

Thrombotic Microangiopathies

Renal mechanisms, morphology, and clinicopathologic interpretation

TTP • Shiga toxin–HUS • Complement-mediated TMA

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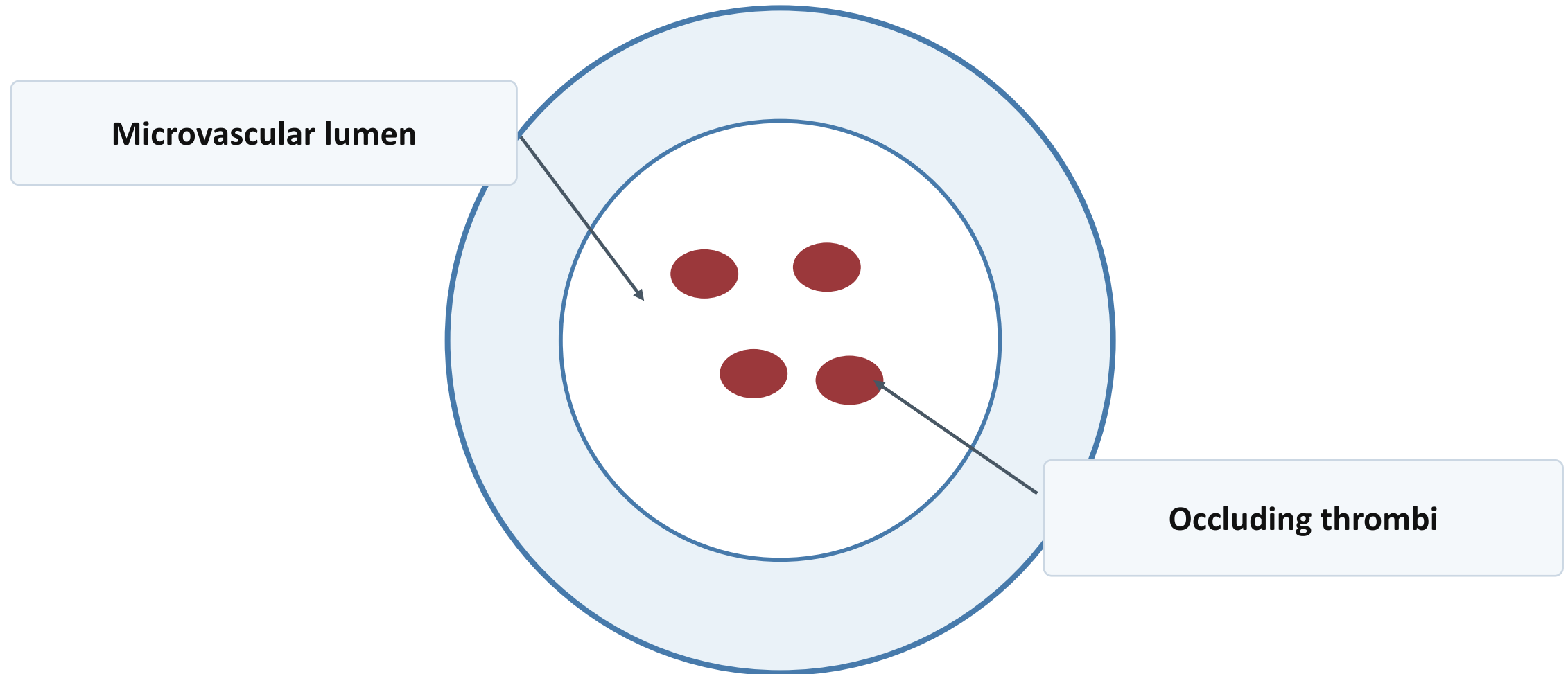
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Learning objectives

- Define the shared pathologic lesion in thrombotic microangiopathy (TMA).
- Contrast the causal pathways of Shiga toxin–HUS, complement-mediated TMA, and TTP.
- Identify acute and chronic renal vascular and glomerular lesions.
- Connect morphology to the clinical pattern and etiologic investigation.

TMA: A syndrome defined by microvascular thrombi



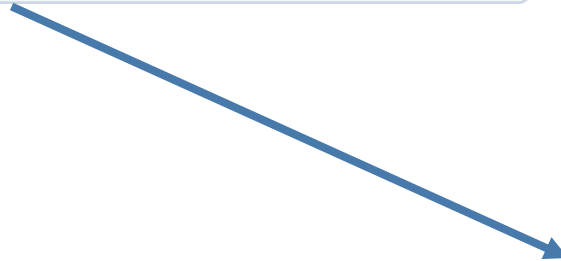
Schematic — not a histologic specimen

The lesion is shared; The triggers differ

Endothelial injury

Excess platelet aggregation

Occlusive microvascular thrombi



From thrombi to the clinical syndrome

Microvascular thrombi

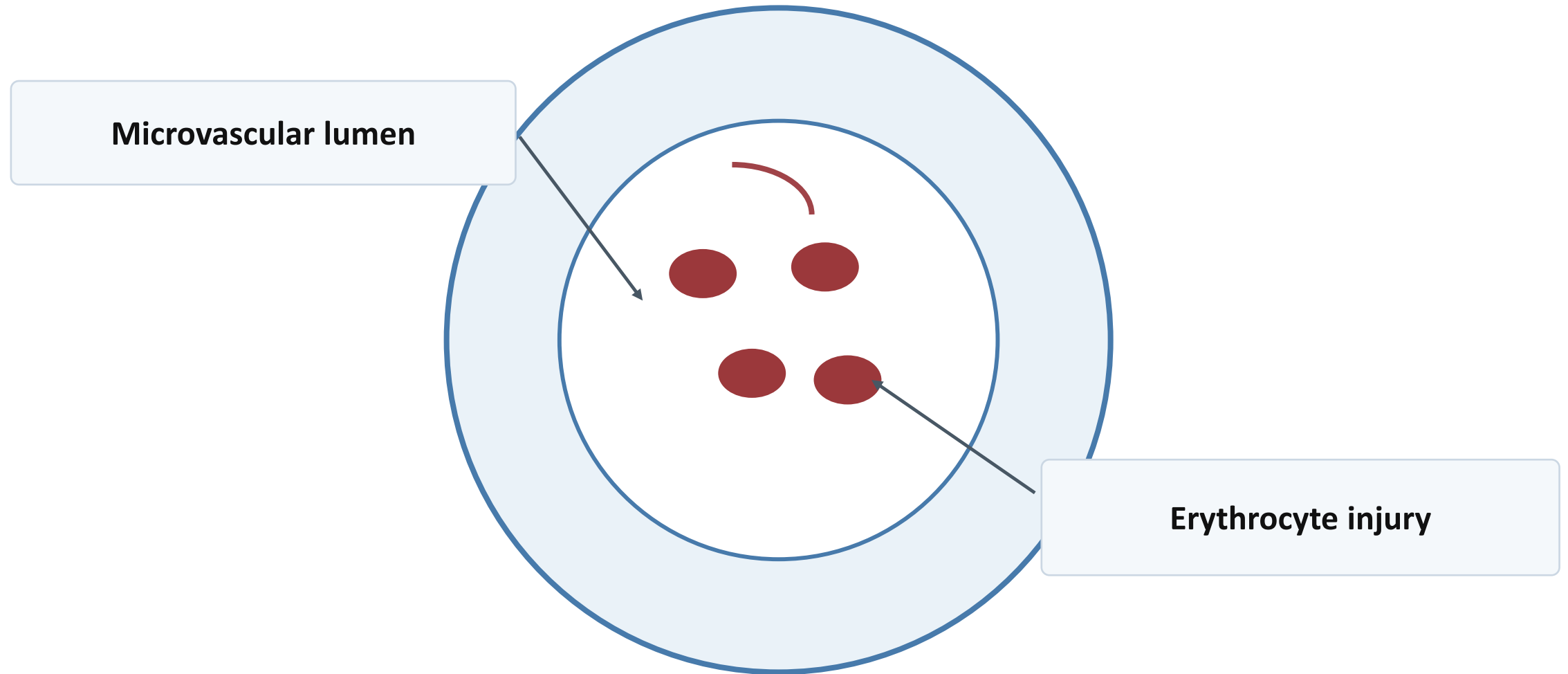


**Platelet consumption +
red-cell injury**



**Organ ischemia /
dysfunction**

Why red cells are injured



Schematic — not a histologic specimen

Why the platelet count falls

Platelet activation



Platelet-rich microthrombi



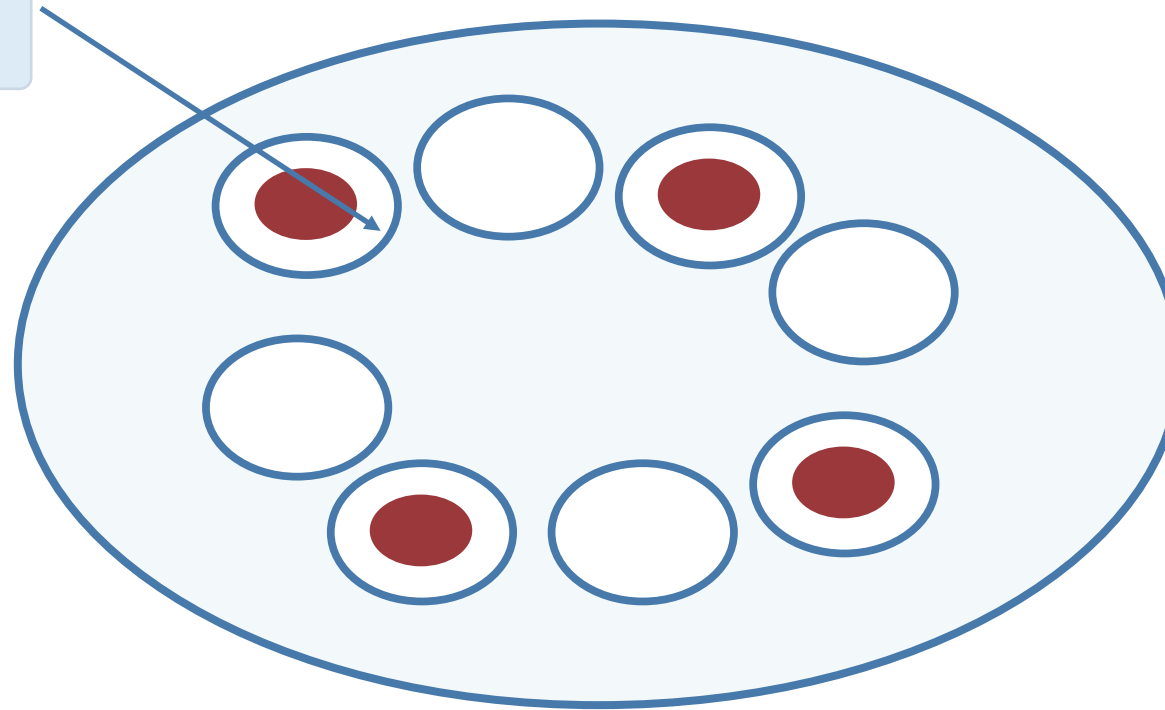
**Consumptive
thrombocytopenia**

Why ischemia follows microvascular occlusion



TMA affects capillaries and arterioles

Capillary thrombi



**Glomerular tuft
(idealized)**

Schematic — not a histologic specimen

Etiologic classification is more useful than symptoms alone

Shiga toxin–HUS

Shiga toxin–producing enteric bacteria

Complement-mediated TMA

Defective complement regulation or regulator antibodies

TTP

Deficient ADAMTS13 activity

Secondary TMA associations

Vascular, autoimmune, gestational or toxic injury

Two dominant pathogenic entry points

**Endothelial injury
(HUS pathways)**

**Excess platelet activation
(TTP pathway)**

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graph TD; A[Endothelial injury (HUS pathways)] --> D[Thrombosis → ischemia]; B[Excess platelet activation (TTP pathway)] --> D;
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Thrombosis → ischemia

Endothelial injury promotes thrombosis

**Endothelial damage /
activation**



Platelet recruitment



Microvascular occlusion

Platelet aggregation can initiate thrombosis

ADAMTS13 deficiency



Very large vWF multimers



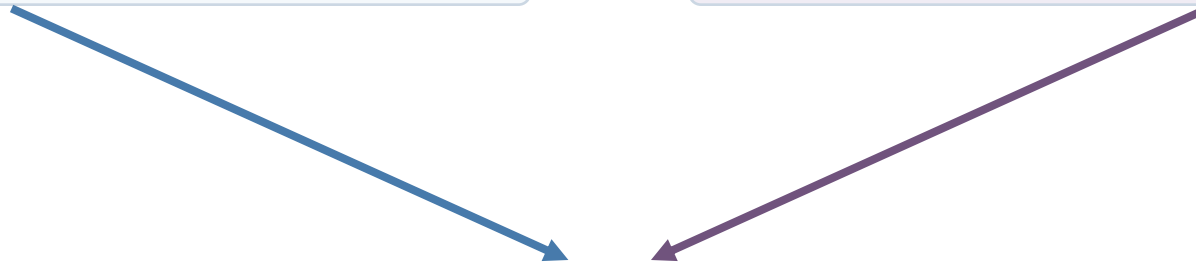
Platelet-rich microthrombi

HUS and TTP converge on the same injury pattern

HUS / endothelial route

TTP / vWF route

Shared microangiopathic morphology



TMA and disseminated intravascular coagulation are distinct

TTP / HUS

Primary platelet/endothelial pathway

Microvascular thrombi

PT / PTT usually normal

DIC

Systemic coagulation activation

Microvascular thrombi

Coagulation tests often abnormal

Clinical overlap does not eliminate etiologic differences

- The traditional TTP pentad is not present in every patient.
- HUS can include fever and neurologic manifestations.
- Clinical distribution suggests a subtype; Mechanism establishes a more reliable distinction.

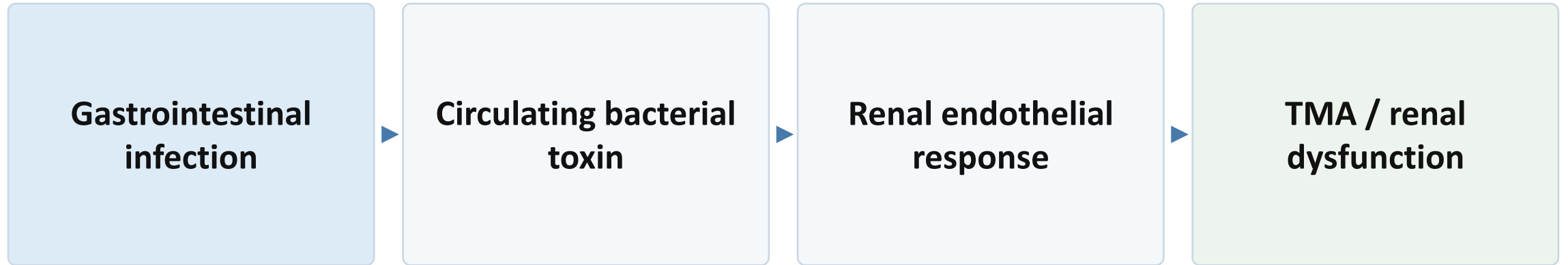
Shiga toxin–mediated HUS: The initiating exposure



Typical HUS is linked to enteric infection

- The offending bacteria produce toxins resembling Shiga toxin.
- Contaminated food may transmit the infection.
- The gastrointestinal illness may precede renal and hematologic findings.

A clinical sequence: Intestine to kidney



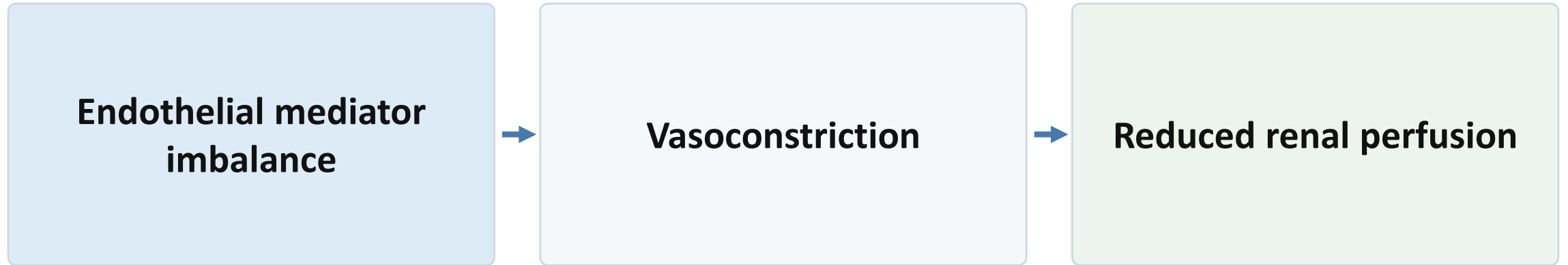
Shiga-like toxin: An endothelial injury model



Changes in endothelial mediators

- Increased leukocyte adhesion molecule expression.
- Endothelin may increase, while nitric oxide production may decrease.
- Such changes can favor vasoconstriction and platelet activation.

Vasoconstriction can amplify endothelial injury



Shiga toxin and factor H: A proposed link



Typical HUS: Clinical sequence

Bloody diarrheal illness



Interval of several days



**Hemolysis +
thrombocytopenia + AKI**

Recovery does not always imply no renal sequelae

- Many survivors of less severe typical HUS regain renal function within weeks.
- Some experience persistent renal damage despite surviving the acute illness.
- Later renal function should not be inferred solely from early recovery.

Complement-mediated TMA: Loss of regulation

Complement dysregulation

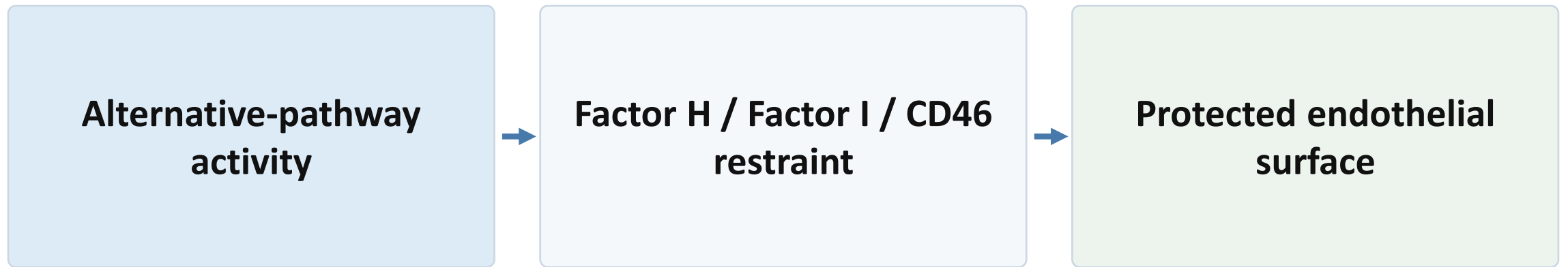


Endothelial injury



**Platelet activation / renal
TMA**

Normal complement regulators protect vascular surfaces



Factor H protects against uncontrolled complement

Impaired factor H



**Excess alternative-pathway
activation**



Renal endothelial injury

Factor I and CD46: Additional regulatory defects

Regulatory protein	Role in disease
Factor I	Inherited dysregulation can permit complement activity
CD46	Membrane-associated protective regulation
Factor H	C3 convertase control

Complement components may also be implicated

**Complement pathway
abnormality**



**Poorly controlled
activation**



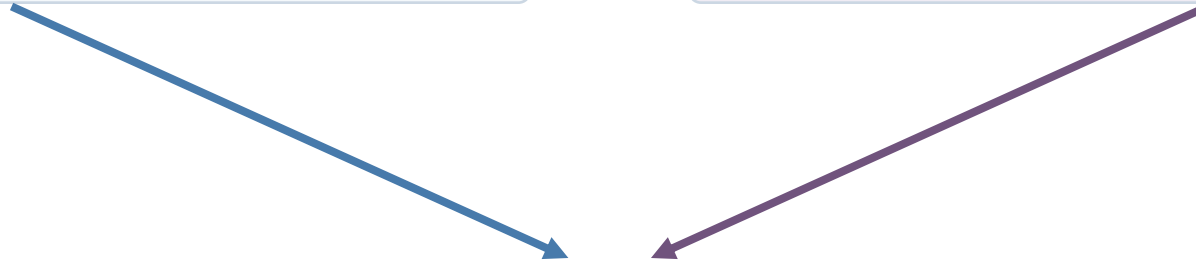
**Endothelial thrombogenic
injury**

Inherited susceptibility may require a second insult

Inherited susceptibility

Superimposed trigger

Clinical complement-mediated TMA



Acquired antibodies can impair complement protection

Complement-mediated TMA

Antibodies to complement regulators

Excess complement activation

Predominantly endothelial trigger

Acquired TTP

Antibodies inhibiting ADAMTS13

Very large vWF multimers

Predominantly platelet trigger

Not all HUS-like TMAs are complement disorders

Immune / thrombotic

Antiphospholipid antibodies

Pregnancy

Pregnancy or postpartum complications

Renal vascular

Systemic sclerosis; Severe hypertension

Exposures

Chemotherapeutic / immunosuppressive drugs; Radiation

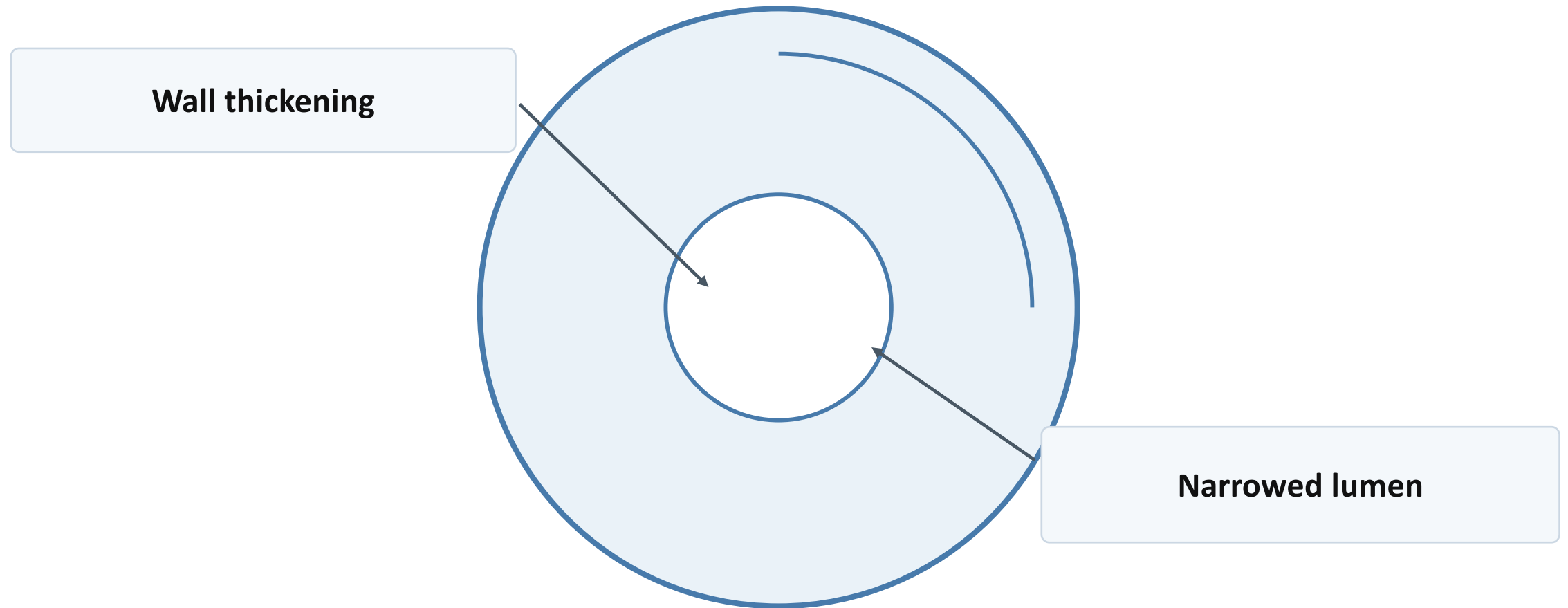
Antiphospholipid syndrome can trigger renal TMA

- Antiphospholipid antibodies are associated with endothelial and thrombotic disease.
- Renal microangiopathy may resemble HUS/TTP microscopically.
- The causative clinical setting is important for etiologic assignment.

Pregnancy and postpartum TMA

- Pregnancy-related complications are recognized settings for TMA.
- Postpartum renal failure can represent a microangiopathic process.
- Some affected patients may have underlying complement regulatory defects.

Systemic sclerosis and severe hypertension



Schematic — not a histologic specimen

Drugs and radiation may damage the endothelium

- Chemotherapeutic and immunosuppressive agents are reported associations.
- Radiation exposure is another recognized endothelial insult.
- Evaluation of exposure is part of etiologic interpretation.

Complement-mediated and secondary TMA may persist



TTP: Deficiency of ADAMTS13

ADAMTS13 deficiency



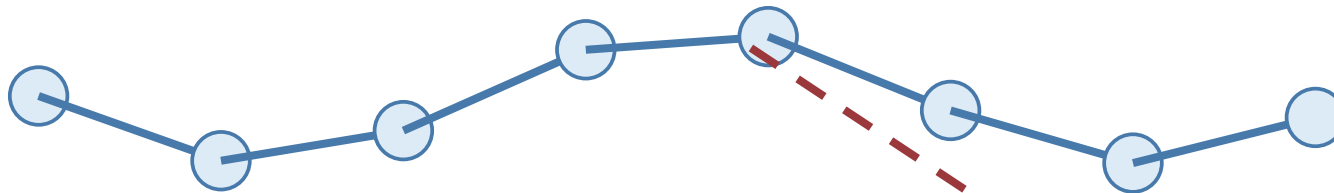
**Large vWF multimers
persist**



Platelet-rich thrombi

Normal ADAMTS13 restrains vWF multimer size

Intact vWF multimer

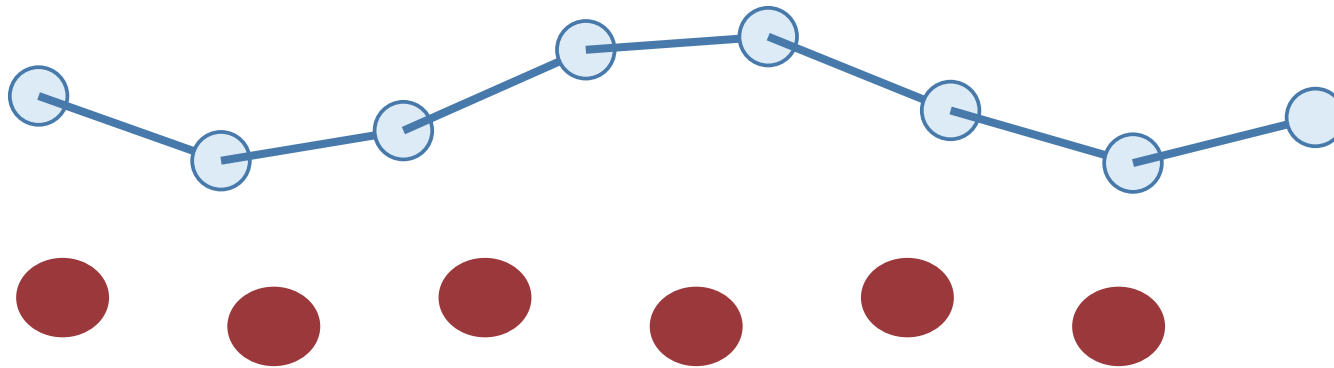


ADAMTS13 proteolysis

Schematic — molecular relationships simplified

Excessively large vWF multimers recruit platelets

Uncleaved very large vWF



Platelet recruitment + aggregation

Schematic — molecular relationships simplified

Acquired TTP is most often antibody-mediated

Inhibitory antibodies



Low functional ADAMTS13



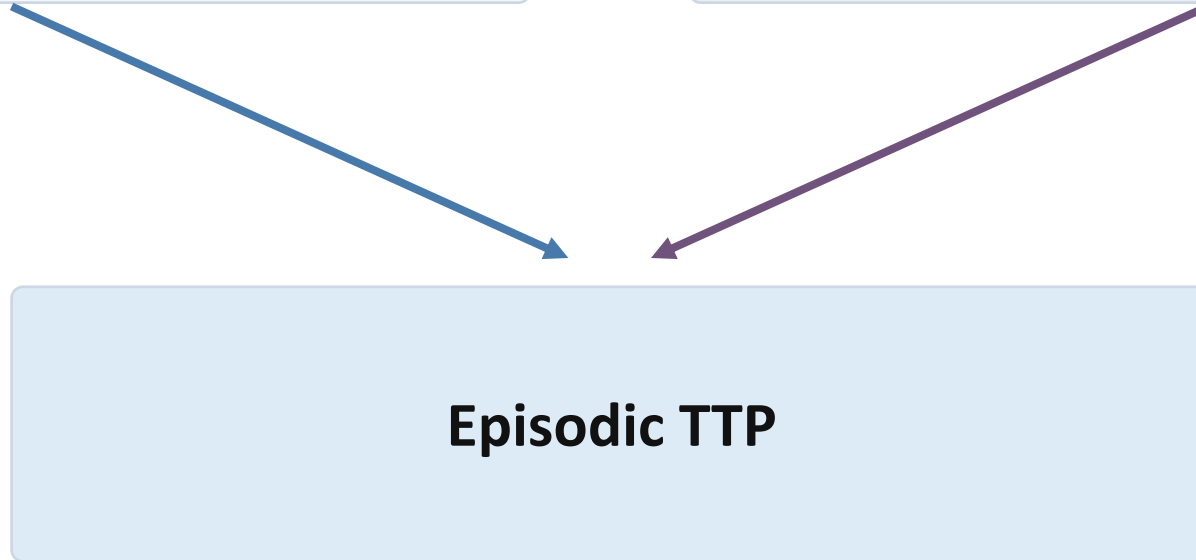
Platelet microthrombi

Inherited TTP arises from ADAMTS13 mutations

Inherited enzyme deficiency

Additional trigger

Episodic TTP



TTP commonly has prominent neurologic involvement

TTP tendency

Neurologic findings often prominent

Thrombocytopenia often marked

Severe kidney failure less typical

HUS tendency

Renal dysfunction often prominent

Thrombocytopenia may be less pronounced

Acute renal failure characteristic

The classic TTP pentad is a historical description

- Fever
- Neurologic abnormalities
- Microangiopathic hemolytic anemia
- Thrombocytopenia and renal dysfunction

Do not require the complete pentad

- Many affected patients lack one or more components of the classic pentad.
- HUS may also produce neurologic manifestations or fever.
- Reasoning should prioritize TMA recognition and the underlying etiology.

ADAMTS13 is a mechanistic discriminator

TTP

Deficient ADAMTS13

Platelet-vWF initiation

Neurologic tendency

Atypical / complement TMA

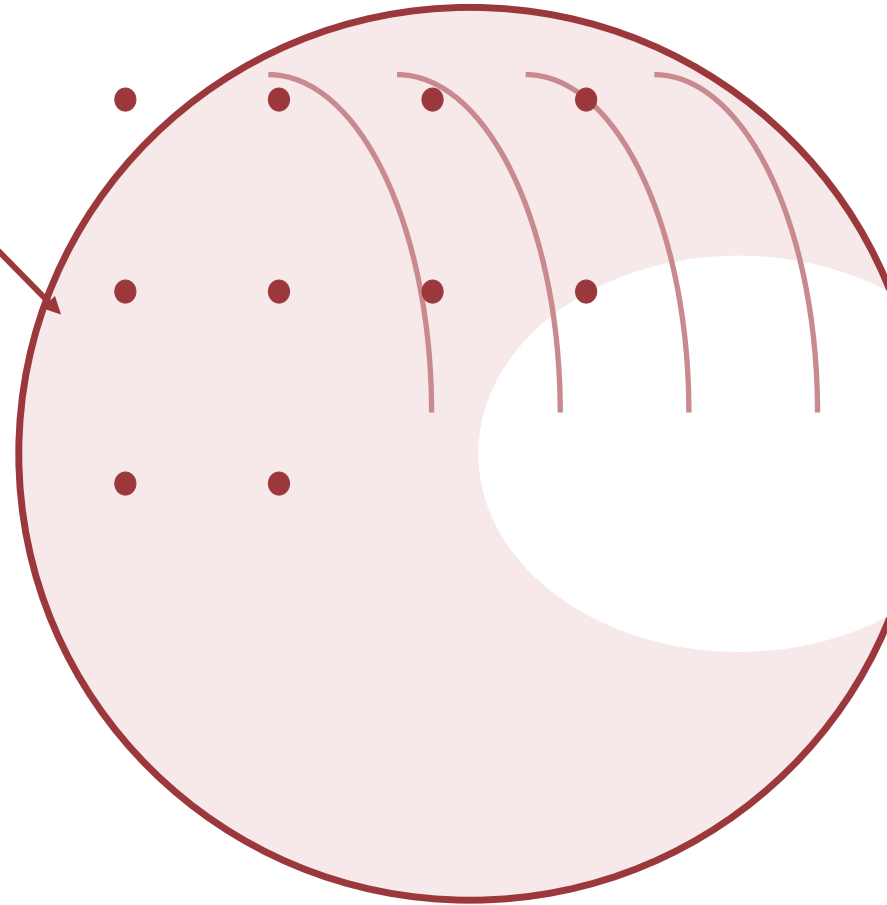
ADAMTS13 generally preserved

Endothelial/complement initiation

Renal tendency

Acute renal TMA: Gross manifestations

**Subcapsular petechiae /
ischemia**

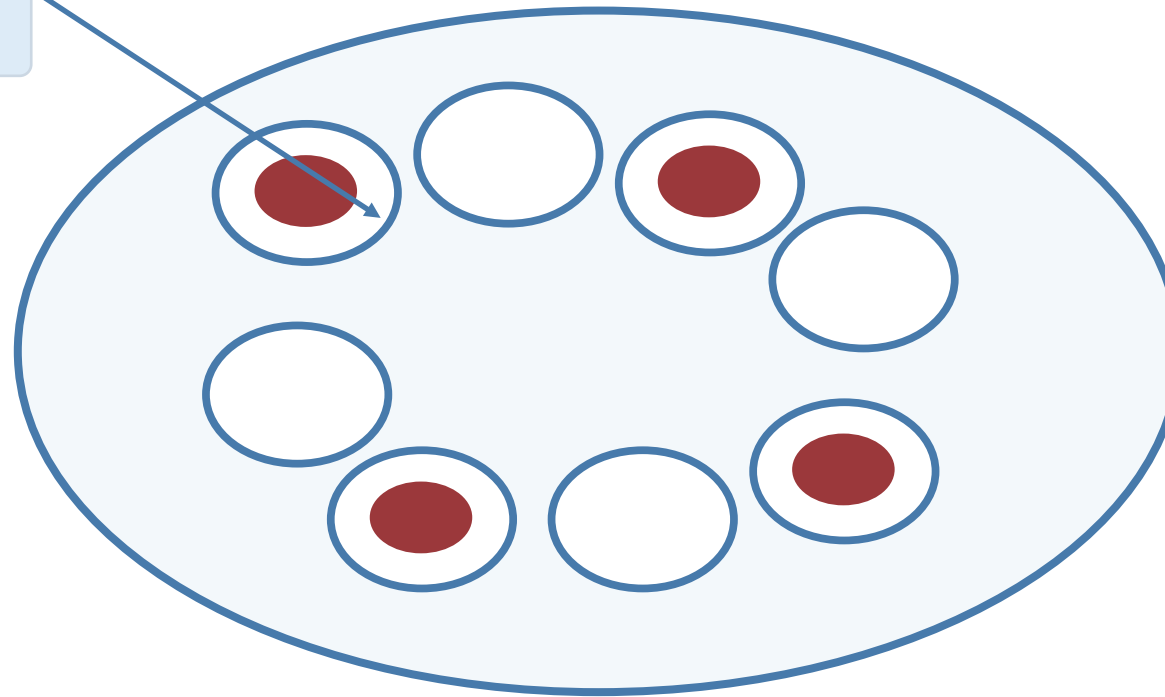


**Simplified kidney
outline**

Schematic — not a gross specimen

Glomerular capillaries may be occluded by thrombi

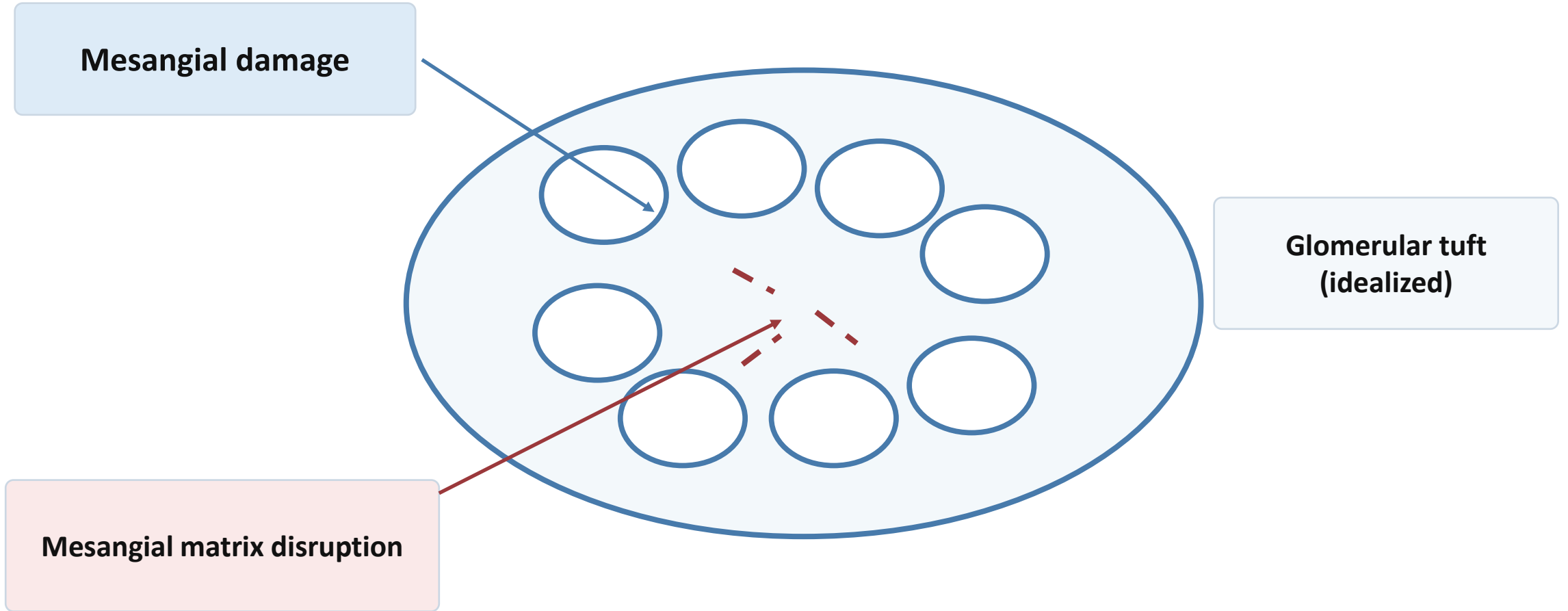
Capillary thrombi



**Glomerular tuft
(idealized)**

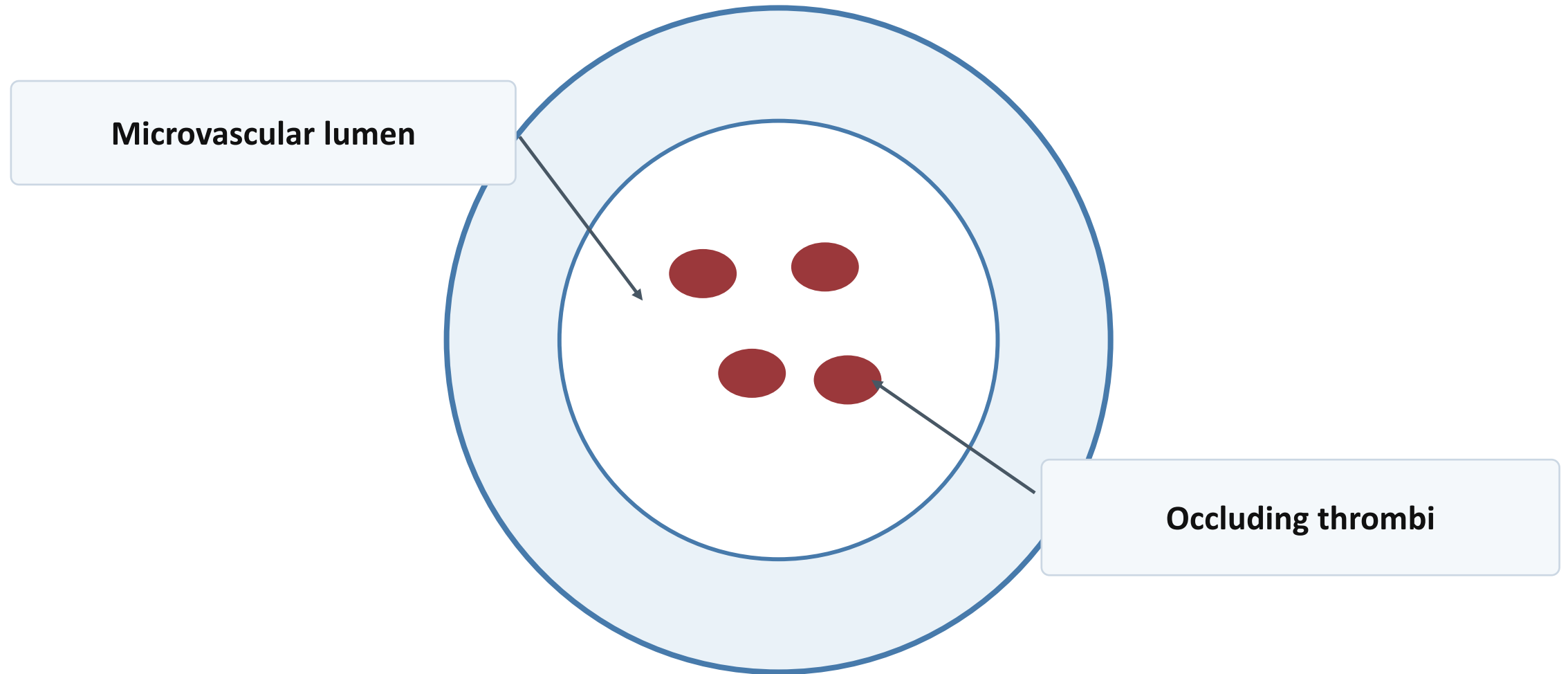
Schematic — not a histologic specimen

Acute mesangial injury: Mesangiolytic



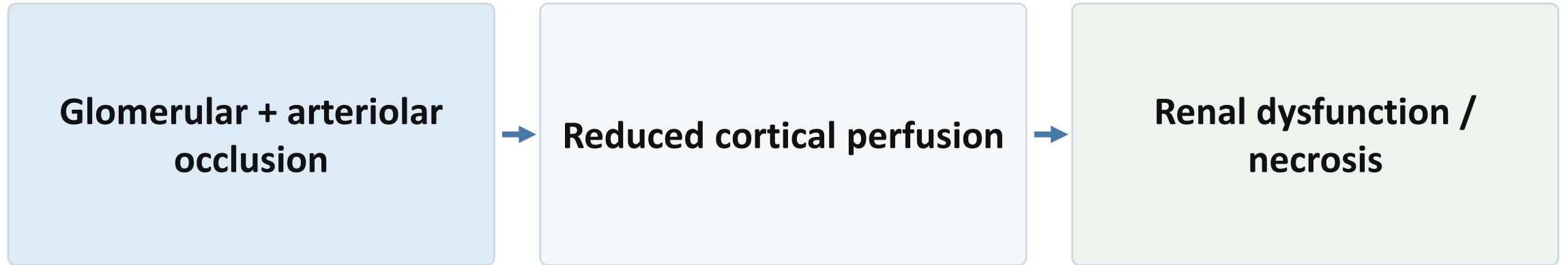
Schematic — not a histologic specimen

Small arteries and arterioles also thrombose



Schematic — not a histologic specimen

The acute pattern links structure to function



Chronic renal TMA reflects repeated injury and repair

**Repeated endothelial
injury**



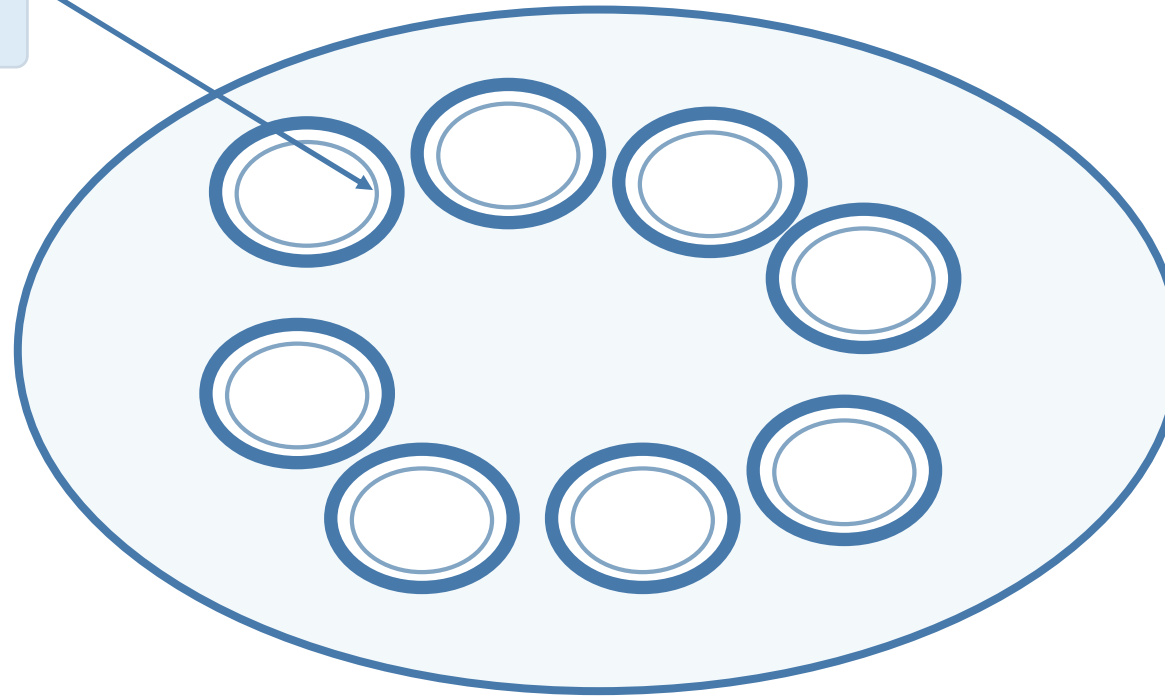
Remodeling and fibrosis



Chronic renal ischemia

Glomerular “double contours” mark chronic injury

Duplicated capillary wall



Glomerular tuft
(idealized)

Schematic — not a histologic specimen

Why basement membrane duplication develops

**Persistent endothelial
injury**

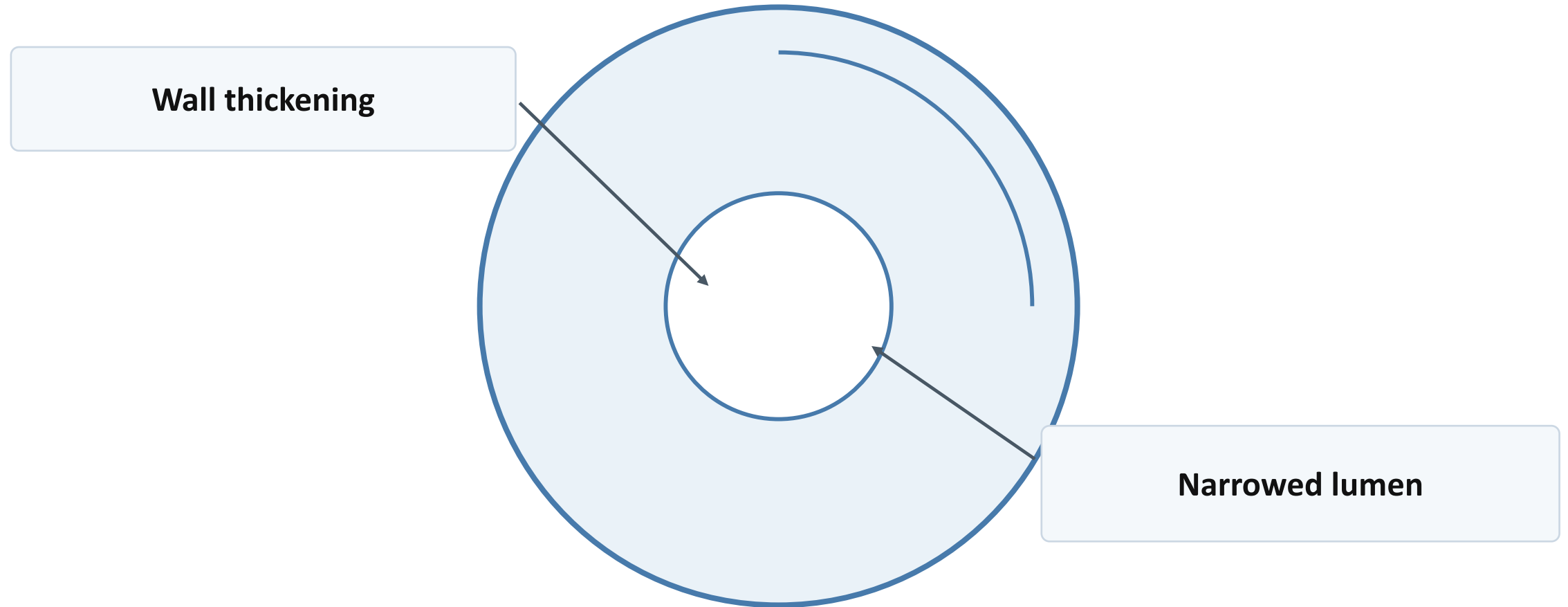


**Repair / basement
membrane remodeling**



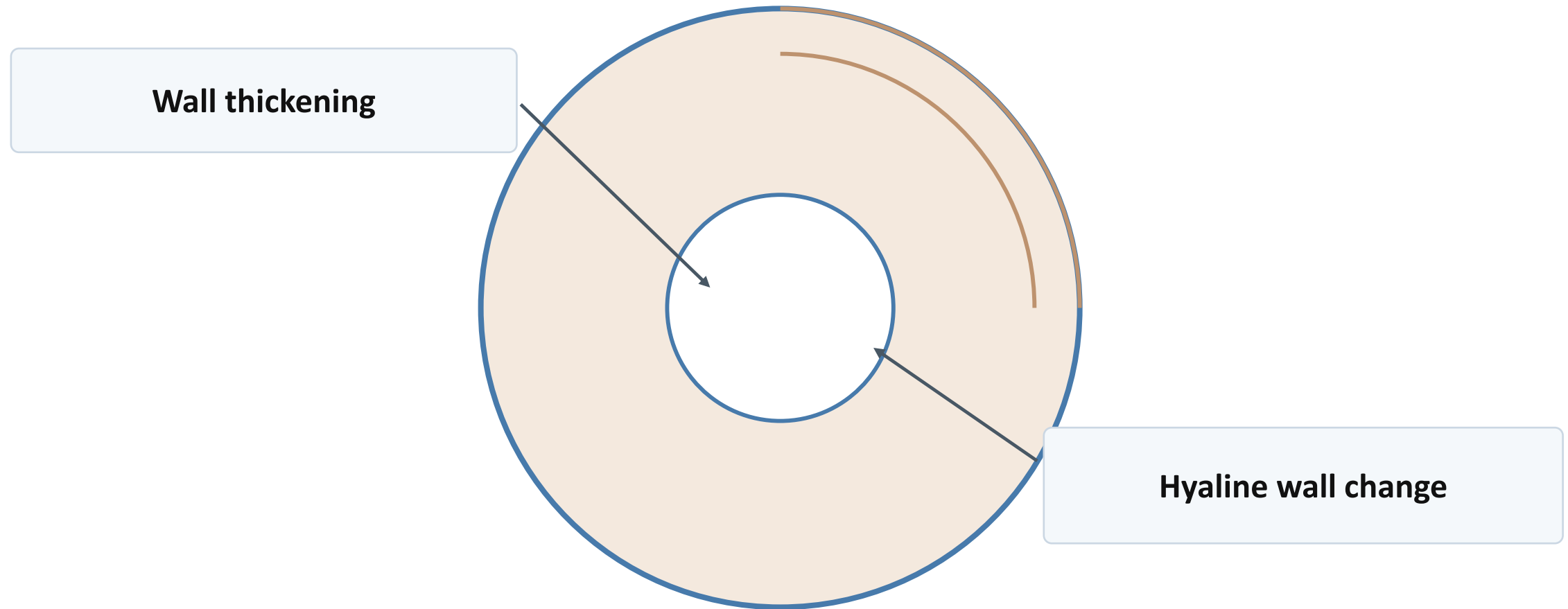
**Duplicated capillary wall
contours**

Chronic arteries develop luminal narrowing



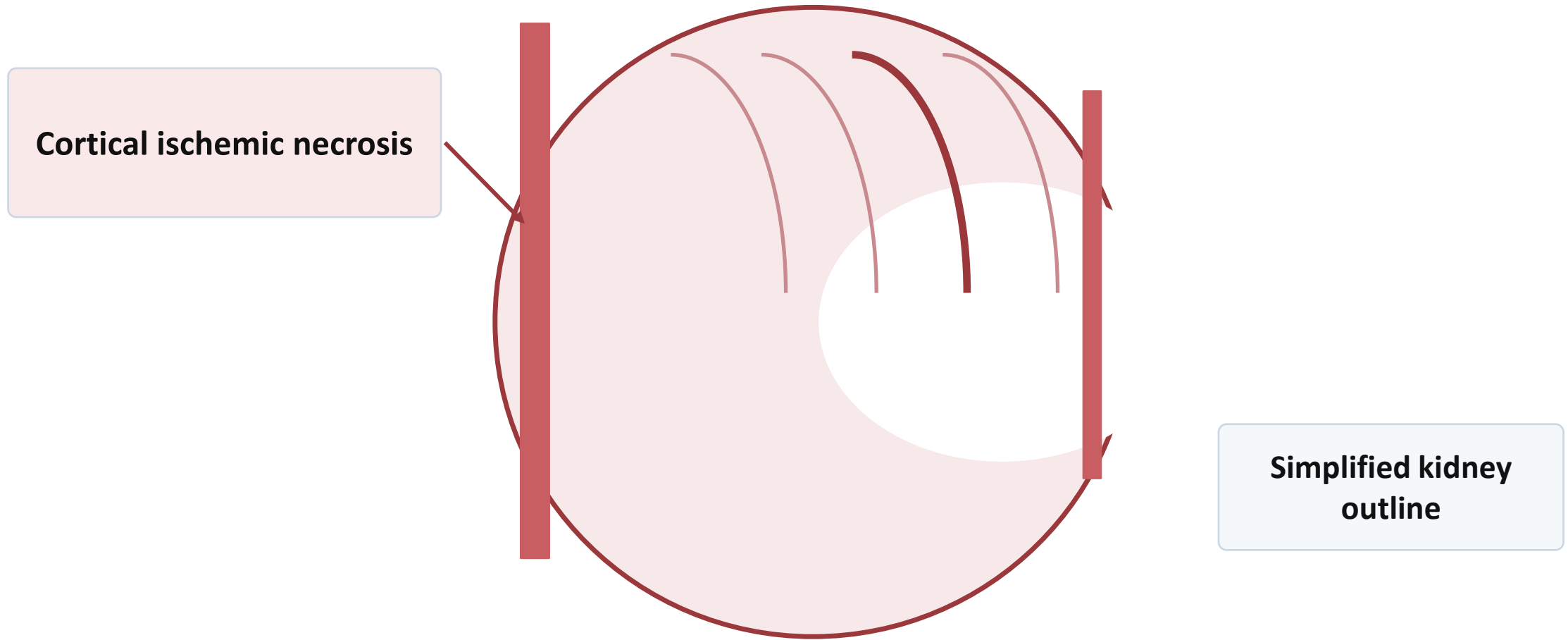
Schematic — not a histologic specimen

Chronic arterioles may show hyalinosis



Schematic — not a histologic specimen

Renal cortical necrosis is an ischemic endpoint



Schematic — not a gross specimen

Acute and chronic morphology differ by timing

Acute dominant lesions

Capillary / arteriolar thrombi

Mesangiolysis

Petechiae or cortical necrosis

Chronic dominant lesions

Capillary-wall duplication

Arterial mural thickening

Scarring, hyalinosis, hypoperfusion

Renal morphology does not identify TMA subtype

What histology demonstrates

Microvascular thrombotic injury

Acute versus chronic changes

Cortical ischemic consequences

What histology alone cannot prove

Shiga toxin exposure

ADAMTS13 deficiency

Complement-regulatory mutation

Distinguish TMA from a coagulopathic process

- TMA is a pathologic pattern, not a single laboratory diagnosis.
- The clinically important differential includes disseminated intravascular coagulation.
- That systemic coagulation cascade activation is not central in HUS/TTP.

A unified etiologic investigation starts with context

Immune / thrombotic

Antiphospholipid antibodies

Pregnancy

Pregnancy or postpartum complications

Renal vascular

Systemic sclerosis; Severe hypertension

Exposures

Chemotherapeutic / immunosuppressive drugs; Radiation

Case: Post-diarrheal renal TMA

- A patient develops bloody diarrhea after gastrointestinal illness.
- Several days later, hemolysis, thrombocytopenia, and acute renal dysfunction appear.
- Which upstream mechanism is most consistent with this sequence?

Discuss: Infer the initiating mechanism before revealing the answer.

Case: Platelet-driven microangiopathy

- A patient has MAHA, marked thrombocytopenia, and neurologic dysfunction.
- Investigation supports deficient ADAMTS13 function.
- What molecular interaction explains the small-vessel thrombi?

Discuss: Infer the initiating mechanism before revealing the answer.

Case: Recurrent renal microangiopathy

- A patient has recurrent episodes of TMA with dominant renal injury.
- An inherited complement-regulatory protein defect is identified.
- What shared tissue event links genotype to kidney dysfunction?

Discuss: Infer the initiating mechanism before revealing the answer.

Three etiologic routes, one renal lesion

Shiga toxin–HUS

Complement-mediated TMA

TTP

Endothelial toxin injury

**Insufficient complement
regulation**

ADAMTS13 deficiency



Platelet-containing microthrombi and renal ischemia

Take-home: Interpret TMA by mechanism and chronicity

- Recognize microvascular thrombosis with hemolysis, platelet consumption, and ischemia.
- Distinguish endothelial pathways from ADAMTS13/vWF platelet-driven TTP.
- In the kidney, separate acute occlusive lesions from chronic vascular remodeling.
- Do not assign an etiology from renal morphology alone.

Selected source

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Renal thrombotic microangiopathy is discussed in “The Kidney.”
- The hematologic pathogenetic context is discussed in “Red Blood Cell and Bleeding Disorders.”