

Sinusoidal Obstruction Syndrome

Pathogenesis • Histopathology • Clinicopathologic diagnosis

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Learning objectives

- Distinguish sinusoidal microvascular obstruction from major hepatic vein thrombosis.
- Explain endothelial injury, red-cell extravasation, and perivenular hepatocyte loss.
- Identify acute, organizing, and fibrous-obliterative histologic lesions.
- Apply contemporary diagnostic categories while recognizing biopsy limitations.
- Connect the pathology with complications and management principles.

Disease definition

Toxic injury to hepatic sinusoidal endothelium impedes outflow through sinusoids and terminal venules.

- The primary lesion is microvascular rather than thrombosis of a major hepatic vein.
- Blood-flow obstruction can produce centrilobular congestion, necrosis, and fibrosis.

Terminology and anatomic target

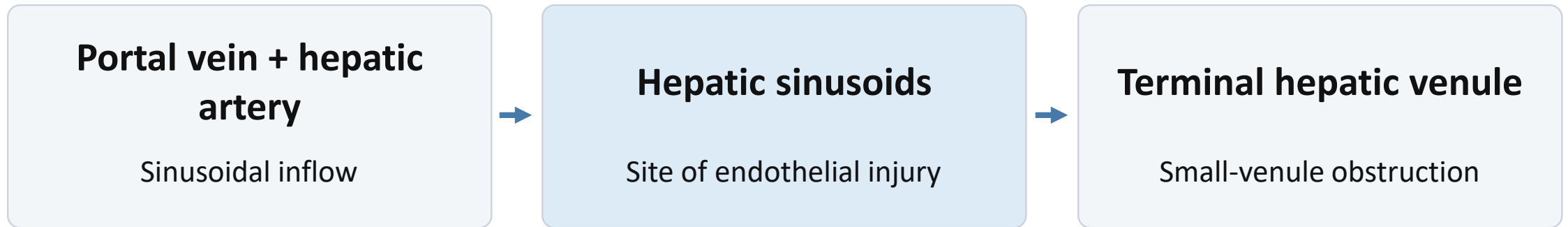
Former nomenclature

- Veno-occlusive disease (VOD)
- Emphasized small hepatic venous lesions
- Term still used in transplant literature

Current descriptive term

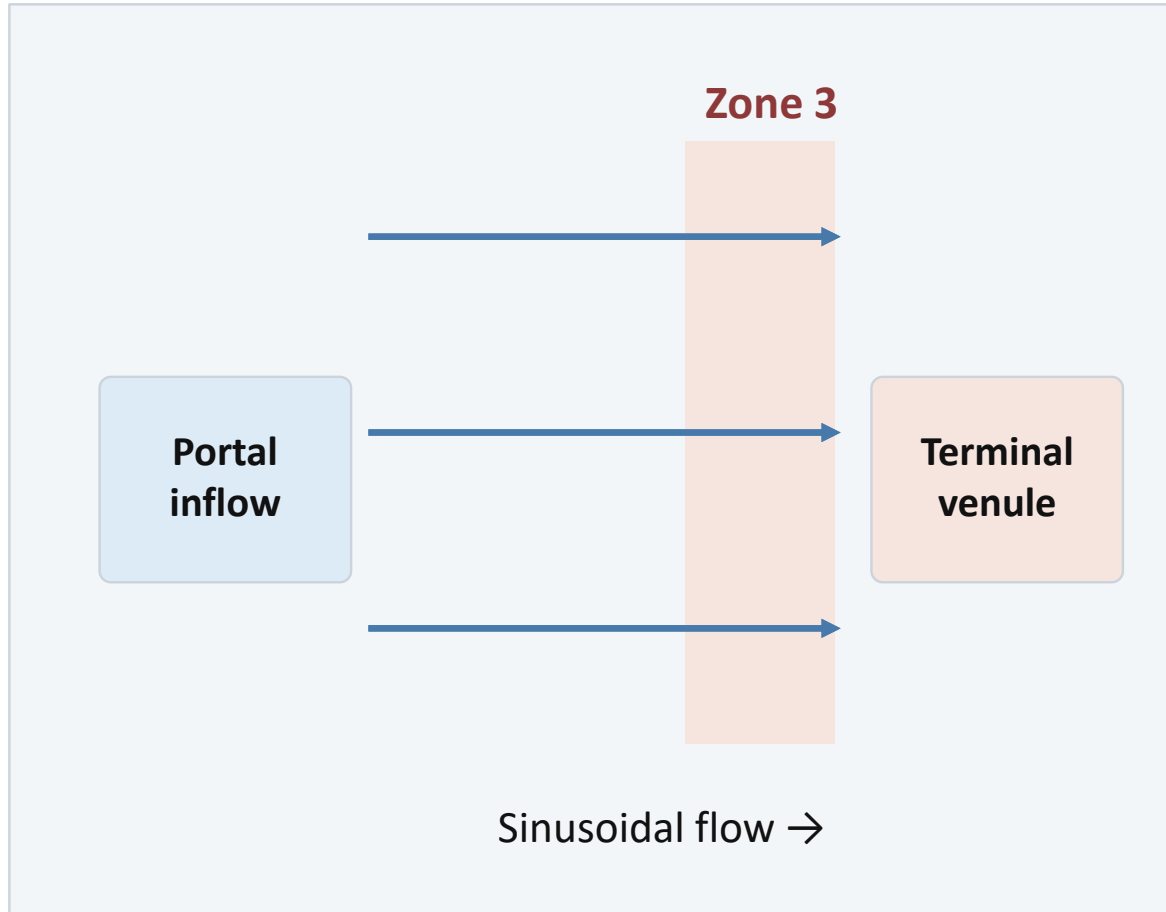
- Sinusoidal obstruction syndrome (SOS)
- Emphasizes sinusoidal endothelial injury
- Common combined usage: SOS/VOD

Where does hepatic blood flow become obstructed?



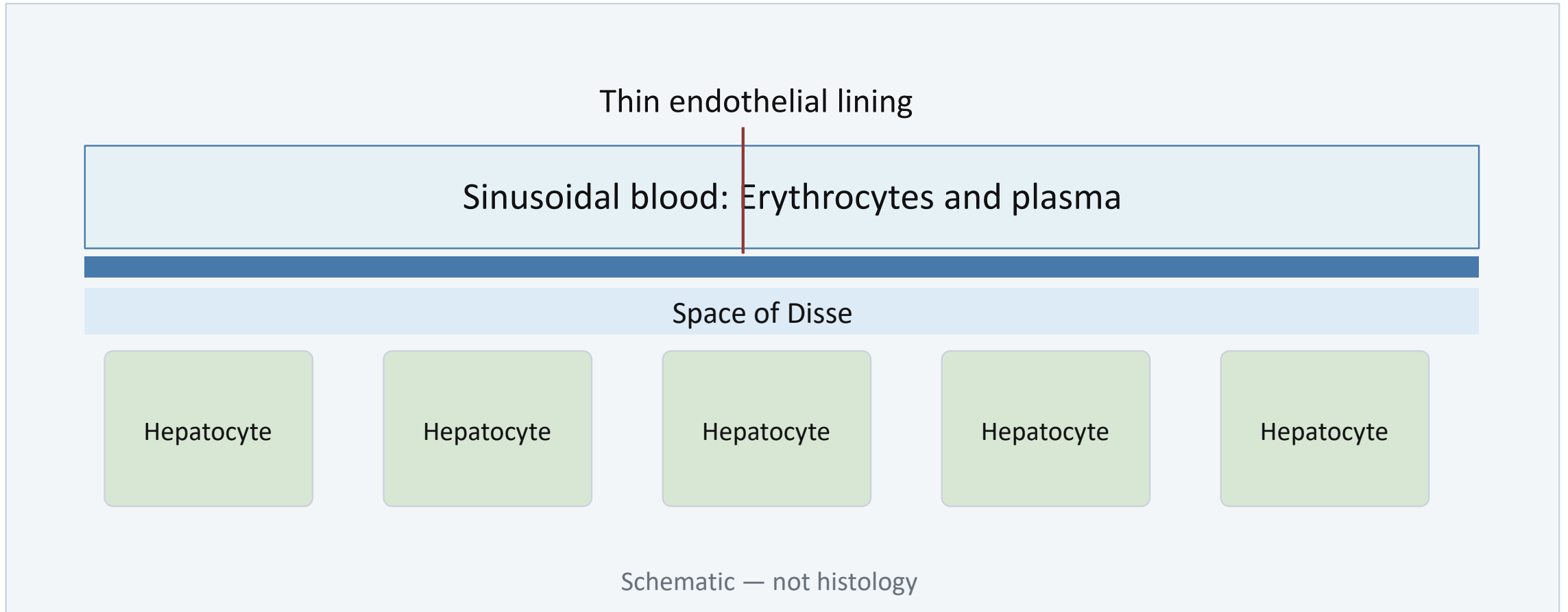
SOS lies upstream of the major hepatic veins; Flow impairment is postsinusoidal in its consequences.

Liver acinus: Why zone 3 matters



- Centrilobular hepatocytes surround the terminal hepatic venule.
- Sinusoidal damage and perfusion failure converge at the venous outflow end.
- Congestion and necrosis therefore predominate around central veins.

Normal sinusoidal barrier: Conceptual architecture



Historical observation: Pyrrolizidine toxicity

- Early cases were described among Jamaican consumers of bush tea containing pyrrolizidine alkaloids.
- The original term “veno-occlusive disease” reflected small-venule obliteration.
- The toxic-vascular mechanism links botanical exposures and chemotherapy-related disease.
- Today, transplantation and selected antineoplastic therapies dominate clinical recognition.

Major clinical settings

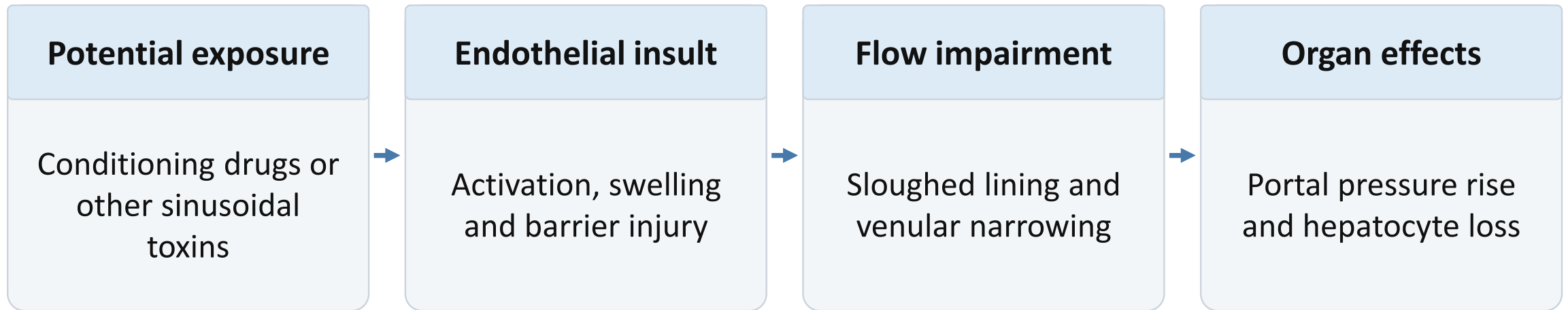
Hematopoietic cell transplantation

- Predominantly after allogeneic HCT
- Classically develops in the first 3 weeks
- Intensity and composition of conditioning matter

Cancer therapy without HCT

- Certain cytotoxic or targeted anticancer agents
- Sinusoidal injury may occur without transplantation
- Interpret the timing relative to drug exposure

Exposure precedes microvascular dysfunction



The clinical syndrome is the downstream consequence of endothelial injury.

Timing after hematopoietic transplantation

- Classical presentation usually arises within 21 days after HCT.
- Late-onset disease occurs after day 21; A rigid time cutoff can miss cases.
- Clinical surveillance should track evolving weight, abdominal findings, bilirubin, and platelet needs.
- Transplantation timing is a diagnostic clue, not proof by itself.

Conditioning-associated endothelial stress

- High-intensity conditioning exposes hepatocytes and sinusoidal endothelium to toxic metabolites.
- Zone 3 sinusoidal endothelial cells are particularly vulnerable to injury.
- Damage amplifies permeability, cellular detachment, and downstream microvascular obstruction.
- The severity reflects both the exposure and the patient's baseline hepatic reserve.

Predisposing factors: Patient versus treatment

Baseline susceptibility

- Preexisting fibrosis or active liver disease
- Iron overload or abnormal liver tests
- Prior HCT or previous SOS/VOD
- Advanced disease and reduced performance status

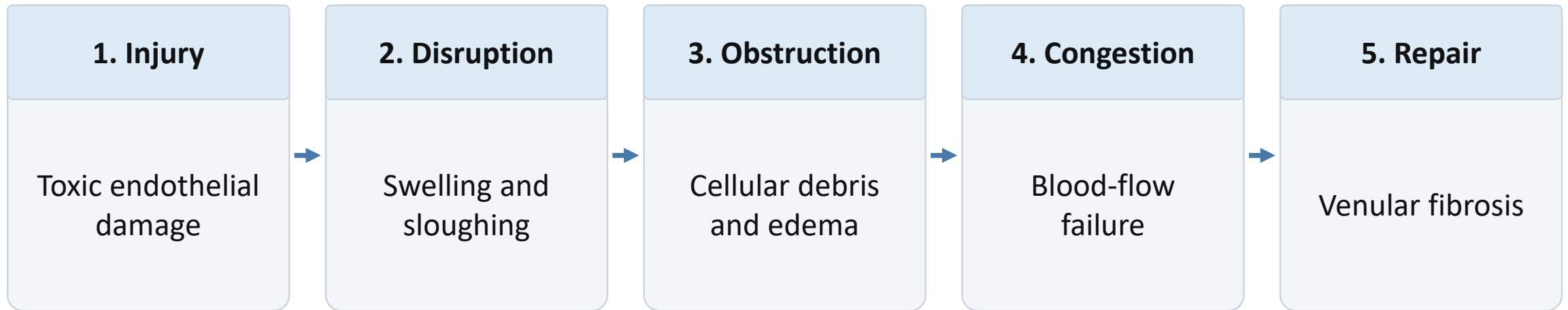
Treatment-related burden

- Myeloablative conditioning
- Busulfan-intensive regimens
- Abdominal or hepatic irradiation
- Selected prior antibody–drug conjugates

Anticancer agents outside transplant conditioning

- Selected chemotherapy exposures as a major modern context.
- In practice, several alkylating agents and sinusoid-toxic anticancer treatments are implicated.
- An isolated post-chemotherapy liver syndrome requires differentiation from diffuse drug-induced hepatitis.
- Drug identity, cumulative exposure, and preexisting hepatic disease modify interpretation.

Pathogenesis: The core morphologic sequence

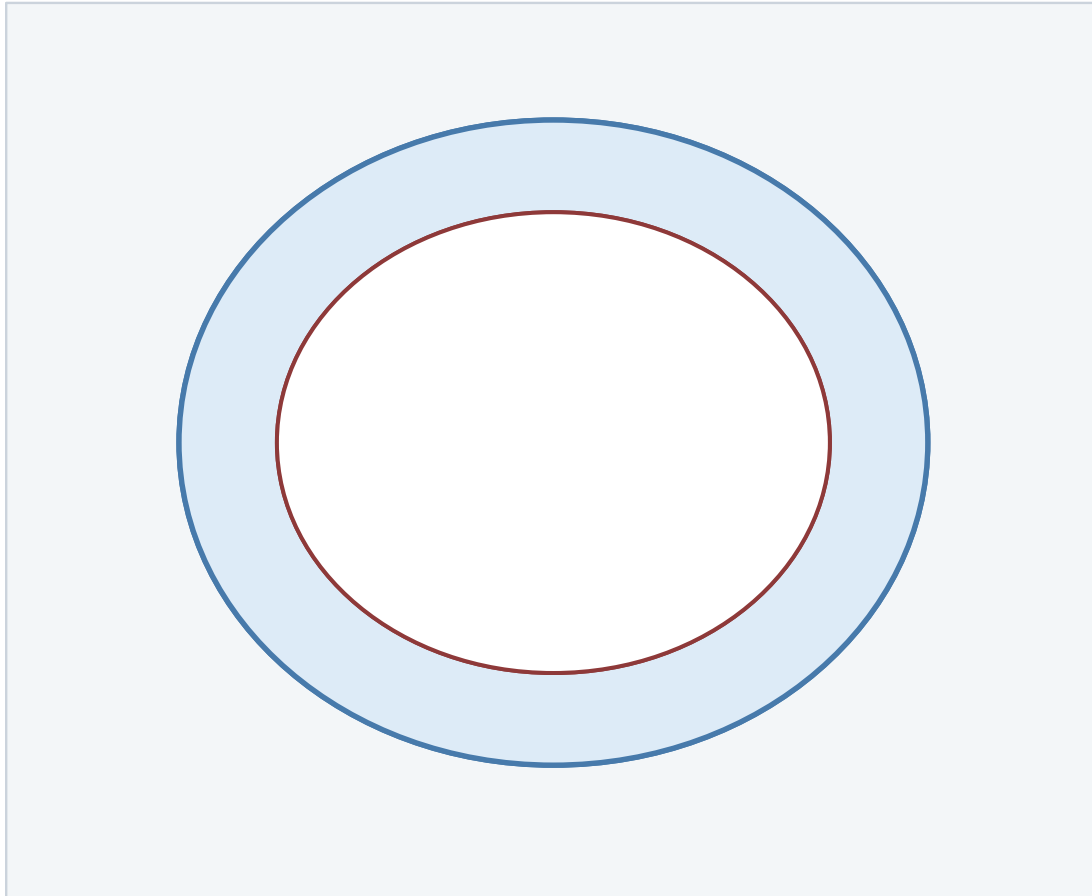


Tissue effects depend on the magnitude and persistence of outflow obstruction.

Endothelial injury is the initiating lesion

- Toxic insult principally involves sinusoidal endothelial cells and terminal venular endothelium.
- Activation and swelling disturb the normal blood–parenchyma barrier.
- Vascular injury precedes many of the secondary hepatocyte changes.
- The histologic appearance therefore differs from a primarily inflammatory hepatitis.

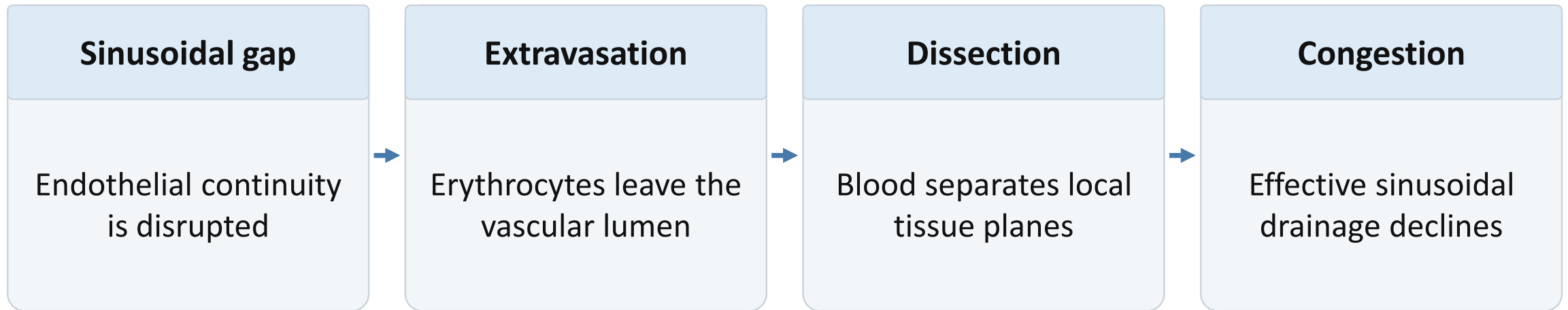
Endothelial swelling narrows the venular lumen



Schematic cross-section of terminal hepatic venule

- Swollen endothelium increases resistance to sinusoidal egress.
- Edema and injured lining contribute to luminal narrowing.
- The illustration depicts the mechanism, not a real biopsy.

Barrier rupture permits blood to enter the space of Disse



Extravasated erythrocytes explain hemorrhage and the tissue reaction.

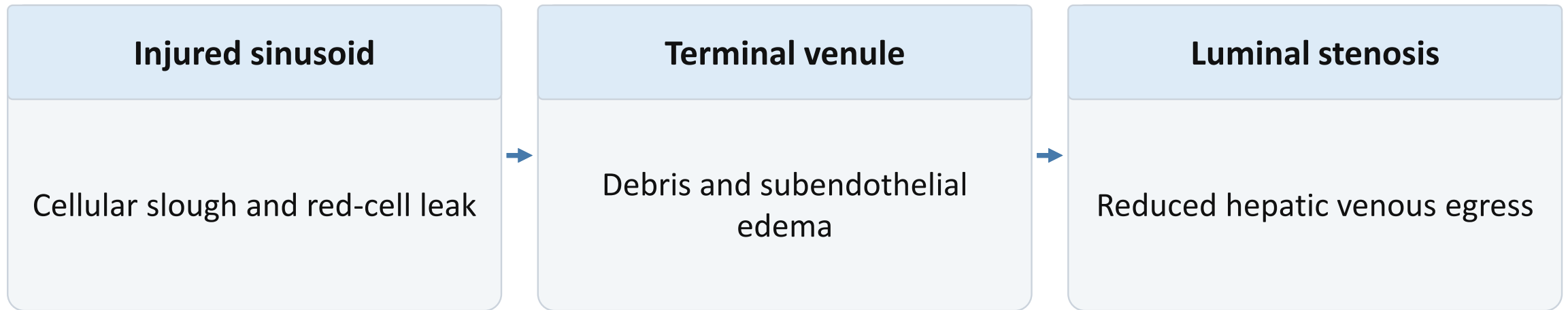
Red-cell extravasation is mechanistically important

- Injured sinusoids permit red cells to enter the space of Disse.
- The blood may dissect beneath residual endothelial surfaces.
- Extravasation produces an appearance of centrilobular hemorrhage on microscopy.
- Space-of-Disse blood is distinct from an uncomplicated dilated vascular lumen.

Endothelial detachment disrupts normal flow

- Necrotic and detached endothelial elements enter sinusoidal channels.
- Cellular debris moves toward the terminal hepatic venule.
- Detachment also enlarges gaps permitting continued hemorrhage.
- The resulting obstruction may be predominantly cellular before collagen is deposited.

Obstruction moves downstream with sinusoidal drainage

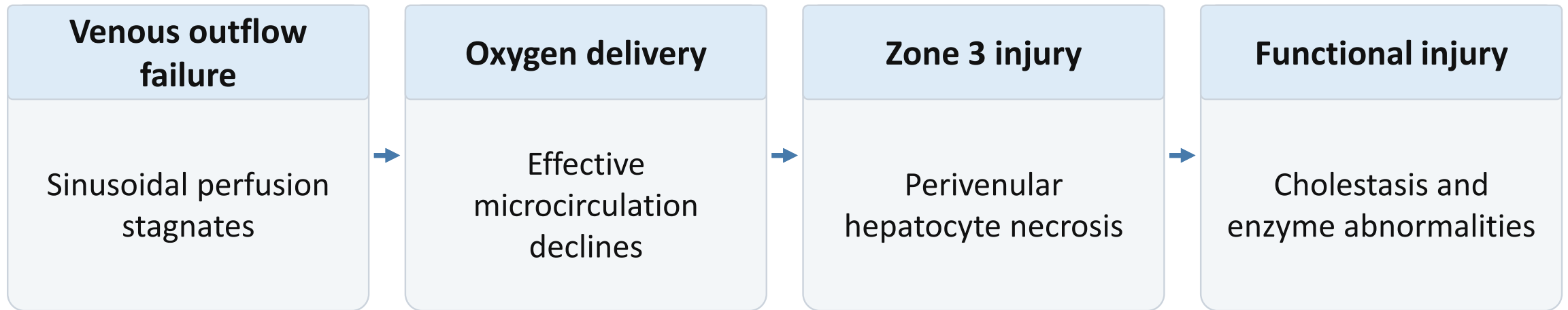


Small-vessel obstruction can occur without thrombosis of a major hepatic vein.

Elevated resistance produces hepatic congestion

- Impaired venous egress raises hydrostatic pressure within sinusoids.
- Centrilobular sinusoidal channels become engorged with blood.
- The pressure burden propagates into clinically detectable fluid retention.
- Congestion reflects the microvascular obstruction—not a portal vein inflow block.

Why perivenular hepatocytes die

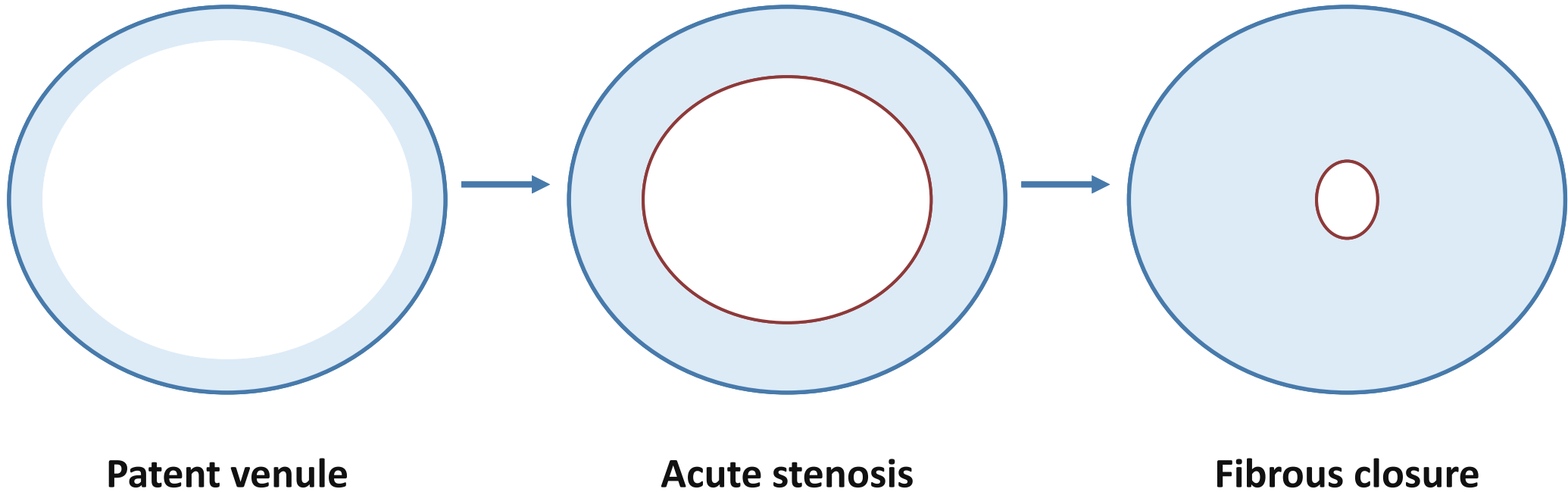


Hepatocyte loss is downstream of vascular injury and hypoperfusion.

Organizing injury recruits fibrosis

- Persistent endothelial damage triggers extracellular-matrix deposition in the venular wall.
- Edema and cellular obstruction evolve toward collagen-rich luminal narrowing.
- Chronic lesions may leave a terminal hepatic venule completely obliterated.
- The eventual scar can persist after the initiating toxic exposure ends.

Anatomical progression: Patent, stenosed, obliterated



Original native-shape schematic — not a clinical specimen

Early microscopy: Centrilobular congestion

- Zone 3 sinusoids contain markedly increased red-cell volume.
- Extravasated erythrocytes may occupy space around hepatocyte plates.
- Endothelial damage need not be easily recognized on routine H&E alone.
- Examine terminal venules for complementary evidence of obstruction.

Venular wall edema and endothelial necrosis

- Swelling and loss of venular endothelial cells are early components of obstruction.
- Subendothelial material narrows the lumen even before mature collagen appears.
- The lesion is centered on terminal hepatic venules rather than the main hepatic veins.
- Patchiness may limit the sensitivity of a small biopsy.

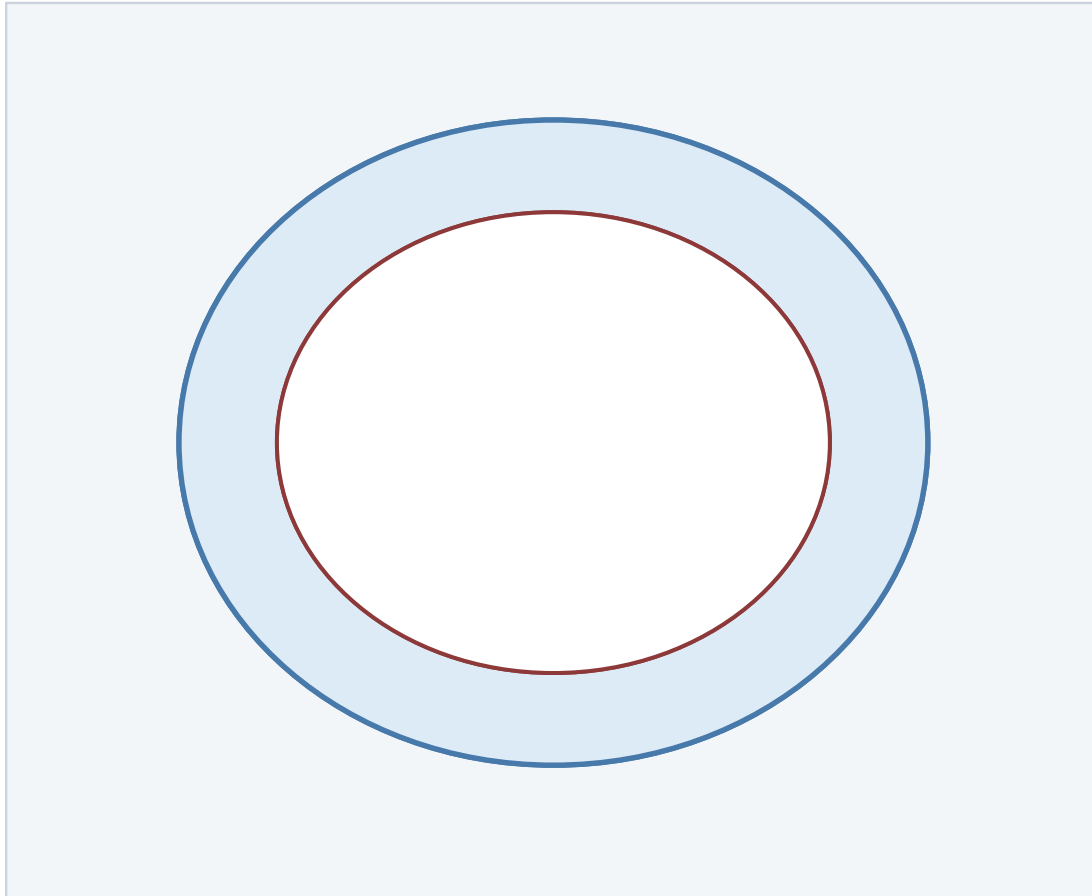
Centrilobular hepatocellular necrosis

- Failure of sinusoidal blood transit injures perivenular hepatocytes.
- Hepatocytes can become atrophic, necrotic, or absent near the central vein.
- Extensive injury may resemble other causes of zone 3 necrosis.
- Coexisting venular injury and exposure history provide specificity.

Hemosiderin-laden macrophages mark prior hemorrhage

- Extravasated erythrocytes are degraded locally by phagocytic cells.
- Hemosiderin-containing macrophages may accumulate within affected areas.
- The finding fits prior hemorrhage but is not independently diagnostic of SOS.
- Interpret iron pigment with the spatial pattern of congestion and venular change.

Organized disease: The terminal venule becomes stenotic



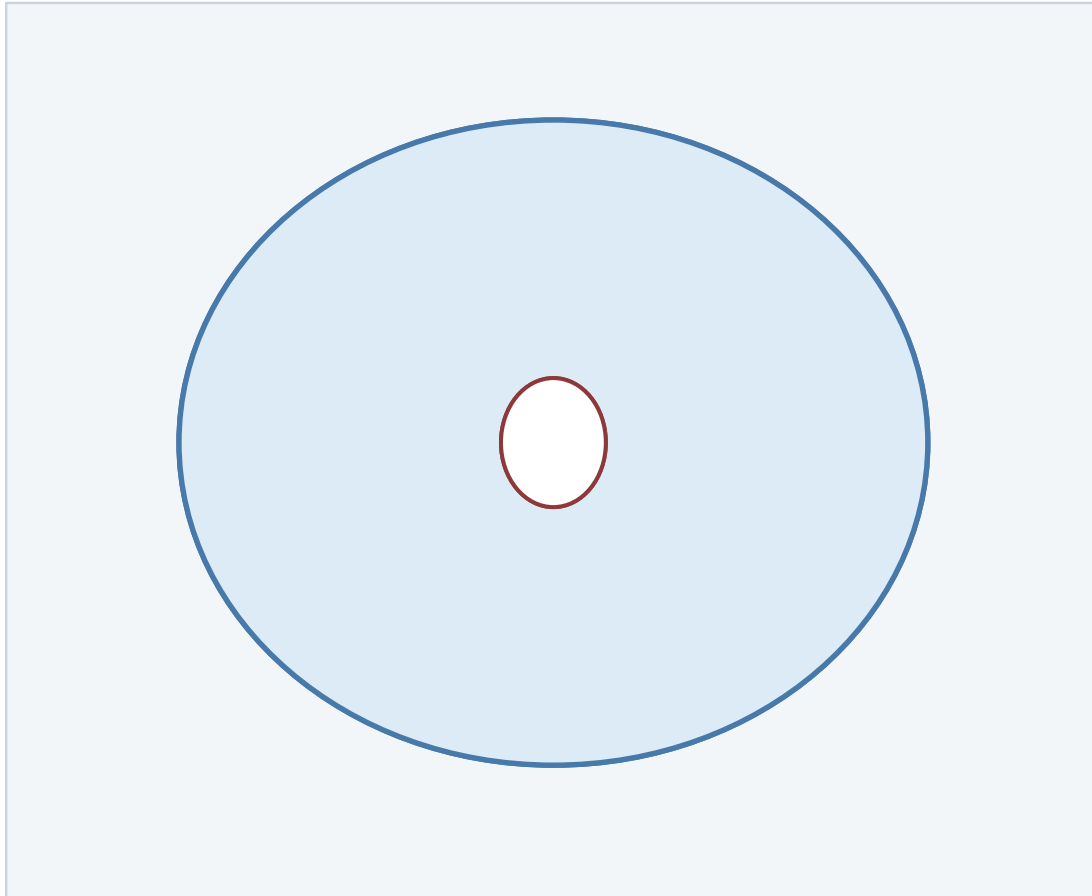
Schematic cross-section of terminal hepatic venule

- The venular lumen is encroached upon by edematous tissue and organizing material.
- Local sinusoidal congestion persists upstream.
- The lesion may be conspicuous on connective-tissue stains.

Masson trichrome: The purpose of a collagen stain

- Special connective-tissue stains demonstrate perivenular or intraluminal fibrous tissue.
- Tracing the venular wall helps recognize a distorted or nearly obliterated lumen.
- Collagen-rich narrowing supports an organizing/chronic obstructive lesion.
- Do not infer a histologic diagnosis from a diagram or staining color alone.

Late disease: Complete fibrous venular obliteration



Schematic cross-section of terminal hepatic venule

- Collagen replaces the functional lumen of a terminal hepatic venule.
- Perisinusoidal fibrosis and parenchymal loss may coexist.
- Advanced fibrosis documents injury but may not reveal its original cause.

Why histology can be heterogeneous

- The disease process affects small sinusoidal and terminal venular channels.
- Tissue sections may sample patent and obstructed venules together.
- Local severity and time since injury vary across the biopsy.
- Multiple levels and suitable stains can improve lesion recognition.

Morphologic timeline

Acute / early disease

- Sinusoidal dilation and congestion
- Red-cell extravasation
- Edema and endothelial necrosis
- Perivenular hepatocellular loss

Organizing / healed disease

- Venular lumen narrowing
- Intraluminal or perivenular collagen
- Persistent sinusoidal fibrosis
- Potential complete fibrous closure

Gross morphology: Assess with restraint

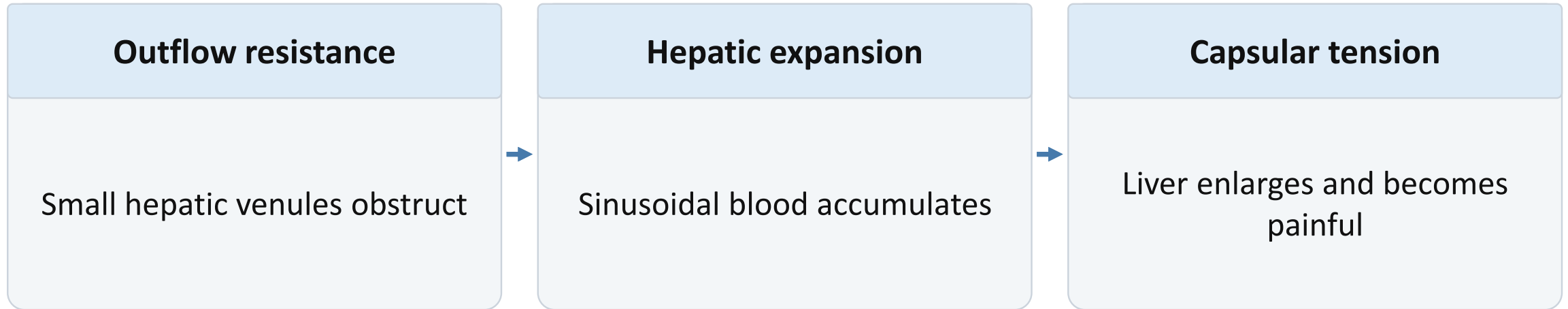
- Microscopic venular obliteration and centrilobular hemorrhagic injury.
- Gross liver appearance alone does not establish SOS.
- Congestion and hepatomegaly may have several hepatic vascular causes.
- For diagnosis, prioritize exposure, clinical course, microvascular changes, and imaging.

Clinical phenotype: Congestion plus fluid retention

Tender hepatomegaly + weight gain/ascites ± jaundice

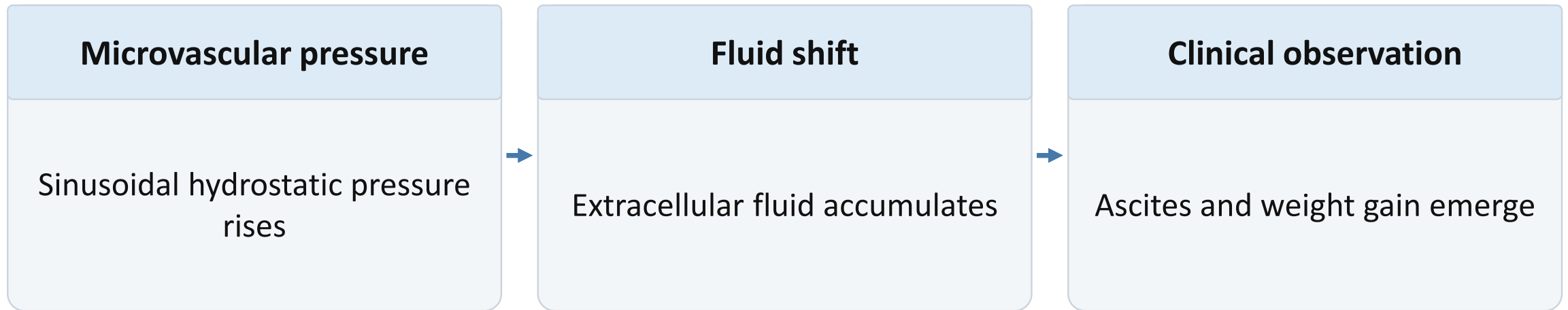
- After HCT, the pattern should prompt consideration of SOS/VOD.
- None of these manifestations alone is sufficiently specific to establish the diagnosis.

Tender hepatomegaly is a consequence of congestion



Pain localizes clinically to the right upper quadrant.

Why ascites and weight gain often evolve together



Weight gain signals fluid accumulation, not necessarily nutritional change.

Hyperbilirubinemia and jaundice

- Jaundice may develop as hepatocellular injury and cholestatic dysfunction progress.
- Bilirubin is required for the EBMT “clinical” category in adults, not “probable.”
- Late-onset and pediatric disease may present without obligatory jaundice.
- A normal early bilirubin does not fully exclude SOS/VOD.

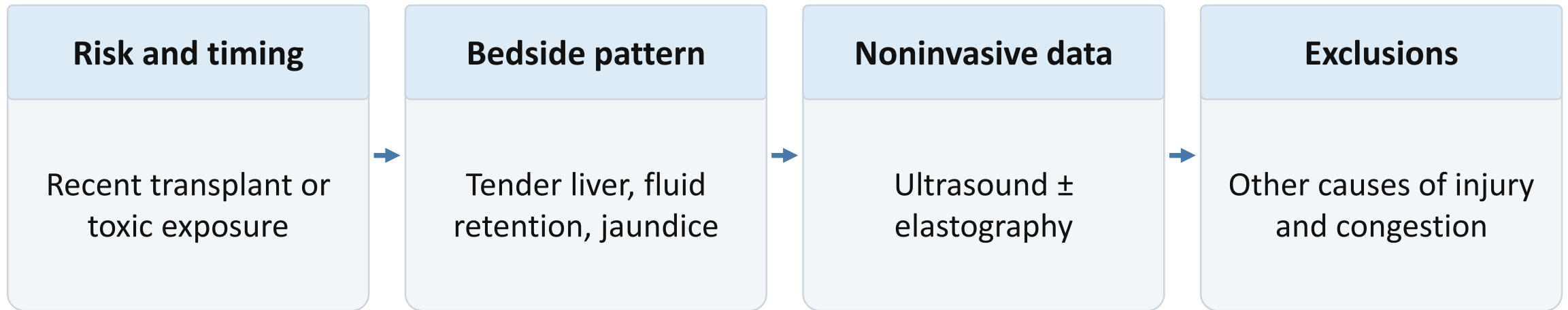
Transfusion-refractory thrombocytopenia

- Post-transplant platelet transfusion requirements may rise early in SOS/VOD.
- It is especially important in pediatric EBMT diagnostic criteria.
- This finding is not specific; Infection, consumption, and marrow dysfunction remain alternatives.
- Interpret platelet refractoriness in the full transplant context.

Laboratory results complement, rather than replace, morphology

- Track total bilirubin and the trajectory of aminotransferases.
- Renal function contributes to determining clinical severity.
- An isolated enzyme rise is not a disease-defining test.
- Laboratory kinetics and evolving clinical findings are more useful than one uncontextualized result.

Diagnostic reasoning in the HCT setting



Clinical diagnosis is common because biopsy can carry significant bleeding risk.

Ultrasound and Doppler findings

- Ultrasound may document hepatomegaly, ascites, and vascular flow changes.
- Attenuated or reversed flow is suggestive but not universally present.
- Doppler abnormalities may evolve later than initial endothelial injury.
- Use the entire ultrasound assessment; No single nonspecific sign proves SOS.

Elastography: A modern complementary modality

- Increased liver stiffness can reflect vascular congestion after transplantation.
- EBMT includes suggestive ultrasound or elastography among “probable” criteria.
- The measurement is context-dependent and not uniquely specific to SOS.
- Availability and operator experience influence its utility.

Adult EBMT 2023: Diagnostic certainty

Probable	Clinical	Proven
≥2 of 5 features	Bilirubin ≥2 mg/dL	Histology consistent with SOS
Bilirubin; Painful liver	Plus ≥2 of: Pain,	Or HVPg ≥10 mmHg
Weight gain >5%; Ascites	Weight gain >5%, ascites	(EBMT definition)
Suggestive US/elastography	Symptoms not otherwise explained	See EASL 2025 caveat

Probable SOS is intended to improve early recognition

- Adult EBMT probable disease requires at least two of five findings.
- Those include bilirubin ≥ 2 mg/dL, painful hepatomegaly, $>5\%$ weight gain, ascites, or suggestive ultrasound/elastography.
- The category may be met before the full conventional clinical criteria.
- Alternative explanations must be assessed before assigning SOS/VOD.

Clinical SOS requires a more restrictive combination

- Adult EBMT clinical SOS includes bilirubin ≥ 2 mg/dL.
- Two additional features are required: Painful hepatomegaly, weight gain $>5\%$, or ascites.
- The combination documents a compatible syndrome but is not itself a biopsy.
- Apply adult HCT criteria to their intended population.

“Proven” SOS: An important guideline difference

EBMT 2023 framework

- Histologic confirmation qualifies
- Hemodynamic confirmation with HVPG ≥ 10 mmHg also qualifies
- The categories reflect diagnostic certainty

EASL 2025 approach

- Reserves “proven” SOS for histology
- HVPG ≥ 10 mmHg supports suspicion only
- A low HVPG does not exclude the disease

Children require pediatric-specific criteria

- Pediatric EBMT rules do not impose a 21-day onset limit.
- Two or more features are assessed, including rising bilirubin, evolving weight, new ascites/hepatomegaly, and refractory thrombocytopenia.
- Anicteric SOS is important in children; Adult bilirubin requirements should not be copied.
- Pretransplant imaging establishes a baseline for liver size and ascites.

Biopsy: Informative but often difficult

Why histology matters

- Can show distinctive small-venule obstruction
- Separates morphological phenotypes
- Helps resolve competing diagnoses

Why biopsy can be hazardous

- Post-HCT thrombocytopenia
- Coagulopathy and fragile clinical condition
- Sampling may miss patchy lesions

Differential I: SOS versus Budd–Chiari syndrome

SOS / small vessels

- Sinusoids and terminal hepatic venules
- Common toxic/conditioning-associated context
- May not show thrombosis of major veins

Budd–Chiari syndrome

- Obstruction of the major hepatic veins
- Often prothrombotic or tumor-related
- Hepatic vein imaging is decisive

Differential II: SOS versus cardiac congestion

Sinusoidal obstruction syndrome

- Primary endothelial injury / small-vessel obstruction
- Temporal association with drugs or HCT
- Terminal venular edema/fibrosis

Cardiac passive congestion

- Elevated systemic venous pressure from right heart failure
- Centrilobular sinusoidal congestion
- Correlate with cardiopulmonary disease

Differential III: Hepatic syndromes after HCT

Conditions to consider

- Drug-induced hepatocellular injury
- Infection or sepsis-related cholestasis
- Hepatic graft-versus-host disease
- Cardiac failure / portal vascular disorders

Features favoring SOS

- Compatible endothelial-toxic exposure
- Weight gain and tender hepatomegaly
- Ascites plus evolving jaundice
- Concordant imaging or histology

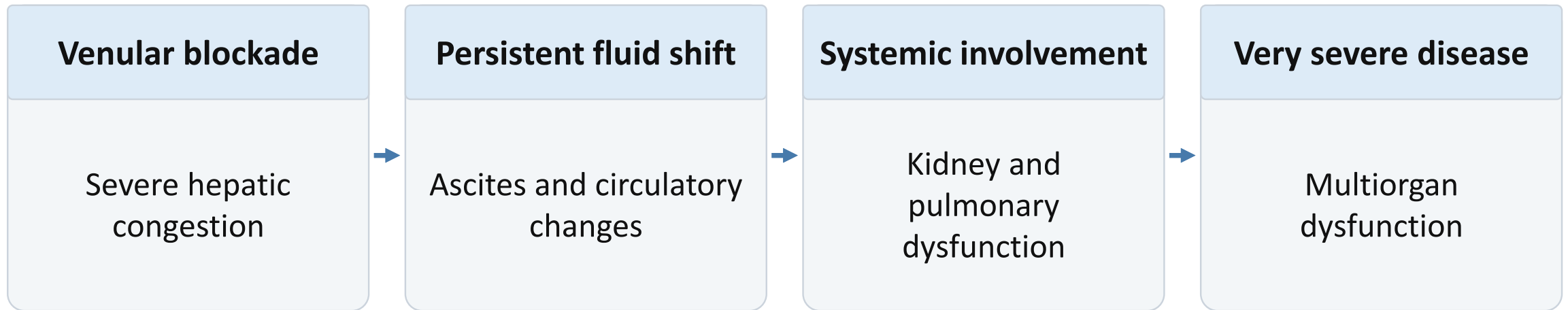
Compare the level of hepatic vascular obstruction

Disorder	Predominant anatomical level	Useful discriminator
Portal vein thrombosis	Inflow through portal venous tree	Portal venous thrombus on imaging
SOS/VOD	Sinusoids and terminal venules	Toxic exposure; Microvascular lesion
Budd–Chiari	Major hepatic veins/outflow	Major-vein occlusion
Cardiac congestion	Systemic venous pressure elevation	Right-sided cardiac disease

Severity is a dynamic clinical assessment

- EBMT severity grades range from mild to very severe.
- Grading incorporates symptom tempo, bilirubin kinetics, aminotransferases, weight gain, and renal function.
- Multiorgan dysfunction places patients in a very severe category.
- Reassess severity as the syndrome evolves rather than relying solely on presentation.

Escalation from local liver injury to organ dysfunction



Organ failure marks high-risk disease and requires urgent specialist management.

Monitoring priorities in suspected SOS/VOD

- Record daily weight and fluid balance during the vulnerable post-HCT interval.
- Follow abdominal findings, bilirubin trajectory, renal function, and platelet support.
- Repeat vascular imaging when symptoms evolve or the first study is inconclusive.
- Escalate rapidly if respiratory or renal dysfunction appears.

Supportive management addresses complications

- Balance fluid status while avoiding intravascular depletion.
- Limit avoidable hepatotoxic and nephrotoxic exposures.
- Manage ascites, coagulopathy, and organ failure with the transplant team.
- Severe cases require early disease-directed therapy in addition to supportive care.

Defibrotide: Contemporary disease-directed therapy

- EBMT guidance recommends prompt defibrotide for severe or very severe SOS/VOD.
- Its early use is also recommended by EBMT in moderate disease.
- Mild cases receive close surveillance and supportive care, with escalation if worsening.
- Defibrotide carries bleeding-related precautions; Treatment is specialist-led.

Prevention: Distinguish established from uncertain

Risk reduction supported by EBMT

- Modify conditioning where feasible
- Identify baseline hepatic risk
- Ursodeoxycholic acid prophylaxis in adult HCT
- Track high-risk patients closely

Important limitation

- Routine prophylactic defibrotide has mixed trial evidence
- 2024 EBMT notes a large trial without benefit
- Preventive drug strategies are not interchangeable with treatment

Interpret older statements against newer evidence

- Early suggestions concerning anticoagulants and ursodeoxycholate after HCT.
- EBMT 2024 supports ursodeoxycholic acid for adult prophylaxis and defibrotide for indicated treatment.
- Routine anticoagulation should not be presented as established SOS treatment.
- Diagnostic and therapeutic claims must be dated and linked to their source.

Teaching vignette: Early clinical suspicion

**Recent HCT → tender hepatomegaly, increasing weight and ascites,
with evolving bilirubin**

- Question: Which hepatic microvascular process should be considered?
- What additional diagnostic and differential information is necessary?

Vignette reasoning: Localize the lesion

- The timing and fluid-retention pattern make SOS/VOD a key differential.
- Assess bilirubin, daily weight, platelet support, ultrasound/elastography, and hepatic vein patency.
- Exclude competing causes such as sepsis-related cholestasis, GVHD, and cardiac congestion.
- Assess severity immediately; Do not wait for biopsy in a deteriorating patient.

Teaching vignette: Pathology interpretation

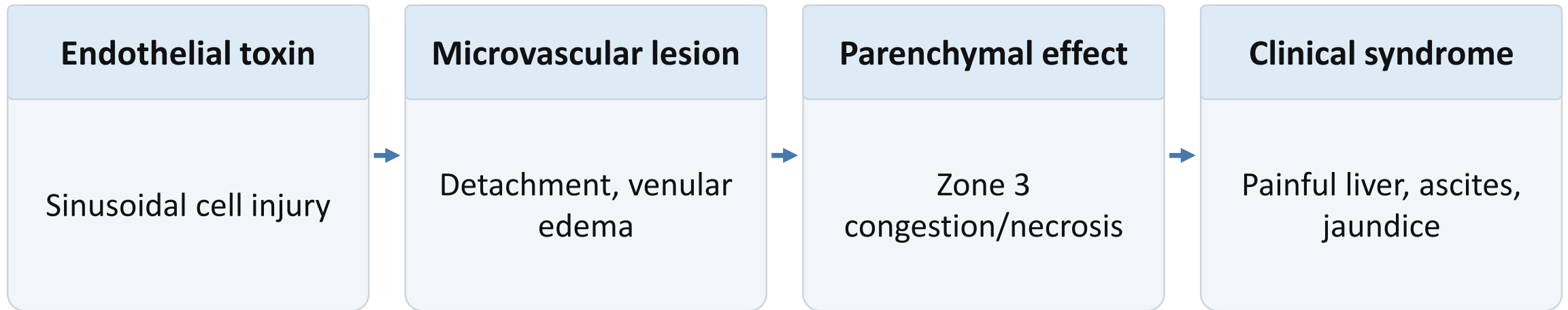
Biopsy shows zone 3 hemorrhage with a narrowed, edematous terminal venule.

- Question: Why does this finding favor SOS over isolated passive congestion?
- What could a connective-tissue stain establish in a later lesion?

Vignette reasoning: Distinguish cause from effect

- Centrilobular hemorrhage is a downstream effect of impeded venous flow.
- Primary endothelial and terminal venular lesions are more informative than congestion alone.
- Trichrome may reveal narrowing or obliteration by collagen during organization.
- Clinical toxic-exposure context remains necessary because histologic findings may overlap.

High-yield synthesis: Injury to syndrome



When recovery is incomplete, venular collagen may produce persistent obliteration.

References and further reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. Chapter 18, “Sinusoidal Obstruction Syndrome.”
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- EASL Clinical Practice Guidelines on vascular diseases of the liver. Journal of Hepatology (2025).
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