

ATYPICAL HEMOLYTIC UREMIC SYNDROME

Nonepidemic / “diarrhea-negative” HUS

Mechanisms • Renal vascular morphology • Clinicopathologic differentiation

Dr Abu Suraih Sakhri

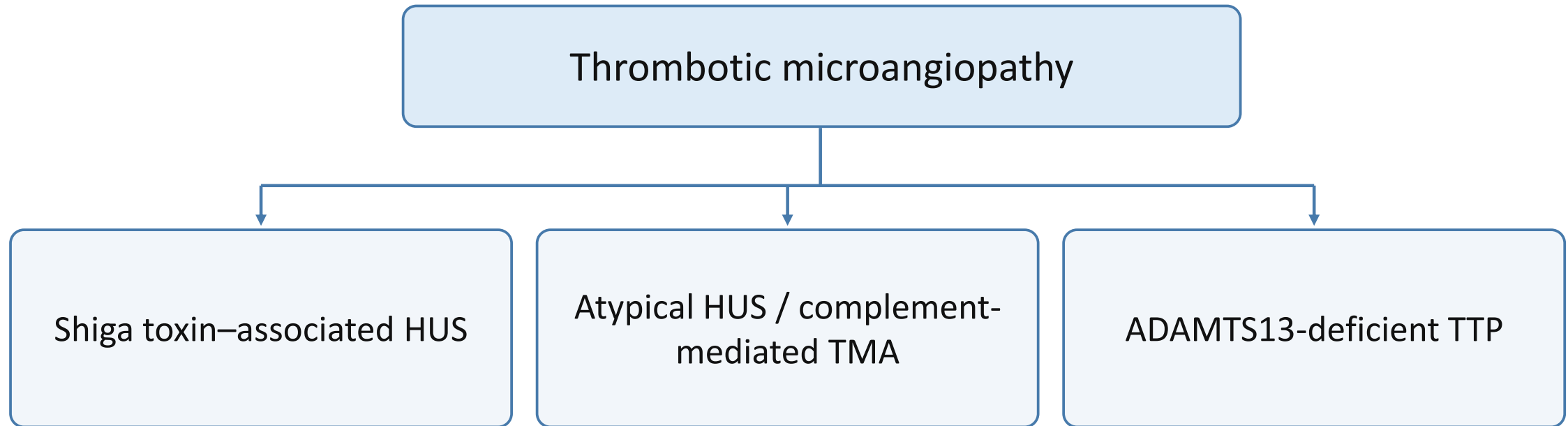
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain the TMA phenotype and locate atypical HUS within its major causal groups.
- Connect impaired complement regulation to glomerular endothelial injury and thrombosis.
- Distinguish acute thrombotic lesions from chronic ischemic remodeling.
- Compare aHUS with Shiga toxin-associated HUS and ADAMTS13-deficient TTP.

Atypical HUS belongs to the TMA spectrum

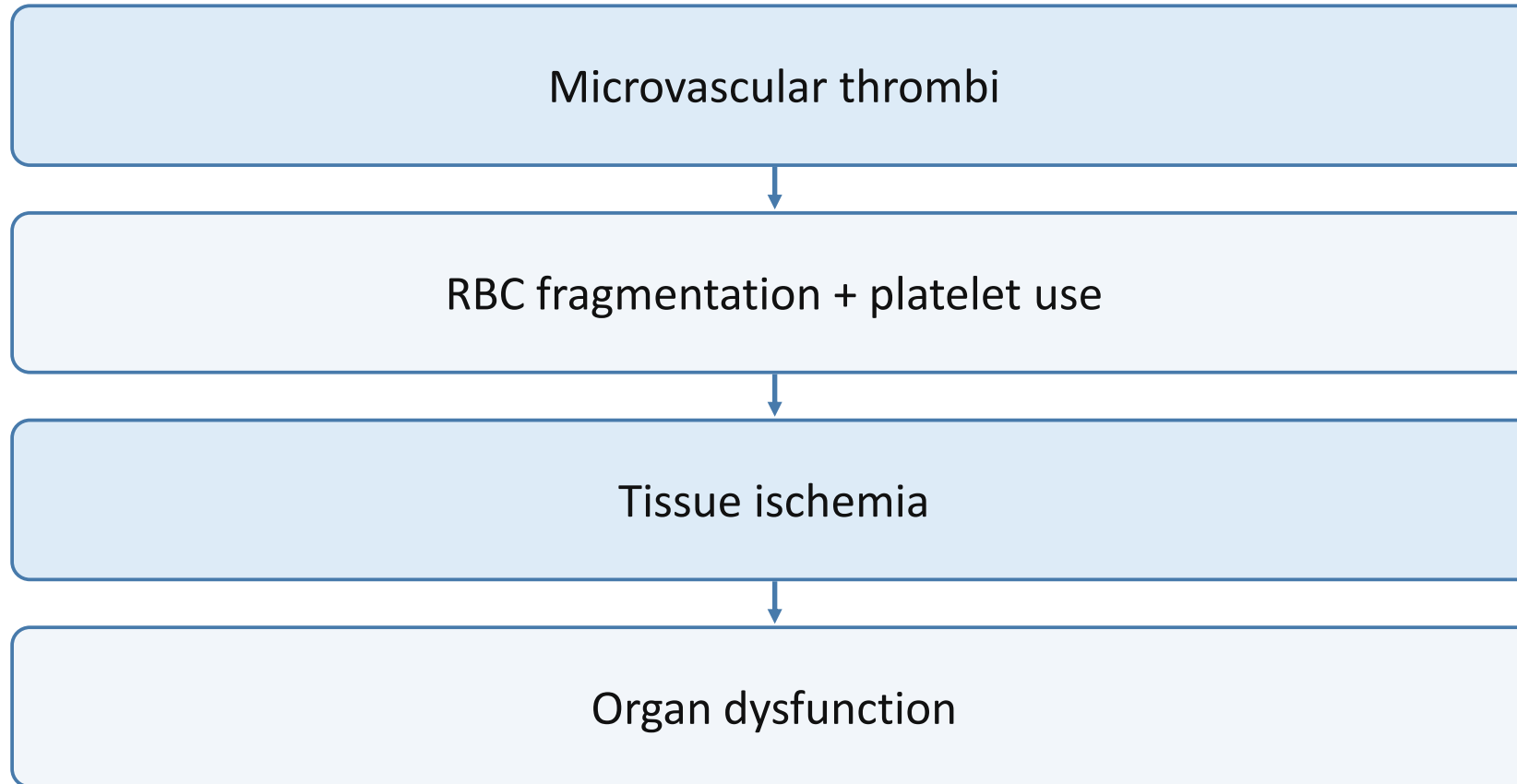


Shared lesions do not imply shared initiating mechanisms

TMA names a vascular injury pattern

- Thrombi form in capillaries and/or arterioles across susceptible organ beds.
- Tissue ischemia and organ dysfunction follow loss of microvascular perfusion.
- Red cell destruction and platelet consumption are linked consequences.
- TMA is a clinicopathologic pattern, not a single etiologic diagnosis.

Four linked consequences of microvascular thrombi



Parallel consequences of narrowed or occluded microvessels

Two dominant initiating routes in TMA

Endothelial injury

Central in HUS

Shiga-like toxin in typical HUS

Excess complement in inherited aHUS

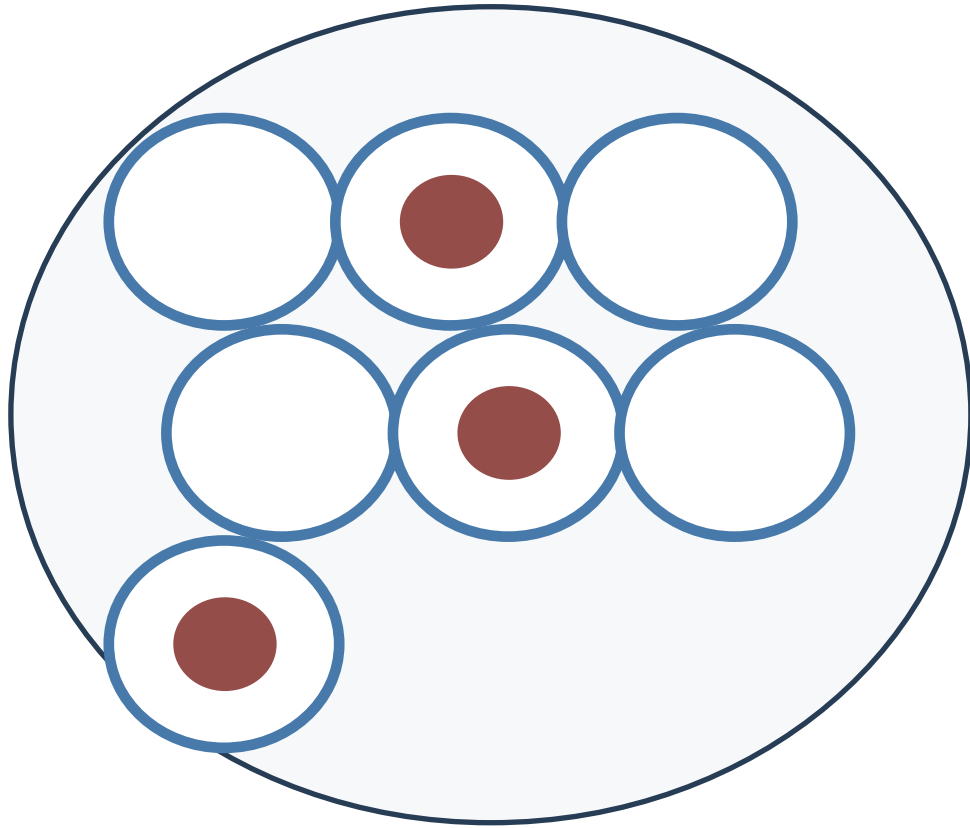
Platelet hyperactivation

Central in TTP

ADAMTS13 deficiency

Ultralarge vWF multimers persist

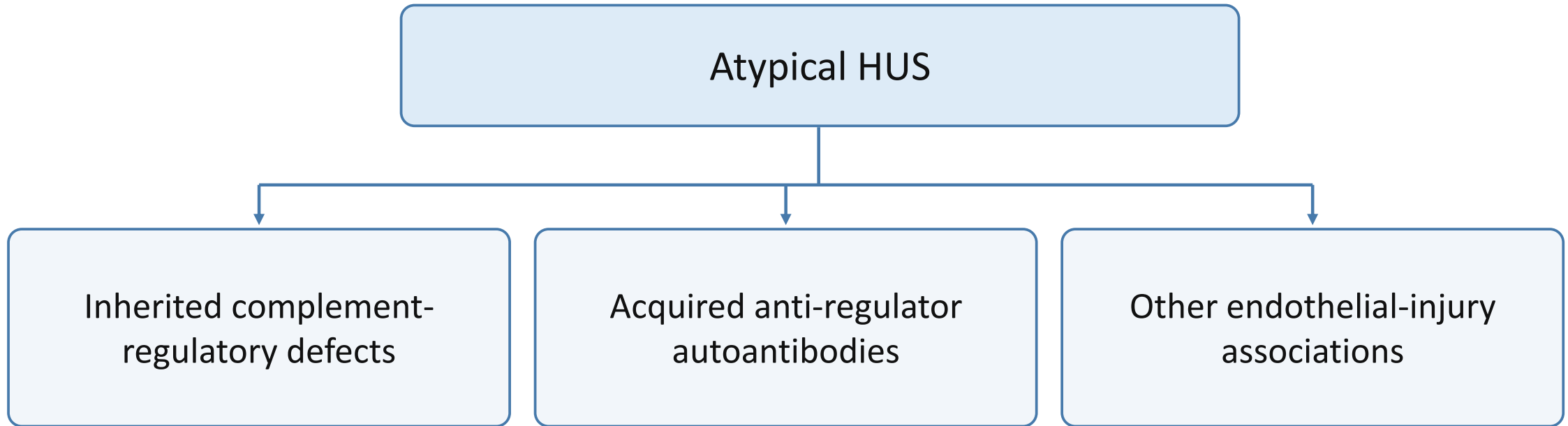
Why the renal microvasculature matters



- Glomerular capillary and arteriolar thrombi compromise cortical perfusion.
- Persistent or extensive vascular occlusion can produce cortical necrosis.
- Chronic injury leads to glomerular and vascular scarring.

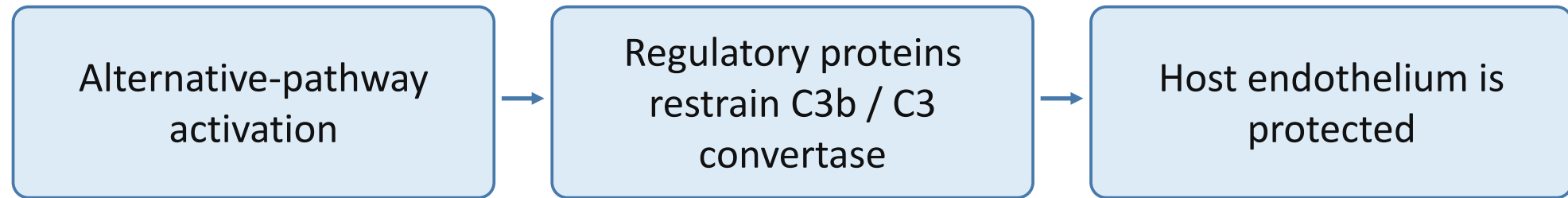
Schematic — not a histologic image

The “atypical HUS” label covers different settings



Mechanism and associated condition must be distinguished

Complement activation needs host-cell safeguards

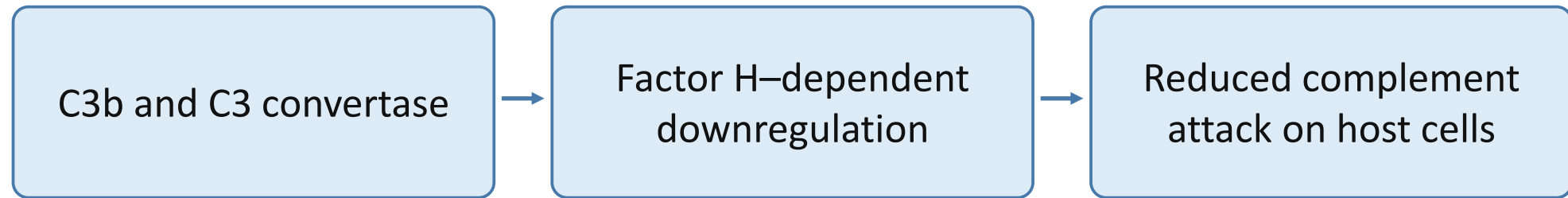


Regulation limits complement damage to normal tissue

Factor H protects cells from complement injury

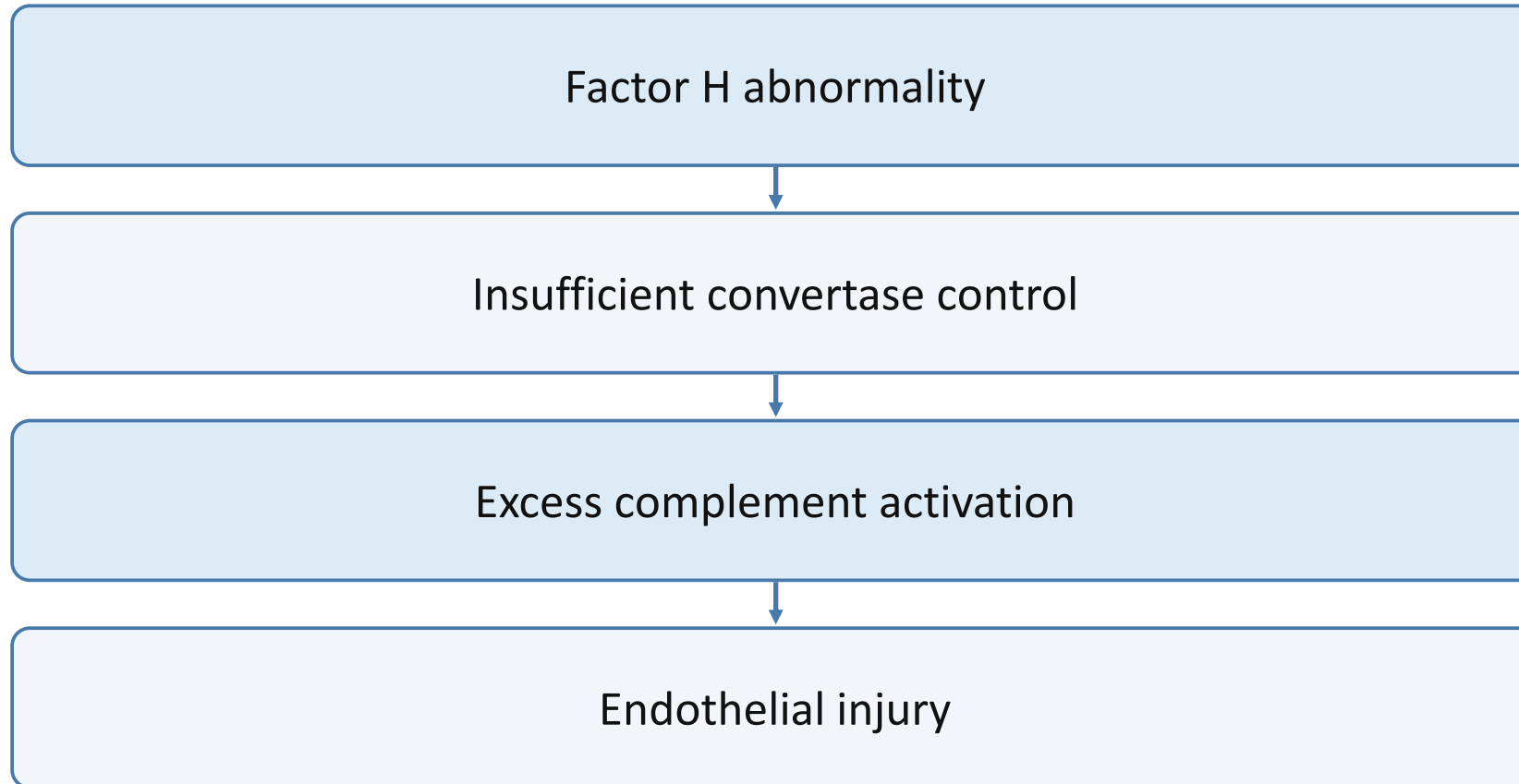
- Factor H is a circulating regulator of the alternative complement pathway.
- It promotes cleavage and destruction of C3b.
- It promotes turnover of C3 convertases, limiting continued activation.
- Defective Factor H regulation allows damage to host microvascular endothelium.

Factor H regulates the C3 amplification step



Factor H acts as a brake, not as an initiating complement trigger

Loss of Factor H function removes a vascular brake



Pathogenetic model described for complement-mediated HUS

Factor H is the most commonly cited regulator

- More than half of affected patients have identifiable complement-regulatory mutations in the cited textbook account.
- Factor H is the most common named regulator among those mutations.
- The mutation-based fraction is a textbook observation—not a diagnostic cut-off.
- Absence of an identified mutation does not negate the clinical TMA phenotype.

Factor I is another complement regulator

- Complement Factor I mutations among aHUS-associated defects.
- This broadens the mechanism beyond a single gene or protein.
- The shared downstream problem is inadequate restraint of complement activity.
- The renal lesion remains TMA rather than a Factor I–specific histology.

CD46 is a membrane-bound cofactor protein

- CD46 is also termed membrane cofactor protein.
- CD46 mutations among complement-regulatory defects in aHUS.
- The role of cell-associated regulators complements circulating regulators.
- Mutations converge on endothelial susceptibility to complement-mediated injury.

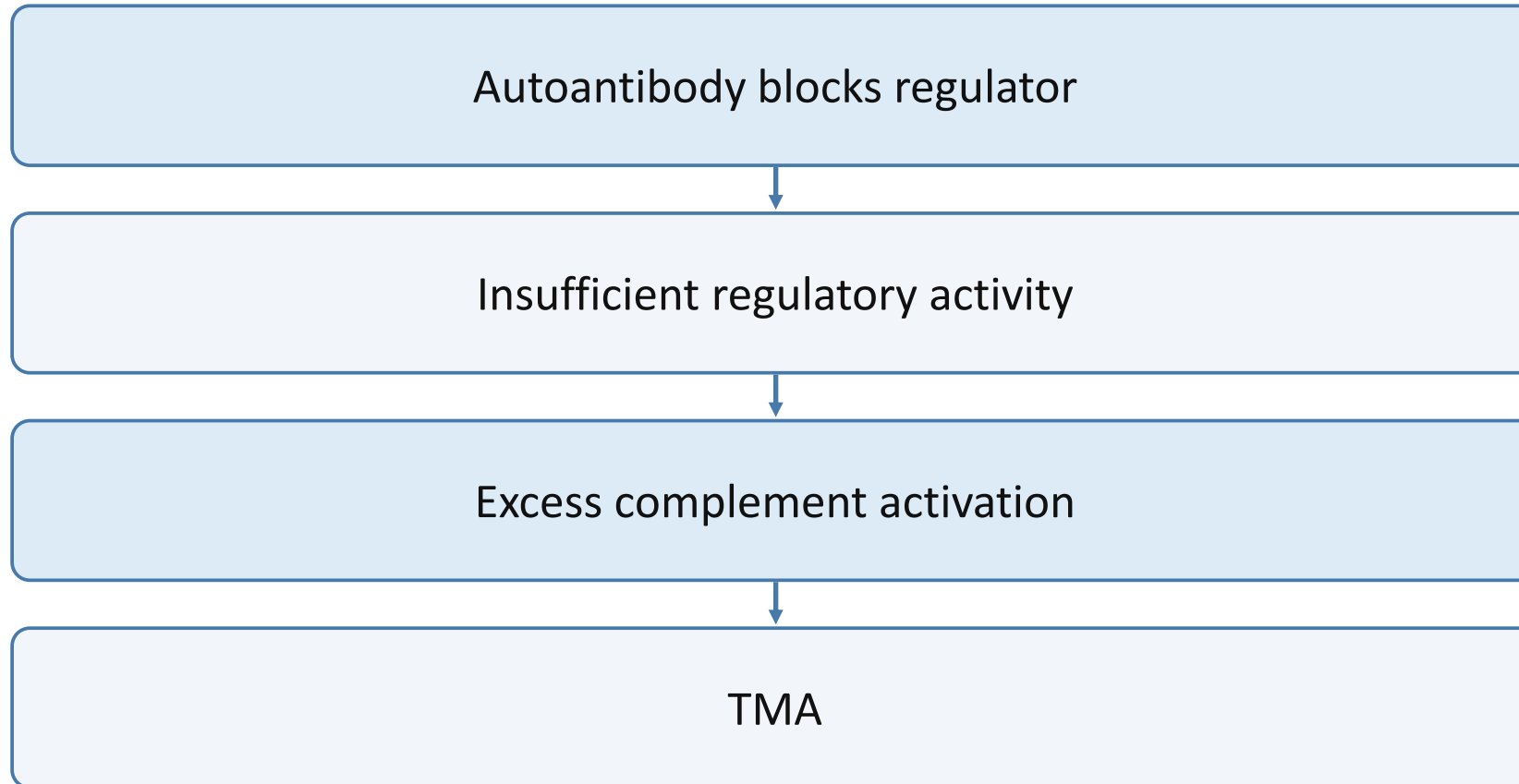
Three named regulators, one pathogenic theme

Regulator	Description in source	Disease relevance
Factor H	Circulating regulator; C3b/C3 convertase control	Most commonly cited mutation
Factor I	Complement regulatory protein	Mutations associated with aHUS
CD46	Membrane cofactor protein	Mutations associated with aHUS

Genetic architecture can modify disease onset

- Multiple complement-regulatory mutations may coexist in a patient.
- Multiple mutations with presentation at a younger age.
- The observation supports a cumulative vulnerability model.
- The source does not provide a penetrance estimate or an age threshold.

Acquired autoantibodies can mimic regulatory loss



An acquired mechanism can reproduce the downstream phenotype

Inherited and acquired mechanisms converge

Inherited

Mutation in regulatory protein

Examples: Factor H, Factor I, CD46

Mutations affect complement-regulatory proteins

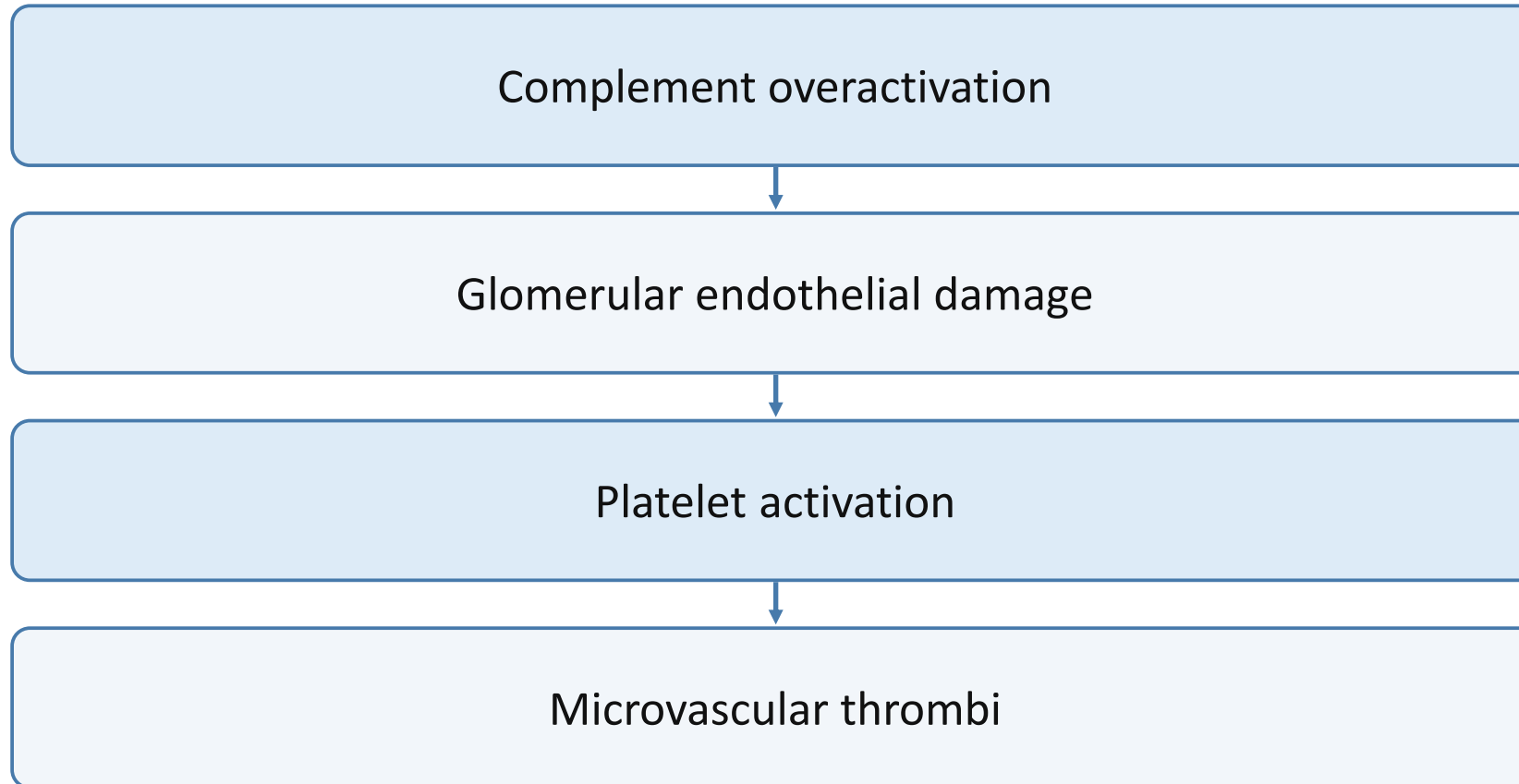
Acquired

Autoantibody blocks regulatory activity

Complement control becomes impaired

Similar downstream endothelial injury

Complement-mediated TMA is endothelial disease

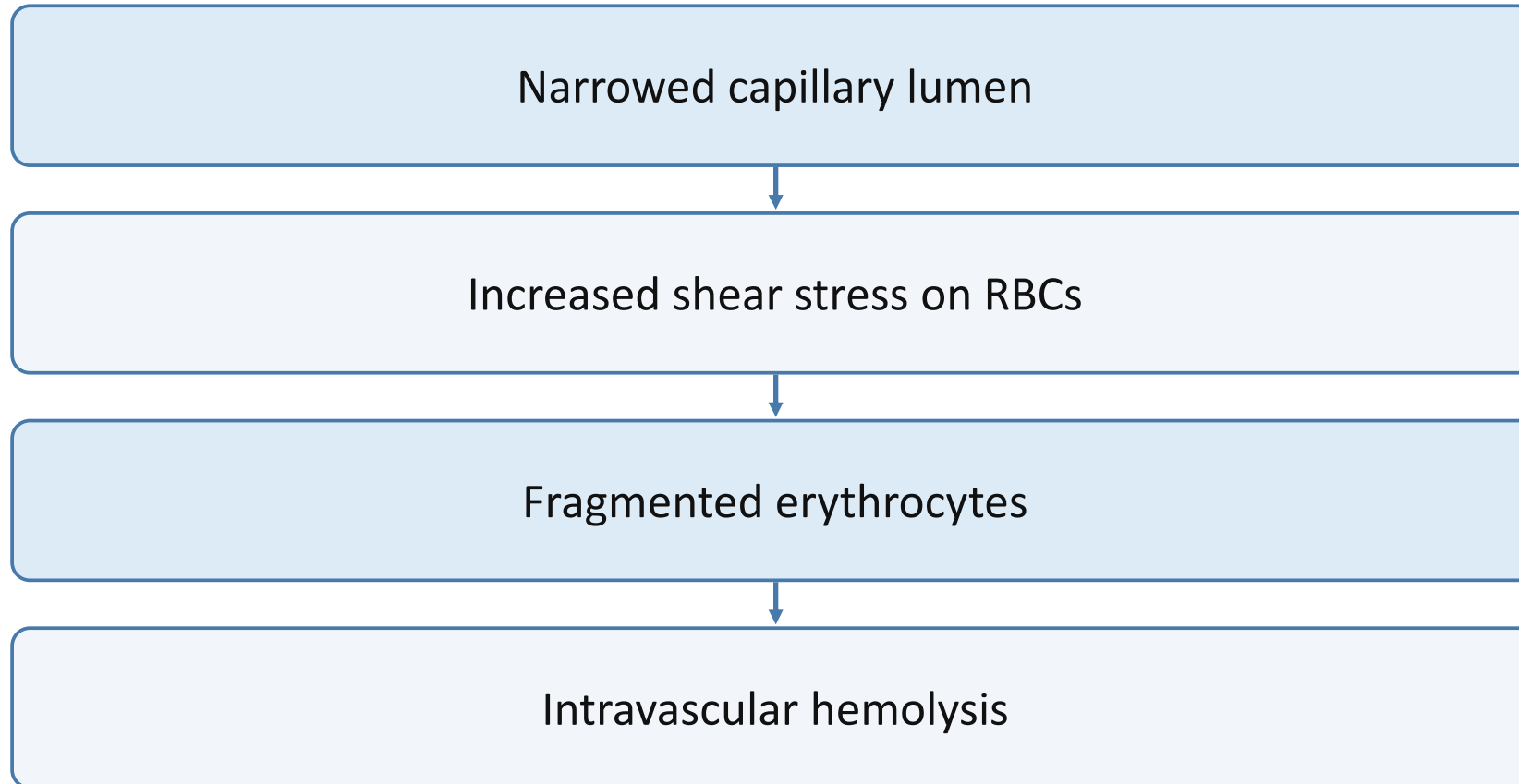


Mechanistic order: Complement dysregulation precedes the platelet-rich lesion

Endothelial injury shifts the vessel toward thrombosis

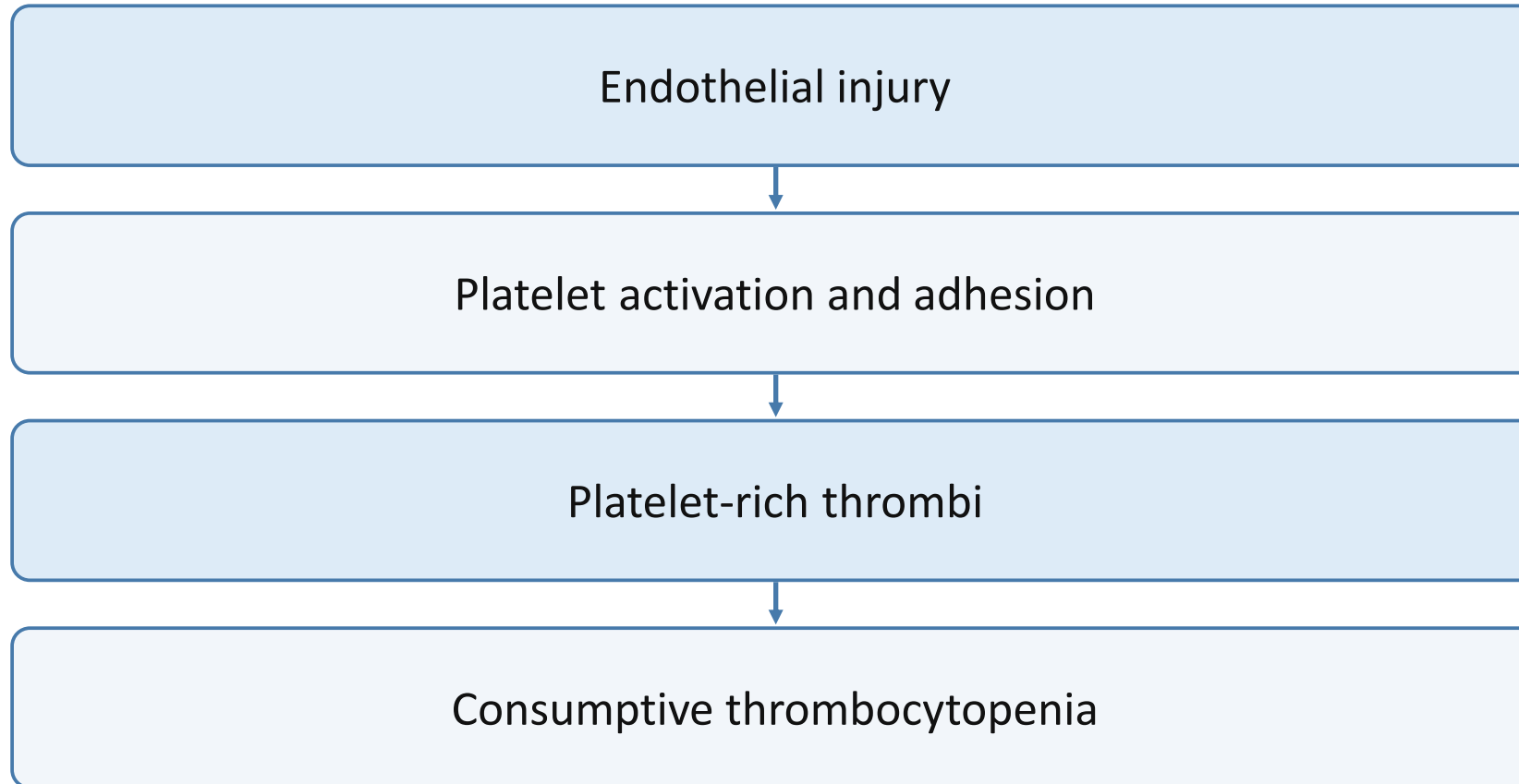
- In HUS, endothelial injury appears to be the primary initiating event.
- Damaged microvascular endothelium promotes platelet activation.
- Platelet-rich occlusion reduces glomerular capillary blood flow.
- Ultimately the clinical phenotype reflects the distribution and severity of thrombi.

Microthrombi mechanically fragment erythrocytes



Schistocytes are a blood-smear manifestation of mechanical red cell trauma

Why platelet counts fall



Consumption links vascular pathology to a systemic blood-count abnormality

One complement defect produces three clinical axes

Complement-mediated microvascular thrombosis

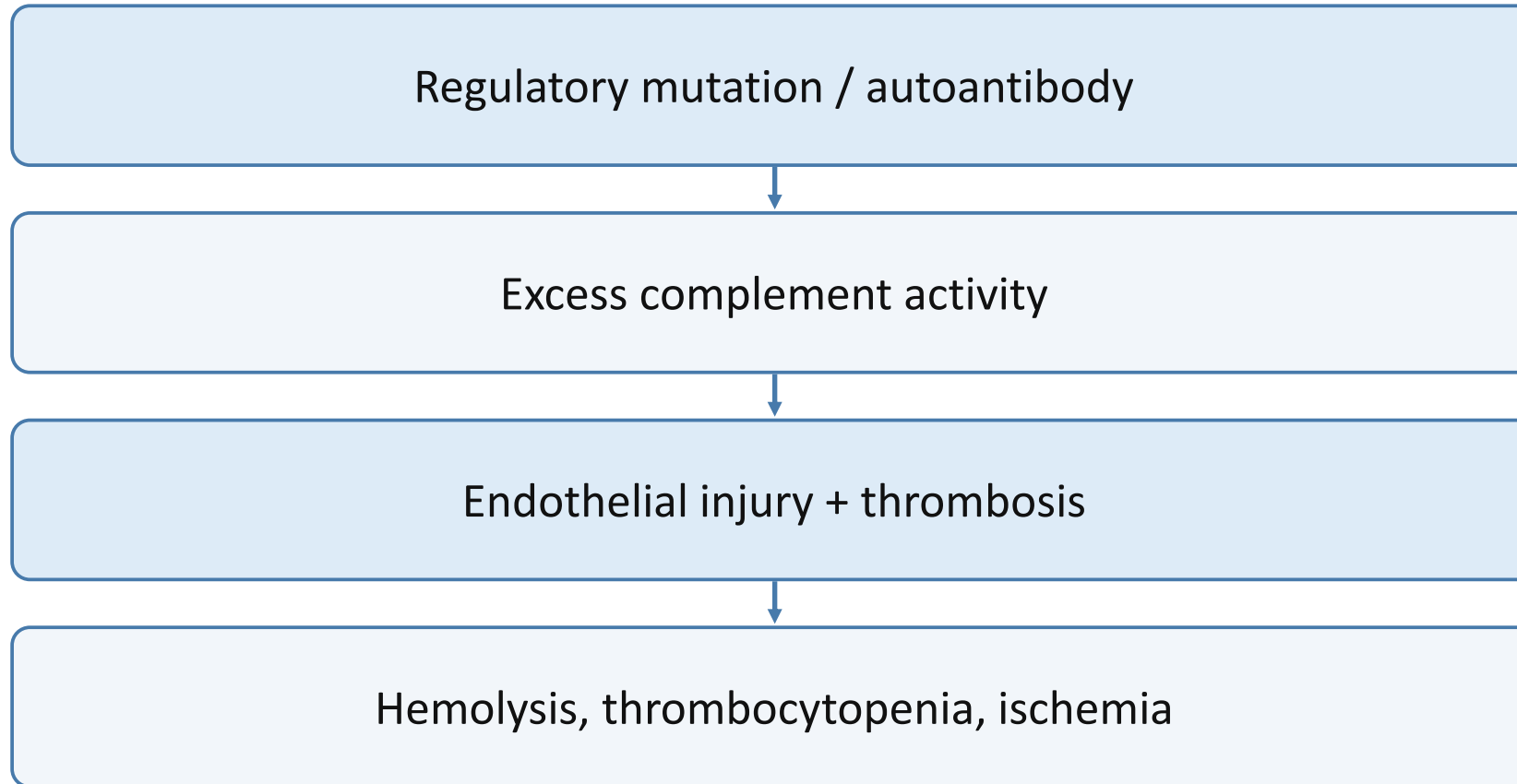
```
graph TD; A[Complement-mediated microvascular thrombosis] --> B[Hemolytic anemia]; A --> C[Thrombocytopenia]; A --> D[Renal dysfunction];
```

Hemolytic anemia

Thrombocytopenia

Renal dysfunction

The aHUS cascade: An integrated model



Original editable mechanism synthesis text

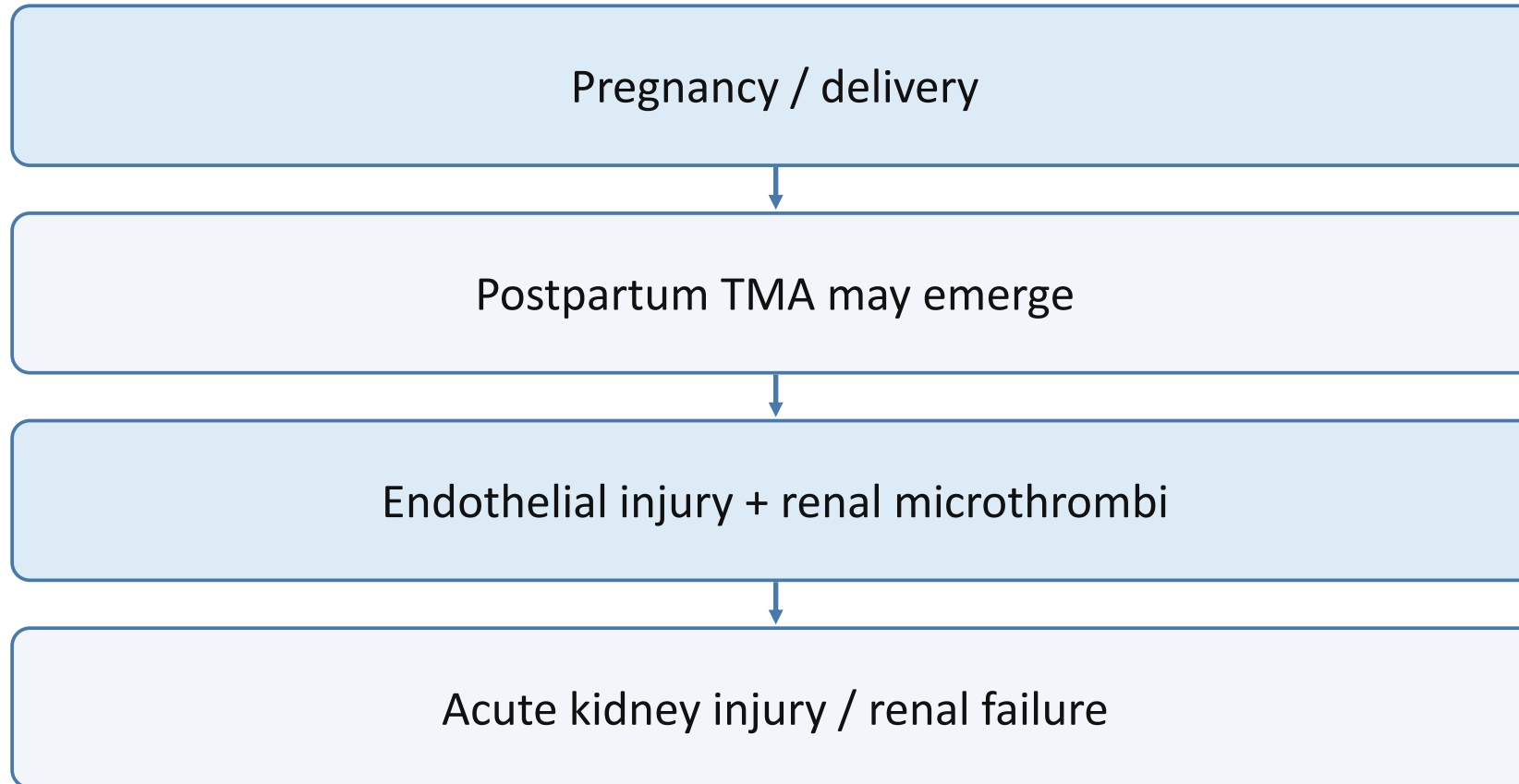
Not every aHUS association is a complement mutation

- Robbins also describes a group associated with heterogeneous conditions or exposures.
- Antiphospholipid syndrome is one named association.
- Pregnancy complications and postpartum renal failure are another setting.
- Vascular renal disease, including systemic sclerosis, is also implicated.

Antiphospholipid syndrome is an associated setting

- Antiphospholipid syndrome among conditions associated with aHUS.
- This belongs to the acquired endothelial-injury context of TMA.
- An aPL-associated TMA should not automatically be labeled a proven inherited complement disorder.
- Morphology alone cannot identify the causative association.

Pregnancy can precede a TMA presentation



Onset from one day to several months after delivery

Postpartum renal failure: Important uncertainty

- The underlying pathogenic mechanism is described as unclear.
- Some patients may carry a complement-regulatory mutation.
- A grave prognosis, although milder cases can recover.
- A pregnancy association does not by itself prove a complement gene defect.

Systemic sclerosis is a vascular renal association

- Systemic sclerosis is listed among vascular diseases affecting the kidney.
- The association is part of the heterogeneous acquired-injury group.
- Kidney microangiopathy may therefore be encountered outside primary regulator defects.
- The microscopic TMA lesion cannot establish systemic sclerosis by itself.

Other endothelial-injury contexts in the parent section

Associated setting	How it
Severe hypertension	Acquired endothelial injury associated with TMA
Chemotherapeutic or immunosuppressive drugs	Drug-associated endothelial injury
Radiation	An exposure associated with endothelial injury
Systemic sclerosis	Vascular disease affecting the kidney

Etiologic categories should not be conflated

Complement-dysregulated aHUS

Inherited regulatory mutations

Blocking anti-regulator antibodies

Complement is the primary described driver

Other associated TMAs

Pregnancy-associated injury

Antiphospholipid syndrome

Systemic sclerosis, drugs, radiation, etc.

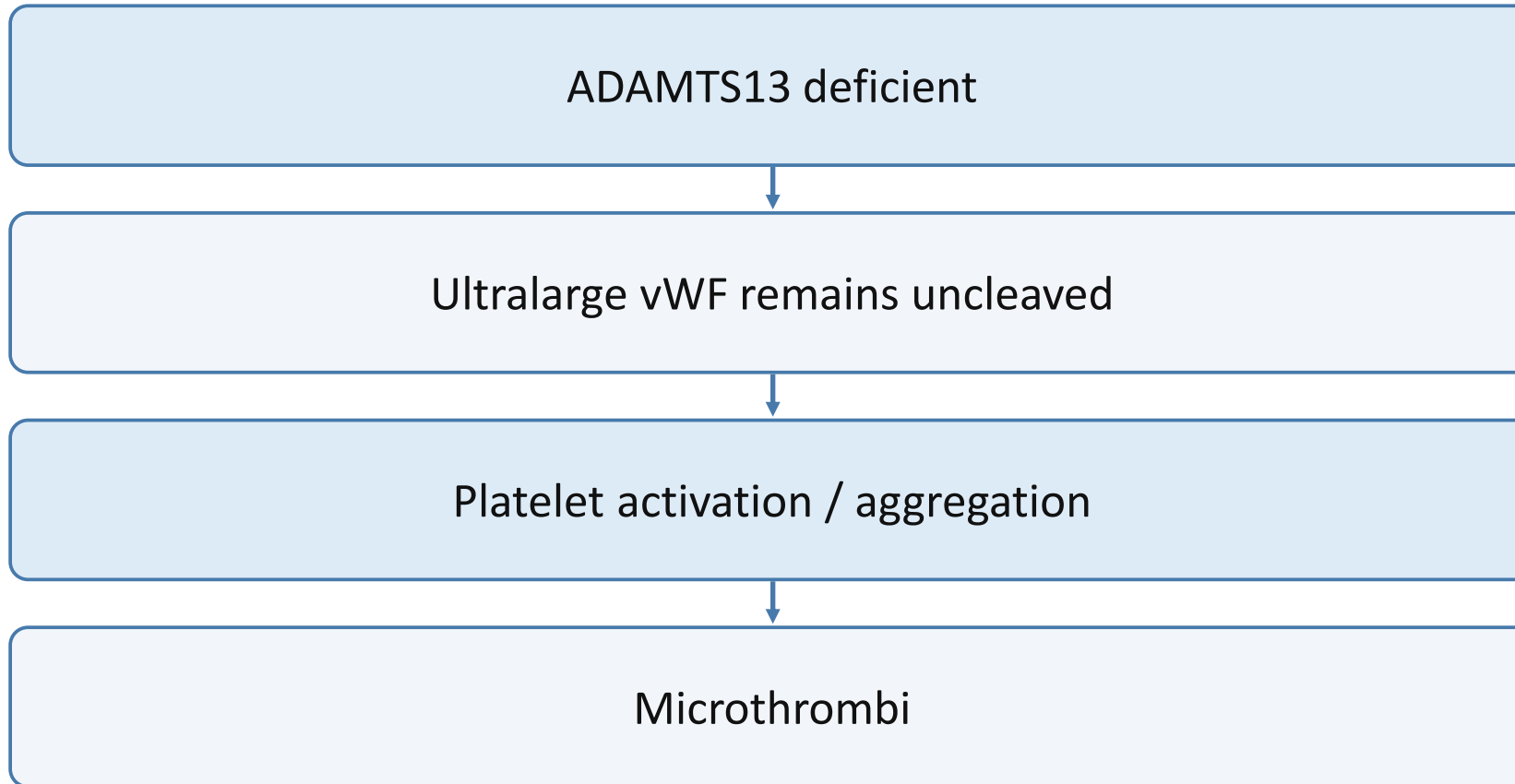
Typical HUS: A different initiating insult

- Most typical HUS cases follow Shiga-like toxin–producing intestinal infection.
- *Escherichia coli* O157:H7 is the most commonly named strain.
- *Shigella dysenteriae* may also cause a related syndrome.
- The toxin is linked to endothelial injury and platelet activation.

Typical HUS endothelial mechanism is not fully settled

- One proposed pathway involves endothelial activation and altered vasoactive signaling.
- Reduced nitric oxide and increased endothelin favor vasoconstriction.
- Cytokine context may contribute to endothelial apoptosis.
- Robbins explicitly acknowledges alternative mechanisms, including possible complement interaction.

TTP: ADAMTS13 deficiency drives platelet activation



Different initiating event; Overlap in TMA consequences

TTP can be acquired or inherited

- Inhibitory autoantibodies are the most common ADAMTS13-deficiency cause.
- Inherited inactivating ADAMTS13 mutations occur less commonly.
- The resulting ultralarge vWF multimers can activate platelets.
- This pathway is pathogenetically distinct from complement-mediated aHUS.

Compare the three principal TMA mechanisms

Syndrome	Initiating mechanism	Emphasis
Typical HUS	Shiga-like toxin–related endothelial injury	Renal involvement prominent
Atypical HUS	Complement-regulatory defect or other endothelial injury	Chronic renal injury common
TTP	ADAMTS13 deficiency → ultralarge vWF	Neurologic signs often dominate

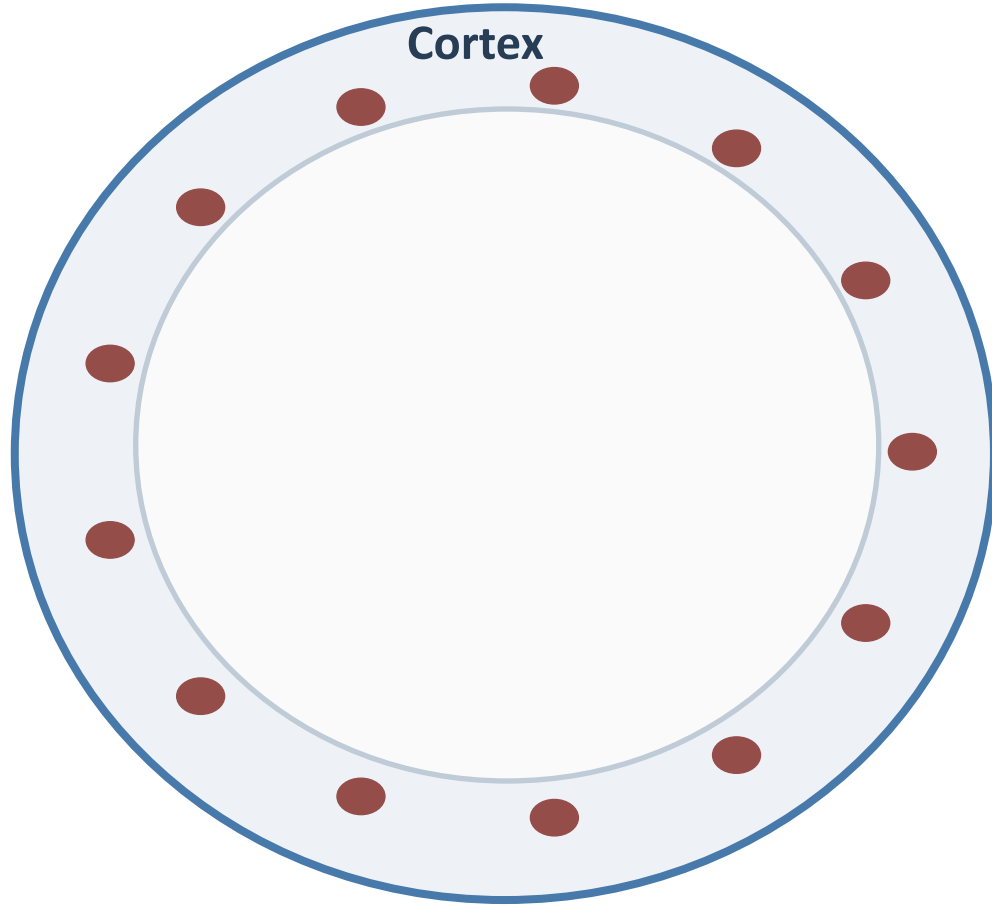
ADAMTS13 distinguishes TTP from aHUS

- Plasma ADAMTS13 levels as normal in aHUS cases with neurologic findings.
- TTP instead involves inherited or acquired ADAMTS13 deficiency.
- This comparison is mechanistically informative when syndromes overlap clinically.
- No numerical activity threshold is provided in the cited textbook section.

All HUS/TTP types share nonspecific morphology

- Morphologic findings across HUS and TTP are indistinguishable.
- Tissue changes differ primarily according to acuity and chronicity.
- A renal thrombus supports TMA—not its specific molecular etiology.
- Clinical and etiologic context is required for classification.

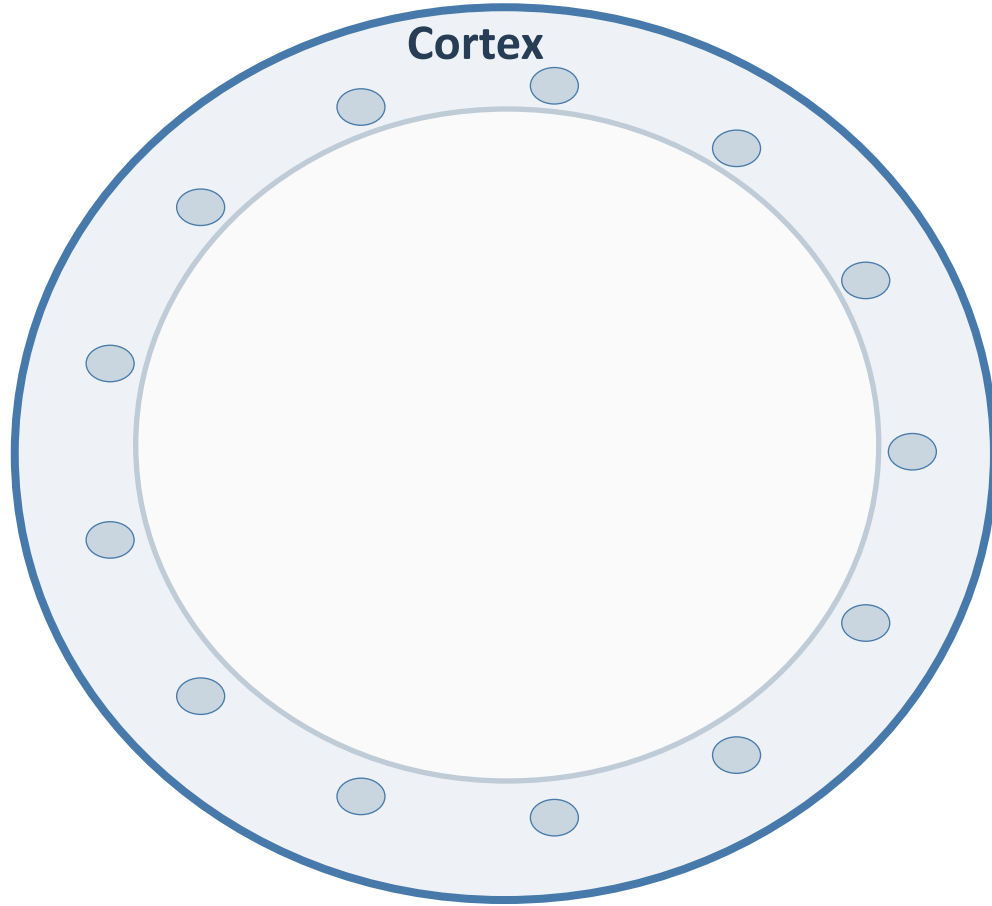
Acute kidney: Subcapsular petechiae and necrosis



- Acute active TMA can yield subcapsular petechial hemorrhages.
- Cortical necrosis may be patchy or diffuse.
- The gross effect is downstream of microvascular ischemia.

Schematic — not a histologic image

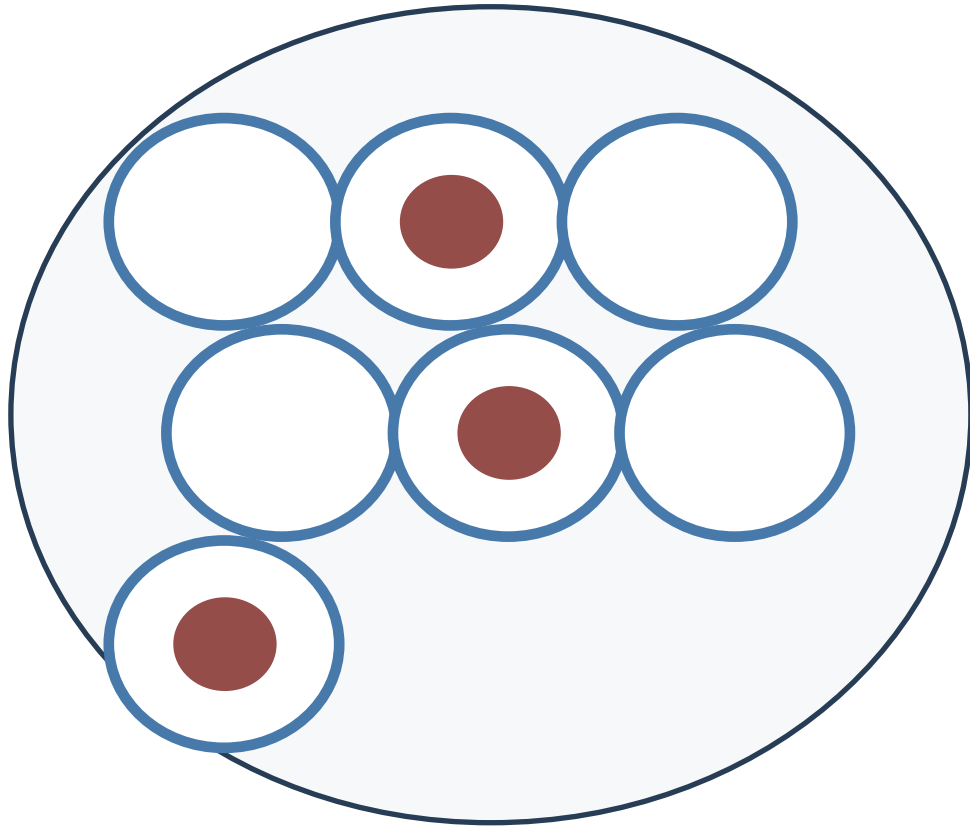
Cortical necrosis may be sharply delimited



- Massive ischemic necrosis is sharply limited to the renal cortex.
- The underlying injury is loss of perfusion within cortical microvasculature.
- Necrotic foci may alternate with relatively preserved cortex.

Schematic — not a histologic image

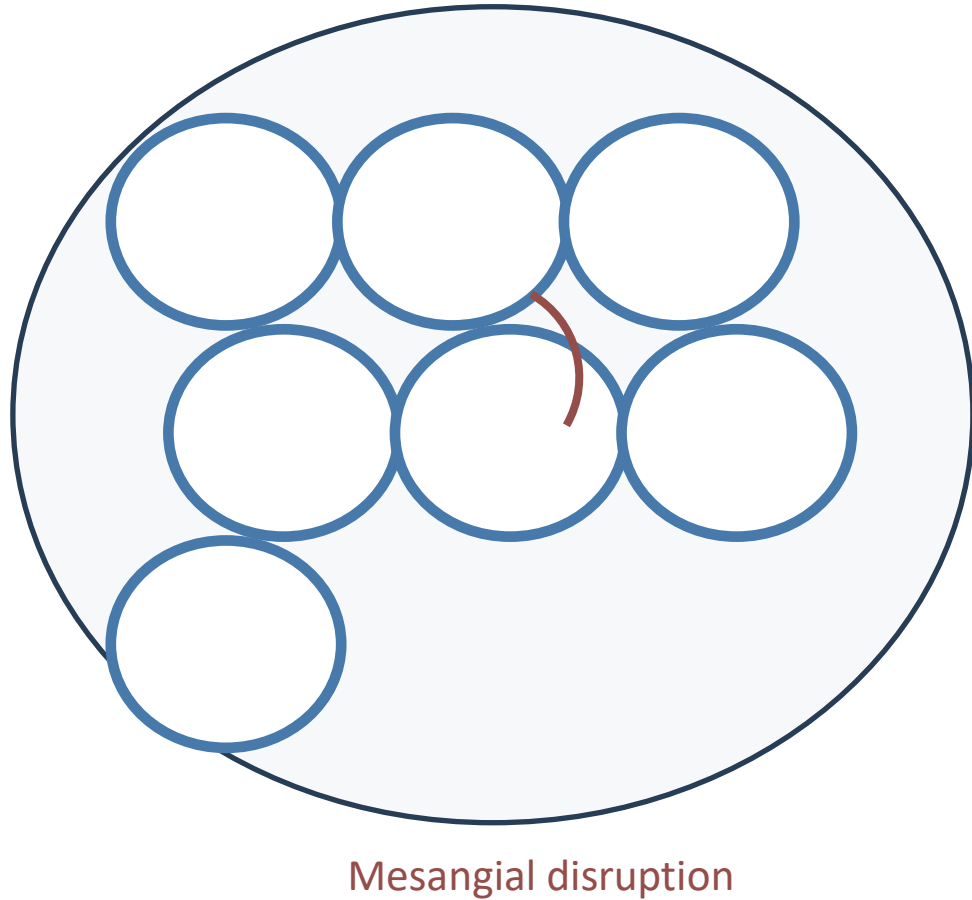
Glomerular capillary thrombi are a core acute lesion



- Capillary loops can be distended by intraluminal thrombi.
- Obstruction reduces effective glomerular blood flow.
- The depicted arrangement is a schematic, not a histologic specimen.

Schematic — not a histologic image

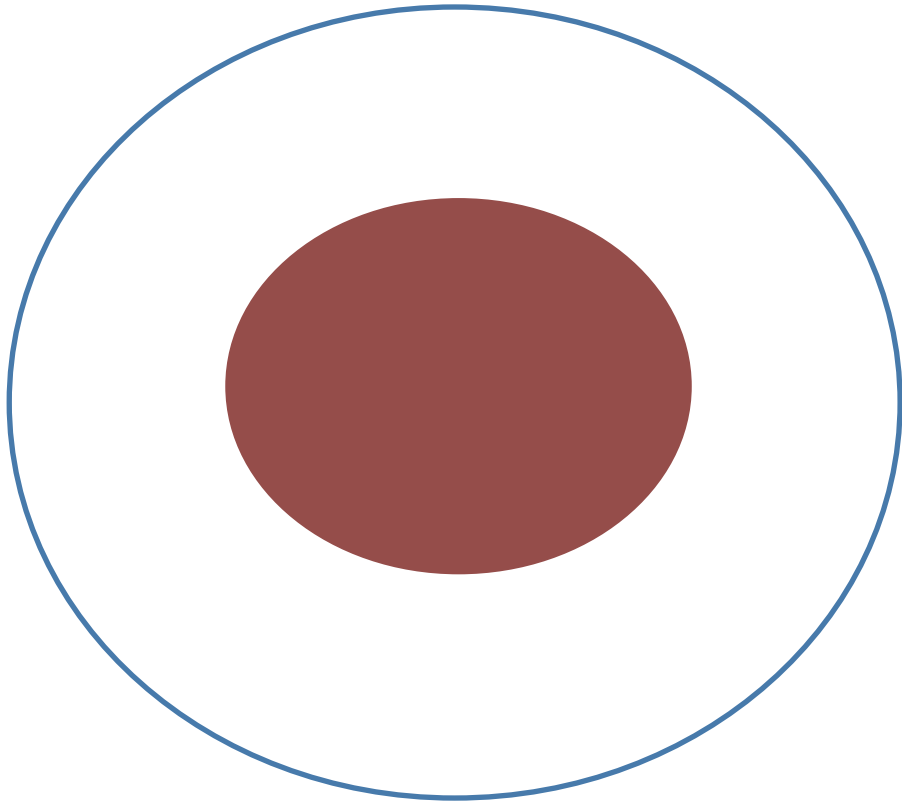
Mesangial matrix destruction is termed mesangiolysis



- Acute injury disrupts mesangial matrix and damages mesangial cells.
- Sufficient damage can produce collapse or loss of mesangial support.
- Mesangiolysis coexists with capillary vascular injury in TMA.

Schematic — not a histologic image

Arterioles and interlobular arteries may thrombose



Occluding thrombus

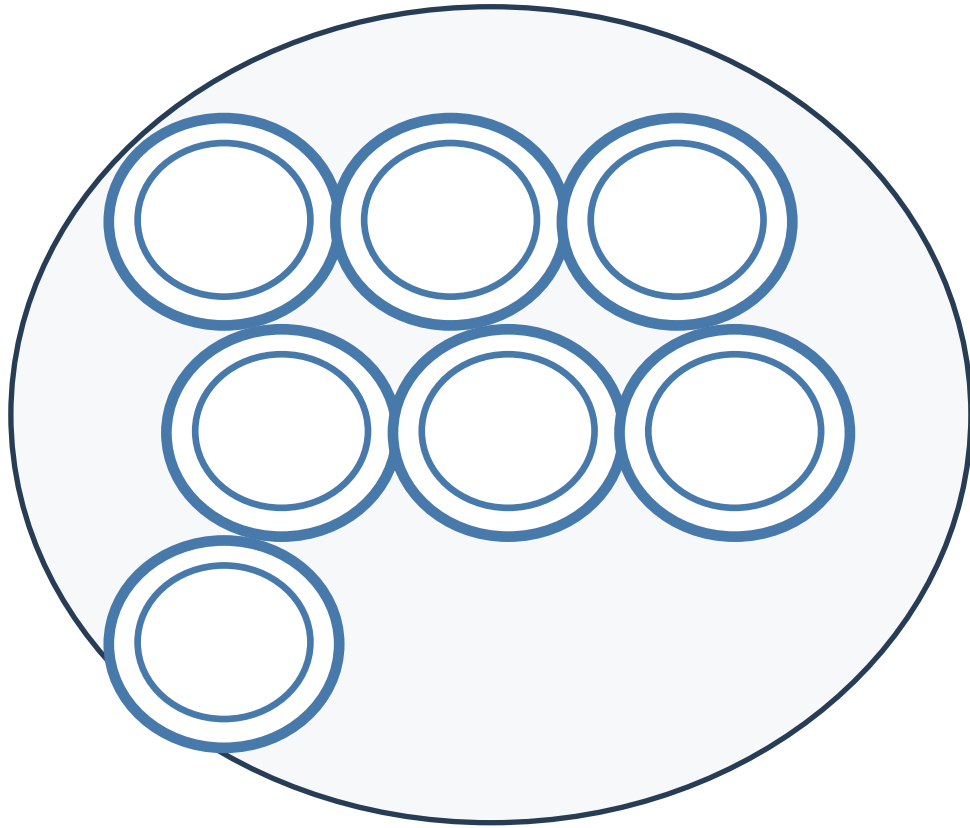
Schematic — not a histologic image

- Occlusive thrombi can involve both arterioles and interlobular arteries.
- The distribution extends beyond glomerular capillary loops.
- Arterial occlusion magnifies cortical ischemia.

Chronic TMA leaves renal cortical scars

- Chronic lesions are especially common in atypical HUS.
- The cortex shows variable scarring after persistent or recurrent injury.
- Scarring records both the original ischemic insult and subsequent healing.
- Chronicity adds irreversible structural damage to active microthrombosis.

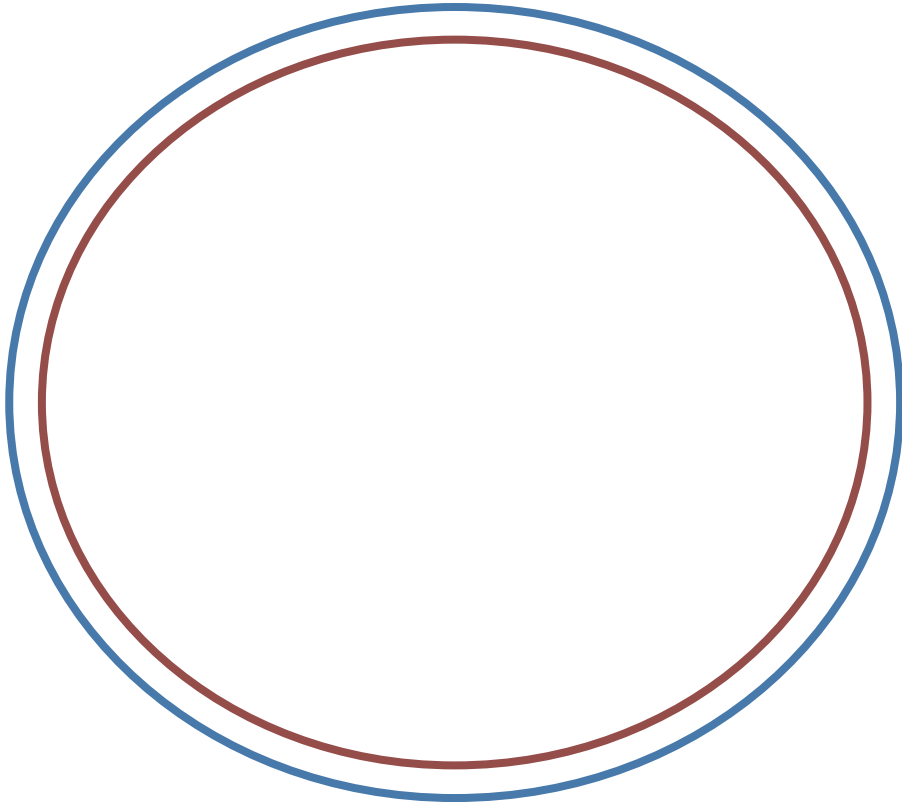
Chronic glomeruli may become shrunken



- Glomerular shrinkage is part of the chronic TMA pattern.
- Capillary wall thickening accompanies chronic glomerular remodeling.
- These changes reflect sustained injury rather than an etiology-specific lesion.

Schematic — not a histologic image

Double contours: Capillary-wall remodeling

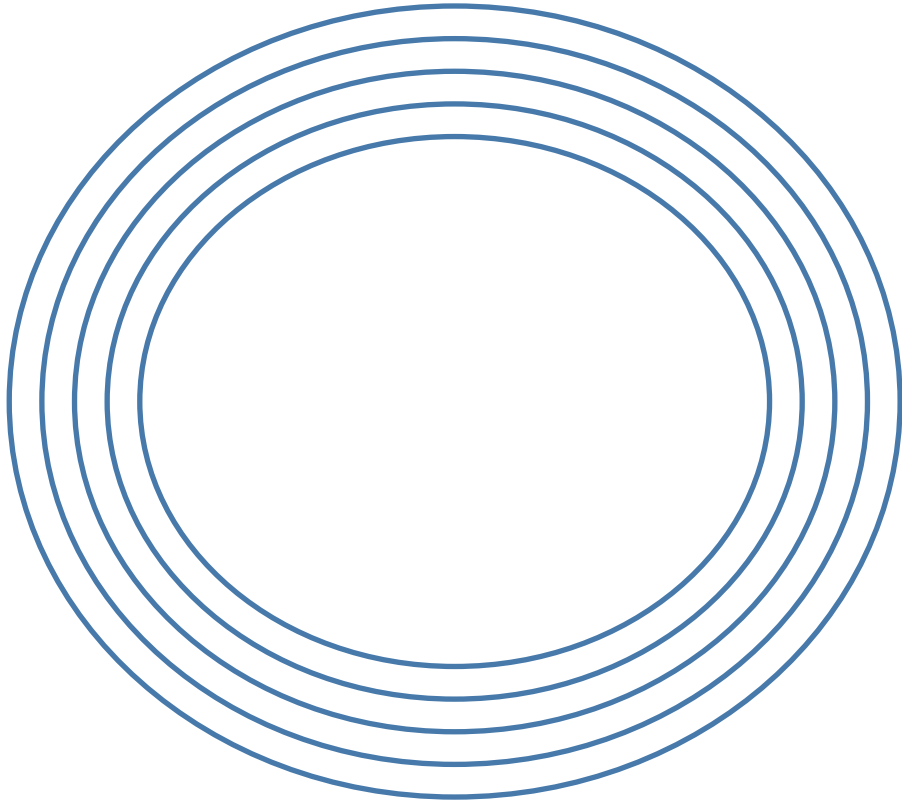


Parallel wall outlines

Schematic — not a histologic image

- Chronic disease may duplicate the glomerular basement membrane.
- The source describes “double contours” or “tram tracks.”
- Duplication is linked to capillary wall thickening and repair after injury.

Concentric arterial wall expansion narrows lumina

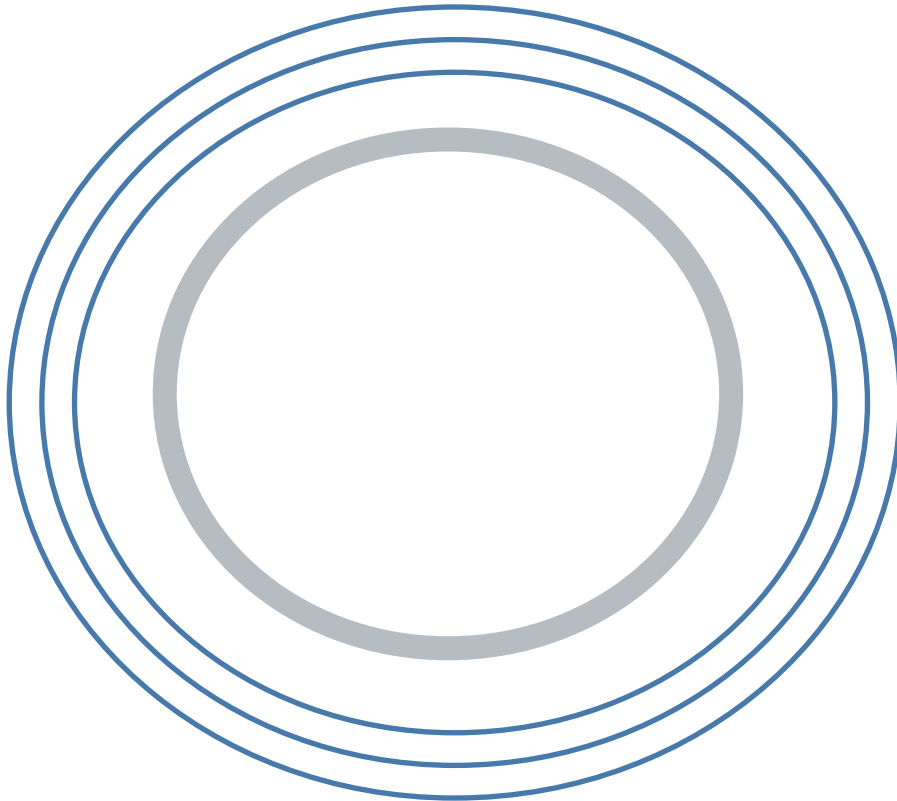


Concentric wall expansion

Schematic — not a histologic image

- Additional layers of cells and connective tissue thicken arterial walls.
- Thickened walls progressively narrow the lumen.
- Persistent vascular narrowing maintains renal hypoperfusion.

Arteriolar hyalinosis can dominate chronic lesions



Thick hyaline wall

Schematic — not a histologic image

- In chronic TMA, arteriolar walls may be thickened by hyalinosis.
- Wall thickening contributes further to luminal narrowing.
- Together with other vascular lesions, this perpetuates ischemic damage.

Acute and chronic renal changes form a continuum

Acute / active

Glomerular and arterial thrombi

Mesangiolysis

Petechiae; Cortical necrosis

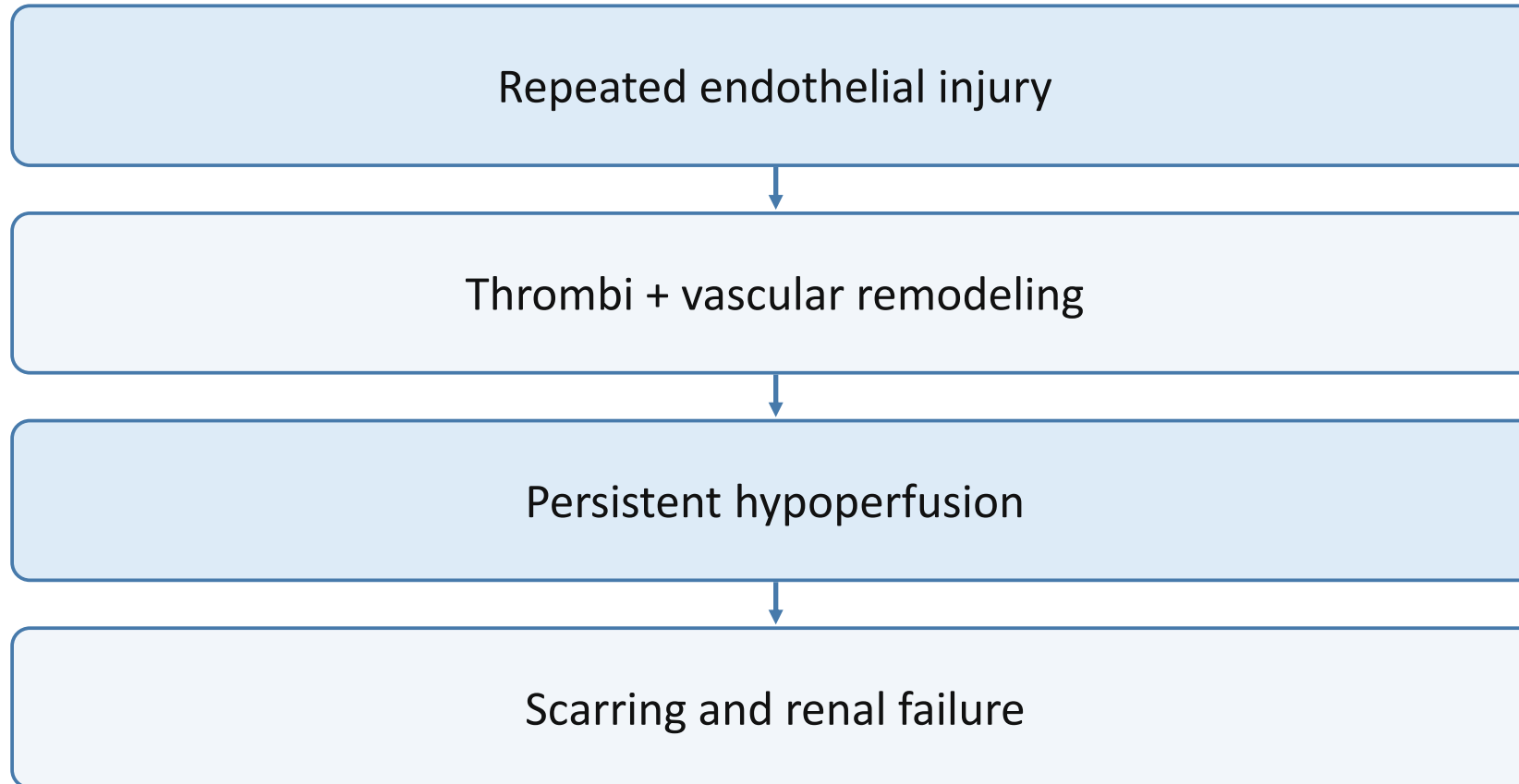
Chronic / reparative

Cortical scar; Small glomeruli

Double-contour capillary walls

Vascular thickening and hyalinosis

Vascular injury can become self-reinforcing



Temporal synthesis: Acute thrombosis evolves into chronic perfusion deficit

RBC fragments are evidence of mechanical hemolysis

- Narrow or thrombus-lined microvessels create shear stress on erythrocytes.
- Peripheral blood may show fragmented cells (schistocytes).
- Microangiopathic hemolysis is shared by several TMA disorders.
- Schistocytes alone cannot identify the underlying TMA cause.

Renal dysfunction is a vascular consequence

- Glomerular thrombosis reduces filtration through affected capillary beds.
- Arteriolar injury diminishes cortical perfusion.
- Severe ischemia can produce cortical necrosis and renal failure.
- Chronic hypoperfusion adds scarring and sustained loss of function.

Neurologic symptoms do not automatically mean TTP

- Some patients with aHUS develop neurologic manifestations.
- Normal plasma ADAMTS13 in these aHUS cases with TTP deficiency.
- TTP typically shows more prominent CNS involvement.
- The entire clinical picture and mechanism must be considered together.

Prognosis: Atypical HUS is often less favorable

Typical HUS

Following infection, many recover kidney function if injury is limited

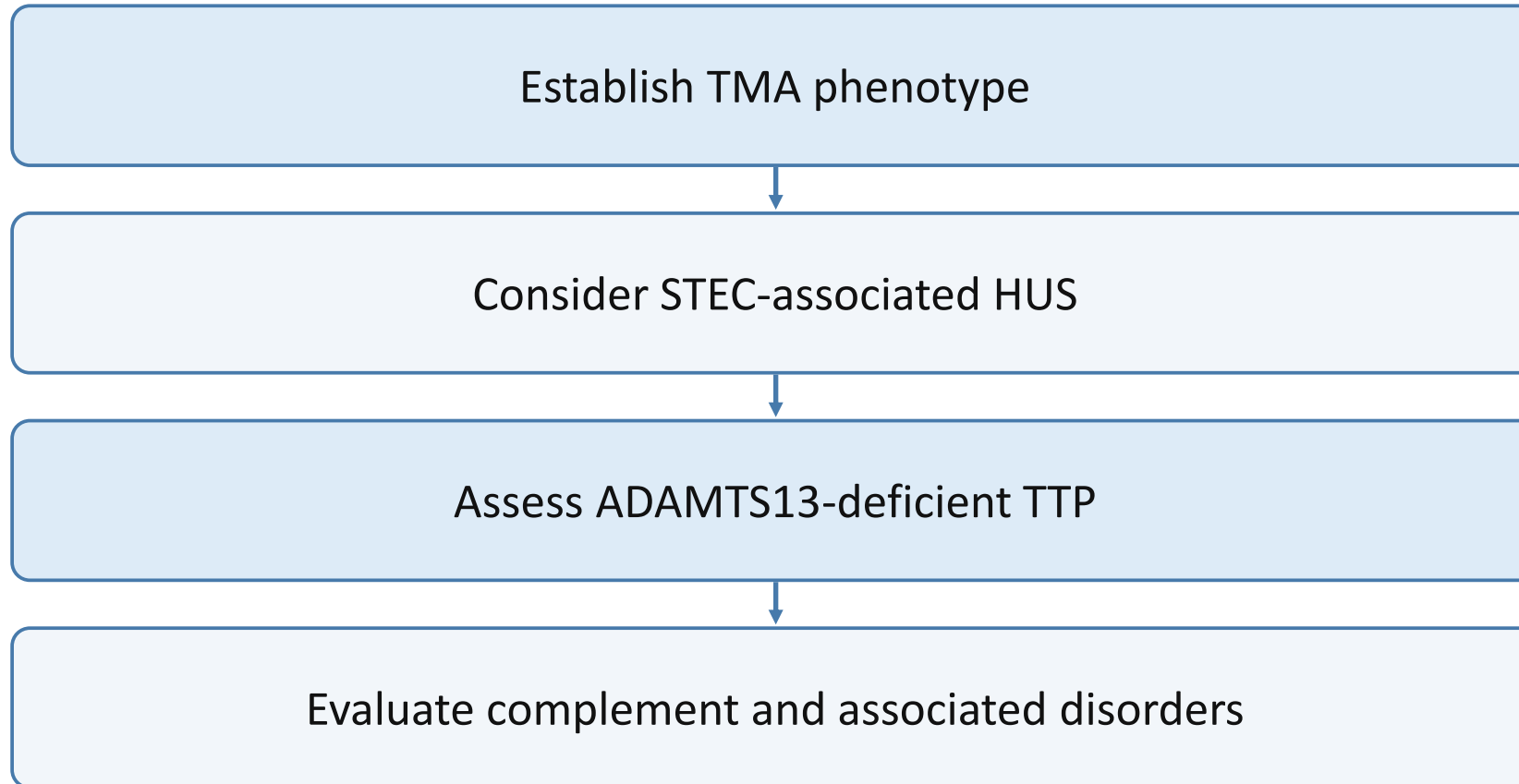
Long-term renal damage remains possible

Atypical HUS

Genetic or persistent underlying conditions may remain active

Chronic lesions and difficult-to-remove triggers worsen outlook

Etiology matters beyond a biopsy diagnosis



Teaching framework, not a clinical practice guideline or formal diagnostic algorithm

Biopsy interpretation: Identify pattern, not subtype

- Acute occlusive thrombi and mesangiolysis support active TMA.
- Double contours, vascular thickening, and scarring suggest chronicity.
- Neither acute nor chronic morphology alone establishes Factor H or CD46 defects.
- Clinicopathologic correlation is mandatory for subtype attribution.

Case 1: Complement-regulatory disease

Clinical reasoning exercise — hypothetical

- A patient develops hemolysis, thrombocytopenia, and acute kidney dysfunction.
- Review identifies a pathogenic complement-regulatory protein defect.
- Question: What order of events links the defect to renal failure?

Teaching interpretation: Impaired complement control → endothelial injury → platelet-rich TMA → glomerular ischemia. Mechanistic application of the Robbins framework; Hypothetical case.

Case 2: Delayed postpartum renal failure

Clinical reasoning exercise — hypothetical

- Renal failure with a TMA phenotype appears weeks after delivery.
- A complement-regulatory defect has not yet been established.
- Question: What can be inferred from pregnancy timing alone?

Teaching interpretation: Postpartum TMA is a recognized association, but its mechanism may be uncertain. The timing does not prove a complement mutation; Hypothetical case.

Case 3: Neurologic TMA and ADAMTS13

Clinical reasoning exercise — hypothetical

- A patient has hemolysis, thrombocytopenia, neurologic symptoms, and renal injury.
- Question: Does prominent neurologic involvement itself establish TTP?
- Which mechanistic feature should be contrasted with aHUS?

Teaching interpretation: No. TTP is associated with ADAMTS13 deficiency; Normal plasma levels in aHUS.
Hypothetical discrimination exercise; Not a management protocol.

Integrated pathologic interpretation

- Complement-regulatory failure is a major route to atypical HUS, but acquired endothelial-injury contexts also occur.
- Endothelial damage → platelet-rich TMA → mechanical hemolysis, platelet consumption, and renal ischemia.
- Acute thrombi/mesangiolysis and chronic double contours/vascular scarring are shared TMA morphologies.
- Cause is assigned by clinicopathologic and mechanistic context—not by renal morphology alone.

Textbook sources and lecture boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Ch 20, pp 853–855: Thrombotic microangiopathies, HUS, TTP.
- Same text, Ch 3, p 82: regulatory proteins of complement, including Factor H.
- Same text, Ch 14: hemolytic anemia due to red cell trauma.
- Source-derived teaching interpretation; no chapter PDF or source figures were supplied for direct image verification.