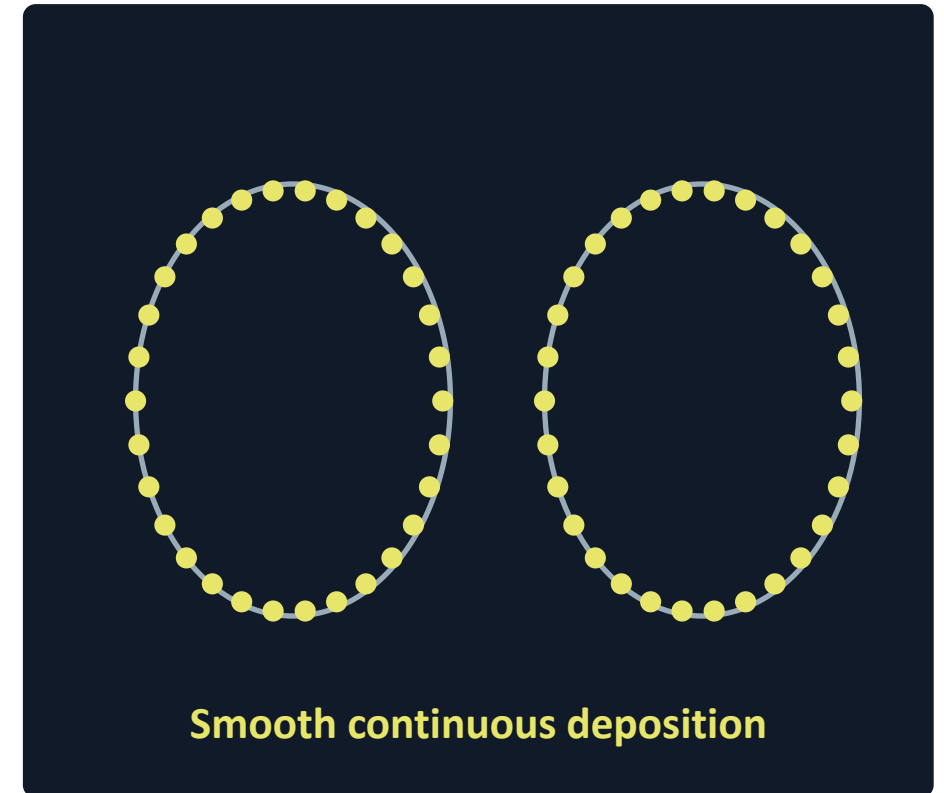
Goodpasture syndrome links nephritis with pulmonary hemorrhage

- Antibodies react with basement membranes of glomeruli and alveoli.
- The kidneys develop inflammatory glomerular injury.
- The lungs may develop hemorrhage due to alveolar basement membrane involvement.



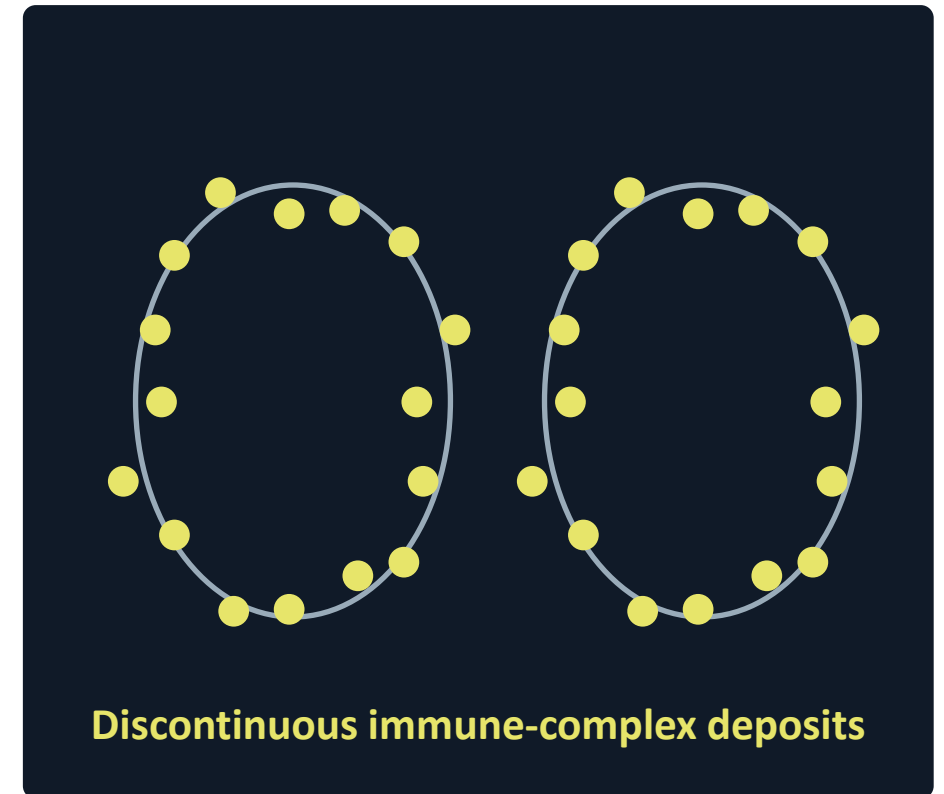
Linear GBM immunofluorescence reflects an intrinsic antigen

- Intrinsic antigen is distributed along the entire GBM.
- Bound IgG therefore outlines capillary walls continuously.
- A linear immunofluorescence pattern supports anti-GBM antibody deposition.



Granular fluorescence reflects discrete immune deposits

- Immune complexes accumulate as discrete deposits rather than continuous binding.
- Their distribution produces a granular fluorescence pattern.

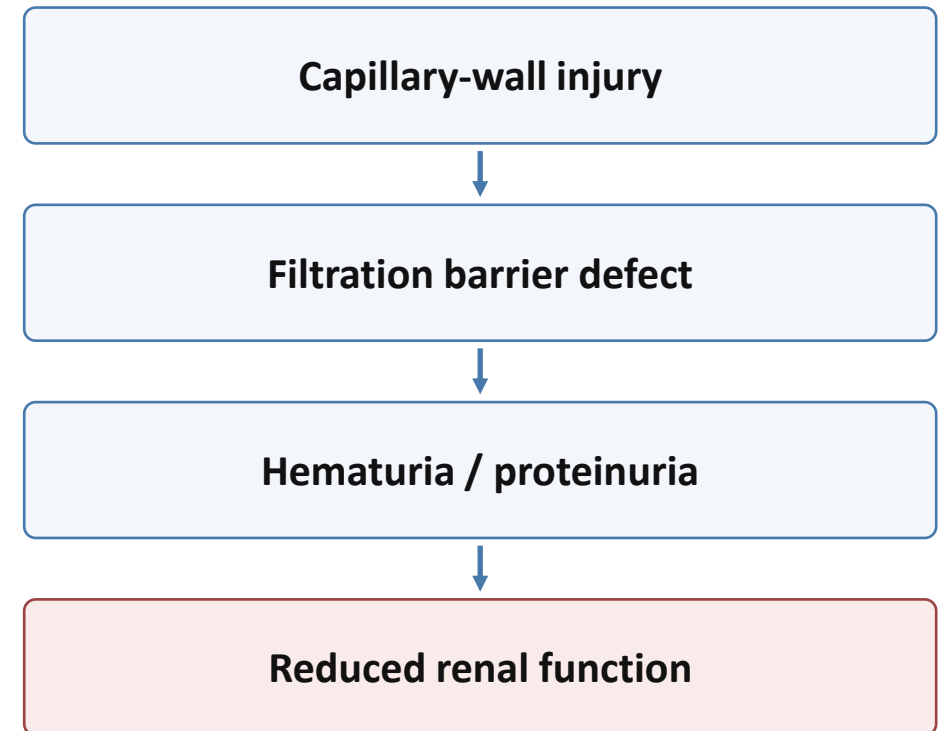


Anti-GBM and immune-complex GN have different origins

Antigen–antibody relationship	Characteristic tissue finding
Anti-GBM disease	IgG recognizes intrinsic GBM → typically linear deposition
Immune-complex GN	Preformed or in situ complexes → typically granular deposits
Shared downstream effectors	Complement / Fc-associated inflammatory injury
Diagnostic implication	Interpret deposits alongside morphology and clinical context

Glomerular inflammation can disrupt filtration

- Inflammation injures glomerular capillary walls.
- Barrier dysfunction may allow blood components and protein into urine.
- Severe injury can rapidly compromise glomerular filtration.



Severe capillary damage may be accompanied by crescents

- Crescent formation is an important response to severe glomerular injury.
- Crescents primarily involve proliferating cells lining Bowman capsule.
- Anti-GBM injury is one cause of rapidly progressive crescentic GN.

**Glomerular capillary
injury**

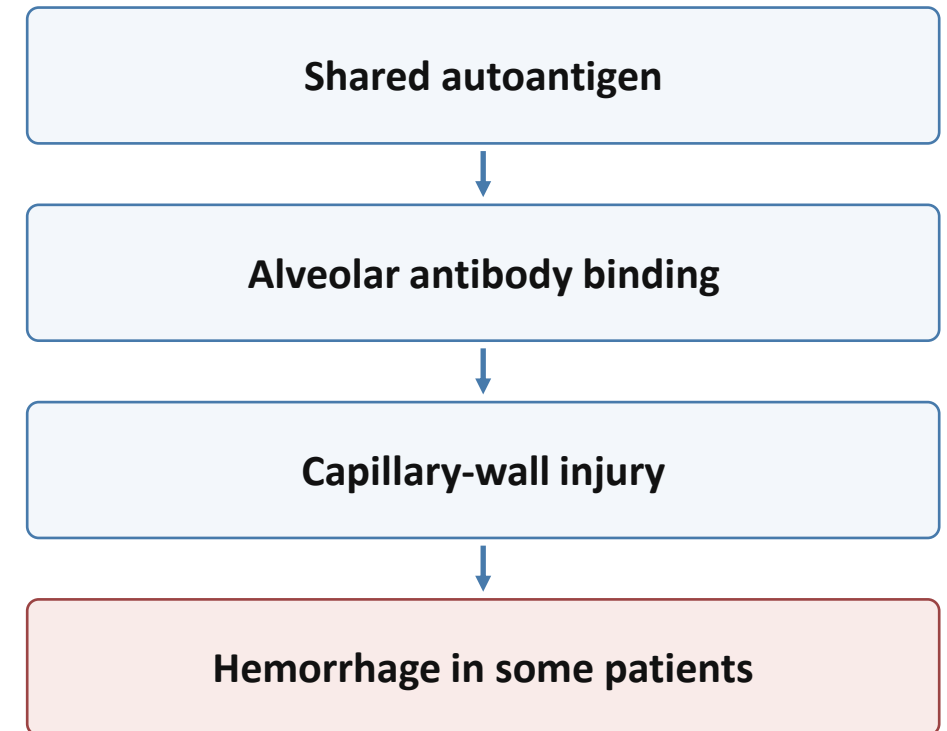
**Bowman-space
response**

Crescent formation

**Rapidly progressive
GN**

Pulmonary involvement reflects the same antigen specificity

- Anti-basement-membrane antibodies can bind in the pulmonary alveolar wall.
- Inflammatory injury can result in alveolar hemorrhage.
- Absence of pulmonary hemorrhage does not exclude renal-limited anti-GBM disease.



Clinical interpretation should integrate organ distribution

- Pulmonary hemorrhage and glomerulonephritis suggest a pulmonary–renal process.
- Anti-GBM disease is an important immune-mediated mechanism in this setting.
- Other causes of pulmonary–renal syndromes exist and require differentiation.

Clinical presentation

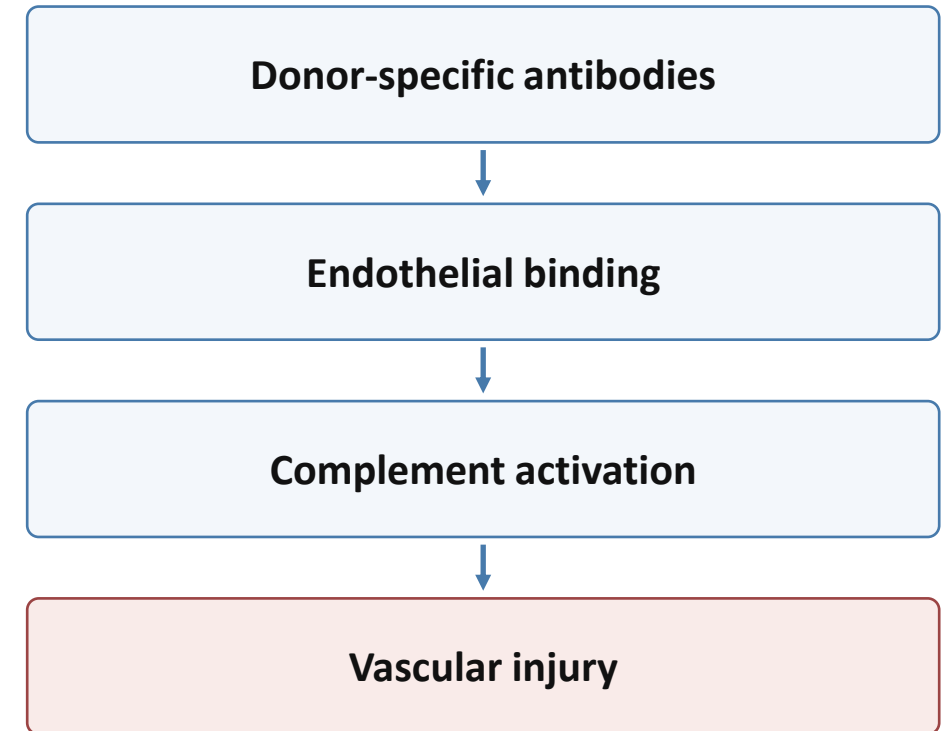
Antibody testing

Renal biopsy pattern

**Competing
mechanisms**

Graft vasculature is another antibody-mediated target

- Antibodies against donor alloantigens can bind graft endothelium.
- Classical complement activation follows local antibody recognition.
- Resultant vascular inflammation and endothelial injury impair graft function.



Acute antibody-mediated rejection injures small vessels

- Typical sites include glomeruli and peritubular capillaries in kidney grafts.
- Inflammatory injury may be associated with complement-product deposition.
- Small-vessel thrombosis may accompany the reaction.

Glomerulitis

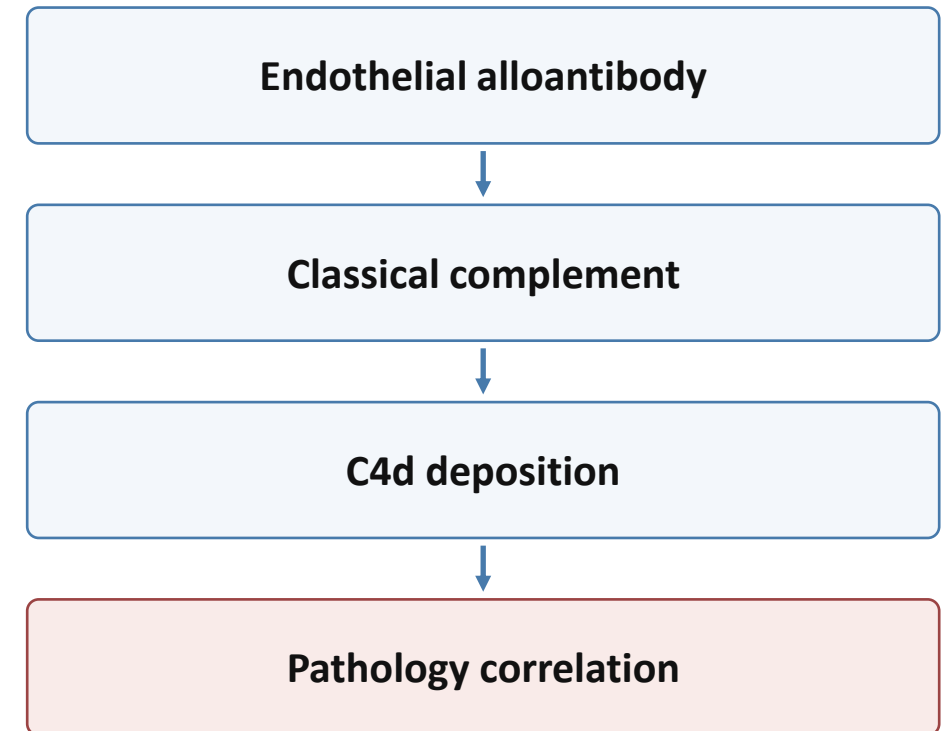
**Peritubular
capillaritis**

**Complement-product
deposition**

**Microvascular
thrombosis**

C4d can indicate complement activation in graft injury

- The classical complement pathway generates C4-derived products.
- C4d deposition is described in the kidney-graft rejection context.
- Interpretation requires graft morphology and appropriate clinical/serologic context.



Antibody-mediated and cellular rejection are not identical

- Grafts can be injured by both humoral and T-cell-mediated immunity.
- Antibody-mediated rejection prominently affects microvasculature.
- Cellular rejection includes tubulitis and lymphocyte-rich endotheilitis.

Antibody-mediated

Endothelial
alloantibody

Complement-
associated capillary
injury

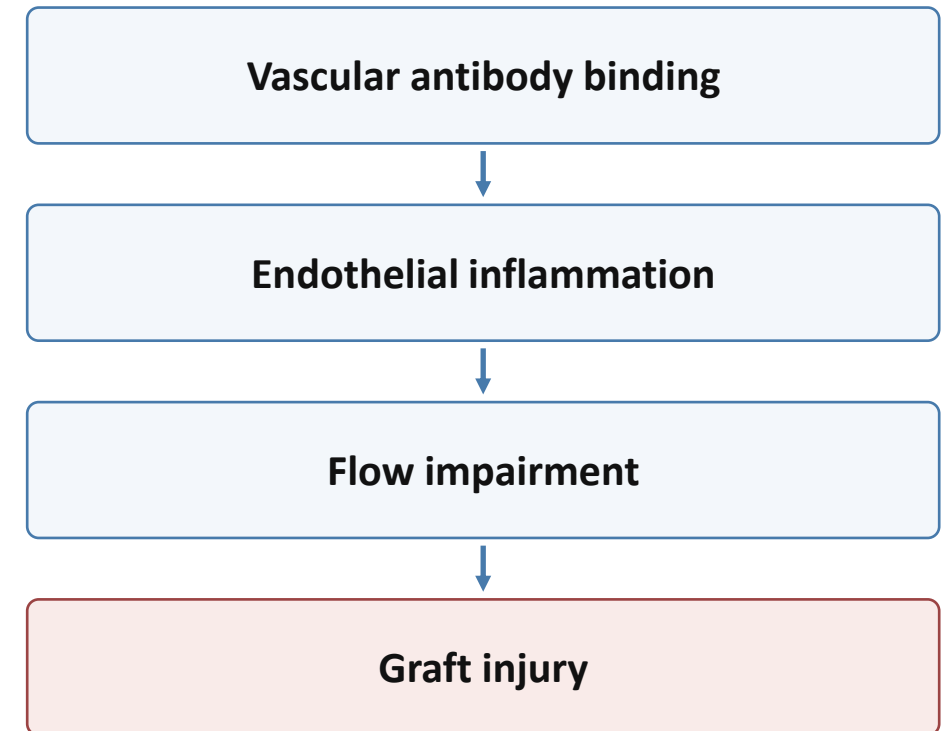
T-cell-mediated

Alloreactive
lymphocytes

Tubulitis /
endotheliitis

Vascular injury can impair a transplanted organ

- Endothelial damage alters microvascular integrity and flow.
- Inflammation and thrombotic changes may coexist.
- Reduced tissue perfusion contributes to graft dysfunction.



ANCA-associated vasculitis is mechanistically distinct

- ANCA reacts with proteins associated with neutrophil granules.
- This differs from antibody binding to a constitutive basement-membrane antigen.
- Neutrophil activation is central to the inflammatory lesion.

Anti-GBM

Antibody binds fixed matrix

Linear deposition

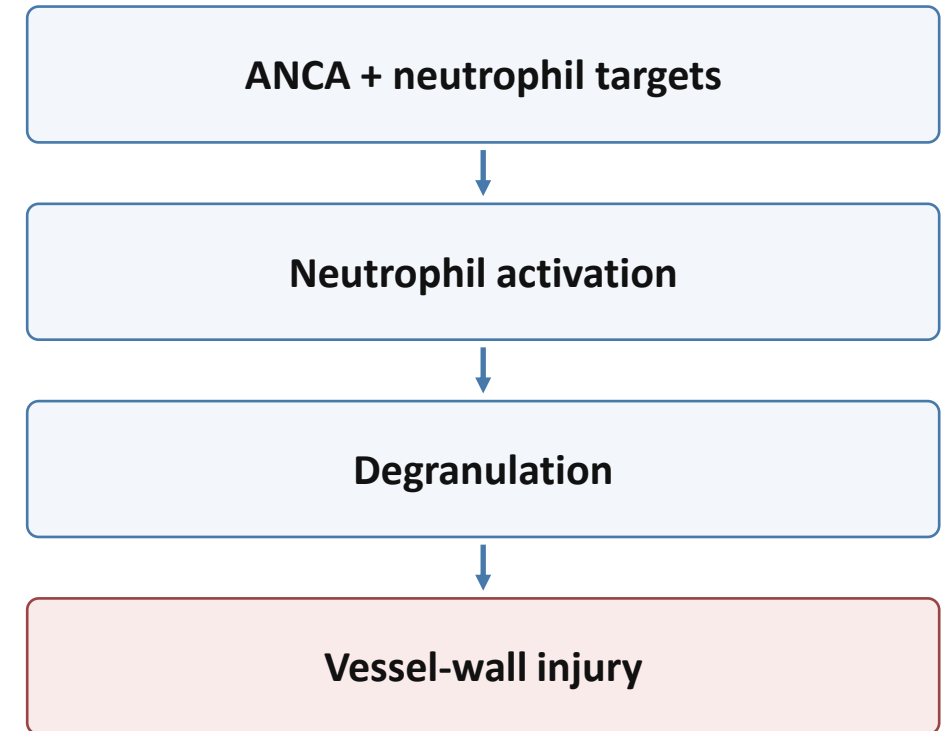
ANCA vasculitis

Antibodies target neutrophil proteins

Pauci-immune glomerular pattern

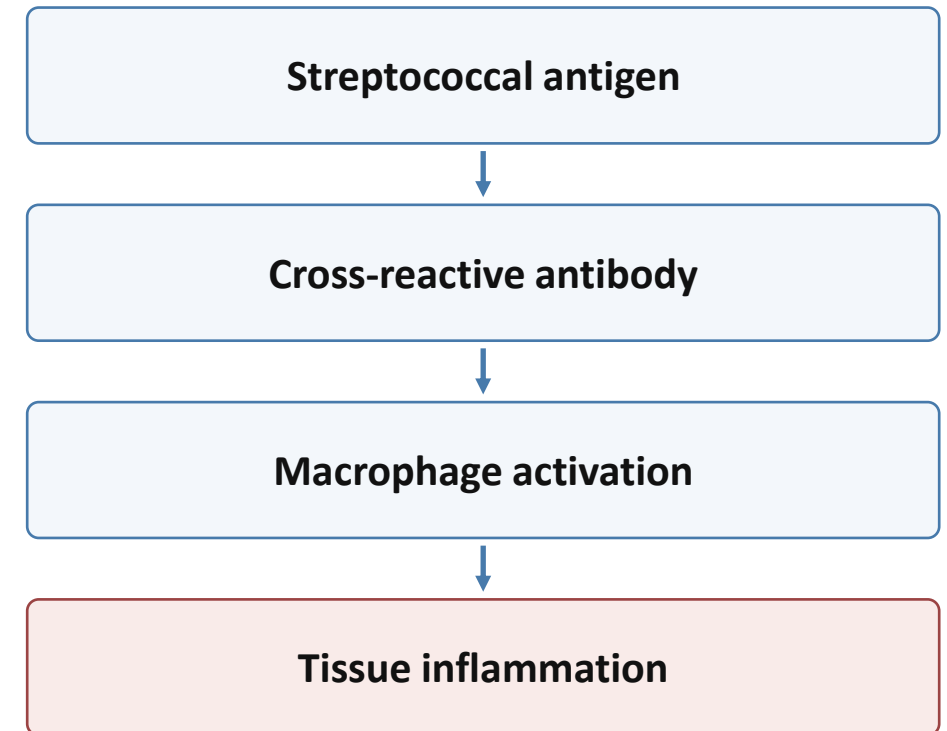
ANCA-related neutrophil activation can damage vessels

- Antibodies recognize neutrophil granule-associated antigens.
- Neutrophil activation and degranulation contribute to vascular inflammation.
- ANCA vasculitis illustrates antibody-triggered inflammation without dense immunoglobulin deposits.



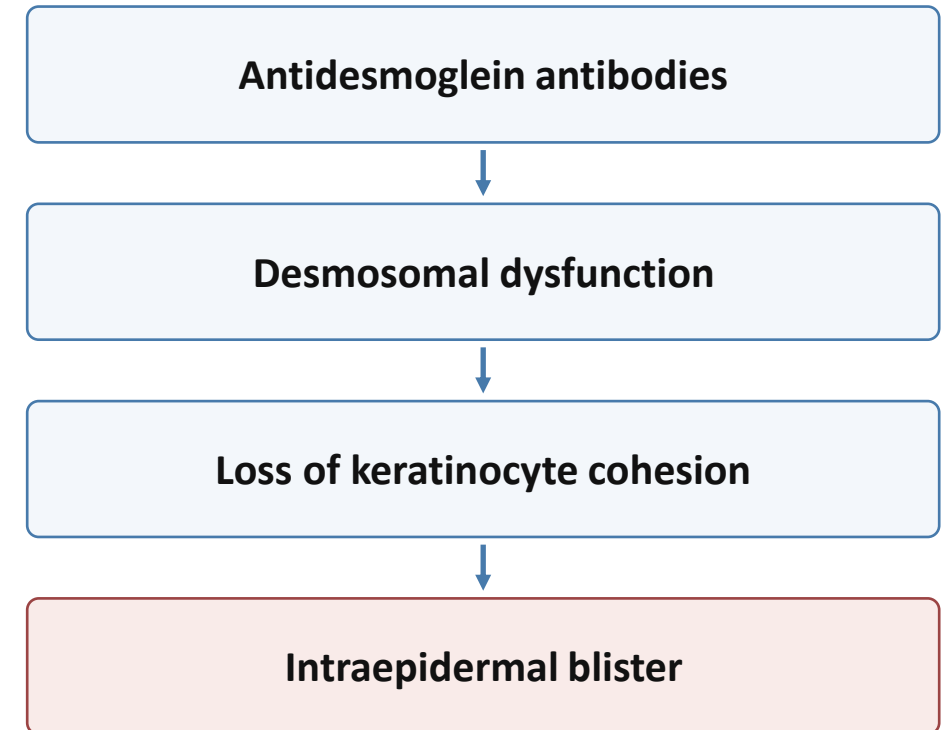
Acute rheumatic fever illustrates antibody cross-reactivity

- Antibody responses to streptococcal antigens can cross-react with host tissue.
- Immune-mediated inflammation contributes to myocarditis and arthritis.
- Cross-reactivity, not direct bacterial invasion, is central to the listed mechanism.



Pemphigus is antibody injury by loss of adhesion

- Autoantibodies target desmogleins in epidermal intercellular junctions.
- Altered cell adhesion and proteolytic mechanisms contribute to skin blistering.
- It is type II antibody-mediated injury, but not the same lesion as complement-driven GBM inflammation.



Opsonization removes cells rather than injuring fixed matrix

- In hemolytic anemia, antibody-coated red cells are removed by phagocytes.
- In fixed-tissue inflammation, recruited leukocytes injure surrounding structures.
- Both are type II, but their immediate tissue targets differ.

Opsonization

Mobile target: Blood cell

Phagocytosis / lysis

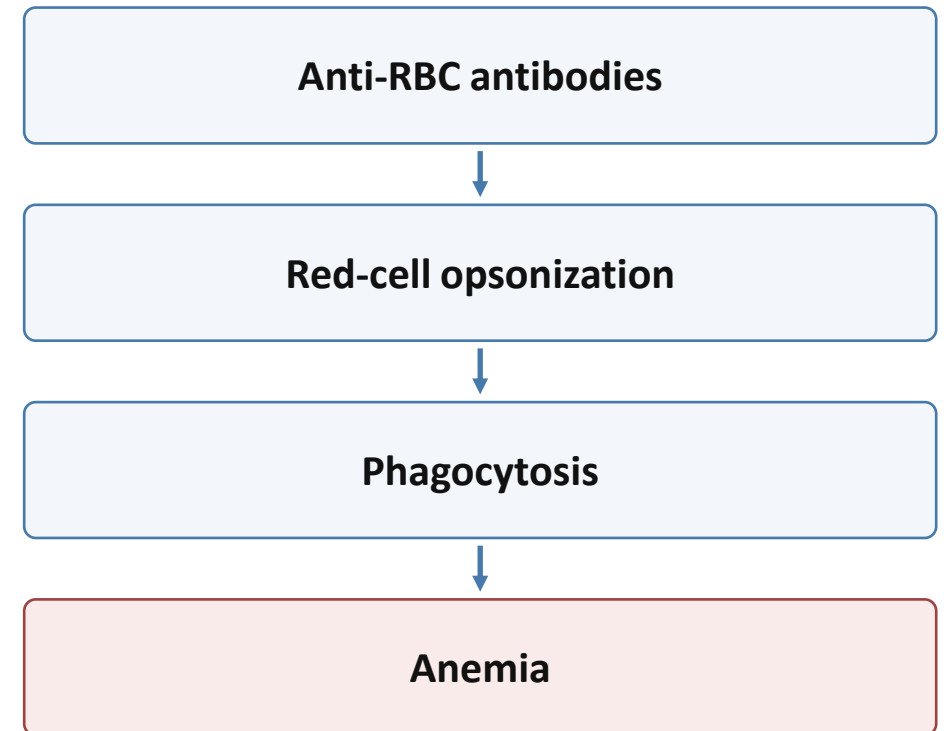
Inflammation

Fixed target: Tissue matrix

Extracellular proteases / ROS

Autoimmune hemolytic anemia highlights the contrast

- Antibodies bind red-cell membrane proteins.
- Fc and complement recognition favors red-cell removal.
- The principal manifestation is hemolysis and anemia—not localized matrix inflammation.



Antibodies may alter receptors without inflammation

- Some type II antibodies impair or stimulate cell-surface receptor function.
- Myasthenia gravis impairs neuromuscular transmission.
- Graves disease stimulates the thyroid-stimulating hormone receptor.

Receptor blockade

Receptor stimulation

Altered physiology

**May lack dominant
inflammation**

Receptor dysfunction and tissue destruction must be separated

- The clinical phenotype cannot be inferred from antibody presence alone.
- An antibody that activates a receptor may produce hyperfunction.
- An antibody that recruits complement to tissue can produce structural damage.

Functional disturbance

Receptor
blockade/stimulation

Altered cell signaling

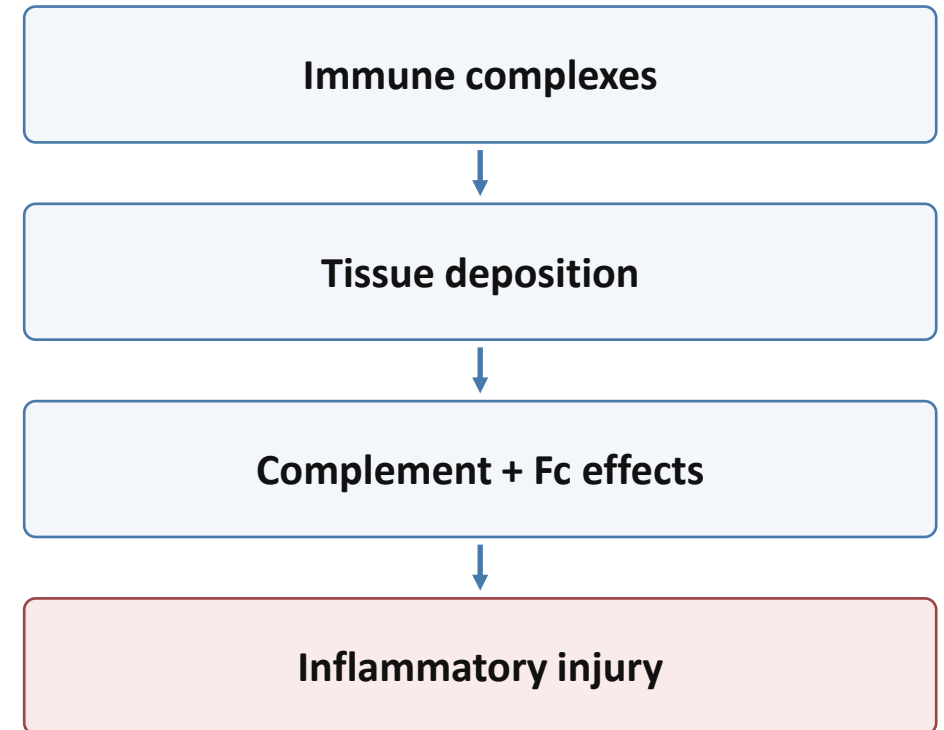
Inflammatory injury

Complement / Fc
engagement

Matrix and cellular
destruction

Type III disease shares many terminal inflammatory mediators

- Antigen and antibody form immune complexes in blood or tissues.
- Deposited complexes activate complement and leukocytes.
- The downstream inflammatory effectors overlap with type II inflammation.



The initiating location separates types II and III

Dimension	Type II inflammation versus type III injury
Antigen distribution	II: Intrinsic / fixed; III: Complex-associated, circulating or in situ
Initial event	II: Antibody binding to tissue; III: Antigen–antibody complex formation/deposition
Downstream pathway	Both may activate complement and Fc receptors on leukocytes
Example	II: Anti-GBM disease; III: Immune-complex glomerulonephritis

Complement consumption is context-dependent

- Circulating immune-complex disease may consume complement systemically.
- Decreased serum C3 during active serum sickness.
- Do not assume every local antibody-mediated lesion causes low serum C3.

Systemic immune complexes

Complement consumption

C3 may decrease

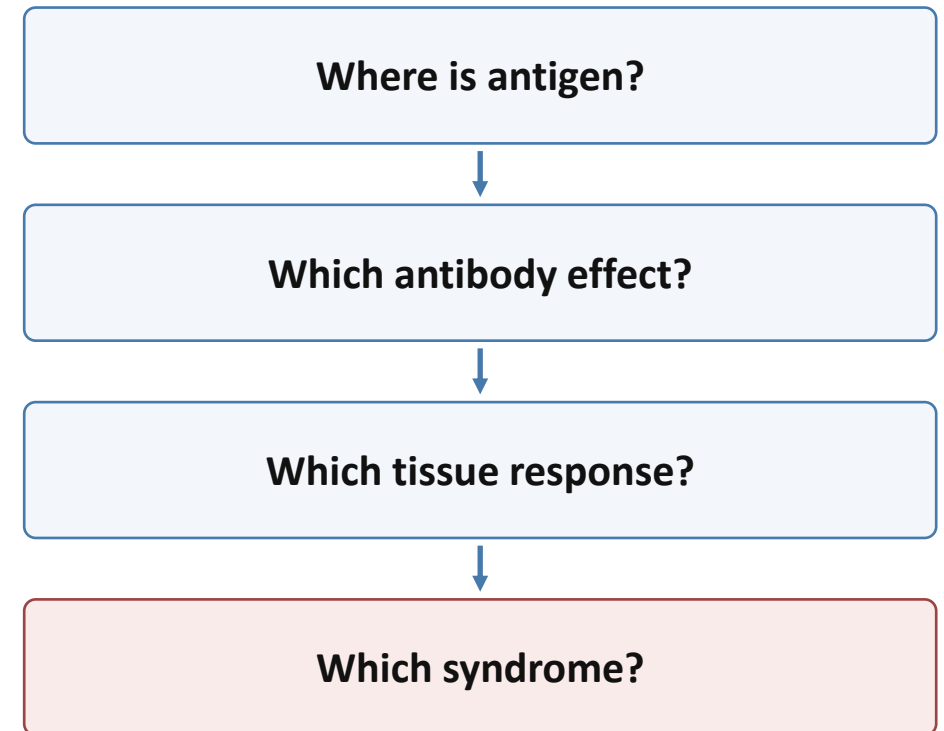
Fixed-tissue antibody

Complement acts locally

Serum level varies by context

Mechanistic pathology begins with the target site

- Locate the antigen: Cell, receptor, matrix, or circulating complex.
- Identify the effector: Phagocytosis, complement/Fc inflammation, or functional change.
- Correlate the tissue pattern and organ manifestations.



Kidney biopsy information can resolve competing mechanisms

- Light microscopy describes the structural injury pattern.
- Immunofluorescence shows distribution of immunoglobulin/complement deposits.
- Electron microscopy can demonstrate discrete electron-dense immune deposits.
- Clinical and serologic data remain essential.

Light microscopy

Immunofluorescence

Electron microscopy

**Clinicopathologic
synthesis**

Linear and granular are patterns—not separate diagnoses

- Linear staining strongly supports antibody binding to intrinsic GBM.
- Granular staining suggests discrete immune-complex deposits.
- Neither pattern should be interpreted without disease morphology and context.

Linear pattern

Continuous GBM
outline

Anti-GBM mechanism

Granular pattern

Discrete deposits

Immune-complex
mechanism

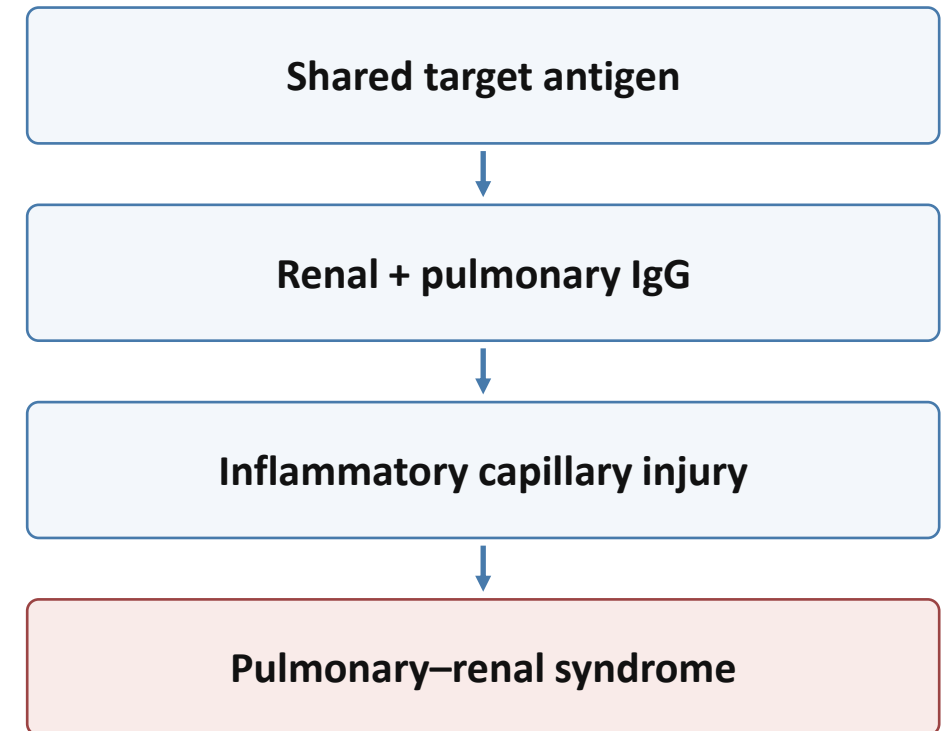
Case application: Pulmonary hemorrhage with nephritic injury

A patient develops hemoptysis, hematuria, and rapidly deteriorating renal function. Which antibody-mediated mechanism could link the lung and kidney findings?

- Consider autoantibody binding to a shared basement-membrane antigen.
- Predict complement/Fc-driven inflammation at both sites.
- Anticipate a linear GBM immunofluorescence pattern if anti-GBM disease is confirmed.

Case resolution: Shared basement membrane explains both organs

- A target within the $\alpha 3$ chain of type IV collagen occurs in kidney and lung.
- IgG binds tissue-fixed antigen and activates inflammatory effectors.
- Organ manifestations follow damage to glomerular and alveolar capillaries.



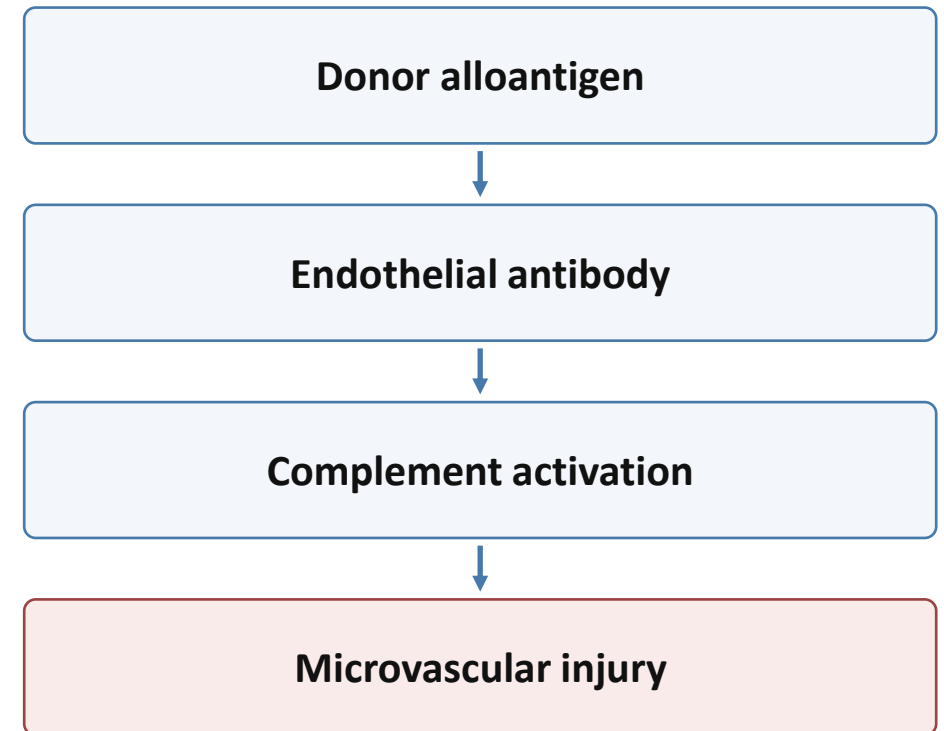
Case application: Early graft microvascular inflammation

A kidney transplant biopsy shows glomerulitis and peritubular capillaritis with complement-product deposition. Which humoral pathway should be considered?

- Assess antibody-mediated rejection in the appropriate context.
- Antibodies may target donor alloantigens on vascular endothelium.
- Classical complement activation links antibodies to microvascular injury.

Case resolution: Vascular antibody binding leads to graft damage

- Alloantibody binding activates complement at graft endothelium.
- The microvascular bed becomes inflamed and injured.
- Focal thrombosis and organ dysfunction may accompany more severe injury.



Case application: Necrotizing vasculitis with sparse deposits

Necrotizing vasculitis occurs with ANCA positivity but little immunoglobulin detected in renal tissue. Is dense tissue-bound IgG deposition required?

- No: ANCA can activate neutrophils through a different antibody-associated process.
- Neutrophil activation and degranulation drive vessel injury.
- Contrast this mechanism with linear anti-GBM antibody deposition.

Case application: Granular deposits in glomeruli

**A glomerular sample has discrete granular immunoglobulin deposits.
Does this pattern identify anti-GBM type II inflammation?**

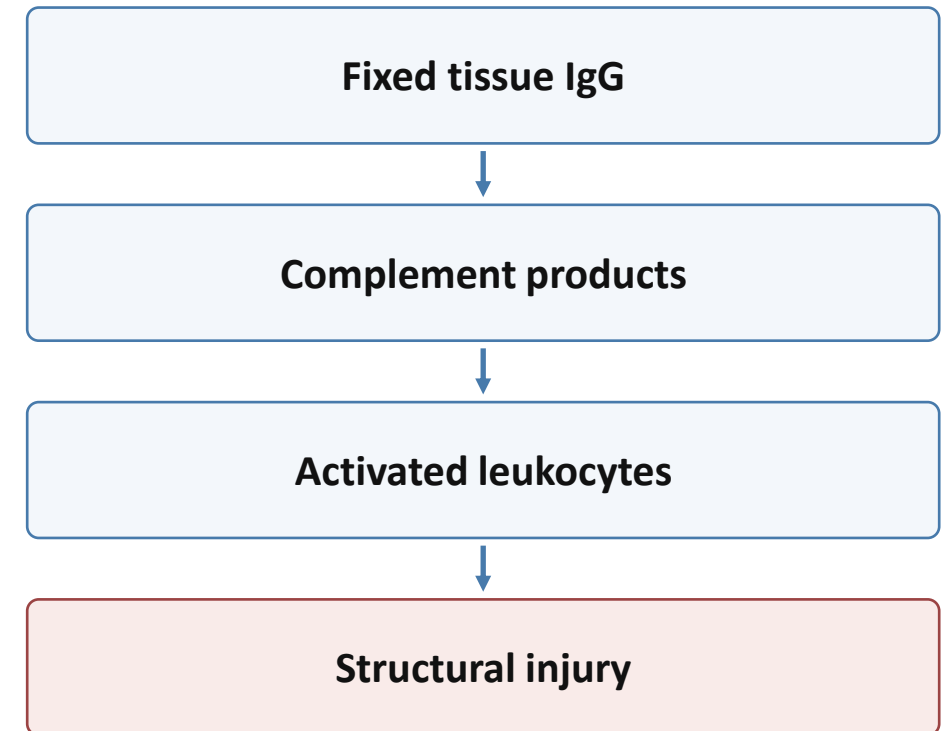
- No: Granular deposition is characteristic of immune-complex-mediated mechanisms.
- Both mechanisms can produce complement and leukocyte injury.
- The source and arrangement of antigen–antibody interaction differ.

Pitfalls when interpreting antibody-associated tissue injury

Common mistake	Correct interpretation
All IgG-mediated injury is inflammatory	Type II also includes opsonization and receptor dysfunction
All glomerular antibodies are immune complexes	Antibodies can bind intrinsic GBM in situ
Complement recruitment equals antigen specificity	Complement acts downstream of antigen–antibody recognition
ANCA vasculitis requires dense fixed deposits	ANCA-associated GN is typically pauci-immune

Integrated pathway from antibody binding to organ dysfunction

- Specific IgG attaches to fixed tissue components.
- Complement fragments recruit cells and alter vascular permeability.
- Fc/C3b-receptor engagement triggers enzyme and ROS release.
- Matrix damage causes organ-dependent dysfunction.



Three questions summarize the pathologic mechanism

- Where is the antigen: Tissue-fixed or within an immune complex?
- Which effector dominates: Inflammatory cells, phagocytes, or receptor regulation?
- What structural injury explains the clinical manifestation?

Target localization

Antibody binding

**Inflammatory
mediator**

Clinical consequence

Test your mechanism-based reasoning

Why does an antibody directed against a basement-membrane antigen produce inflammation instead of simple removal of the antigen?

- The antigen is fixed in the tissue and cannot be engulfed like a circulating blood cell.
- Complement activation and Fc receptor engagement recruit activated leukocytes.
- Extracellular proteases and ROS injure the surrounding structural matrix.

Selected textbook sources and figure contexts

Source section	Teaching material used
Chapter 6, pp. 181–182	Hypersensitivity definition and four-type classification
Chapter 6, pp. 185–188	Type II injury mechanisms, Fig. 6.16 and Table 6.3; type III contrast
Chapter 6, pp. 209–210	Acute antibody-mediated vascular graft rejection
Chapter 20, glomerular injury	Anti-GBM disease, linear/granular IF and crescentic GN