

Typical hemolytic uremic syndrome

Shiga toxin–associated thrombotic microangiopathy

Etiology · endothelial injury · renal morphology · clinical consequences

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Learning objectives

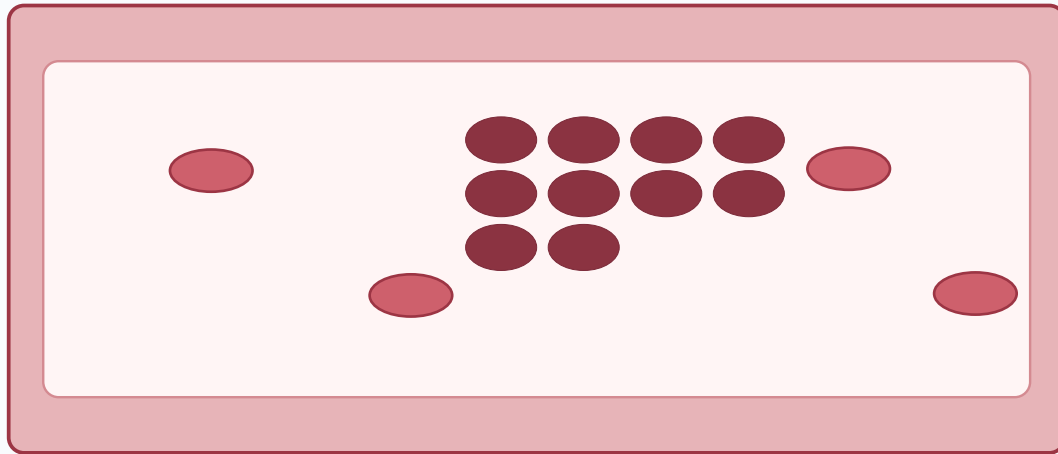
- Relate typical HUS to the broader family of thrombotic microangiopathies.
- Trace the proposed link from intestinal Shiga toxin exposure to endothelial injury and microthrombi.
- Interpret shared renal morphology and the clinical pattern of hemolysis, thrombocytopenia, and renal dysfunction.
- Distinguish typical HUS from complement-mediated HUS and thrombotic thrombocytopenic purpura.

Thrombotic microangiopathy defines the parent lesion

- Thrombotic microangiopathy (TMA) is a group of syndromes with thrombi in capillaries and/or arterioles.
- The thrombi compromise perfusion and produce tissue ischemia and organ dysfunction.
- Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are major examples.

The microvessel is the decisive anatomic site

Schematic: Microvascular lumen



Occluding platelet thrombus

- Capillary and arteriolar lumens may be narrowed or occluded by thrombi.
- Passing erythrocytes encounter increased mechanical stress.
- Microvascular obstruction links blood abnormalities to organ injury.

A single vascular process generates three consequences

Erythrocyte injury

Microangiopathic hemolytic
anemia

Platelet consumption

Thrombocytopenia

Vascular occlusion

Renal ischemia and
dysfunction

Typical HUS is a cause-defined member of TMA

Typical HUS

- Shiga toxin–associated enteric infection
- Endothelial injury appears to initiate TMA
- Renal involvement is prominent

Other major TMAs

- Complement-mediated HUS: Dysregulated complement
- TTP: Deficient ADAMTS13 activity
- Microscopic thrombi overlap across categories

What do “typical,” “epidemic,” and “diarrhea-positive” denote?

- These historical names refer to the classic enteric-infection–associated HUS syndrome.
- The preferred causal framing is Shiga toxin–mediated HUS.
- Clinical labels describe an association; They do not identify a unique histologic lesion.

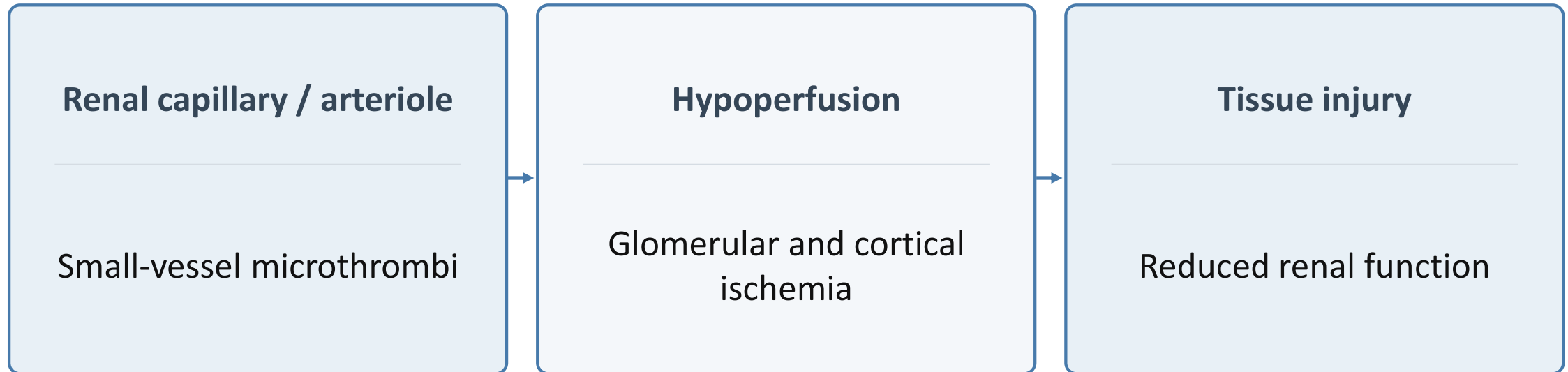
TMA classification follows the initiating disturbance

Syndrome	Principal trigger	Mechanistic emphasis
Typical HUS	Shiga toxin–producing infection	Endothelial injury
Complement-mediated HUS	Complement dysregulation	Endothelial injury
TTP	ADAMTS13 deficiency	Platelet activation

TMA phenotypes overlap more than the labels suggest

- HUS and TTP share microangiopathic anemia, platelet consumption, and tissue injury.
- Neurologic symptoms may occur in HUS; Not every patient with TTP exhibits its classic pentad.
- A causal classification is more discriminating than the clinical triad alone.

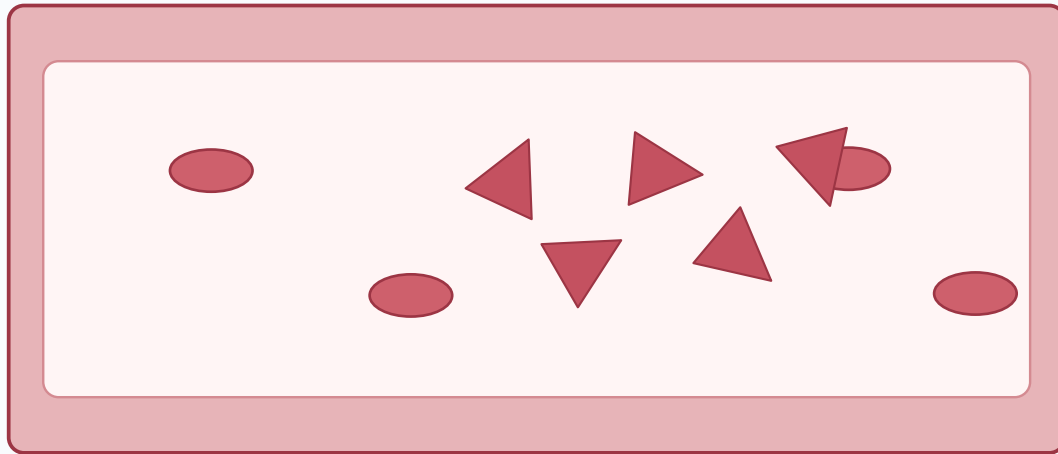
Why the kidney is a major target in HUS



The renal manifestations reflect microvascular ischemic injury.

Red cell fragmentation is mechanical, not marrow failure

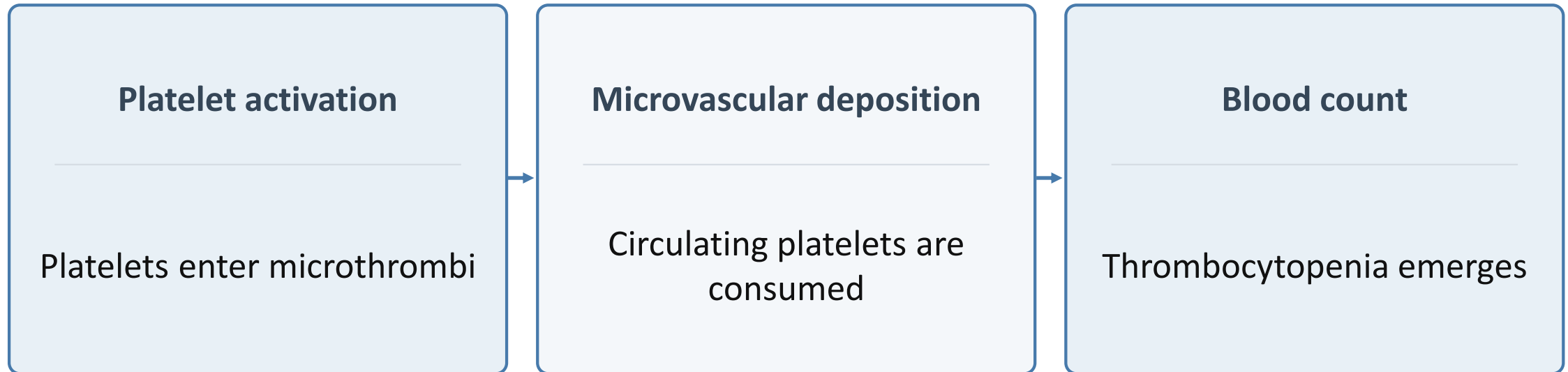
Schematic: Microvascular lumen



Fragmentation under shear

- Thrombi and narrowed lumens impose shear stress on circulating erythrocytes.
- Erythrocytes fragment within the circulation.
- The consequence is a microangiopathic hemolytic anemia.

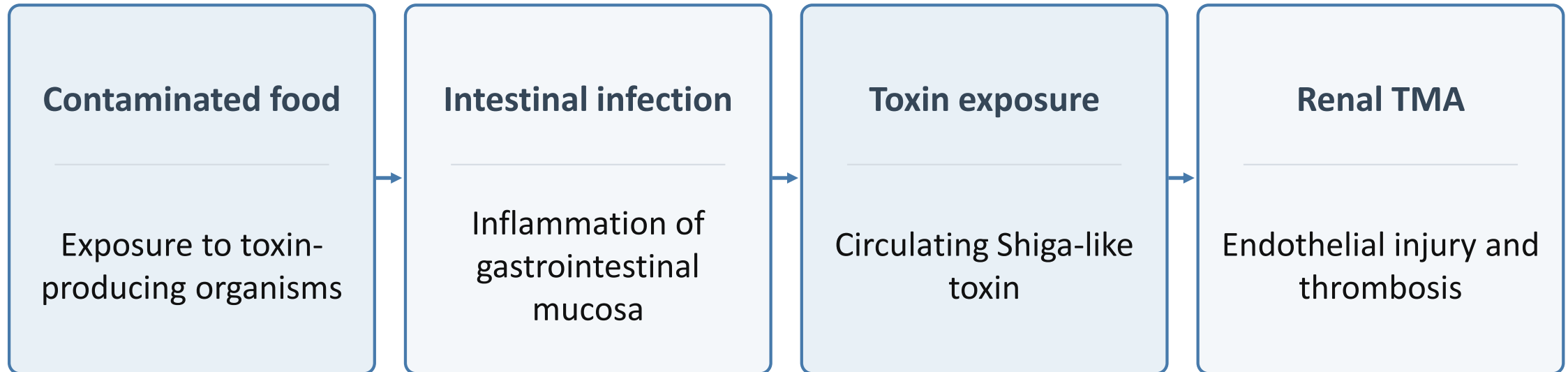
Thrombocytopenia reflects platelet consumption



Renal dysfunction is a consequence of vascular occlusion

- Glomerular capillaries and intrarenal arterioles may become thrombosed.
- Loss of perfused microvascular surface impairs function.
- Severe, extensive ischemia may progress to cortical necrosis.

Typical HUS commonly follows enteric infection



Shiga toxin–producing *Escherichia coli* is central

- Most classic HUS cases follow intestinal infection with Shiga-like toxin–producing *E. Coli*.
- The bacterial toxin, rather than a primary ADAMTS13 defect, anchors the etiologic explanation.
- The organism–toxin association defines the classical acquired form.

E. Coli O157:H7 is the textbook's leading example

- The most commonly implicated strain named is E. Coli O157:H7.
- The serotype is an illustrative frequent cause, not the definition of all Shiga toxin-mediated HUS.
- Etiologic thinking should begin with the toxin-producing infection.

Why “Shiga-like toxin” is the textbook term

- The toxins produced by the implicated E. Coli strains resemble Shiga toxin.
- The name refers to the toxin made by *Shigella dysenteriae*.
- The shared toxin mechanism explains why more than one organism may trigger this TMA pattern.

Shigella dysenteriae is a less common association

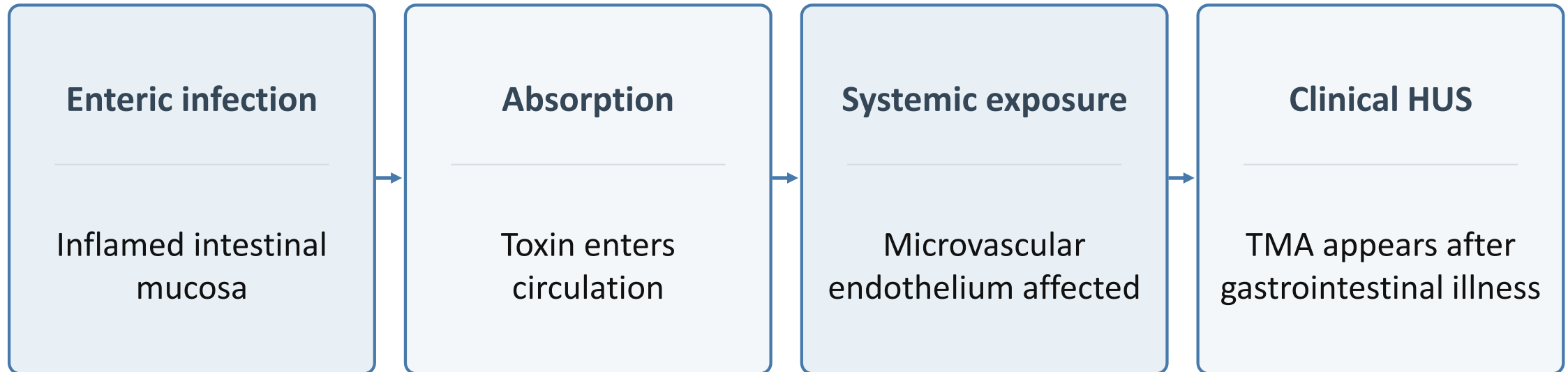
Common association

- Shiga toxin–producing E. Coli
- O157:H7 highlighted in the text
- Intestinal infection preceding HUS

Less common association

- Shigella dysenteriae
- A similar toxin-associated syndrome
- Different microorganism; Convergent endothelial injury

The intestine is the entry point for circulating toxin



Bloody diarrhea often precedes the renal syndrome

- The Chapter 14 account describes bloody diarrhea during the gastrointestinal illness.
- HUS typically emerges a few days after this enteric phase.
- The temporal sequence is an important diagnostic clue, not a unique pathognomonic sign.

Children and older adults are described as higher-risk

- Children and older adults as groups at greatest risk for infection-associated HUS.
- The epidemiologic context can strengthen suspicion after an enteric illness.
- Age does not replace etiologic or hematologic evaluation.

The precise molecular pathogenesis remains incompletely resolved

- How Shiga-like toxin causes HUS is not fully understood.
- The endothelial activation model is presented as one proposed explanation.
- A Factor H–complement link is discussed as an additional possibility.

Endothelial injury is the initiating emphasis in HUS

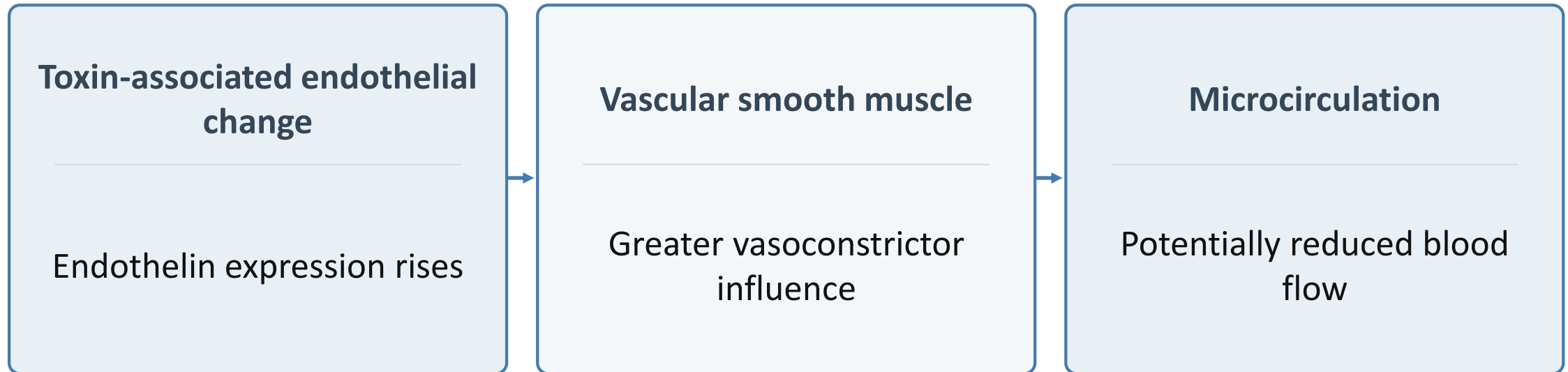


This is the dominant pathophysiologic model, not a fully settled molecular sequence.

Leukocyte adhesion molecules increase in one model

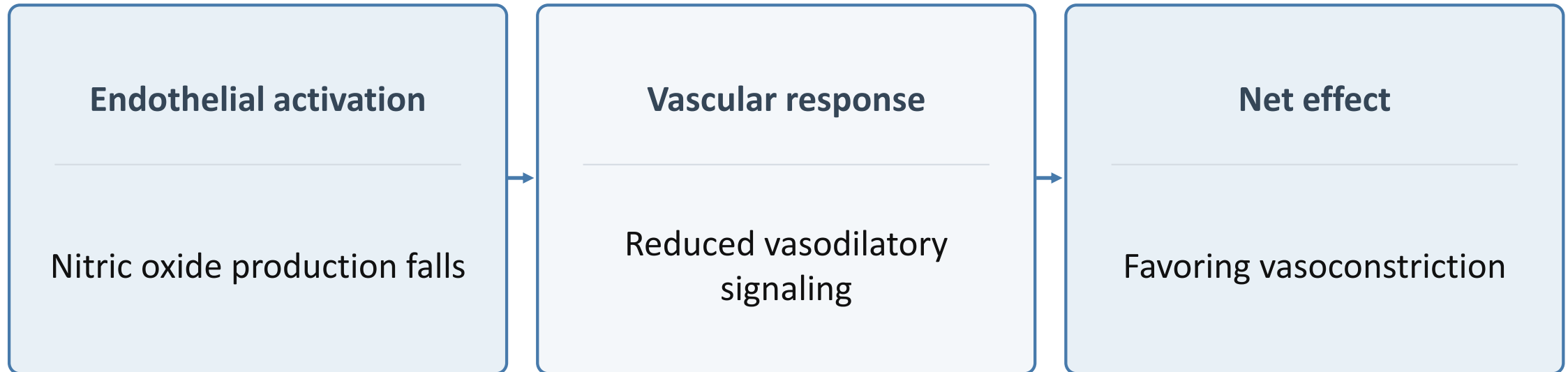
- Toxin-exposed endothelial cells are proposed to increase adhesion-molecule expression.
- The change denotes a more activated endothelial phenotype.
- This response is one component of a wider injury state linked to thrombosis.

Endothelin expression contributes to vasoconstriction



Endothelin induction is proposed in the Robbins mechanistic model.

Reduced nitric oxide removes a vasodilatory influence



Vascular tone and thrombosis amplify ischemia

Vasoconstriction

- Endothelin increased
- Nitric oxide reduced
- Further restricts blood flow

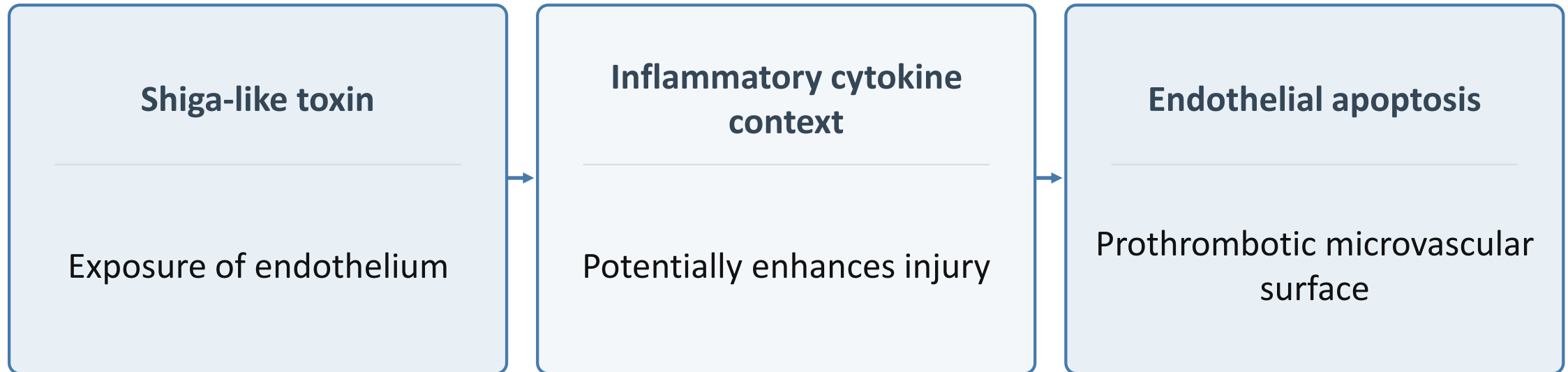
Microthrombi

- Endothelial injury activates platelets
- Aggregates narrow or occlude vessels
- Ischemic consequences converge

TNF is a conditional cofactor for endothelial apoptosis

- That cytokines such as tumor necrosis factor (TNF) may modify toxin responses.
- In their presence, Shiga-like toxin may induce endothelial apoptosis.
- This interaction is hypothesis-dependent; It is not an obligatory step in every case.

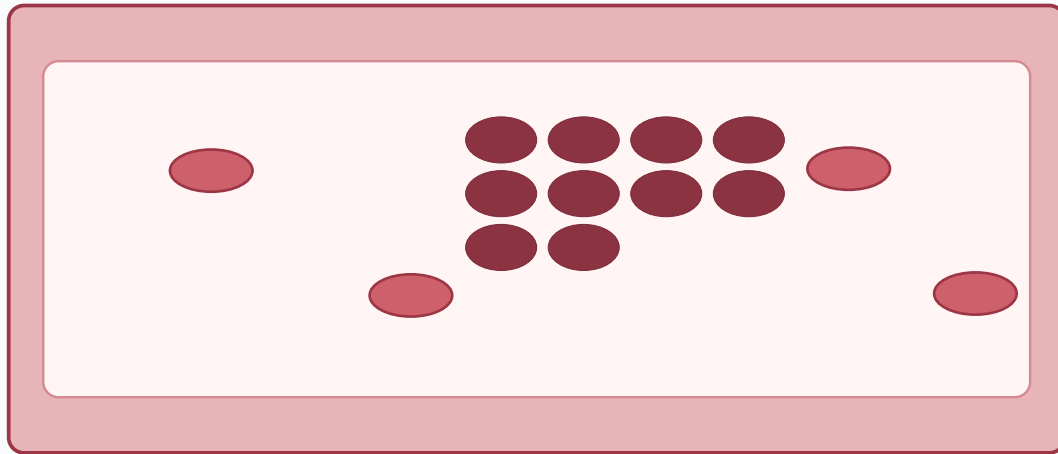
Endothelial apoptosis is one proposed lesion mechanism



Apoptosis is a conditional mechanism's model.

Endothelial injury provides a substrate for platelet activation

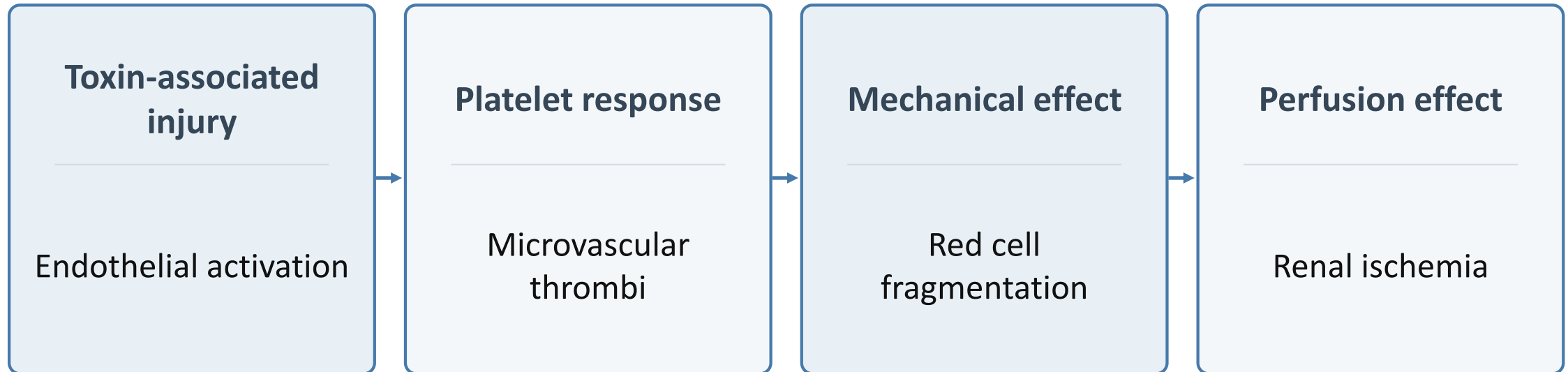
Schematic: Microvascular lumen



Occluding platelet thrombus

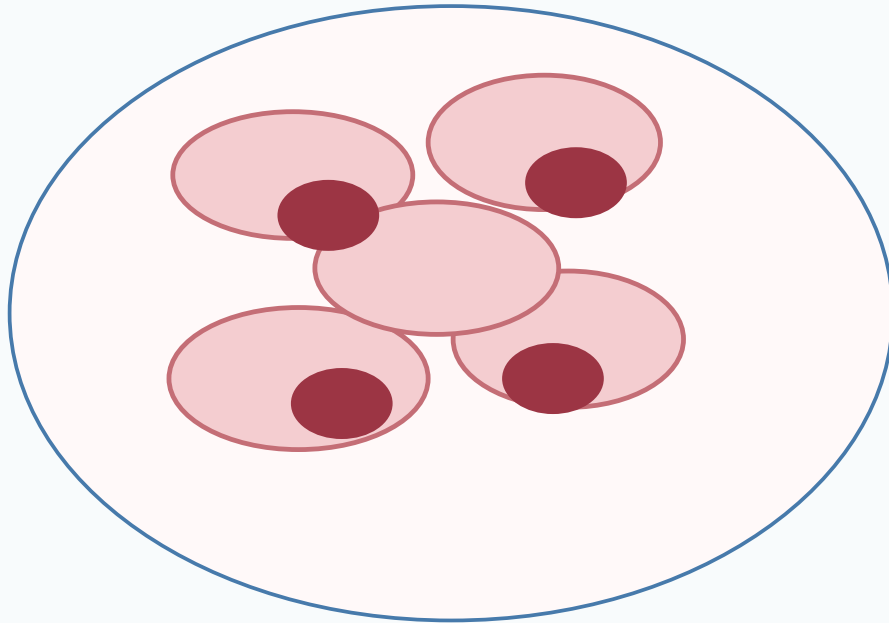
- Activated or damaged endothelium changes the local vascular environment.
- Platelet activation and aggregation are favored.
- The resulting occlusive lesions constitute thrombotic microangiopathy.

Platelet microthrombi connect toxin exposure to organ injury



The renal glomerulus is a microvascular target

Schematic glomerular capillary bundle

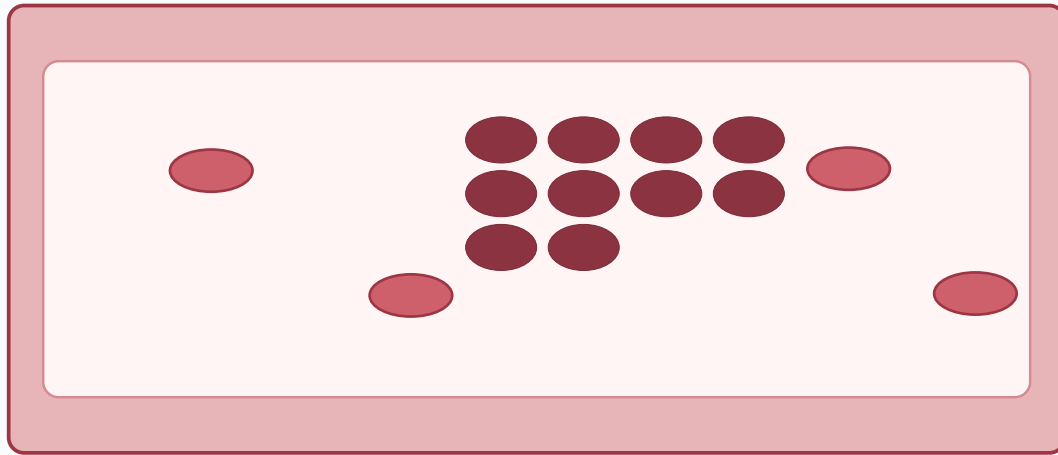


Thrombi within loops

- Glomerular capillary loops may contain thrombi.
- Occluded lumens disturb local flow and filtration.
- TMA morphology is not exclusive to Shiga toxin-mediated HUS.

Intrarenal small vessels are also involved

Schematic: Microvascular lumen



Occluding platelet thrombus

- Interlobular arteries and arterioles may contain occlusive thrombi.
- Capillary and arteriolar lesions can coexist.
- Widespread involvement increases the risk of ischemic damage.

An integrated proposed pathogenesis

Enteric infection

Shiga-like toxin

Endothelial response

Activation ± apoptosis

Hemodynamic change

↑ endothelin · ↓ nitric oxide

Platelet thrombosis

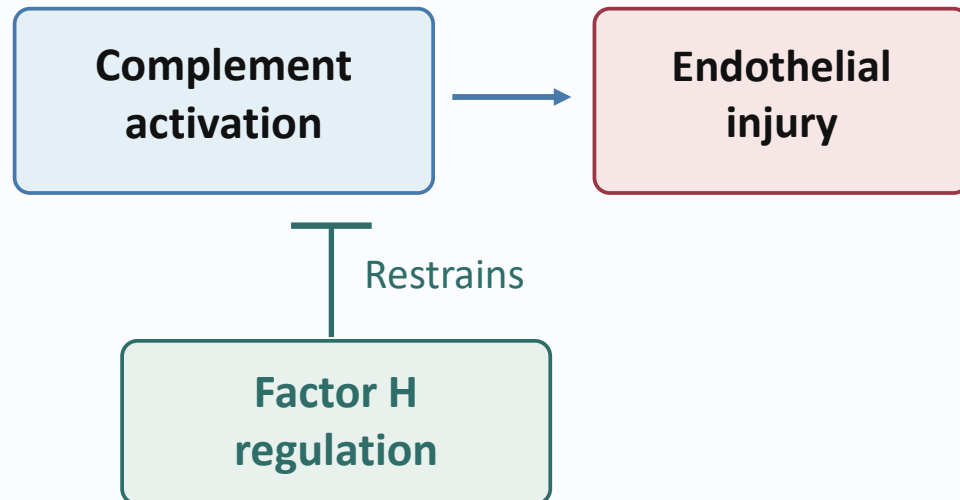
Occlusive microthrombi

TMA phenotype

Hemolysis · ↓ platelets · renal injury

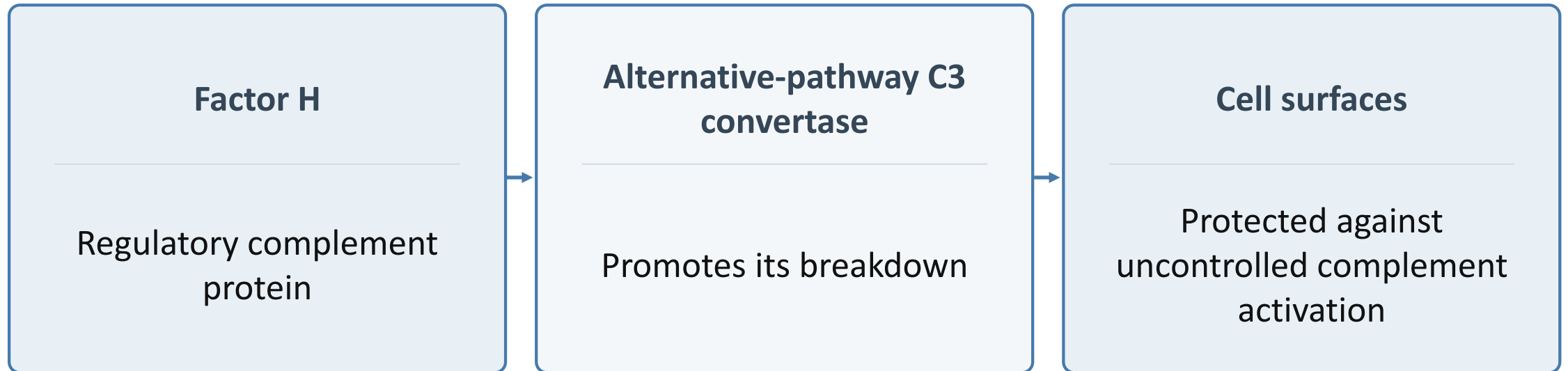
Factor H offers a possible complementary mechanism

Proposed mechanism · not definitive



- A proposed toxin–Factor H interaction could impair complement regulation.
- Reduced regulation might permit excessive complement activation.
- This link as intriguing evidence, not an established universal pathway.

Factor H normally restrains alternative-pathway activity



Do not equate a toxin hypothesis with inherited HUS

Typical HUS

- Shiga-like toxin exposure is the usual initiating insult
- Factor H interference is a proposed contribution
- A preceding intestinal infection is characteristic

Complement-mediated HUS

- Primary dysregulation of complement regulation
- Mutations or regulatory autoantibodies described
- Triggers and course differ by etiology

HUS and TTP start from different dominant events

HUS: Endothelium first

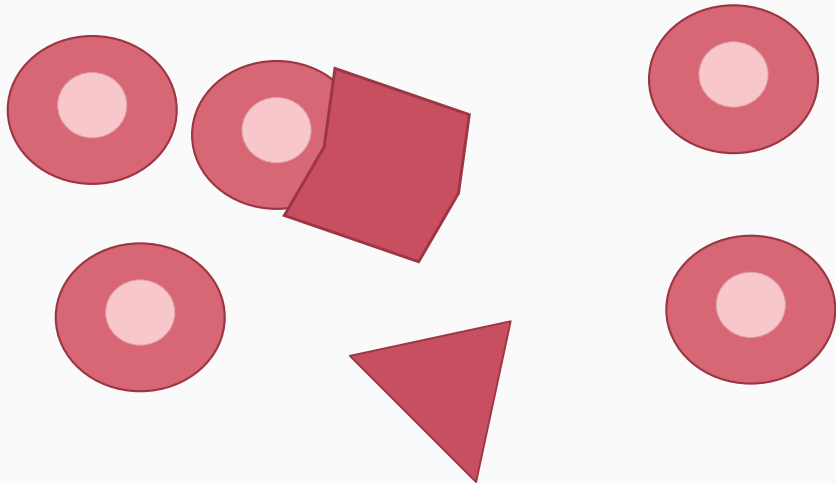
- Toxin or complement disturbance
- Endothelial injury / activation
- Secondary platelet activation

TTP: Platelets first

- ADAMTS13 function deficient
- Ultra-large vWF multimers persist
- Platelet activation initiates microthrombi

Schistocytes reflect shear across damaged microvessels

Schematic red-cell forms — not a blood film



Fragmented erythrocytes

- Luminal narrowing imposes mechanical stress on erythrocytes.
- Fragmented red cells may appear as schistocytes or helmet-shaped forms.
- Morphology supports microangiopathic hemolysis, but does not establish its cause.

Microangiopathic anemia is a shared TMA manifestation

- TTP and HUS both develop intravascular mechanical hemolysis.
- The anemia is downstream of microvascular thrombi and altered flow.
- Hemolysis alone cannot distinguish infectious HUS from other thrombotic microangiopathies.

PT and PTT are usually normal in TTP and HUS

TMA (HUS/TTP)

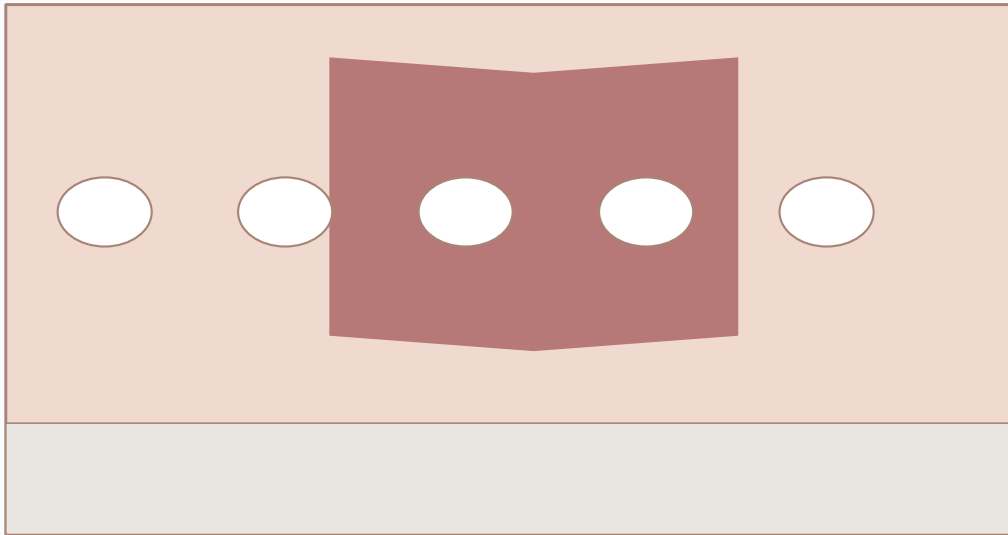
- Platelet-rich microvascular thrombi
- Coagulation cascade not the primary initiating mechanism
- PT and PTT usually normal

DIC

- Pathogenetically distinct process
- Activation of coagulation is central
- Some findings, including hemolysis, overlap

Acute renal TMA may cause cortical necrosis

Schematic renal cortical ischemia

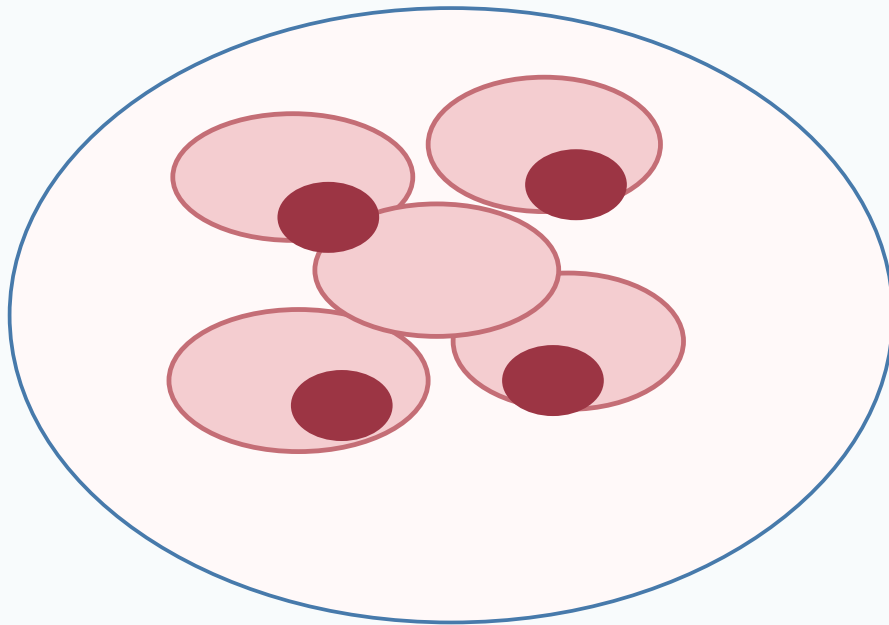


Ischemic cortical region

- Kidneys may exhibit patchy or diffuse cortical necrosis.
- Subcapsular petechiae may accompany acute injury.
- Severe perfusion disturbance can produce sharply cortex-limited infarction.

Glomerular thrombi distend and obstruct capillary loops

Schematic glomerular capillary bundle



Thrombi within loops

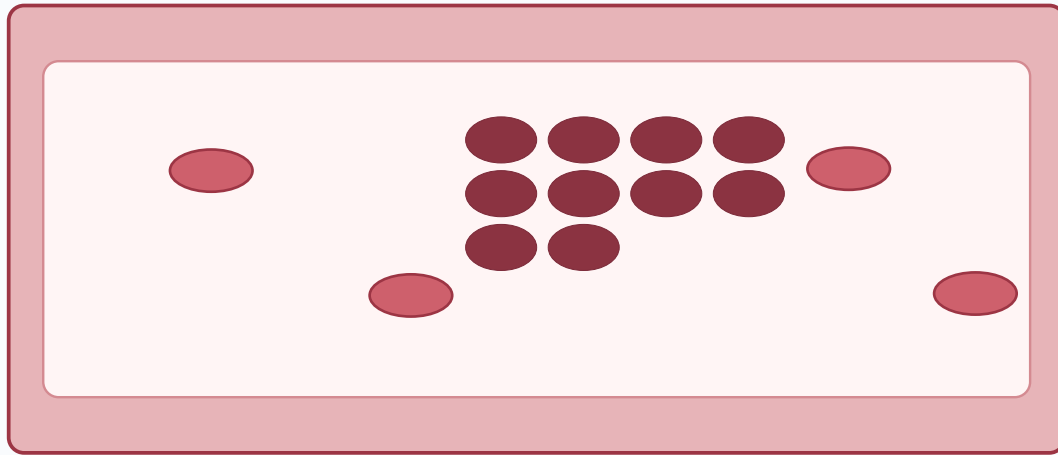
- Glomerular capillaries are described as distended by thrombi.
- Occlusion interrupts local perfusion.
- This morphologic pattern is shared by different HUS/TTP etiologies.

Mesangial matrix and cells may be damaged

- Active renal TMA can disrupt mesangial matrix.
- Damage to mesangial cells may culminate in mesangial destruction.
- These lesions accompany capillary thrombosis in the shared morphology account.

Interlobular arterial and arteriolar thrombi

Schematic: Microvascular lumen

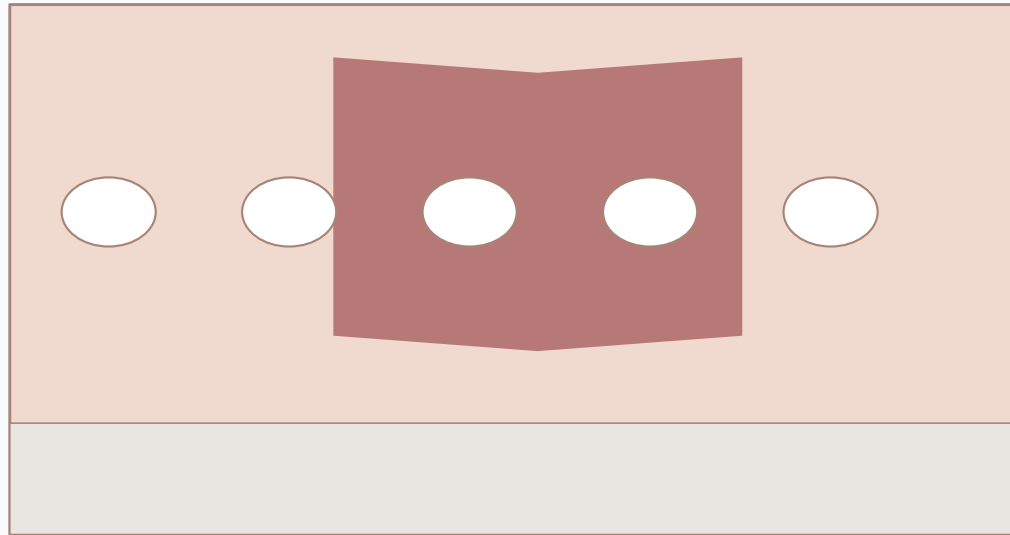


Occluding platelet thrombus

- Small arterial lumens may be obstructed by thrombi.
- Vessel occlusion contributes to cortical ischemia.
- The anatomic distribution explains why diffuse injury can follow small-vessel disease.

Extensive ischemia can produce cortical infarction

Schematic renal cortical ischemia



Ischemic cortical region

- When severe, the ischemic process may be sharply confined to the cortex.
- Histology may show coagulative necrosis with relatively preserved adjacent areas.
- A large ischemic territory can manifest clinically as renal failure.

Repeated endothelial damage leaves chronic vascular scars

- The shared HUS/TTP morphology varies with disease chronicity.
- Persistent or prior microvascular injury may leave cortical scarring.
- Chronic features are particularly emphasized in the atypical HUS section; They are not diagnostic of infection-associated HUS.

Double contours reflect chronic capillary-wall remodeling

Acute lesion

- Capillary distension
- Microthrombotic occlusion
- Mesangial injury

Chronic remodeling

- Shrunken glomeruli
- Basement-membrane duplication
- Double contours / “tram tracks”

Arterial remodeling may perpetuate hypoperfusion

- Chronically injured arteries may accumulate extra cell and connective-tissue layers.
- The resultant wall thickening narrows the lumen.
- Arteriolar hyalinosis may become prominent when chronic features predominate.

Renal TMA morphology does not specify its trigger

Shared pathologic observation	What it supports	What it cannot prove
Glomerular thrombi	Active microvascular thrombosis	Shiga toxin etiology
Mesangial injury	Microvascular tissue damage	Specific HUS subgroup
Double contours	Chronic endothelial injury	Unique infectious cause

Renal-predominant HUS and neurologic-predominant TTP

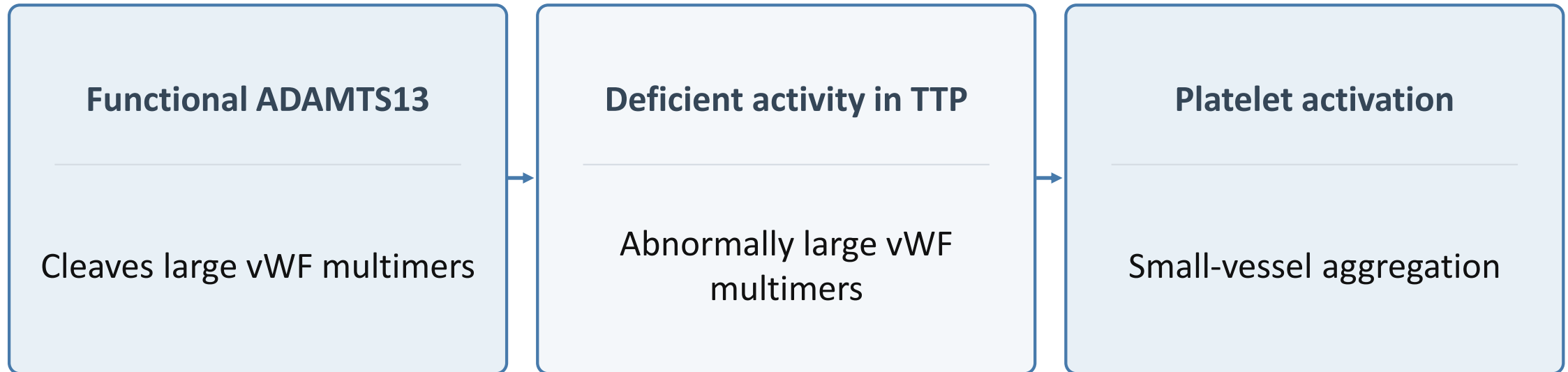
HUS pattern

- Renal failure often prominent
- Hemolytic anemia and thrombocytopenia
- Some patients still develop neurologic symptoms

TTP pattern

- Neurologic involvement classically prominent
- Severe renal injury less common
- The clinical spectra overlap

ADAMTS13 distinguishes TTP mechanism from HUS



The Chapter 14 source describes normal ADAMTS13 levels in HUS.

Toxin history and complement dysregulation are different clues

Clinical–causal clue	Typical HUS	Complement-mediated HUS
Trigger	Enteric toxin-producing infection	Inherited/acquired regulation defect
Initiating emphasis	Endothelial toxin injury	Complement-mediated endothelial injury
Course	Recovery often occurs after acute episode	May recur or persist

The diagnosis should integrate cause, blood and organ findings

Causal setting

Recent enteric illness /
Shiga toxin association

Hematologic syndrome

Hemolysis + platelet
consumption

Organ injury

Acute renal dysfunction /
ischemic TMA

Do not assign “typical HUS” from a renal biopsy alone

- Active HUS and TTP lesions may be morphologically indistinguishable.
- Biopsy establishes microvascular injury and its chronicity, not the precise causal trigger.
- The infectious context and the broader hematologic differential remain essential.

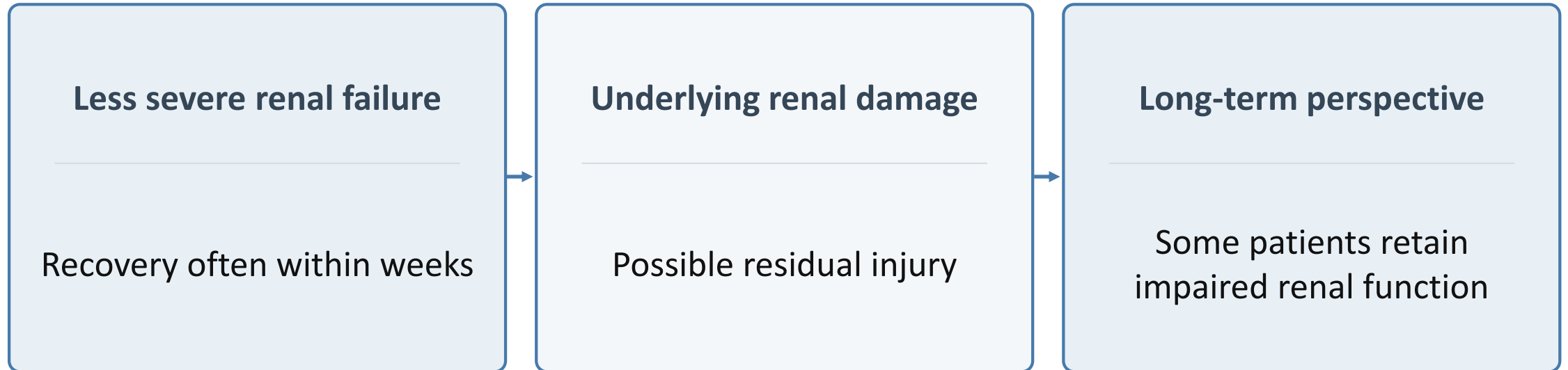
DIC can mimic the hemolytic microvascular pattern

- DIC and TMA can both produce microvascular occlusion and red cell fragmentation.
- Unlike HUS and TTP, coagulation-cascade activation is central to DIC.
- Interpret the coagulation profile within the full clinical context.

Renal recovery commonly occurs over weeks in milder disease

- That most patients with less severe renal failure recover renal function within weeks.
- This describes an acute recovery pattern, not assurance of lifelong renal normality.
- The extent of initial renal damage influences later risk.

Greater initial renal injury changes the prognosis



Long-term renal risk persists despite acute improvement

- The chapter cautions that 15–25-year renal outcomes are less reassuring than short-term recovery.
- Residual structural injury may remain clinically relevant after the infection resolves.
- Follow-up cannot be replaced by the observation that acute renal function improved.

A quoted follow-up study is a cohort, not a prevalence

Normal renal function in 10 of 25 patients with prior typical HUS at long-term assessment.

10

Normal renal function

15

Not normal renal function

One historical cohort (n = 25); Not a population-level probability or prediction.

Supportive care is the textbook's treatment emphasis

- Chapter 14 describes infection-associated HUS as managed supportively.
- Some survivors have permanent kidney damage and may require renal replacement therapy.
- Specific modern testing or treatment algorithms are outside the source-defined scope of this lecture.

Case: Renal failure after bloody diarrheal illness

A child has a bloody diarrheal illness, followed several days later by anemia, thrombocytopenia, and acute renal dysfunction.

Which initiating association best explains this pattern?

Shiga toxin–producing enteric infection causing typical HUS; The evidence is a constructed teaching vignette, not a patient record.

Case: Identical biopsy, different etiologic mechanism

Two patients show glomerular capillary thrombi and mesangial damage. One had preceding enteritis; The other has a defect in complement regulation.

Can the shared renal microscopic changes identify which patient has typical HUS?

No. HUS/TTP forms share a TMA morphologic pattern; Causal context is required to type the syndrome.

Case: Neurologic deficits do not automatically exclude HUS

A patient with microangiopathic hemolysis, thrombocytopenia and kidney injury also develops neurologic symptoms.

Does neurologic dysfunction alone establish TTP?

No. The source explicitly notes overlap and neurologic findings in some patients with HUS.

Clinical synthesis: Trace cause to consequence

Cause

Shiga toxin enteric illness

Primary process

Endothelial injury / activation

Microvascular lesion

Platelet-rich thrombosis

Blood effects

Schistocytes + thrombocytopenia

Kidney effects

Ischemia / renal impairment

Five conclusions to retain

- Typical HUS is a Shiga toxin–associated thrombotic microangiopathy.
- Endothelial injury, platelet activation, and microvascular obstruction explain its renal and blood manifestations.
- The precise toxin-to-TMA mechanism remains incompletely understood.
- Morphologic TMA does not identify its specific etiology.
- Acute renal recovery does not exclude important long-term consequences.

Textbook sources and interpretive boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026. Chapter 20, “The Kidney,” pp. 853–855.
- Same textbook, Chapter 14, “Red Blood Cell and Bleeding Disorders,” pp. 605–606 and section on red cell trauma.
- Source text was supplied in Markdown; original chapter-page images were not available for direct verification.
- Vascular, blood-smear, and renal figures in this deck are original editable schematics, not clinical specimens.