

Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

Mechanisms • morphology • clinicopathologic reasoning

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Learning objectives

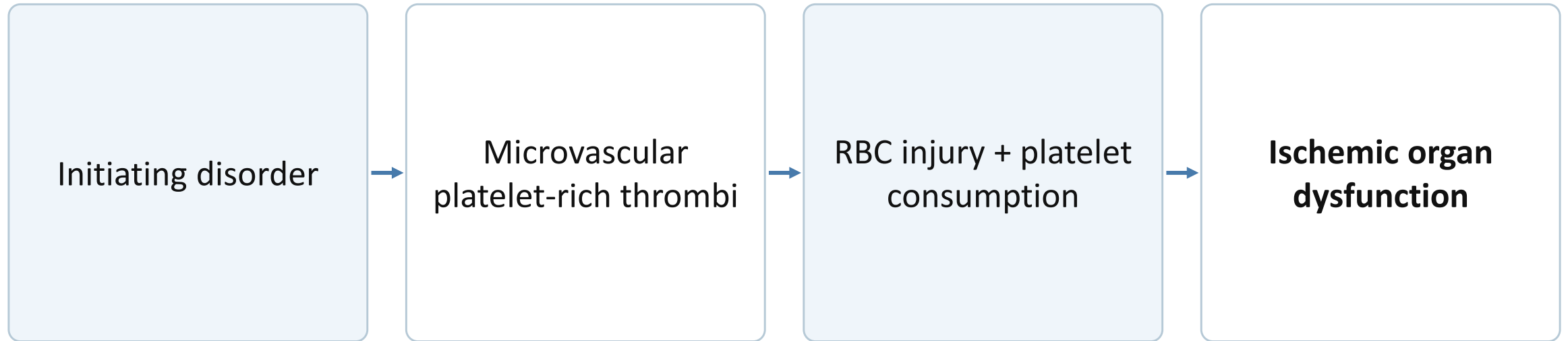
- Recognize the shared consequences of small-vessel platelet-rich thrombosis.
- Explain how ADAMTS13 deficiency initiates TTP.
- Distinguish Shiga toxin–associated from complement-mediated HUS.
- Interpret the renal morphology and major clinicopathologic differentials.

TMA is a clinicopathologic syndrome

Shared vascular lesion

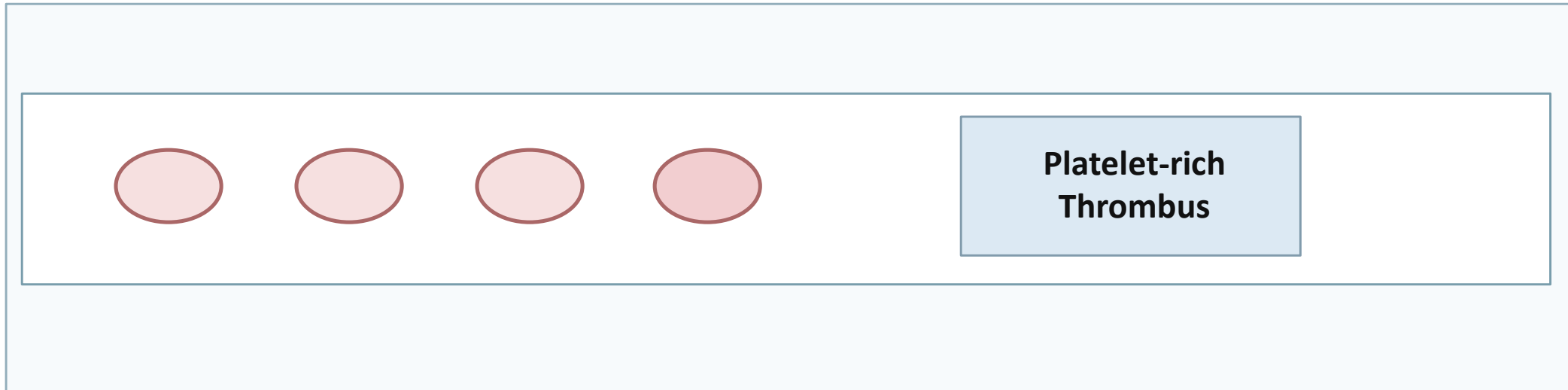
Microvascular thrombi link hemolysis, platelet consumption, tissue ischemia, and organ dysfunction.

The shared thrombotic microangiopathy cascade



Why microthrombi have systemic consequences

Schematic: Capillary obstruction links thrombosis and hemolysis



Flow direction →

RBC fragmentation under shear

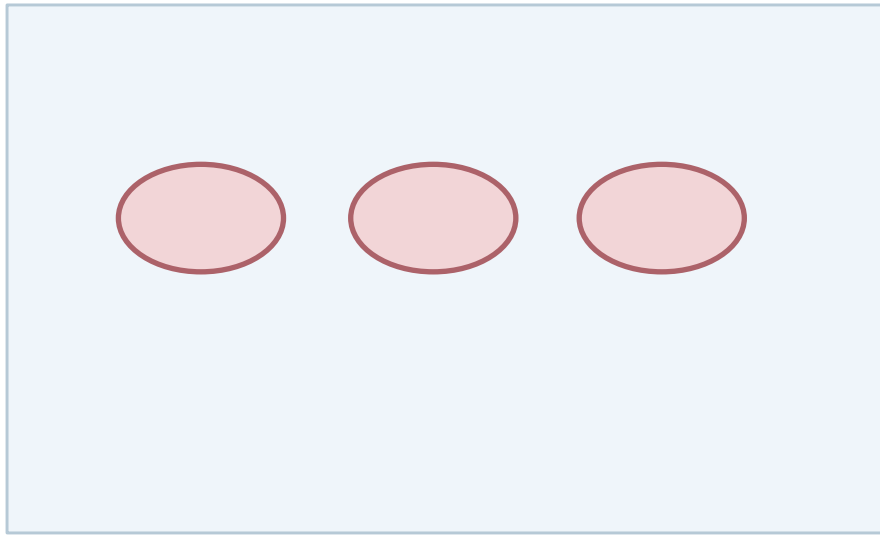
Native schematic • not a histologic image

Microangiopathic hemolytic anemia is mechanical

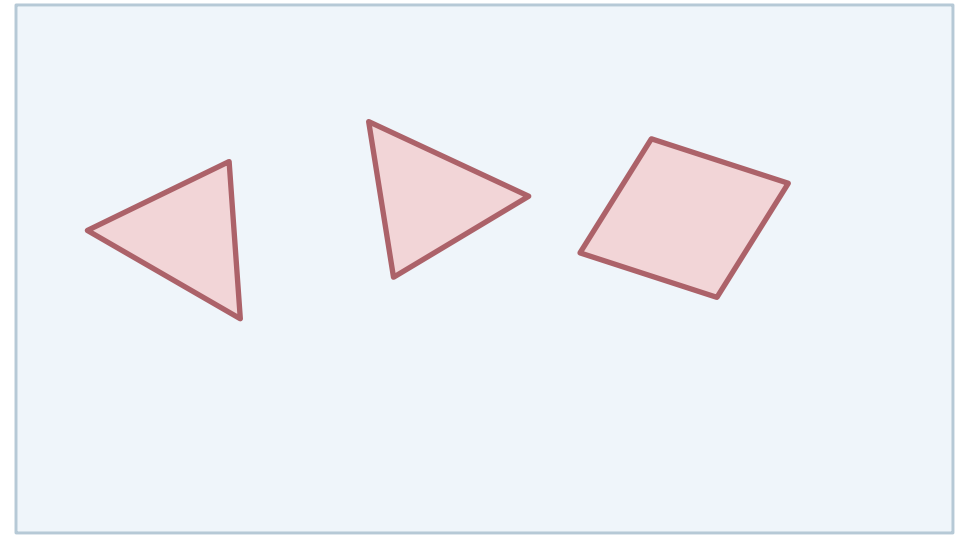
- Microvascular lesions narrow the vessel lumen.
- Passing erythrocytes are subjected to abnormal shear stress.
- Fragmentation produces intravascular hemolysis and red-cell fragments.
- The mechanism is distinct from immune-mediated erythrocyte destruction.

Fragmented erythrocytes in TMA

Before microvascular passage



After high-shear obstruction



Schistocytes / helmet forms

Conceptual cell silhouettes; Not a blood film

Why platelet counts fall in TMA

Excessive platelet
activation



Formation of platelet
microaggregates



Peripheral platelet
consumption



Thrombocytopenia

Organ dysfunction reflects thrombus distribution

- Microvascular occlusion deprives downstream tissue of perfusion.
- Renal microvasculature is a major target in HUS.
- Neurologic involvement is often prominent in TTP.
- The distribution and severity of thrombosis vary between patients.

TMA: The shared clinical and laboratory picture

Feature	Clinicopathologic explanation
Thrombocytopenia	Platelet consumption into microthrombi
Hemolytic anemia	Red-cell fragmentation within narrowed small vessels
Renal dysfunction	Microvascular ischemic injury
Neurologic symptoms	Microvascular dysfunction in nervous tissue

The historical TTP pentad

- Fever
- Thrombocytopenia and microangiopathic hemolytic anemia
- Transient neurologic deficits
- Renal dysfunction or failure

Why the historical pentad is insufficient

- Many patients diagnosed with TTP do not exhibit all five classical features.
- Some patients with HUS develop neurologic dysfunction or fever.
- Diagnostic distinction is better based on initiating pathogenesis.
- Do not exclude TTP merely because the complete pentad is absent.

Typical clinical emphasis is not absolute

TTP

- Neurologic dysfunction often dominates
- Renal injury can occur
- Thrombocytopenia is often more pronounced

HUS

- Acute renal dysfunction often dominates
- Neurologic symptoms can occur
- Frequently affects children in typical infection-associated HUS

Clinical overlap makes etiology central.

TMA and disseminated intravascular coagulation

TMA

- Primarily platelet/endothelial mechanisms
- Coagulation cascade is not the dominant driver
- PT and PTT are usually normal

DIC

- Systemic coagulation activation
- Widespread fibrin-rich microthrombosis
- Clotting factors may be consumed

Both can produce fragmented erythrocytes and organ ischemia.

Why PT and PTT often remain normal

- TTP and HUS do not begin with widespread activation of the coagulation cascade.
- Platelet aggregation and endothelial injury dominate the pathogenic events.
- Routine PT and PTT are consequently usually normal.
- Coagulation results support—but do not alone establish—the differential.

Etiologic classification of TMA

Entity	Principal initiating abnormality
TTP	ADAMTS13 deficiency: autoantibodies or inherited mutation
Shiga toxin–associated HUS	Bacterial toxin-associated endothelial injury
Complement-mediated HUS	Excessive alternative complement activation
Other secondary TMAs	Drug, radiation, infection, autoimmunity, pregnancy or vascular disease associations

Three major pathogenic routes to microthrombosis

TTP → ADAMTS13 deficiency → Unusually large vWF multimers → Platelet aggregation

Typical HUS → Shiga-like toxin exposure → Endothelial injury / activation → Platelet activation

Complement-mediated HUS → Alternative complement dysregulation → Endothelial injury → Platelet activation

TTP: The defining molecular defect

ADAMTS13 deficiency

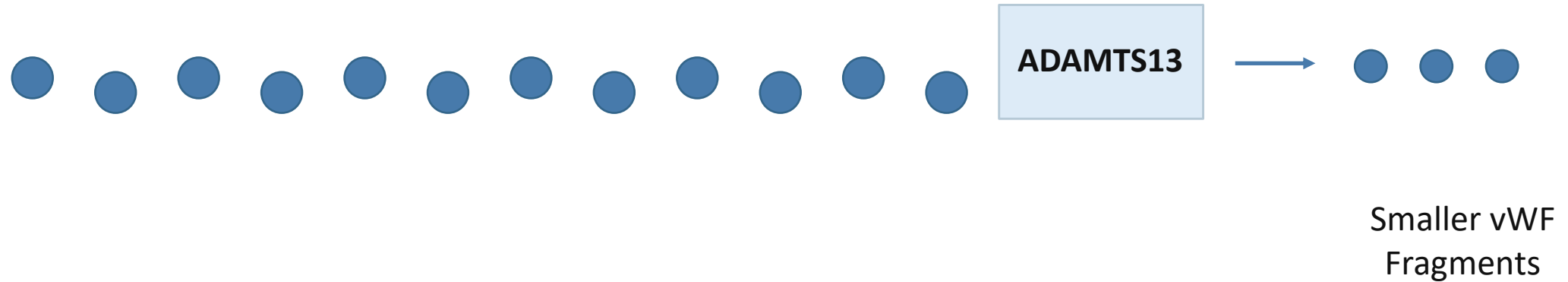
Failure to process very-high-molecular-weight von Willebrand factor permits pathogenic platelet aggregation.

Von Willebrand factor supports normal hemostasis

- VWF mediates platelet adhesion to exposed subendothelial matrix.
- Circulating vWF is organized into multimers of different sizes.
- Very-large multimers have high capacity to recruit platelets.
- Physiologic proteolysis limits persistence of unusually large multimers.

ADAMTS13 normally trims vWF multimers

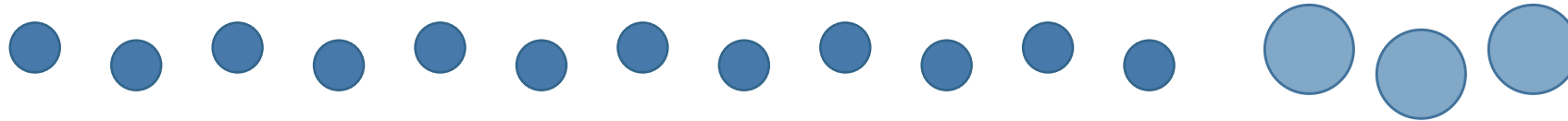
Normal ADAMTS13 cleaves very-large vWF multimers



Native mechanism schematic

ADAMTS13 deficiency preserves large vWF multimers

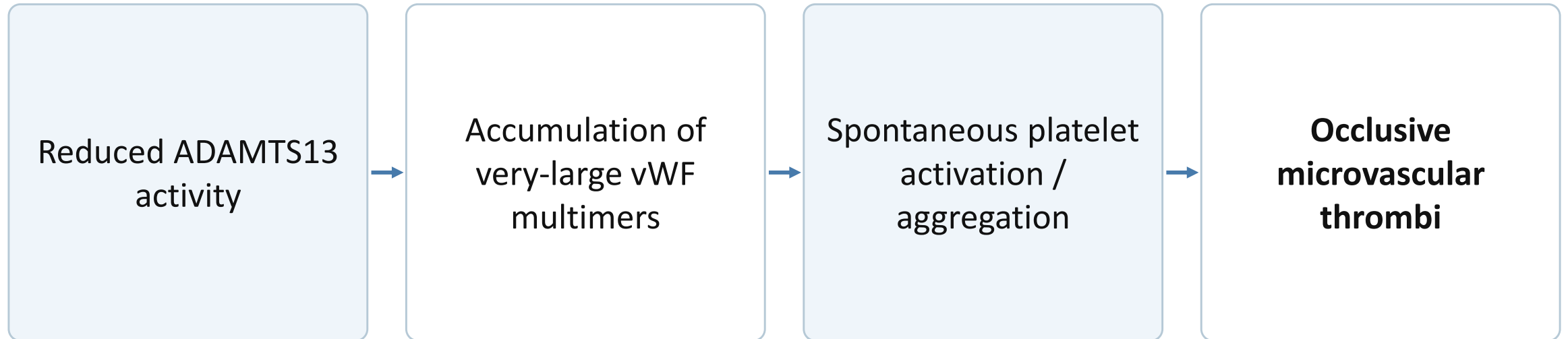
Deficient ADAMTS13: Unusually large vWF multimers persist



**Spontaneous platelet activation
And aggregation**

Native mechanism schematic

TTP pathogenesis from enzyme deficiency to injury



Acquired versus inherited TTP

Acquired TTP

- Inhibitory autoantibodies against ADAMTS13
- Metalloprotease activity is impaired
- Plasma exchange removes inhibitory antibody

Inherited TTP

- Inactivating ADAMTS13 variants
- Enzyme deficiency is constitutive
- Additional triggers may precipitate attacks

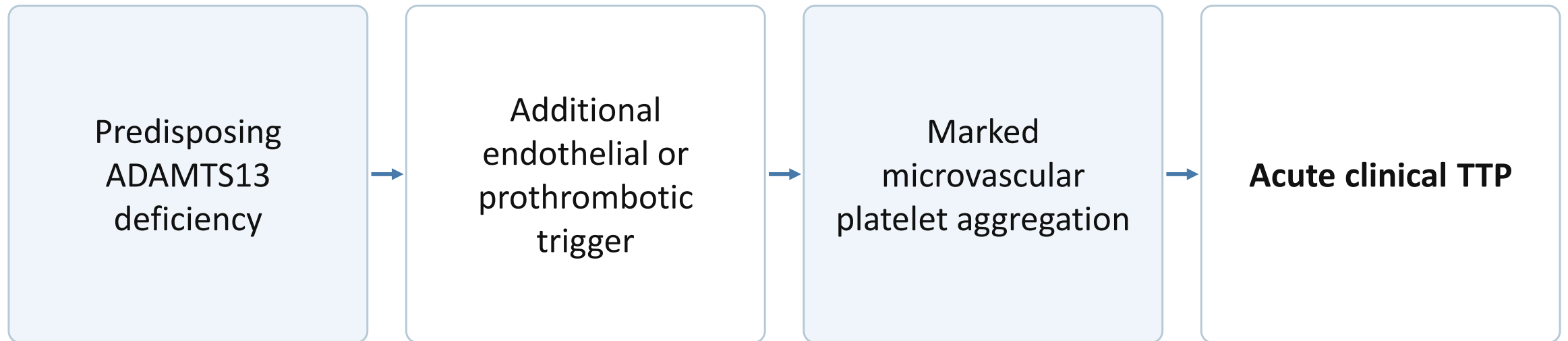
Acquired TTP: An antibody-mediated protease defect

- Autoantibodies inhibit ADAMTS13 metalloprotease activity.
- Persisting high-molecular-weight vWF multimers activate platelets.
- Plasma exchange addresses both the inhibitor and deficient enzyme.
- This is not a disorder of primary clotting-factor deficiency.

Inherited TTP: Deficiency does not guarantee an attack

- ADAMTS13-inactivating mutations are less common than acquired inhibitors.
- Symptoms may be episodic, with onset delayed until adolescence.
- Additional endothelial injury or prothrombotic states may precipitate clinical disease.
- The genotype creates susceptibility; A trigger influences expression.

A two-component model of clinical TTP



TTP: Neurologic and renal involvement

- Occlusive microthrombi develop in systemic arterioles.
- Central nervous system dysfunction is a prominent feature.
- Severe renal injury is less common than in HUS.
- Clinical findings follow the distribution of involved microvascular beds.

Recognizing a possible TTP presentation

- Concurrent thrombocytopenia and microangiopathic hemolysis are a critical signal.
- Fever, transient neurologic changes, or renal abnormalities may accompany the syndrome.
- Absence of some classical manifestations does not exclude TTP.
- Urgent evaluation is essential because delays can be fatal.

Why plasma exchange is effective in acquired TTP

Remove inhibitory
antibodies



Replace plasma
ADAMTS13 activity



**Reduce propagation of
vWF-mediated
thrombosis**

TTP: Treatment illustrates causation

- Plasma exchange removes antibodies inhibiting ADAMTS13.
- Replacement plasma supplies functioning ADAMTS13.
- Successful treatment in more than 80% of patients.
- The therapeutic response reinforces the pathogenic role of the enzyme defect.

HUS: The dominant pathogenic setting

Endothelial injury

Unlike TTP, typical and complement-mediated HUS generally begin with endothelial injury, followed by platelet activation.

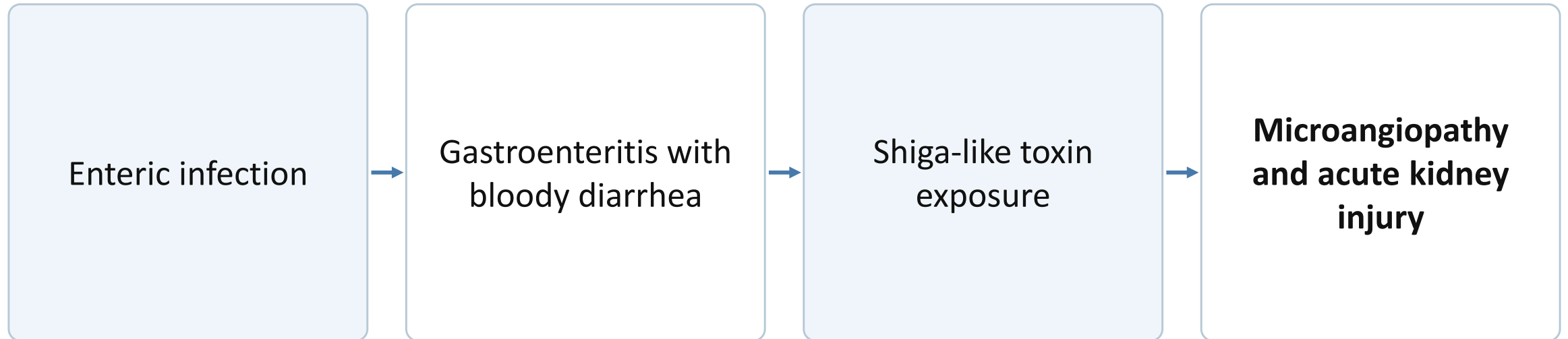
HUS: Major etiologic categories

Category	Biologic trigger	Clinical tendency
Typical / Shiga toxin–associated	Shiga-like toxin–producing enteric bacteria	Often follows bloody diarrhea
Complement-mediated	Alternative pathway dysregulation	Can be episodic and relapsing
Secondary TMA associations	Drugs, systemic disease, pregnancy or radiation	Context-dependent organ injury

Typical HUS often follows enteric infection

- Most cases follow intestinal infection with Shiga-like toxin–producing bacteria.
- *Escherichia coli* O157:H7 is a frequent causative strain.
- *Shigella dysenteriae* and other toxin-producing organisms can also be implicated.
- Children and older adults are particularly vulnerable' account.

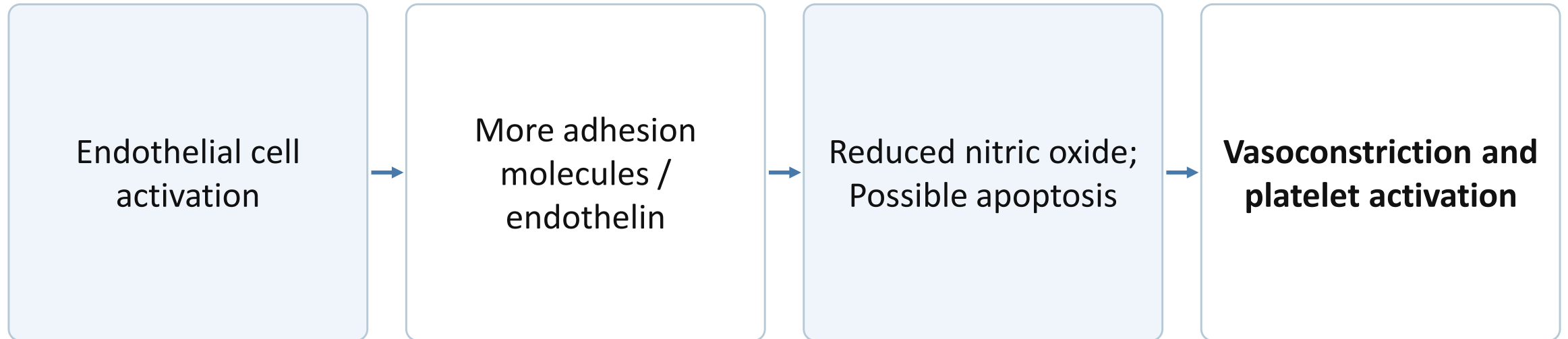
Typical HUS: Clinical sequence



How bacterial toxin reaches the circulation

- Gastroenteritis produces inflamed gastrointestinal mucosa.
- The toxin can be absorbed from the affected mucosa.
- Systemic exposure precedes endothelial perturbation.
- The precise molecular route from toxin exposure to HUS remains incompletely established.

Proposed endothelial effects of Shiga-like toxin



Endothelin and nitric oxide in a toxin model

Endothelin

- Endothelial activation increases endothelin expression
- Favors vasoconstriction
- Can exacerbate impaired microvascular flow

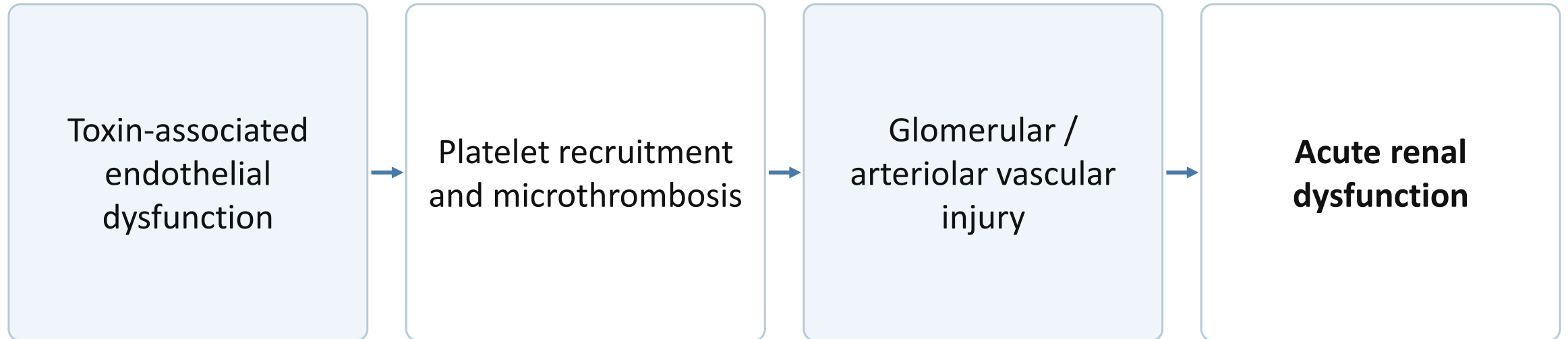
Nitric oxide

- Endothelial toxin effects may reduce nitric oxide
- Loss of a vasodilatory influence
- May worsen microvascular perfusion

The proposed Shiga-toxin mechanism has uncertainty

- The text describes endothelial activation as a model, not an established complete pathway.
- Inflammatory cytokines may enhance toxin-associated endothelial apoptosis.
- Possible disruption of factor H and complement control has also been suggested.
- These possibilities should not be presented as fully proven mechanisms.

Typical HUS: Converging consequences



Renal injury dominates typical HUS

- Small-vessel thrombi compromise the glomerular and arteriolar circulation.
- The kidney may develop acute ischemic injury and loss of function.
- The clinical syndrome often emerges days after the diarrheal illness.
- Neurologic manifestations are possible, despite the classic clinical distinction.

Typical HUS: Short- and long-term outcomes

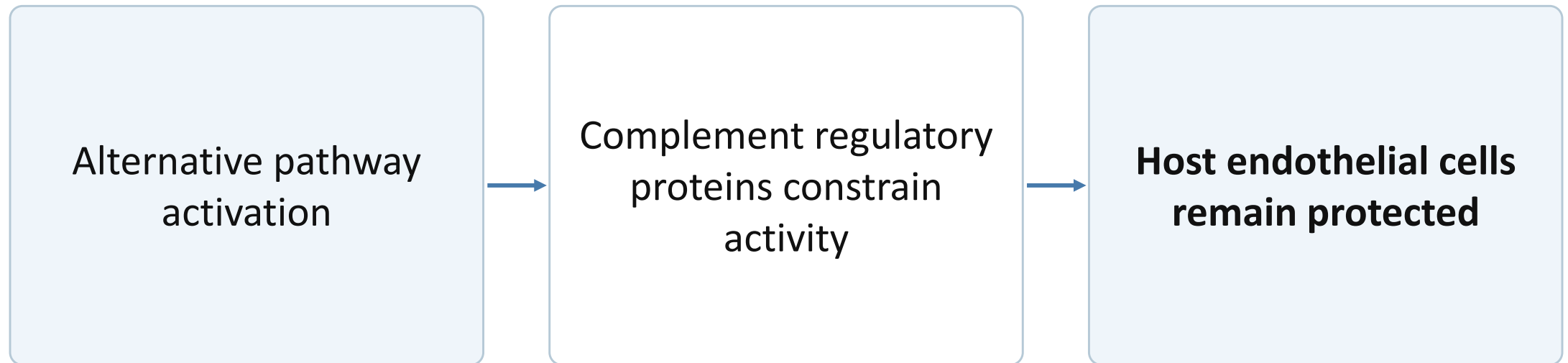
- Patients with less severe renal failure frequently recover function over weeks.
- Survival of the acute episode does not exclude residual renal injury.
- Long-term renal function may remain impaired in some survivors.
- Persistent renal follow-up rather than assuming complete recovery.

Complement-mediated HUS

Loss of complement control

Alternative complement activation becomes excessive and injures microvascular endothelium.

Normal alternative complement control



Factor H is a major complement regulator

- Factor H promotes breakdown of alternative pathway C3 convertase.
- This protects host cells from excessive complement activation.
- Inherited factor H abnormalities are prominent among complement-mediated HUS causes.
- Loss of restraint permits self-tissue microvascular injury.

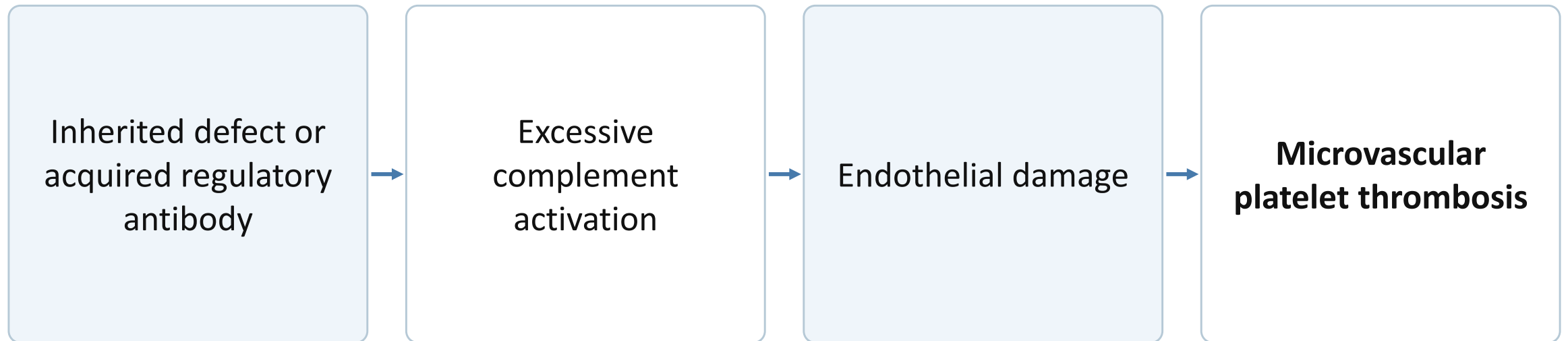
Complement-associated proteins named by Robbins

Protein / component	Relevance to complement-mediated HUS
Factor H	Limits alternative pathway activity
Factor I	Regulatory protease; inherited variants described
CD46 (membrane cofactor protein)	Cell-surface complement regulatory protein
C3 and factor B	Alternative pathway components with associated variants

Inherited complement defects may produce episodic HUS

- Genetic susceptibility does not necessarily imply a continuous active syndrome.
- Infection or another event may trigger complement overactivation.
- Episodes may recur because the underlying defect persists.
- Some affected individuals have more than one regulatory-gene variant.

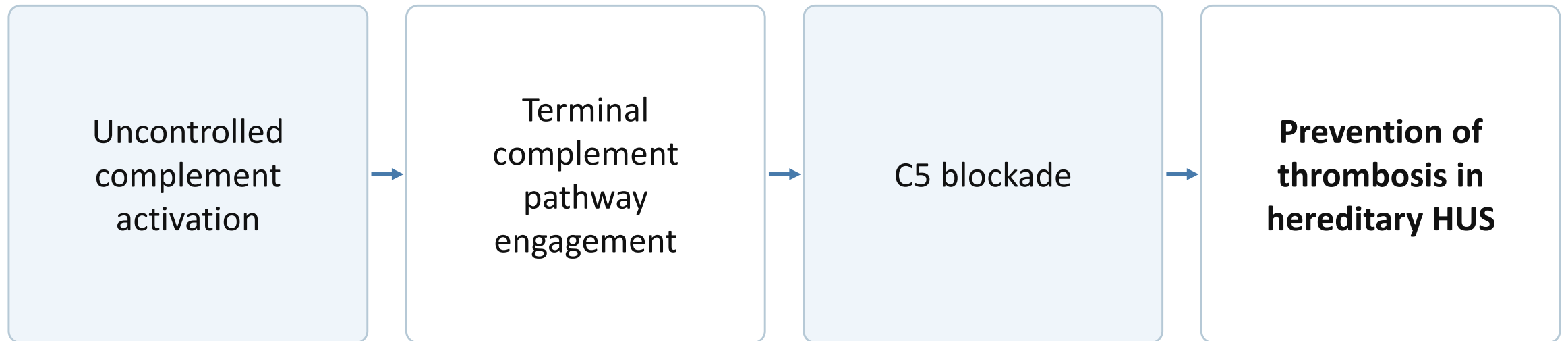
Complement-mediated HUS: Pathogenesis



Acquired complement-mediated HUS

- Inhibitory autoantibodies can target complement regulatory proteins.
- Regulatory loss resembles the functional effect of pathogenic inherited variants.
- Excess complement activation damages microvascular endothelium.
- A potential role for immunosuppression when inhibitory antibodies are involved.

Complement inhibition demonstrates mechanism



Why complement-mediated HUS can relapse

- The initiating regulatory abnormality may be persistent.
- Intercurrent illness can act as a trigger in a susceptible host.
- Recurrent endothelial injury can cause progressive renal damage.
- This clinical pattern differs from a single resolved enteric infection.

Secondary TMAs: Acquired endothelial insults

- Certain chemotherapeutic and immunosuppressive drugs are recognized associations.
- Radiation exposure and transplantation settings may precede TMA.
- Other infections and autoimmune or lymphoid conditions may be implicated.
- Such associations need etiologic evaluation; They are not equivalent to ADAMTS13-deficient TTP.

Examples of secondary TMA associations

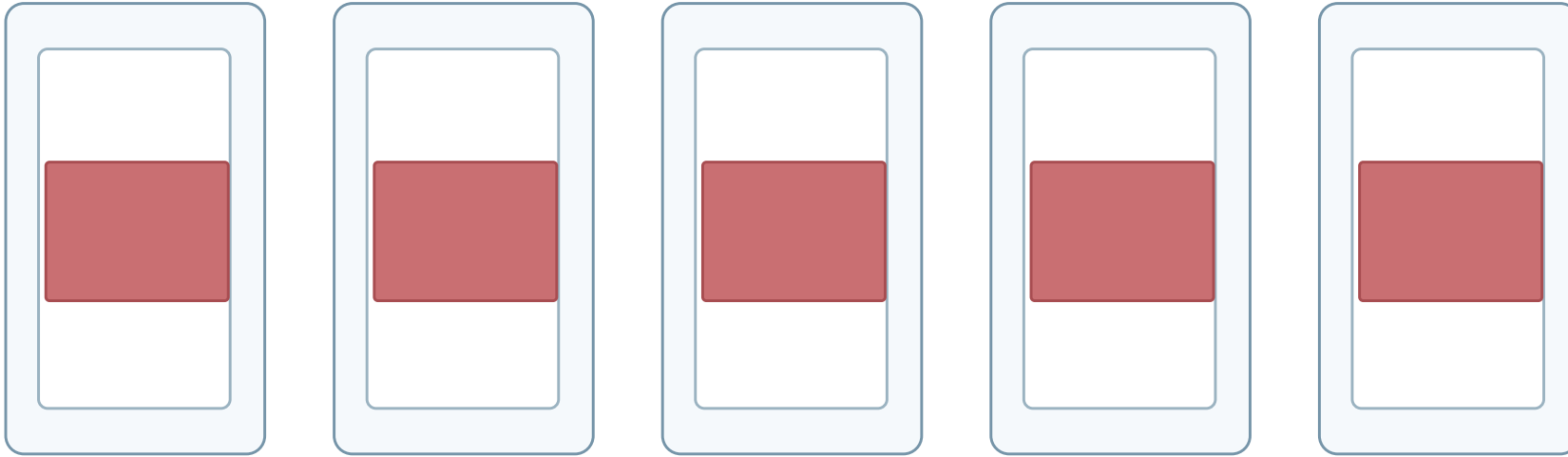
Clinical setting	Examples mentioned in Robbins
Drug exposure	Cyclosporine; chemotherapeutic agents
Other infections	HIV infection; pneumococcal sepsis
Autoimmune / vascular	Antiphospholipid syndrome; systemic sclerosis; severe hypertension
Other contexts	Pregnancy / postpartum; transplantation; radiation

Pregnancy-associated TMA requires context

- Pregnancy and the postpartum period are associated with TMA syndromes.
- Postpartum renal failure can develop from one day to months after delivery.
- A complement-regulatory variant may be involved in some cases.
- The pathogenesis is not settled and clinical prognosis can be serious.

Acute TMA in glomerular capillaries

Schematic of renal microvascular pathology



Occlusive thrombi in glomerular capillaries

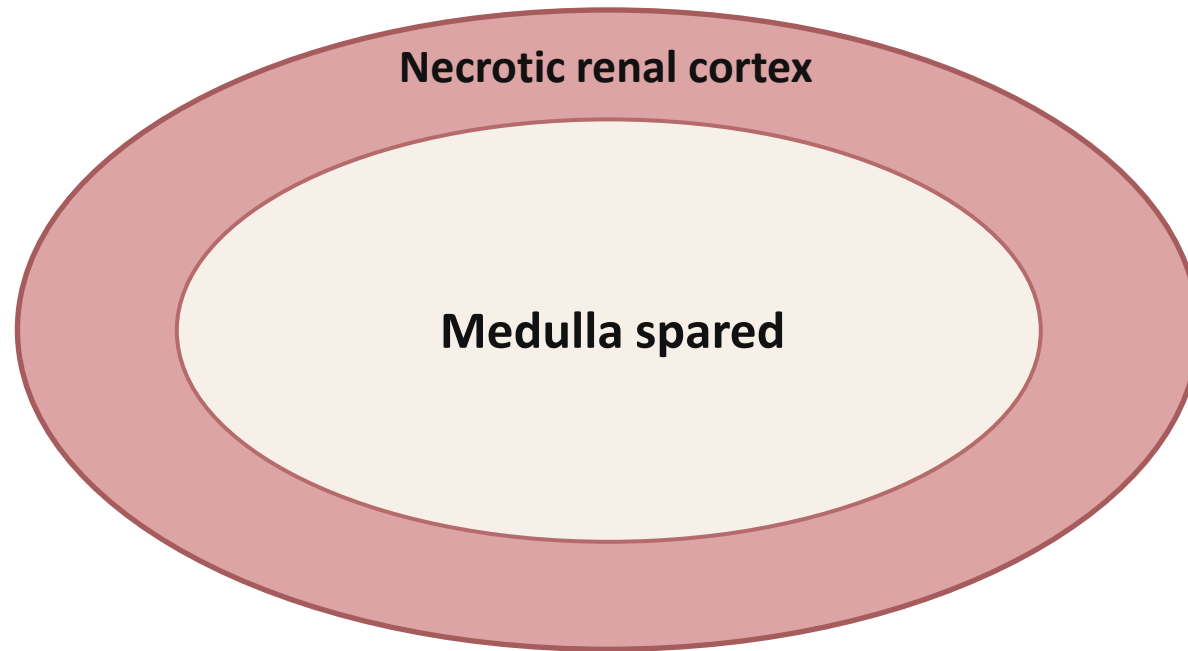
Original conceptual schematic • not a photomicrograph

Acute glomerular injury: The principal lesions

- Glomerular capillary lumens are distended or occluded by thrombi.
- Mesangial cell and matrix injury may disrupt the mesangium.
- Interlobular arteries and arterioles can also contain occlusive thrombi.
- These lesions reduce perfusion and contribute to acute kidney dysfunction.

Ischemic damage may produce cortical necrosis

Schematic of renal microvascular pathology



Cortical necrosis may be patchy or extensive

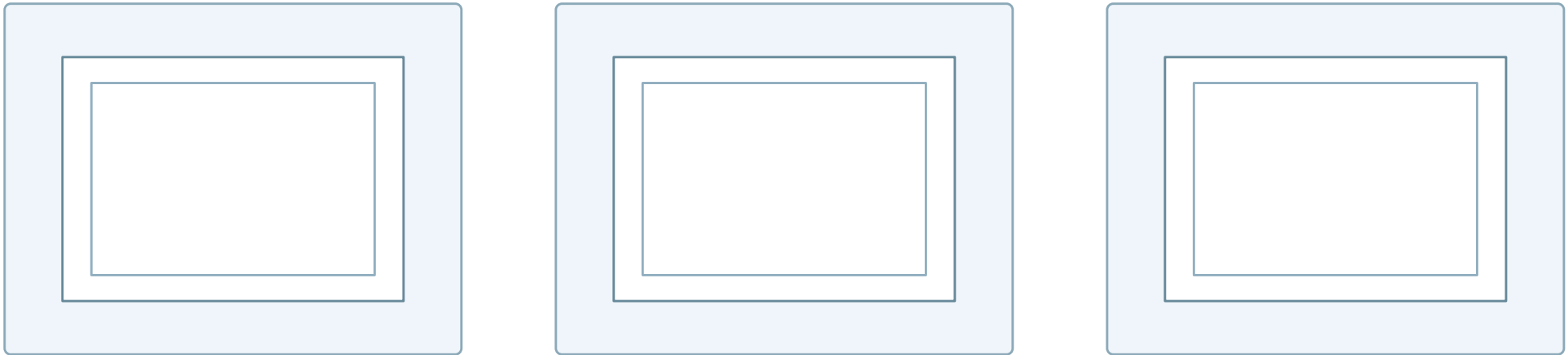
Original conceptual schematic • not a photomicrograph

Gross kidney changes in active TMA

- Subcapsular petechiae may be present.
- Cortical necrosis can be patchy or diffuse.
- Severe ischemia can produce sharply cortex-limited necrosis.
- Extent of the vascular lesion influences the severity of renal failure.

Chronic TMA: Double-contour capillary walls

Schematic of renal microvascular pathology



Basement-membrane duplication (“double contours”)

Original conceptual schematic • not a photomicrograph

Chronic TMA reflects repeated vascular injury

- Glomeruli may shrink and develop conspicuous capillary-wall thickening.
- Basement-membrane duplication creates double contours (“tram tracks”).
- Arterial intimal cellular/connective tissue layering narrows the lumen.
- Arteriolar wall thickening and hyalinosis may accompany chronic disease.

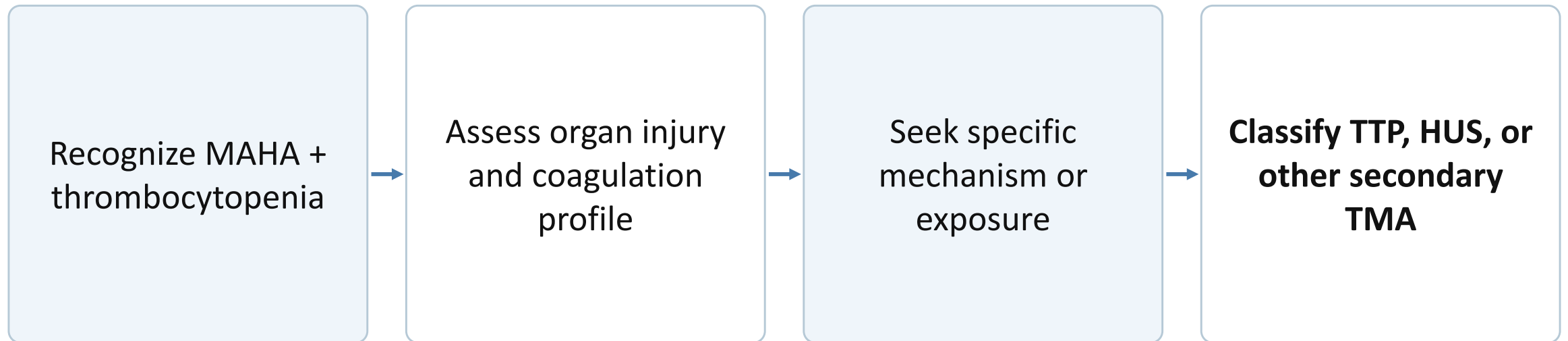
Acute and chronic renal TMA compared

Acute / active	Chronic / healed or ongoing
Capillary and arteriolar thrombi	Glomerular capillary-wall thickening and double contours
Mesangial disruption	Shrunk and scarred glomeruli
Subcapsular petechiae / cortical necrosis	Intimal proliferation and narrowing
Rapid ischemic dysfunction	Persistent hypoperfusion and renal scarring

TTP and HUS cannot be classified by morphology alone

- The renal lesions overlap substantially between pathogenetic subtypes.
- Appearance varies more with acute versus chronic disease than with syndrome label.
- Biopsy demonstrates microvascular injury but does not by itself establish its trigger.
- Mechanistic classification requires clinical and laboratory correlation.

A clinicopathologic approach to suspected TMA



High-yield etiologic discriminators

Possible entity	Mechanistic clue	Clinical pattern
TTP	ADAMTS13 deficiency	Often prominent neurologic manifestations
Typical HUS	Toxin-producing intestinal infection	Often bloody diarrhea → renal injury
Complement-mediated HUS	Complement regulation abnormality	Possible recurrent renal TMA
DIC	Systemic coagulation activation	Clotting-factor consumption; abnormal coagulation profile

Case 1: TTP-directed reasoning

An adult develops thrombocytopenia, red-cell fragmentation, and transient neurologic deficits. PT and PTT are normal. The full historical pentad is absent.

Which initiating mechanism deserves urgent consideration?

Case 1: ADAMTS13 deficiency is central

- The combination suggests a thrombotic microangiopathy.
- Incomplete pentad does not rule out TTP.
- ADAMTS13 deficiency, commonly from an inhibitory antibody, explains vWF-mediated platelet aggregation.
- Urgency because a delay can be fatal.

Case 2: Diarrheal prodrome

A child develops bloody diarrhea after a gastrointestinal illness. Several days later there is microangiopathic hemolysis, thrombocytopenia, and acute renal dysfunction.

Which pathogenic category best explains the presentation?

Case 2: Shiga toxin–associated HUS

- The temporally preceding diarrheal illness points toward typical HUS.
- Shiga-like toxin-producing E. Coli is a major initiating pathogen.
- Endothelial injury favors microvascular thrombosis and acute renal injury.
- The detailed toxin-to-HUS pathway remains incompletely established.

Case 3: Recurrent kidney-predominant TMA

A patient experiences repeated episodes of acute renal dysfunction with microangiopathic hemolysis and thrombocytopenia. There is no consistent antecedent diarrheal infection.

What inherited or acquired pathway warrants consideration?

Case 3: Complement dysregulation

- Recurrent HUS can reflect insufficient regulation of the alternative complement pathway.
- Factor H, factor I, CD46, C3, and factor B are implicated.
- Inherited regulatory defects or acquired antibodies can produce the phenotype.
- Complement-mediated endothelial damage distinguishes this route from TTP.

What the different therapies teach about causation

Acquired TTP

- Plasma exchange removes ADAMTS13 inhibitors
- Replacement plasma supplies functional enzyme
- The target is a vWF-cleaving enzyme defect

Hereditary complement-mediated HUS

- C5-directed therapy inhibits downstream complement activation
- Effective control of thrombosis supports complement causality
- The target is complement-mediated injury

Mechanism-specific treatment follows accurate etiologic classification.

Integrating the TTP–HUS spectrum

TTP → ADAMTS13 deficiency → Unusually large vWF multimers → Platelet aggregation

Typical HUS → Shiga-like toxin exposure → Endothelial injury / activation → Platelet activation

Complement-mediated HUS → Alternative complement dysregulation → Endothelial injury → Platelet activation

Five clinically useful principles

- MAHA with thrombocytopenia raises the possibility of TMA.
- A missing TTP pentad feature does not exclude disease.
- TTP is defined mechanistically by ADAMTS13 deficiency.
- Typical HUS follows Shiga toxin exposure; Complement-mediated HUS involves complement dysregulation.
- Acute and chronic renal lesions overlap and require clinicopathologic interpretation.

Selected primary references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026). Chapter 14, “Red Blood Cell and Bleeding Disorders,” pp. 605–606.
- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026). Chapter 20, “The Kidney,” pp. 853–855.
- Supporting context: Chapter 14, “Hemolytic anemia due to red cell trauma” and “Disseminated intravascular coagulation.”
- Original diagrams in this lecture are explanatory schematics, not clinical specimens.