

Patterns and mechanisms of graft rejection

Alloimmune recognition, renal allograft morphology, and mechanisms of graft failure

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Learning objectives

- Distinguish hyperacute, acute, and chronic rejection by mechanism and pathology.
- Explain direct and indirect allorecognition and their effector pathways.
- Recognize the principal renal allograft patterns: Tubulitis, arteritis, capillary injury, and fibrosis.
- Connect morphology to temporal context and implications for graft function.

Rejection is an alloimmune attack on the graft

- The recipient identifies transplanted tissue as foreign.
- T lymphocytes and antibodies against graft antigens injure the transplanted organ.
- The resulting damage may affect graft parenchyma, blood vessels, or both.
- Anatomic injury patterns reflect the dominant immune mechanism.

Allograft and xenograft are different settings

Allograft

- Donor and recipient are of the same species.
- The focus of standard clinical graft-rejection pathology.
- Recipient responses to donor alloantigens are central.

Xenograft

- Donor and recipient are different species.
- Distinct antigenic barriers may apply.
- Not the focus of the textbook morphology discussion.

HLA polymorphism drives donor–recipient disparity

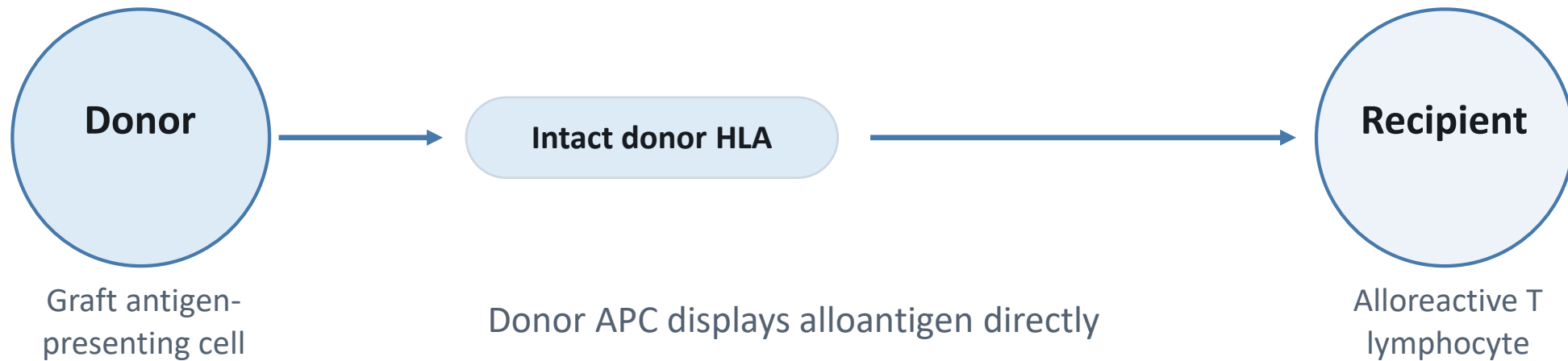


- Exception: Identical twins generally lack these major HLA differences.

Why allografts provoke strong T-cell responses

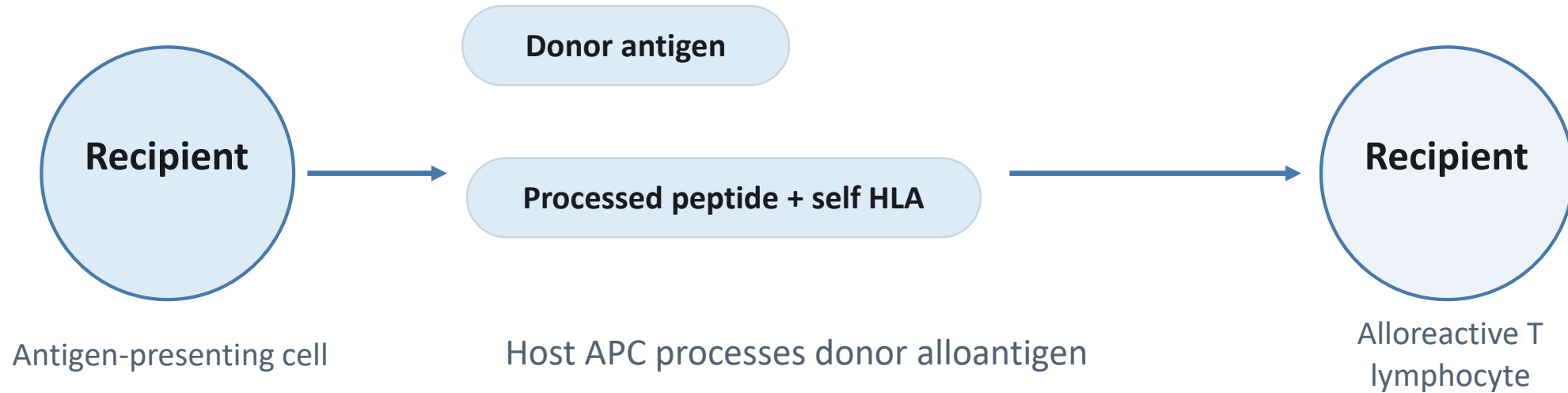
- Alloreactive T-cell precursors occur at unusually high frequency.
- The response to an allograft can exceed responses mounted against microbes.
- Without immune suppression, a vigorous response may rapidly destroy tissue.
- The intensity of allorecognition explains the need for potent immunosuppression.

Direct pathway of alloantigen recognition



Graft antigen-presenting cells display donor HLA directly to recipient T cells.
The pathway is especially relevant to cytotoxic T-cell responses in acute rejection.

Indirect pathway of alloantigen recognition



Host antigen-presenting cells take up and process graft alloantigens.

Peptides are presented to host T cells on recipient HLA.

Direct and indirect pathways differ mechanistically

Direct recognition

- Antigen-presenting cell comes from the donor graft.
- Intact donor HLA is recognized by recipient T cells.
- May be particularly important in CTL-mediated acute rejection.

Indirect recognition

- Recipient antigen-presenting cell processes graft antigen.
- Antigen is presented in a conventional peptide–HLA context.
- May have a greater role in chronic rejection.

Relative contributions are described as tendencies, not exclusive assignments.

CD8+ and CD4+ cells provide distinct effector functions

CD8+ T lymphocytes

- Differentiation into cytotoxic T lymphocytes.
- Direct destruction of graft cells.
- A major effector of acute cellular rejection.

CD4+ T lymphocytes

- Predominantly cytokine-producing effector cells, especially Th1.
- Recruitment and activation of inflammatory cells.
- Contribution to graft inflammation and chronic remodeling.

B-cell alloimmunity generates donor-reactive antibody



- Alloantibodies can cause endothelial injury in acute and chronic rejection.

Two effector arms converge on graft injury

Cellular arm

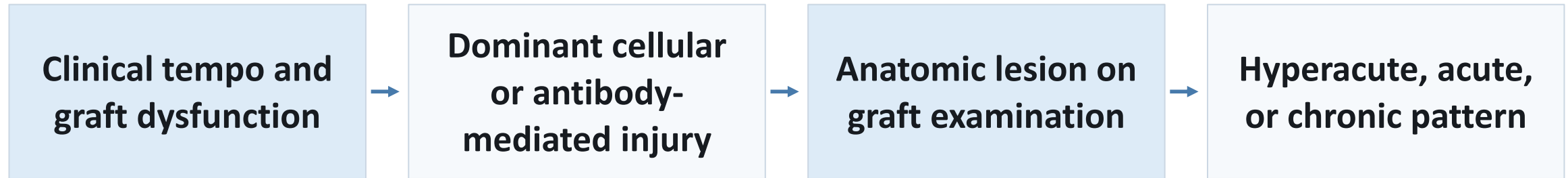
- CD8+ cytotoxic lymphocytes kill graft cells.
- CD4+ cells produce inflammatory cytokines.
- Interstitial and vascular cellular injury may follow.

Humoral arm

- Alloantibodies bind graft vascular antigens.
- Complement activation amplifies endothelial injury.
- Capillary injury and thrombosis may follow.

Both arms may operate in the same transplanted organ.

Classification links mechanism to pathologic pattern

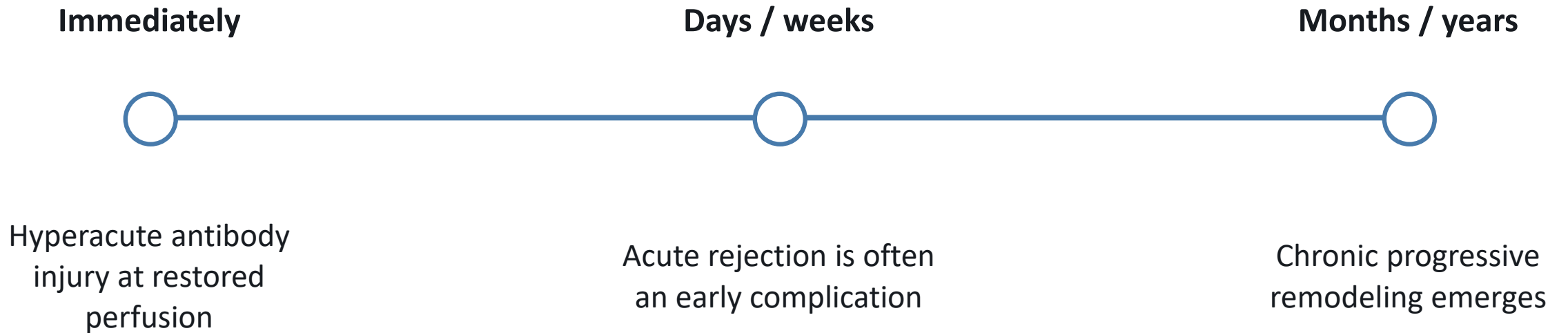


- This historical framework was developed chiefly from kidney allografts.

Three classic rejection patterns at a glance

Pattern	Typical tempo	Dominant mechanism	Major lesion
Hyperacute	At reperfusion / immediately	Preformed antibody	Thrombosis and ischemic necrosis
Acute	Days to weeks; sometimes later	T cells and/or antibodies	Tubulitis, arteritis, capillary injury
Chronic	Months to years	Chronic T-cell effects + alloantibodies	Vascular narrowing and fibrosis

Elapsed time helps, but does not define the mechanism



- Acute rejection can arise much later if immunosuppression is reduced or stopped.

The microvasculature is a recurrent target

- Circulating antibodies contact donor vascular endothelium immediately.
- Complement activation can injure endothelial surfaces.
- Vascular damage promotes thrombosis or long-term remodeling.
- Parenchymal dysfunction may therefore result from impaired perfusion.

Hyperacute rejection requires pre-existing antibody

Anti-blood-group antibody

- Naturally occurring IgM can recognize graft blood-group antigens.
- ABO incompatibility produces an immediate vascular target.

Anti-HLA alloantibody

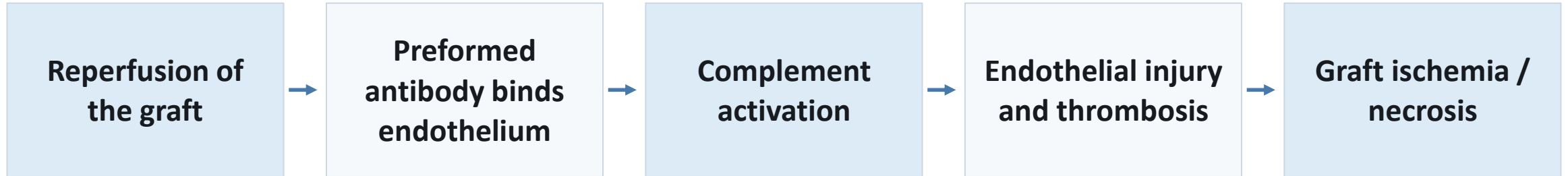
- Antibody can arise after exposure to allogeneic cells.
- Donor HLA on vascular cells becomes a target after reperfusion.

Prior exposure can sensitize a recipient



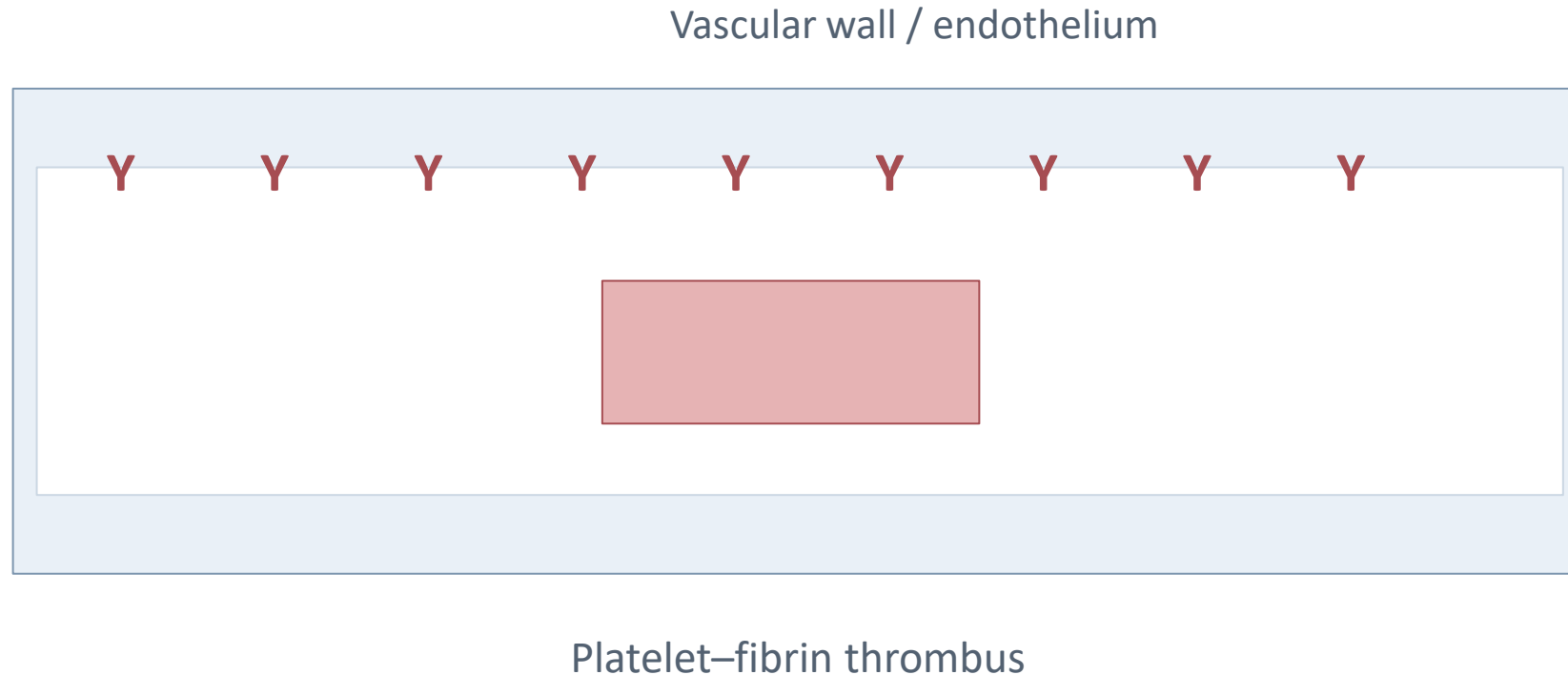
- Each exposure can introduce allogeneic cells and induce anti-HLA antibodies.
- Preformed anti-donor antibody changes risk at the next transplant.

Hyperacute injury begins when blood flow resumes



- The initiating antibody is present before implantation.

Antibody binding triggers vascular thrombosis



Antibody-endothelial binding activates complement.

Endothelial disruption promotes platelet-fibrin thrombi and ischemic damage.

Hyperacute rejection has a dramatic gross phenotype

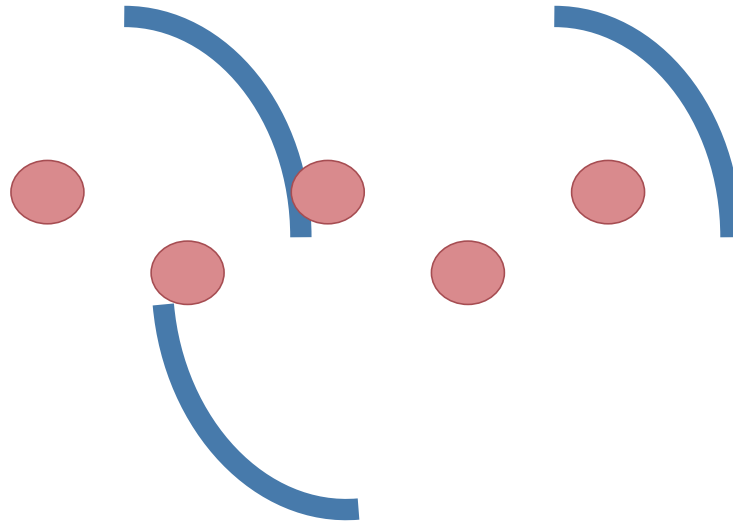
- The transplanted kidney rapidly becomes cyanotic and mottled.
- Perfusion failure is accompanied by abrupt loss of urine production.
- The injury begins almost immediately after implantation and reperfusion.
- Gross changes reflect widespread vascular occlusion and ischemia.

Small arteries show fibrinoid necrosis and occlusion

- Acute arterial and arteriolar wall injury may become fibrinoid.
- Platelet–fibrin thrombi narrow or obstruct vascular lumens.
- The vascular injury mechanism predicts rapid tissue ischemia.
- The lesion is not primarily a slow process of fibrosis.

Hyperacute glomerular injury is thrombotic

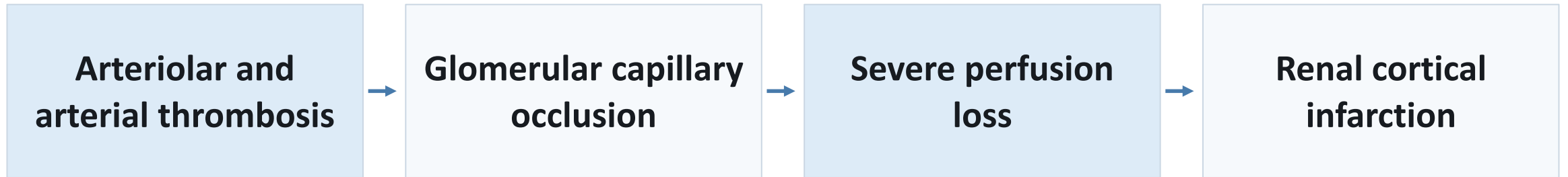
Schematic: Capillary loops (not histology)



Capillary thrombi

Glomerular capillaries may undergo thrombotic occlusion.
Neutrophils also accumulate in glomeruli and small graft vessels.

Ischemia progresses toward cortical infarction

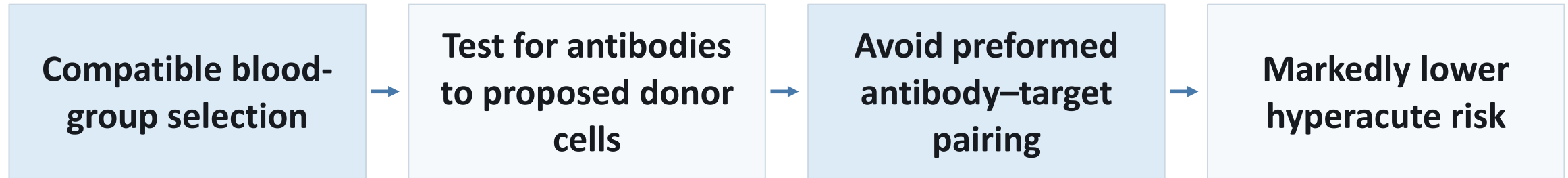


- Established hyperacute injury renders the graft nonfunctional.

Hyperacute injury is often irreversible

- Severe endothelial injury rapidly compromises essentially the entire graft.
- Diffuse thrombosis culminates in necrotic kidney cortex.
- An affected kidney as nonfunctional and requiring removal.
- Pretransplant antibody prevention is therefore essential.

ABO compatibility and crossmatch are preventive safeguards



- The textbook attributes rarity of hyperacute rejection to ABO matching and crossmatch screening.

Case: Immediate anuria following reperfusion

Clinical / pathologic vignette

A kidney becomes mottled and cyanotic almost as soon as vascular clamps are removed. Urine output ceases. The vascular lesions consist of extensive platelet–fibrin thrombi.

Most likely rejection pattern?

1. Hyperacute antibody-mediated rejection
2. Acute T-cell–mediated rejection
3. Chronic graft arteriosclerosis

Hyperacute pattern: Explain the discriminating evidence

- Immediate onset after restored perfusion is a defining temporal clue.
- Preformed anti-endothelial antibody explains rapid complement activation.
- Diffuse intravascular thrombi account for mottling and anuria.
- The central lesion is acute ischemic injury, not established intimal fibrosis.

Acute rejection may appear early or after later tapering

- Typical appearance: Days to weeks after transplantation.
- It is an important cause of early graft failure.
- A later episode can occur abruptly when immunosuppression is reduced or stopped.
- Time alone cannot exclude an acute immune lesion.

Acute rejection is mechanistically heterogeneous

Acute cellular rejection

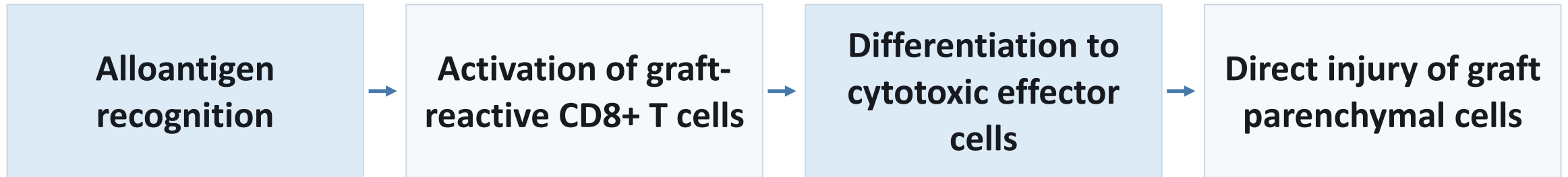
- Alloreactive CD8+ and CD4+ T lymphocytes.
- Direct parenchymal killing and inflammatory recruitment.
- Tubulointerstitial or vascular lesions.

Acute antibody-mediated rejection

- Antibodies reactive with vascular alloantigens.
- Classical complement activation.
- Glomerular and small-vessel injury.

Many rejecting grafts show more than one mechanism.

Cytotoxic T cells can directly injure graft cells



- CTL-mediated cell killing is part of acute T cell–mediated rejection.

CD4+ T cells amplify rejection through cytokines



- CD4+ cytokine effects and CD8+ direct killing as complementary mechanisms.

Acute cellular rejection has two morphologic patterns

Tubulointerstitial

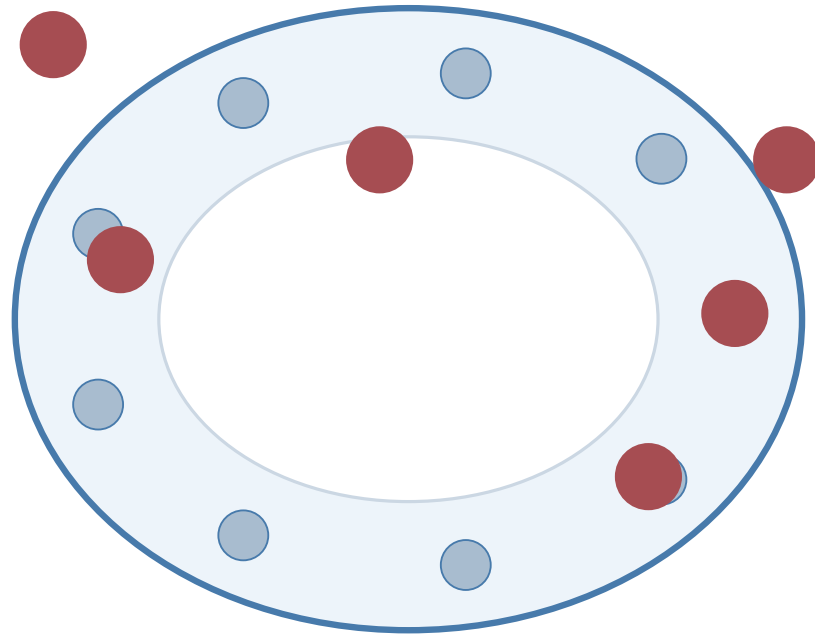
- Interstitial lymphocytic inflammation.
- Tubulitis: Inflammatory cells between tubular epithelial cells.
- Focal tubular cell injury.

Vascular

- Inflammation involving vessels.
- Swollen endothelium and lymphocytes in the intima.
- Sometimes vascular wall necrosis.

Tubulitis: Inflammatory cells within tubular epithelium

Schematic: Section of one renal tubule



Tubular epithelium

Lymphocytes within tubular epithelium

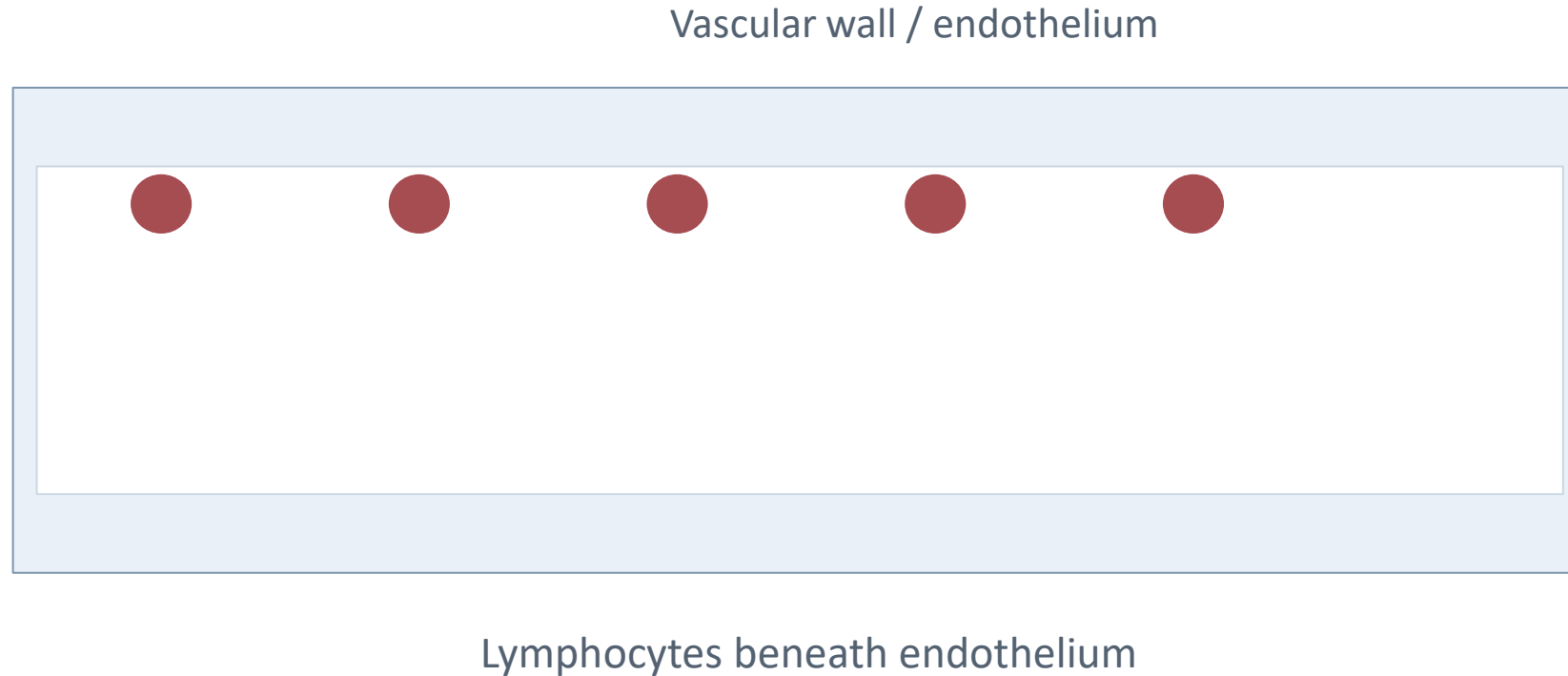
Tubulitis signifies lymphocytes entering and lying among epithelial cells of renal tubules.

Concurrent interstitial inflammation and tubular injury are typical.

Interstitial inflammation is T-cell rich

- Activated CD4+ and CD8+ T cells populate the interstitium.
- The infiltrate is accompanied by focal tubular injury.
- Inflammation outside tubules plus tubulitis defines the tubulointerstitial pattern.
- The finding is rooted in T cell–mediated cytotoxic and cytokine effects.

Intimal arteritis locates the immune attack in vessels



Lymphocytes are present between the vessel endothelium and the vessel wall.

Robbins also uses the term endotheliitis for this lesion.

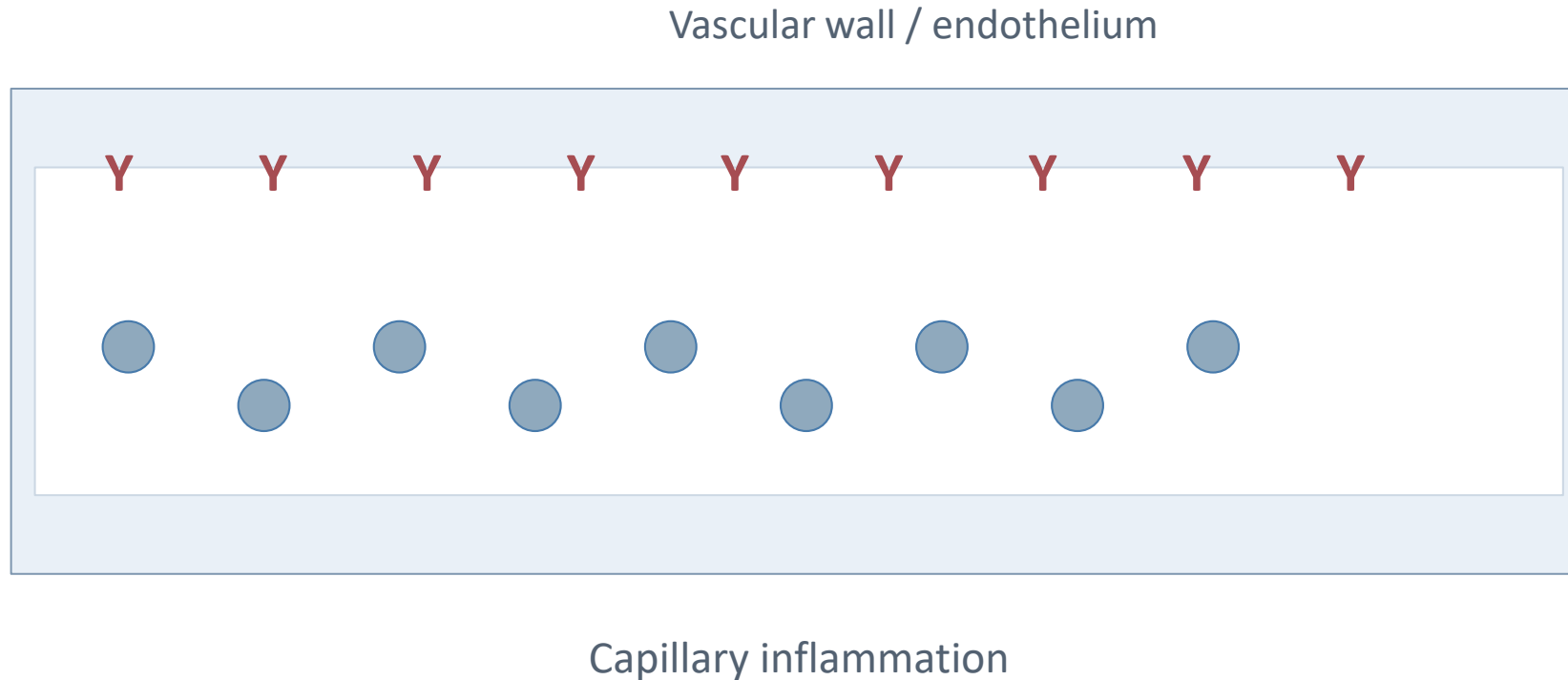
Vascular cellular rejection may damage vessel walls

- Vessel endothelium becomes swollen during immune attack.
- Lymphocytes may undermine or traverse the endothelial layer.
- Some lesions advance to necrosis of vessel walls.
- Recognition of this pattern distinguishes vascular injury from isolated tubular inflammation.

Why identifying cellular rejection matters clinically

- Acute cellular rejection is specifically susceptible to T-cell-directed immunosuppression.
- Many cases without concomitant humoral rejection respond well.
- An antibody-mediated component changes the mechanistic interpretation.
- Recognition of both patterns is important for therapeutic planning.

Acute humoral rejection begins on the endothelium



Antibodies bind the vascular endothelium and activate complement via the classical pathway.

The result is vascular inflammation and endothelial injury.

Classical complement activation leaves a C4d footprint



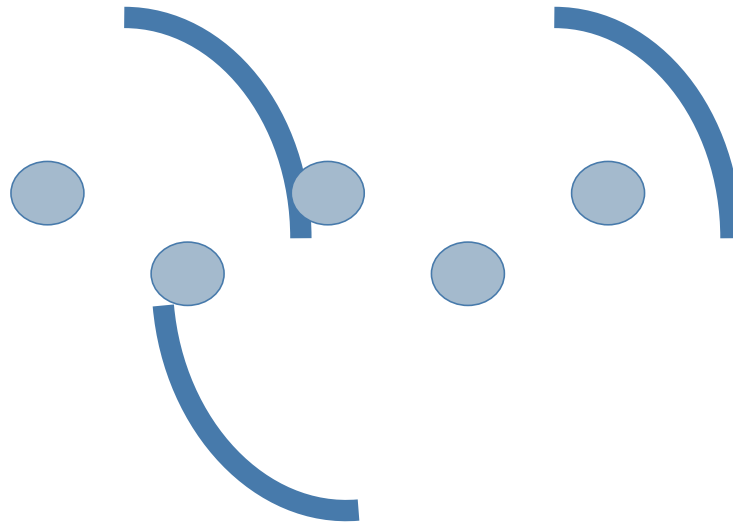
- C4d deposition is described in glomerular and peritubular capillary locations.
- This is a mechanistic marker, not a standalone classification algorithm.

Antibody-mediated injury centers on capillaries

- Glomerular inflammation is a typical feature.
- Peritubular capillaries may show inflammatory cell accumulation.
- Complement products, including C4d, may deposit in affected sites.
- Small-vessel thrombosis can accompany the capillary lesion.

Glomerulitis represents intraglomerular inflammation

Schematic: Capillary loops (not histology)



Glomerular capillary inflammation

Glomerular inflammation as a characteristic of acute antibody-mediated rejection.
The schematic depicts involvement of small capillary structures without simulating microscopy.

Peritubular capillaritis signals microvascular injury

- Peritubular capillaries are a second major site of humoral graft injury.
- Inflammatory accumulation follows antibody- and complement-related endothelial activation.
- Associated capillary C4d deposition supports complement engagement.
- Interpret capillary inflammation together with the overall graft pattern.

A vascular thrombus can also occur in acute humoral injury

- Antibody-mediated endothelial injury is not limited to leukocyte accumulation.
- Small vessels may develop focal thrombi.
- Compared with hyperacute rejection, the setting need not involve preformed antibody at immediate reperfusion.
- The same vascular target can yield a different clinical tempo.

Cellular versus humoral acute rejection: Tissue clues

Finding	T cell–mediated	Antibody-mediated
Tubulitis	Characteristic	Not emphasized as primary lesion
Intimal arteritis	Characteristic vascular pattern	Vascular injury may coexist
Glomerular / peritubular capillaritis	Not defining pattern in this account	Characteristic microvascular pattern
C4d deposits	Not a central mechanistic feature	Reflect classical complement activation
Predominant target	Parenchyma and vessels	Glomeruli and small vessels

Mixed rejection is common

- Cellular and antibody-mediated injury are separate explanatory categories.
- Most rejecting grafts may exhibit both patterns.
- A biopsy can therefore include tubular, vascular, and capillary abnormalities.
- Do not presume a single effector pathway explains every lesion.

Case: Tubulitis with intimal lymphocytes

Clinical / pathologic vignette

Several weeks after kidney transplantation, graft dysfunction develops. A biopsy shows interstitial T-cell infiltrates, lymphocytes between tubular epithelial cells, and lymphocytes beneath arterial endothelium.

Which mechanism dominates?

1. Acute T-cell–mediated rejection
2. Hyperacute preformed-antibody rejection
3. Chronic rejection alone

Case explanation: Two cellular compartments

- Tubulitis demonstrates direct inflammatory involvement of tubular epithelium.
- Intimal lymphocytes identify the vascular form of cellular rejection.
- The coexistence of both lesions is compatible with acute T-cell–mediated rejection.
- Additional evidence would be needed to characterize any simultaneous humoral lesion.

Case: Capillary inflammation with C4d

Clinical / pathologic vignette

A renal allograft biopsy shows inflammation of glomeruli and peritubular capillaries. Complement-product deposition, including C4d, is demonstrated in the microvasculature.

Which effector pathway is suggested?

1. Antibody with classical complement activation
2. Exclusive CTL-mediated tubular injury
3. Only chronic smooth-muscle proliferation

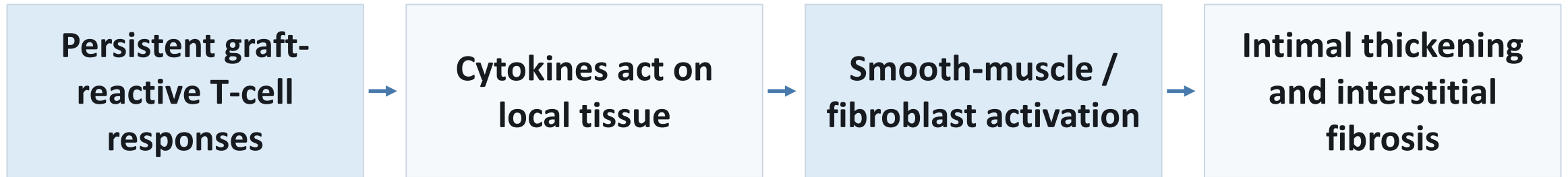
Case explanation: Link C4d to the mechanism

- Glomerular and peritubular capillary injury identify the microvascular compartment.
- C4d deposition is consistent with activation of the classical complement pathway.
- The combination is characteristic of acute antibody-mediated injury.
- Complement deposition should be interpreted with the morphologic setting.

Chronic rejection is progressive, not explosive

- Graft dysfunction evolves insidiously over months or years.
- The principal pathologic themes are vascular narrowing and parenchymal scarring.
- Both T-cell effects and alloantibodies are implicated.
- The injury becomes increasingly resistant to reversal with therapy.

Chronic T-cell cytokines drive structural remodeling



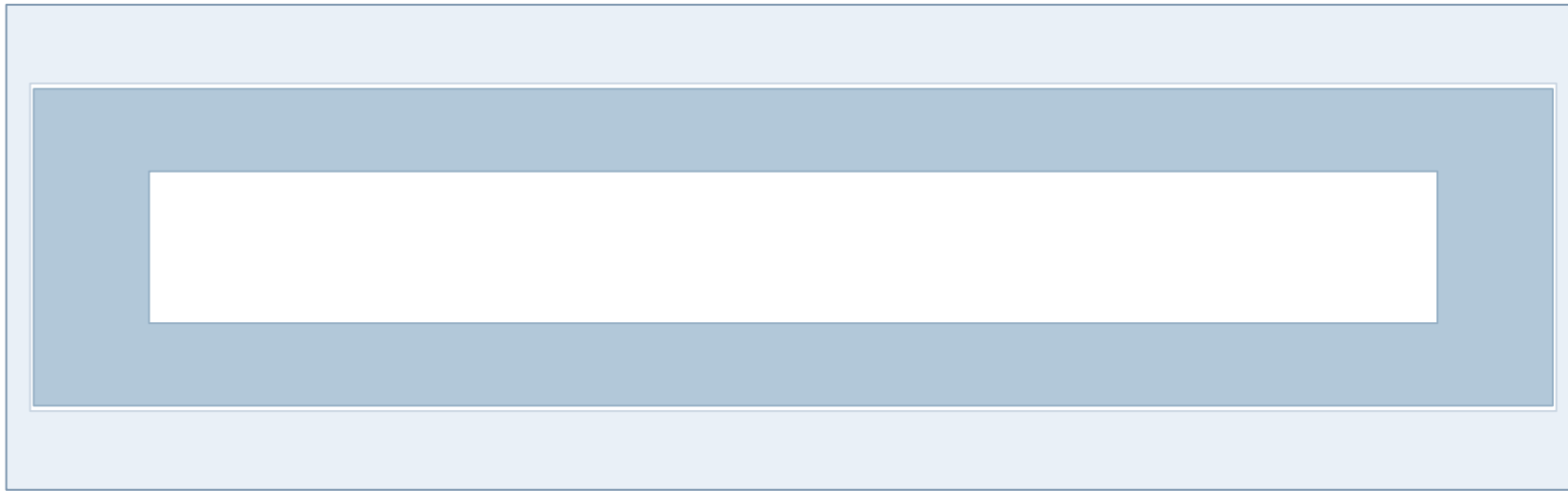
- These cells are believed to be key drivers; This is not an exclusive mechanism.

Alloantibodies also contribute to chronic rejection

- The chronic lesion is not explained by T lymphocytes alone.
- Donor-reactive antibody may sustain vascular endothelial injury.
- Repeated endothelial damage helps account for chronic glomerular changes.
- The result is cumulative microvascular and parenchymal remodeling.

Graft arteriosclerosis progressively narrows the lumen

Vascular wall / endothelium

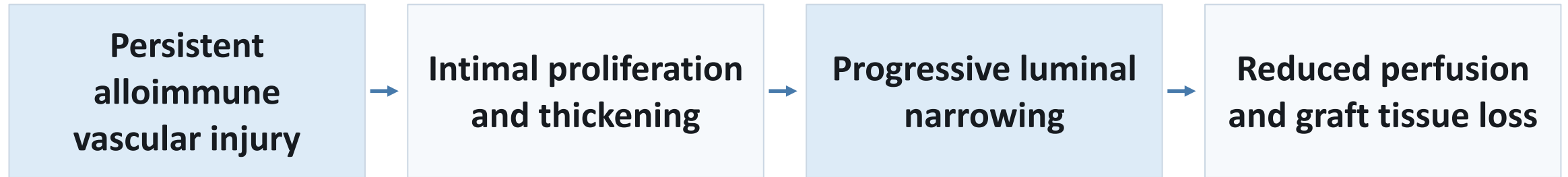


Intimal thickening narrows the lumen

Intimal thickening progressively reduces available lumen diameter.

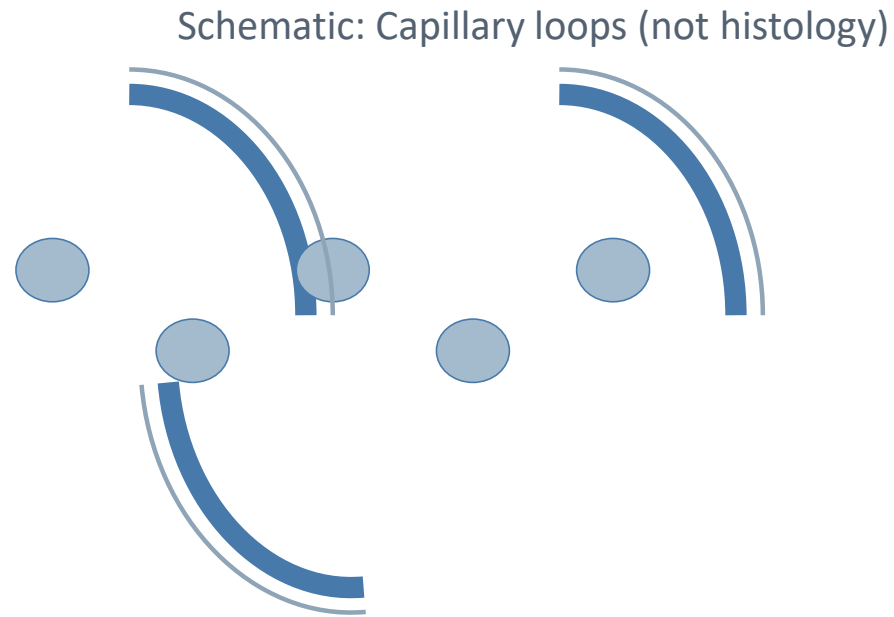
This native vector diagram is schematic, not a specimen image.

Chronic vascular narrowing links immunity to ischemia



- Structural vascular changes help explain chronic parenchymal atrophy and fibrosis.

Transplant glomerulopathy involves basement-membrane duplication



Duplication of capillary basement membranes

Chronically rejecting kidney grafts can develop duplication of glomerular basement membranes.

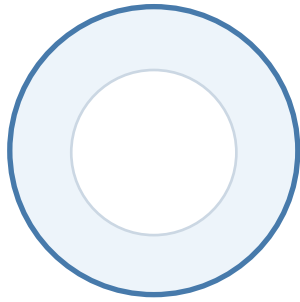
Robbins relates this finding to chronic endothelial injury.

Peritubular capillary basement membranes also remodel

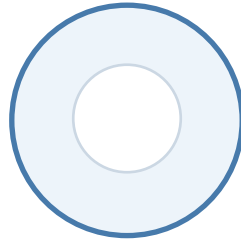
- Chronic capillary damage may lead to multilayered basement membranes.
- Peritubular capillaritis can accompany this microvascular remodeling.
- The lesion fits the broader theme of repeated endothelial injury.
- It differs from immediate thrombotic occlusion of hyperacute rejection.

Tubular atrophy and interstitial fibrosis replace parenchyma

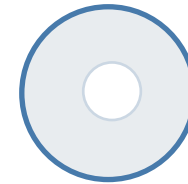
Schematic: Relative tubular atrophy



Preserved tubule



Atrophic tubule



Marked atrophy

Interstitial fibrous matrix replaces functioning parenchyma

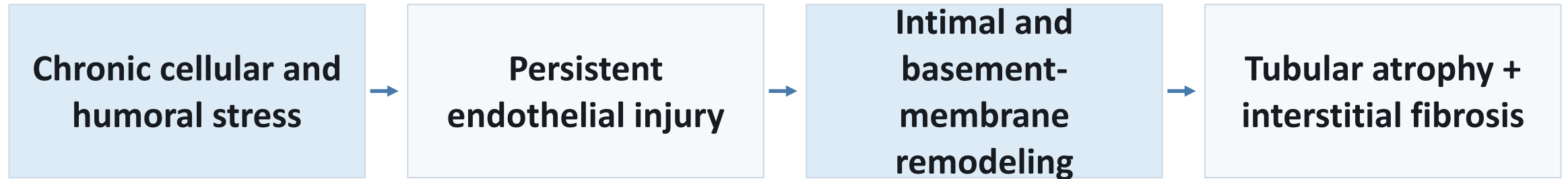
Chronic kidney allografts develop tubular atrophy with interstitial fibrosis.

These changes may occur secondary to vascular lesions and parenchymal loss.

Chronic rejection may contain little visible inflammation

- Interstitial mononuclear infiltrates are often sparse in chronic rejection.
- Established scarring and vascular remodeling can dominate the biopsy.
- Sparse inflammation does not exclude a prior or ongoing immune contribution.
- Pathologic interpretation must assess structural damage as well as leukocyte density.

Chronic pathology is the cumulative outcome of injury



- This is a conceptual synthesis of Robbins morphology, not a validated clinical scoring pathway.

Chronic rejection: Major tissue compartments

Compartment	Prominent change	Pathogenetic implication
Arteries	Intimal thickening / occlusion	Long-standing vascular remodeling
Glomeruli	Basement-membrane duplication	Chronic endothelial injury
Peritubular capillaries	Capillaritis; BM multilayering	Sustained capillary damage
Tubules / interstitium	Atrophy and fibrosis	Progressive parenchymal loss

Chronic rejection is difficult to reverse

- Control of acute rejection has improved early transplant outcomes.
- Chronic rejection remains refractory to most available therapies.
- The lesion consists substantially of fixed vascular and fibrotic remodeling.
- It is an increasingly important cause of late graft failure.

Case: Slowly progressive graft dysfunction

Clinical / pathologic vignette

Several years after kidney transplantation, graft function gradually declines. A biopsy demonstrates diffuse intimal thickening, duplication of glomerular basement membranes, interstitial fibrosis, and tubular atrophy.

Most consistent pattern?

1. Chronic allograft rejection
2. Hyperacute rejection
3. Isolated acute tubulitis

Case explanation: Structural injury predominates

- Gradual deterioration over years is consistent with chronic rejection.
- Intimal thickening identifies graft arteriosclerosis.
- Glomerular basement-membrane duplication suggests chronic endothelial injury.
- Fibrosis and tubular atrophy account for progressive nephron loss.

Anatomical localization sharpens interpretation

Dominant site	Principal lesion	Mechanistic association
Renal tubules	Tubulitis	Acute T-cell effect
Arterial intima	Endotheliitis / intimal arteritis	Acute cellular vascular injury
Glomerular / peritubular capillaries	Capillaritis with C4d	Acute antibody + complement
Small-vessel lumen	Thrombi at reperfusion	Hyperacute antibody injury
Vessel wall and interstitium	Intimal thickening + fibrosis	Chronic remodeling

The same vascular target produces distinct patterns

Immediately

- Preformed antibody.
- Complement, widespread thrombi.
- Severe ischemic necrosis.

Acute episode

- Graft-reactive antibody and/or T cells.
- Capillaritis or intimal arteritis.
- Potentially reversible inflammation.

Long term

- Ongoing cellular and antibody effects.
- Intimal thickening; Basement-membrane remodeling.
- Progressive fibrosis.

Morphology is interpreted with mechanism and tempo

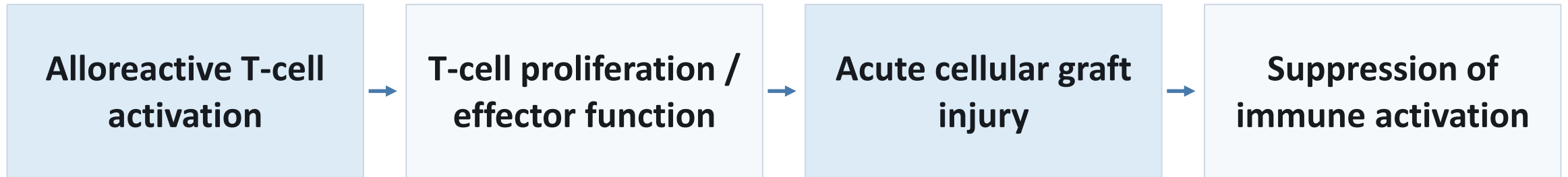


- This is an educational approach—not a substitute for contemporary organ-specific diagnostic criteria.

Organ effects vary; The immune principles recur

- Detailed rejection morphology primarily for the kidney.
- Allografts of heart, lungs, liver, and pancreas also experience rejection.
- Cellular attack, endothelial antibody injury, and chronic remodeling are broad mechanisms.
- Organ-specific lesion definitions require organ-specific reference material.

Immunosuppression preferentially limits acute T-cell responses



- Current drugs are described as principally designed to reduce acute rejection by limiting T-cell responses.

Calcineurin blockade interrupts T-cell cytokine signaling



- Tacrolimus and cyclosporine inhibit calcineurin, reducing NFAT-dependent T-cell activation.
- This is a simplified explanation from the adjacent graft-survival section.

Graft protection requires balancing immune suppression

Prevent rejection

- HLA matching can benefit kidney grafts.
- Immunosuppressive agents suppress alloreactive responses.
- Additional therapies target antibody-mediated injury.

Recognize tradeoffs

- Susceptibility to opportunistic infection rises.
- Viral reactivation can damage a transplant.
- Risk of some malignancies also increases.

These are implications from the adjacent Robbins section on graft survival.

Three mechanism–morphology chains to retain

Rejection pattern	Immune initiating event	Diagnostic tissue consequence
Hyperacute	Preformed antibody + complement	Thrombosis → infarction
Acute cellular	Activated CD8+/CD4+ cells	Tubulitis / arteritis
Acute humoral	Endothelial alloantibody + complement	Glomerulitis / capillaritis ± C4d
Chronic	Persistent cellular and antibody injury	Arteriosclerosis / fibrosis

Apply the framework: Three contrasting presentations

At reperfusion

- Pre-existing antibody.
- Thrombi in small vessels.
- Abrupt graft failure.

Weeks after grafting

- Tubulitis or microvascular inflammation.
- T-cell and/or antibody effects.
- Potential for treatment response.

Years after grafting

- Intimal narrowing and glomerular remodeling.
- Interstitial fibrosis and atrophy.
- Progressive loss of function.

Summary: Immunologic mechanism predicts the lesion

- Preformed antibody → complement and thrombosis → hyperacute ischemic necrosis.
- T cells → tubulitis and/or arteritis → acute cellular rejection.
- Alloantibody → complement and capillary injury → acute humoral rejection.
- Persistent alloimmune injury → vascular remodeling and fibrosis → chronic rejection.

Primary reference and scope

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

- Chapter 6: Diseases of the Immune System.
- Primary teaching section: Patterns and Mechanisms of Graft Rejection.
- Parent context: mechanisms of allograft recognition; adjacent section: graft-survival strategies.
- Morphology is presented for renal allografts; schematic illustrations are not diagnostic photomicrographs.