

Acute Liver Failure

Pathogenesis · Morphology · Clinicopathologic consequences

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Learning goals

- Define acute liver failure by temporal course, encephalopathy, and coagulopathy.
- Differentiate direct toxic injury, immune-mediated necrosis, and metabolic dysfunction.
- Recognize the gross and microscopic patterns of hepatocyte loss.
- Explain encephalopathy, synthetic failure, cholestasis, and renal complications.

The defining syndrome

Acute liver illness

+

Coagulopathy

+

Encephalopathy

All components arise within 26 weeks of initial injury, without preexisting liver disease.

Time window for acute liver failure



Measure symptom onset → liver failure interval; Timing helps suggest the cause.

Why the time course matters

- Rapid progression particularly suggests a drug or toxin.
- Acetaminophen-associated failure may follow symptoms within one week.
- Virus-associated failure usually develops over a longer interval.
- Timing is etiologic context—not proof of a specific cause.

Liver reserve versus acute collapse

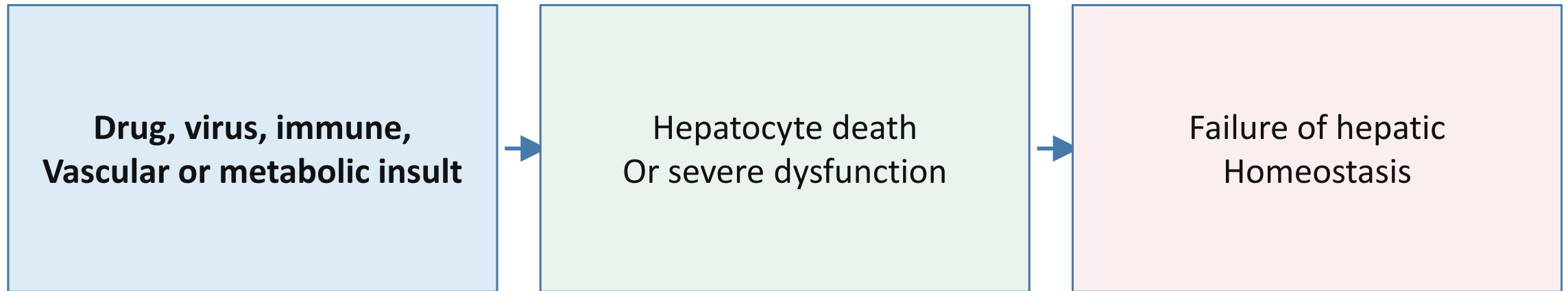
Preserved hepatic reserve

- Mild injury may be clinically silent.
- Remaining hepatocytes sustain metabolic and synthetic tasks.
- Abnormal tests may precede symptoms.

Rapid loss of reserve

- Diffuse acute injury overwhelms functional reserve.
- Excretion, synthesis, and detoxification become impaired.
- Neurologic and bleeding manifestations can follow.

How different insults converge



Acute failure is a functional syndrome; Massive necrosis is common but not universal.

Major etiologic classes

Class	Representative causes in Robbins
Toxic or drug-related	Acetaminophen; other drugs and toxins
Immune/infectious	Autoimmune hepatitis; hepatitis A, B or E
Other uncommon causes	Abnormal blood flow; metabolic disorders; malignancies
Unknown	No cause established despite evaluation

Geographic differences in etiology

United States (adults)

- Acetaminophen is a leading cause.
- Autoimmune hepatitis and other drugs contribute.
- Acute hepatitis A and B are important causes.

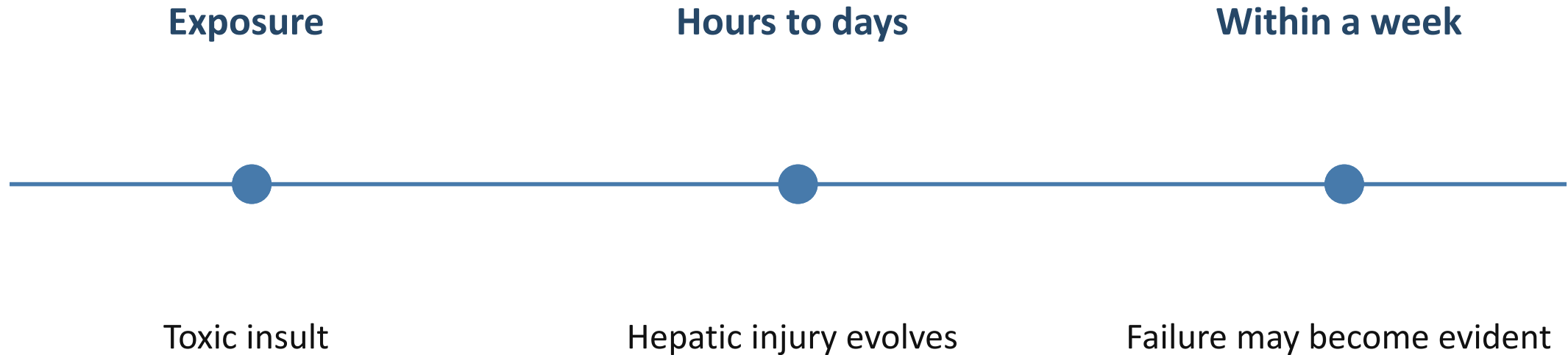
Asia

- Acute hepatitis B and E predominate in the text.
- Regional infectious epidemiology differs.
- The textbook gives geographic context, not a universal hierarchy.

Acetaminophen: Epidemiologic importance

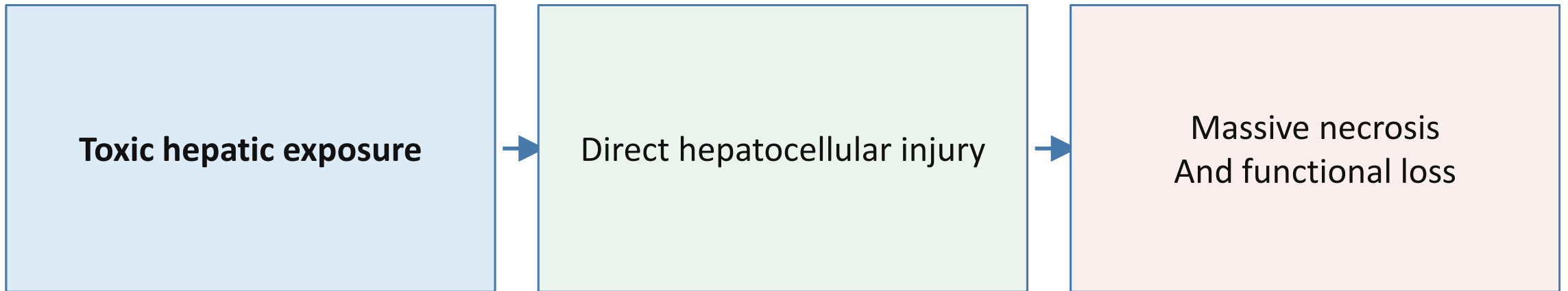
- Accidental or deliberate ingestion can cause acute liver failure.
- Almost 50% of adult ALF cases in the United States to acetaminophen.
- This figure is the textbook's geographic estimate; It is not generalized globally.
- Clinical history should therefore specifically consider exposure.

Acetaminophen: Rapid deterioration



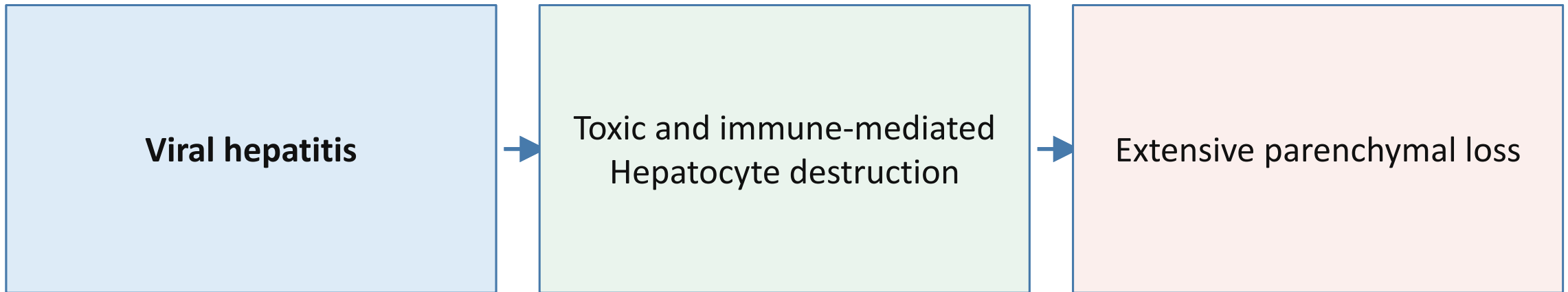
The course may be too rapid for appreciable scarring or regeneration.

Direct toxin-mediated hepatocyte death



Acetaminophen is the exemplar of direct toxic injury in the source.

Immune-associated hepatocyte injury



The immune response can amplify hepatocyte injury during infection.

Toxic versus viral failure

Direct toxic pattern

- Often abrupt clinical progression.
- Extensive necrosis may occur in hours to days.
- Little time for scar or regenerative response.

Viral hepatitis pattern

- Often evolves over weeks to months.
- Injury continues while repair attempts occur.
- Regeneration and scarring can coexist.

Autoimmune hepatitis and acute failure

- Autoimmune hepatitis is among the important non-acetaminophen causes in adults.
- Immune-mediated hepatocyte destruction can be severe enough to cause acute failure.
- Histologic injury may overlap patterns of severe hepatitis from other etiologies.
- Etiology cannot be assigned from necrosis alone.

Other drug- and toxin-related causes

- Not all toxic failure follows acetaminophen exposure.
- Some drugs induce extensive cell death; Others profoundly impair metabolism.
- Nature and duration of the injury influence the morphologic pattern.
- A severe toxin-associated syndrome may occur without substantial fibrosis.

Circulatory injury as an uncommon cause

- Abnormal hepatic blood flow is a rare cause of acute liver failure.
- Ischemic or hypoxic insults can produce marked hepatocyte necrosis.
- Confluent injury may be accentuated near central veins.
- Secondary vascular insults may enlarge areas of necrosis during hepatitis.

Metabolic causes of acute liver failure

- Metabolic disorders are among the uncommon etiologies.
- Severe failure need not correspond to massive hepatocyte dropout.
- Mitochondrial dysfunction can impair cellular energy metabolism.
- Diffuse microvesicular steatosis is an important morphologic clue.

Malignancy-associated acute liver failure

- Malignancies are an uncommon cause of the acute failure syndrome.
- The text particularly identifies leukemia and lymphoma.
- Metastatic malignancies, including breast and colon cancer, also appear among reported causes.
- Hepatic dysfunction may follow widespread infiltration rather than a typical toxin pattern.

When the cause remains unknown

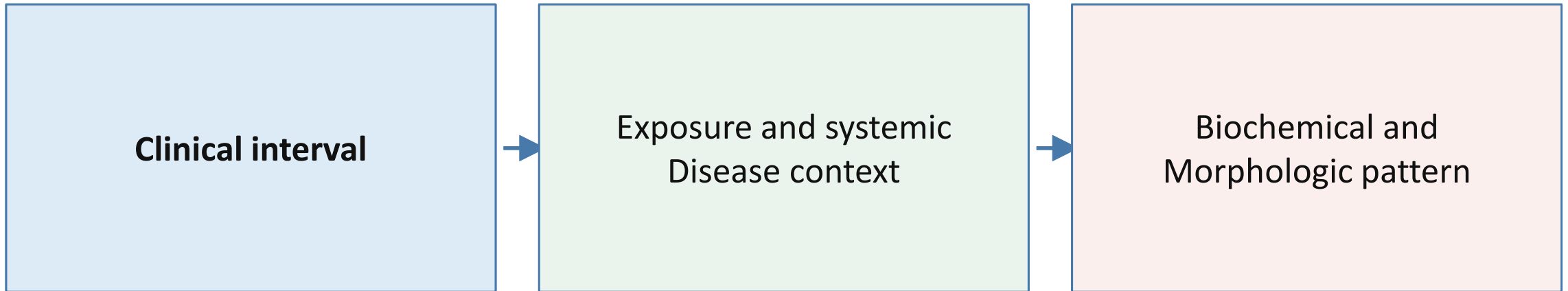
Adults

- No established cause in approximately 15% of cases.
- An indeterminate designation is descriptive.

Children

- No established cause in approximately 50% of cases.
- Do not infer a specific mechanism from the absence of a diagnosis.

Interpreting an acute failure presentation



Combine observations; Any single laboratory test or necrosis pattern is insufficient to establish etiology.

Hepatocyte dysfunction and cell death

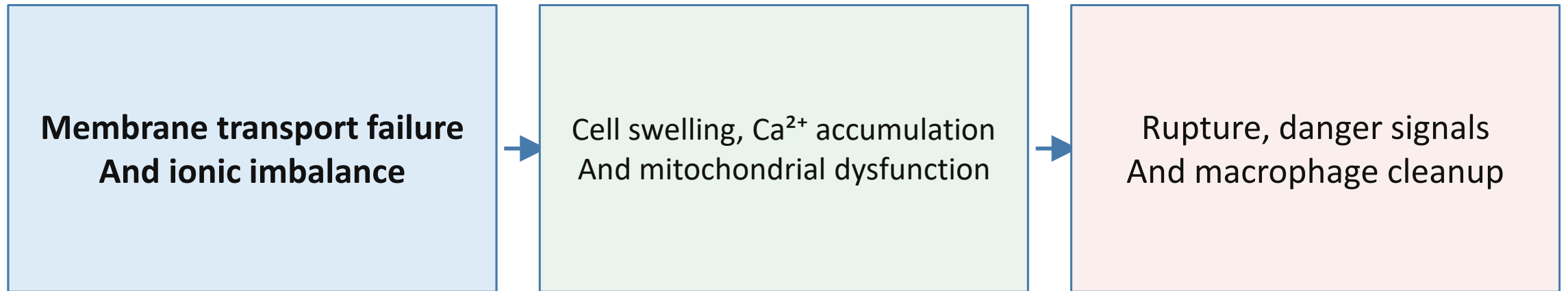
Potentially reversible changes

- Steatosis or intracellular bilirubin retention.
- Hepatocyte ballooning and cytoplasmic changes.
- Cellular dysfunction before loss of viability.

Irreversible injury

- Necrosis: Swelling, membrane damage and rupture.
- Apoptosis: Shrinkage and acidophil bodies.
- Confluent death can destroy wide lobular territories.

Cellular events in hepatocyte necrosis

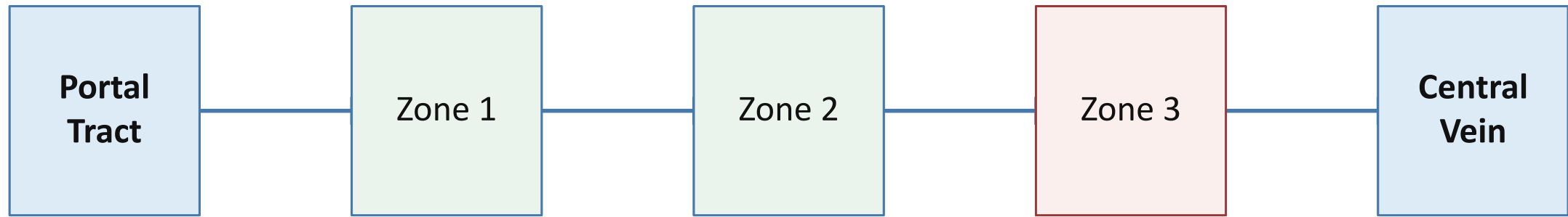


Necrotic loss of hepatocytes reduces the mass available for hepatic function.

Apoptosis as an additional hepatocyte response

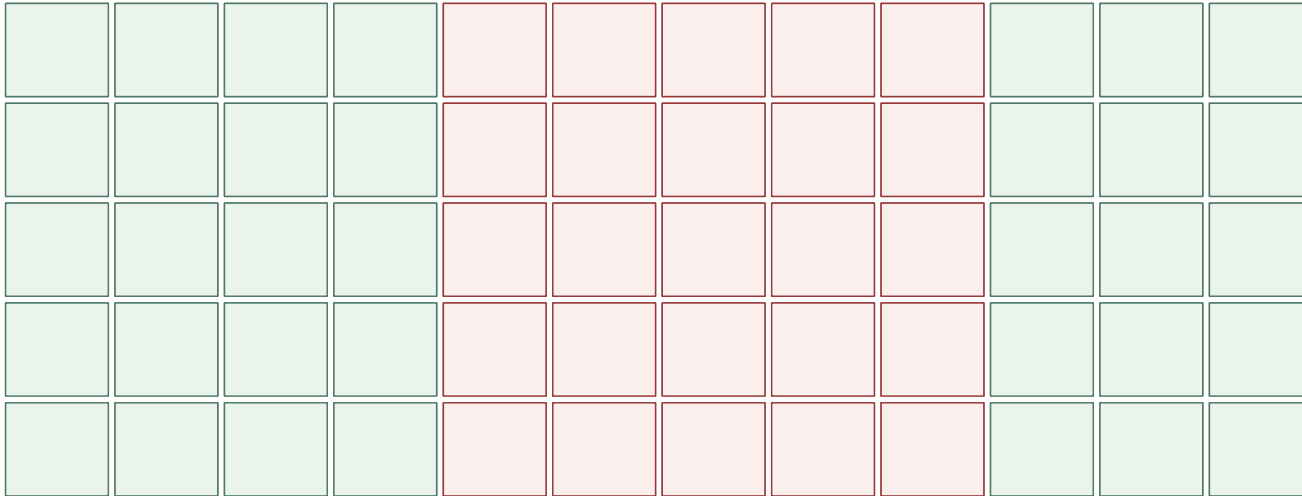
- Programmed cell death produces cell shrinkage and nuclear condensation.
- Nuclear fragmentation and acidophilic apoptotic bodies may be present.
- Acidophil bodies can occur in acute and chronic hepatitis.
- Apoptosis is distinct from confluent necrosis, which removes contiguous groups of cells.

Hepatic acinar zonation and injury



Schematic acinar sequence: Zone 1 is periportal; Zone 3 is perivenular and relatively less oxygenated.

Confluent necrosis: Contiguous cell loss



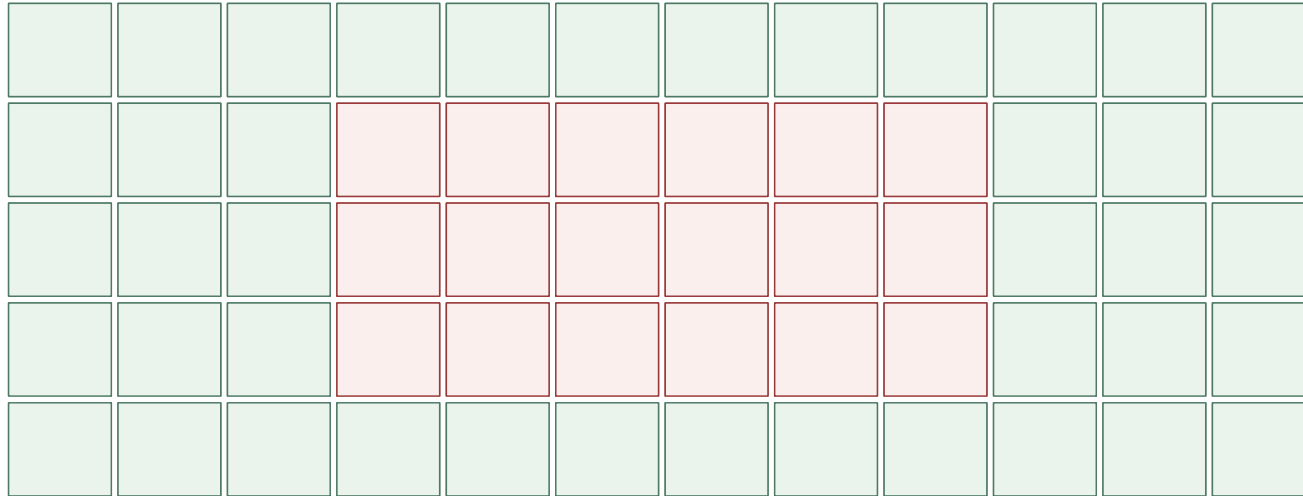
Conceptual parenchyma map

Muted red: Hepatocyte dropout
Green: Retained parenchyma

Contiguous hepatocyte loss can create a broad zone of necrosis.

Schematic only — not a histologic specimen or measured distribution.

Bridging necrosis: Injury across landmarks



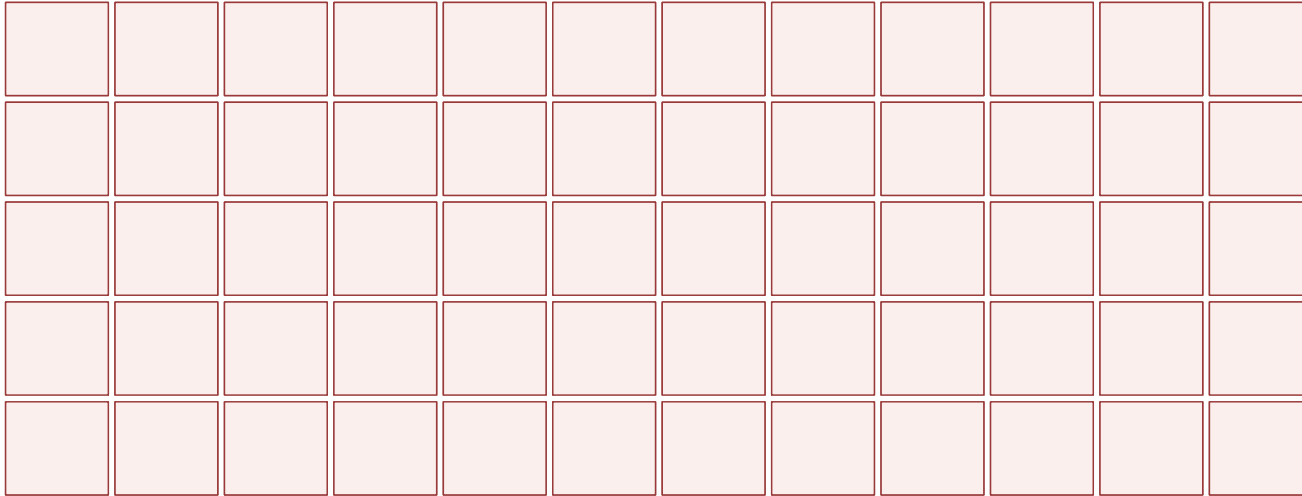
Conceptual parenchyma map

Muted red: Hepatocyte dropout
Green: Retained parenchyma

Confluent injury may connect
vascular landmarks within a
lobule.

Schematic only — not a histologic specimen or measured distribution.

Pan-acinar necrosis: Whole-lobule loss



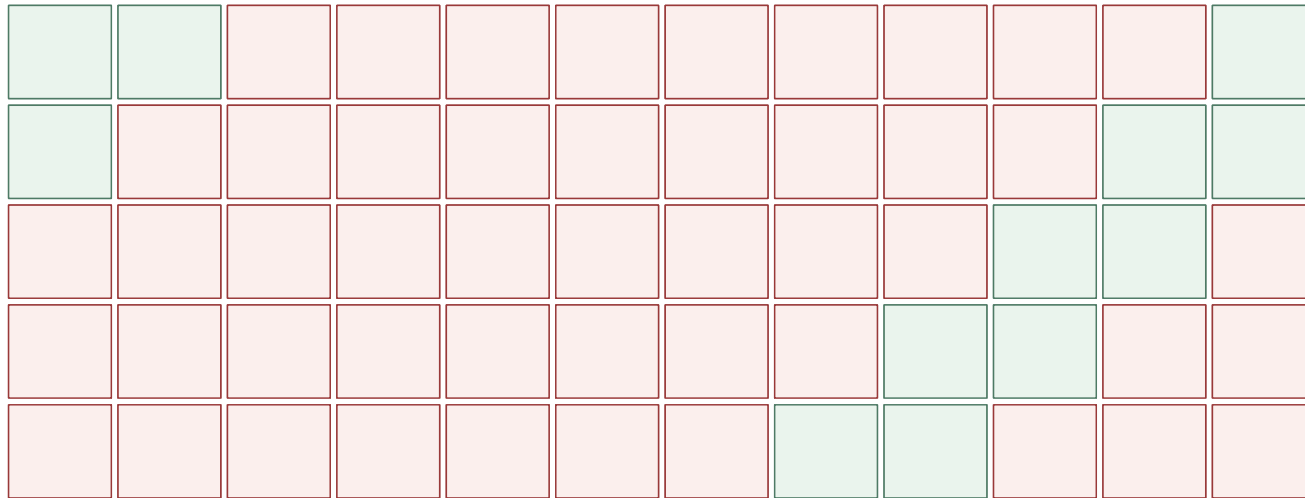
Conceptual parenchyma map

Muted red: Hepatocyte dropout
Green: Retained parenchyma

The whole lobule may be obliterated in pan-acinar necrosis.

Schematic only — not a histologic specimen or measured distribution.

Massive hepatic necrosis in acute failure



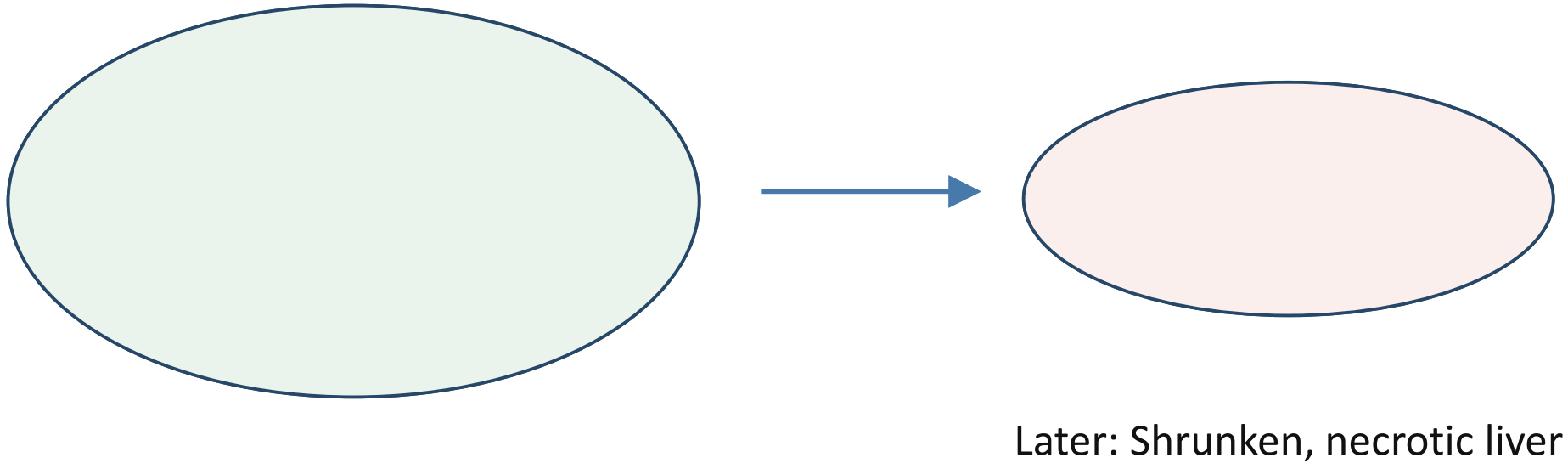
Conceptual parenchyma map

Muted red: Hepatocyte dropout
Green: Retained parenchyma

ALF may leave only scattered islands of viable or regenerating hepatocytes.

Schematic only — not a histologic specimen or measured distribution.

Acute failure: Enlargement may precede shrinkage



Early: Swelling, edema, infiltrates

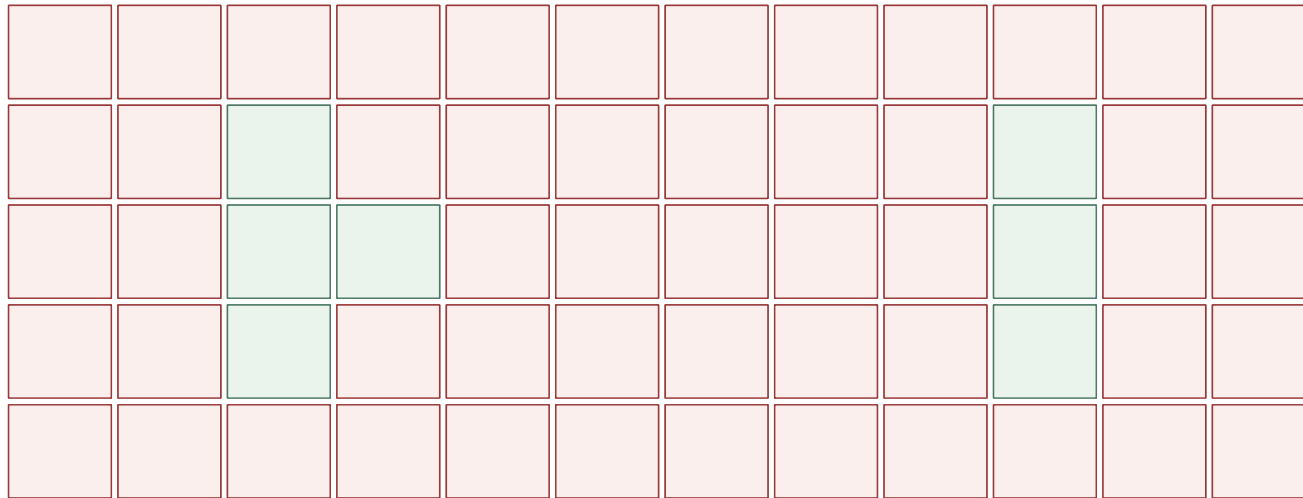
Later: Shrunken, necrotic liver

Schematic outline comparison, not an anatomical illustration or size measurement.

Gross appearance of massive necrosis

- With severe destruction, the liver may become small and shrunken.
- The textbook example is bile-stained, soft, and congested.
- Broad zones of parenchymal loss may coexist with surviving islands.
- A macroscopic pattern alone does not identify the initiating insult.

Surviving hepatocytes after extensive injury



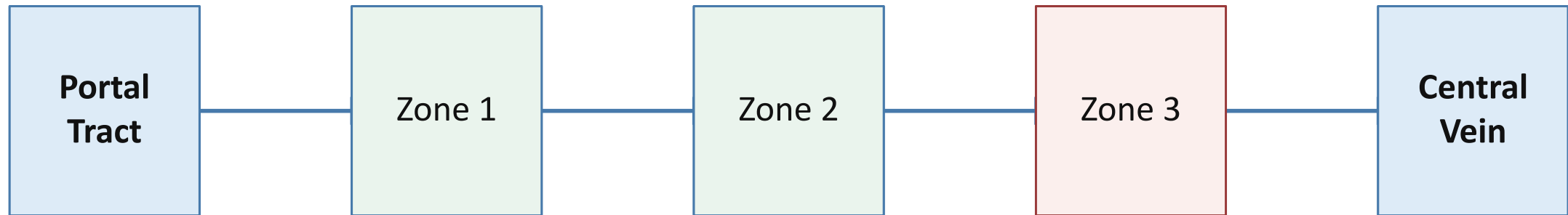
Conceptual parenchyma map

Muted red: Hepatocyte dropout
Green: Retained parenchyma

Preserved cell islands can
coexist with extensive
parenchymal destruction.

Schematic only — not a histologic specimen or measured distribution.

Acetaminophen and perivenular necrosis



Acetaminophen-associated confluent necrosis may be perivenular (zone 3).

Histologic evolution: Tempo shapes repair

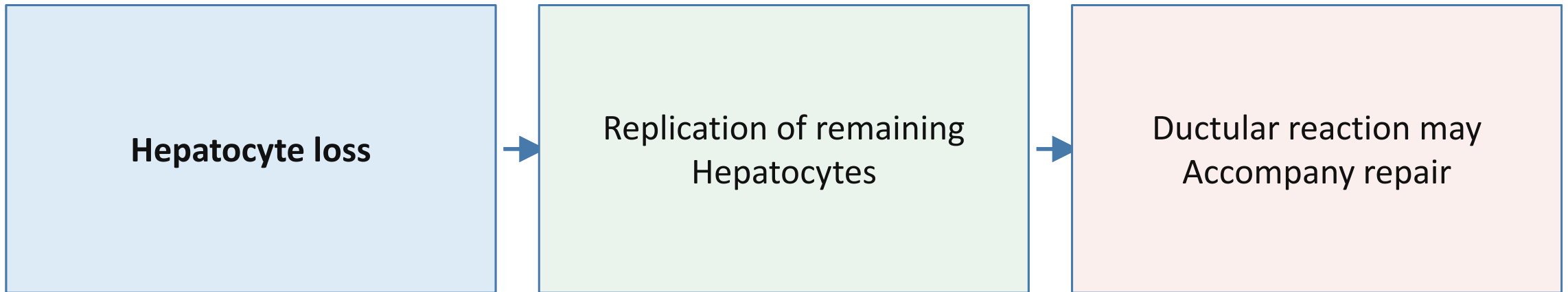
Hours to days

- Toxic necrosis may progress too quickly for scar formation.
- Little regenerative response may be visible early.

Weeks to months

- Viral injury may persist while hepatocytes regenerate.
- Ductular reactions and scarring can become apparent.

Regeneration during severe parenchymal injury



The balance between ongoing loss and regeneration governs the resulting tissue pattern.

Why scarring varies in acute failure

Rapid toxic insult

Sustained injury

Longer course



Minimal interval for scar
deposition

Persistent cell loss and repair

Scarring may become visible

Fibrosis is not a required morphologic feature of acute liver failure.

Acute failure with little visible necrosis

Usual pattern

- Massive parenchymal necrosis.
- Marked hepatocyte dropout.
- Small and shrunken liver late in disease.

Unusual functional pattern

- Widespread metabolic dysfunction.
- Little overt hepatocyte death may be evident.
- Diffuse microvesicular steatosis is a key example.

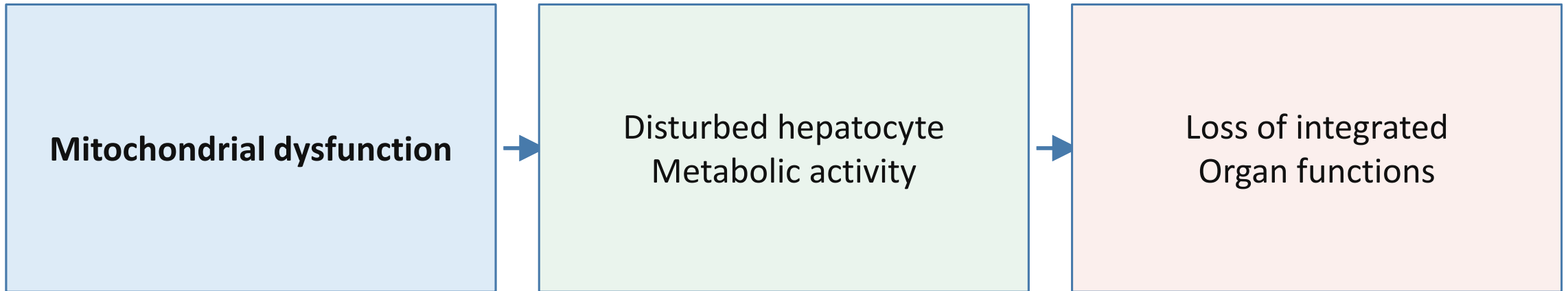
Acute fatty liver of pregnancy

- The source identifies acute fatty liver of pregnancy as a setting of diffuse microvesicular steatosis.
- Severe failure may arise despite relatively limited overt hepatocyte death.
- The functional disturbance is generally linked to mitochondrial dysfunction.
- The hallmark distinction is metabolic incapacity versus massive necrosis.

Idiosyncratic drug reactions and steatosis

- Valproate and tetracycline as examples.
- Diffuse microvesicular steatosis may accompany profound metabolic failure.
- Mitochondrial dysfunction can prevent normal hepatocellular functions.
- This path is different from a predominantly necrotic drug injury.

Mitochondrial failure → functional collapse

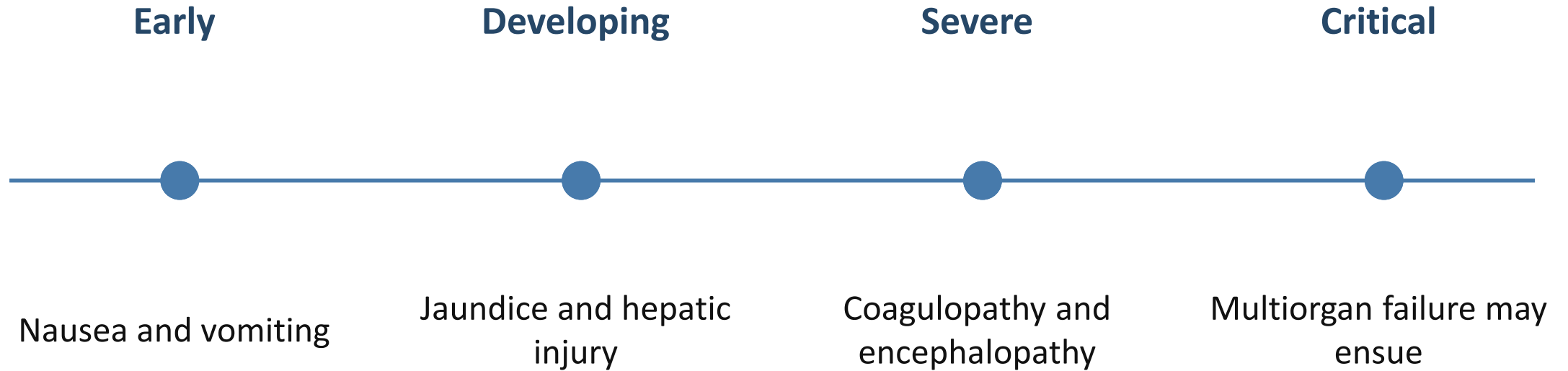


Extensive hepatocyte necrosis is not necessary for a severe functional syndrome.

Non-hepatotropic viruses in immunodeficiency

Viruses named	Clinical setting noted
Cytomegalovirus	Advanced immunodeficiency and posttransplant suppression
Herpes simplex viruses	Immunodeficient patients
Adenovirus	Immunodeficient patients

Typical clinical evolution



The sequence is illustrative; Not every patient follows identical timing.

What serum aminotransferases represent

- AST and ALT are cytosolic hepatocellular enzymes.
- Marked elevations commonly accompany acute failure.
- Enzyme release indicates hepatocellular injury—not directly the remaining liver reserve.
- Interpret the trajectory alongside bilirubin, synthesis, and neurologic status.

A falling transaminase level may mislead

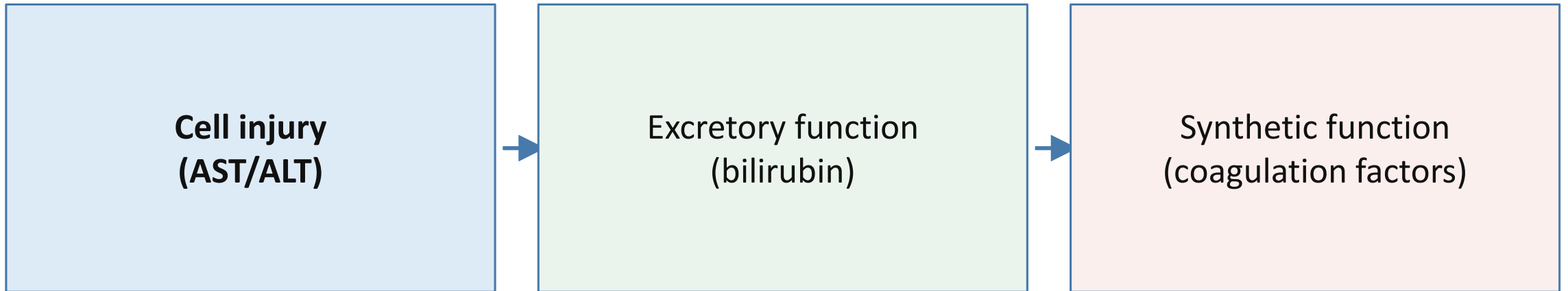
Recovery is plausible when...

- Clinical status stabilizes or improves.
- Jaundice and coagulopathy do not progress.
- Neurologic status does not deteriorate.

Extensive cell loss is plausible when...

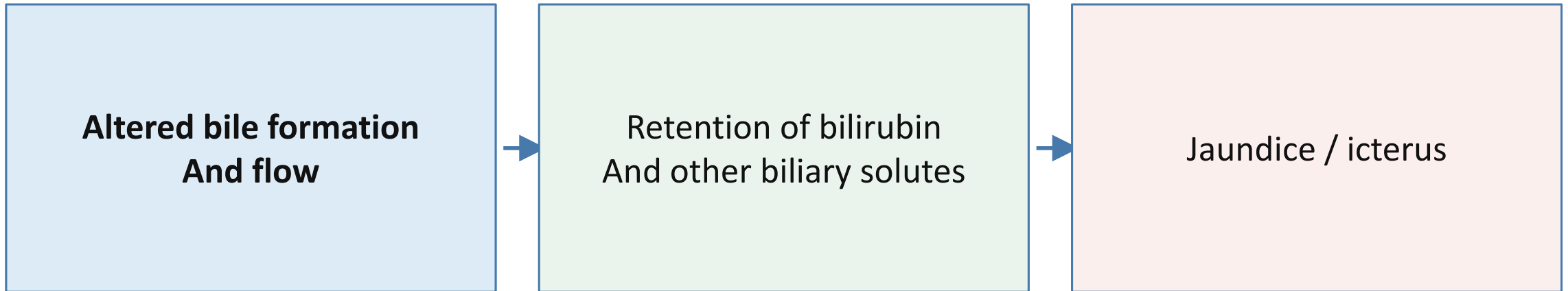
- Few viable cells remain to release enzymes.
- Jaundice and coagulation failure worsen.
- Encephalopathy progresses despite falling AST/ALT.

Functional tests reveal hepatic failure



No single analyte substitutes for the combined clinical syndrome.

Cholestasis from hepatocellular dysfunction



Cholestasis is a functional consequence of severe hepatic injury.

Jaundice and icterus

Jaundice

- Yellow discoloration of skin.
- Linked to retained bilirubin.

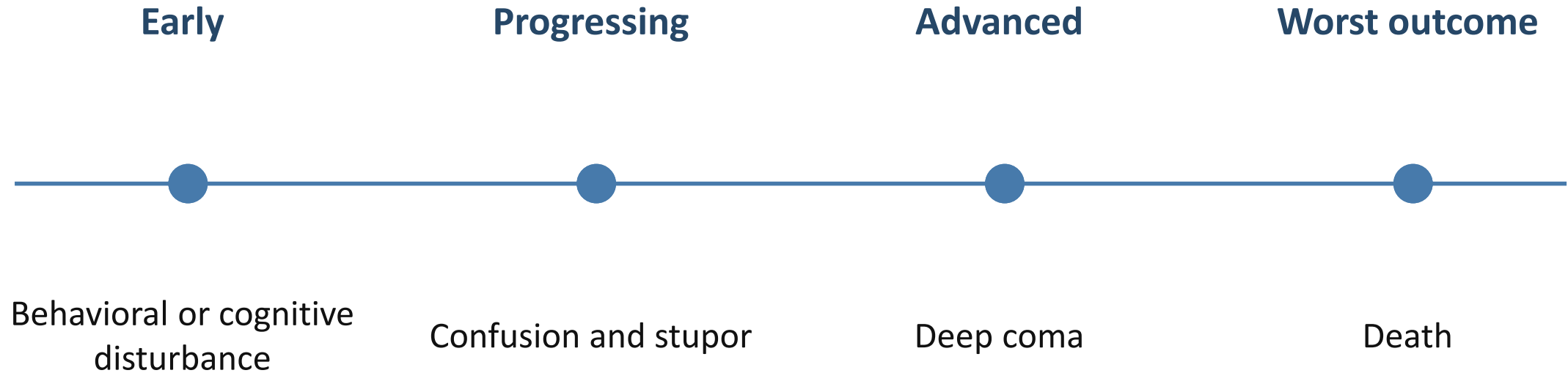
Icterus

- Yellow discoloration of conjunctivae.
- Also reflects bilirubin retention.

Infection risk in acute failure

- Severe liver dysfunction is associated with increased bacterial infection risk.
- The textbook particularly notes potentially life-threatening infection in this setting.
- Infection can compound the physiologic burden of hepatic failure.
- A worsening patient requires attention beyond hepatic biochemical results alone.

Hepatic encephalopathy: Clinical spectrum

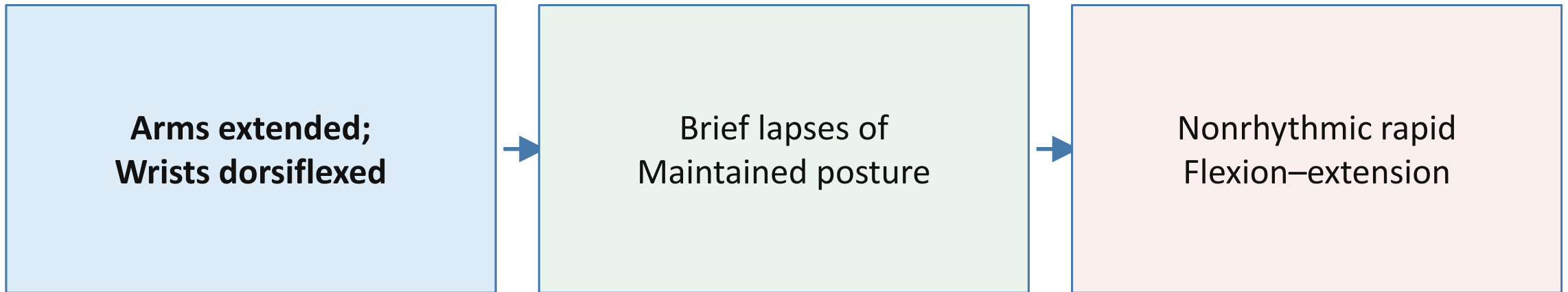


Changes in consciousness are essential to the syndrome definition.

Neurologic findings in encephalopathy

- The patient may display fluctuating neurologic signs.
- Rigidity and hyperreflexia are described in the source.
- Asterixis is particularly characteristic, though not specific to a cause.
- Encephalopathy may develop quickly or over a longer interval after hepatic injury.

Asterixis: What the examiner observes



Asterixis is a bedside sign, not a histologic or biochemical test.

Ammonia production and hepatic clearance



Acute liver failure disrupts the final detoxification step.

Normal and failed ammonia handling

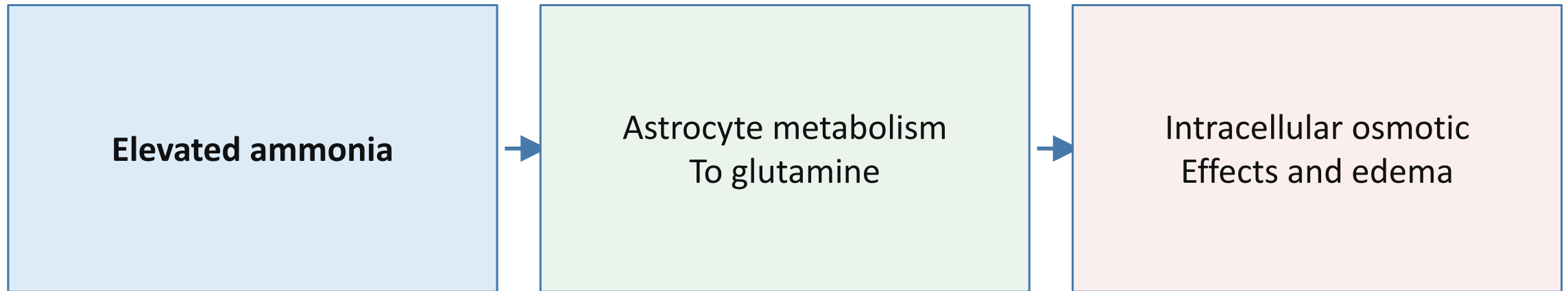
Working liver

- Ammonia reaches hepatocytes through portal blood.
- Urea-cycle activity detoxifies ammonia.
- Systemic exposure is constrained.

Severe hepatic failure

- Ammonia removal becomes insufficient.
- Increased ammonia is associated with CNS dysfunction.
- Cerebral edema can accompany the syndrome.

A proposed pathway to cerebral edema



This as a proposed mechanism, not the only cause of encephalopathy.

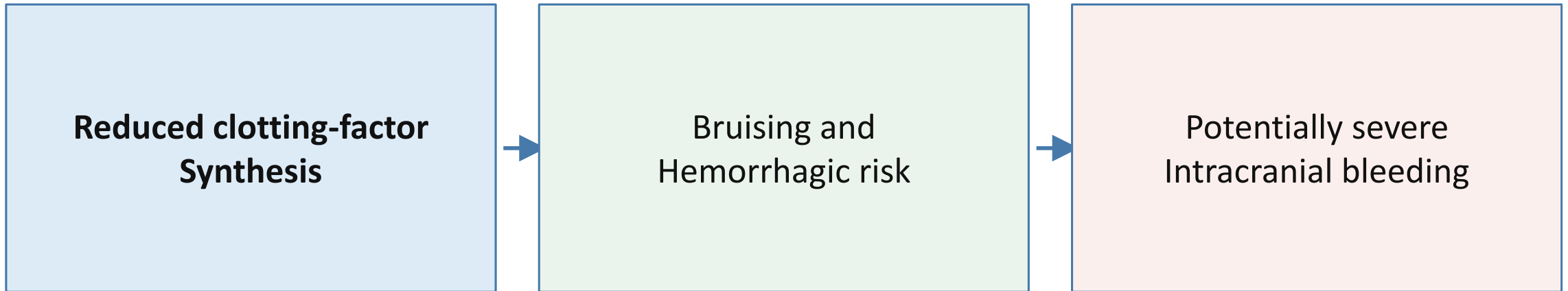
Why encephalopathy can be fatal

- Neurologic impairment can advance from subtle behavior change to coma.
- Hyperammonemia correlates with impaired neuronal function and cerebral edema.
- The source notes both direct neuronal and indirect astrocytic mechanisms as proposals.
- Cerebral edema represents a severe neurologic complication.

Hepatocellular synthesis and coagulation

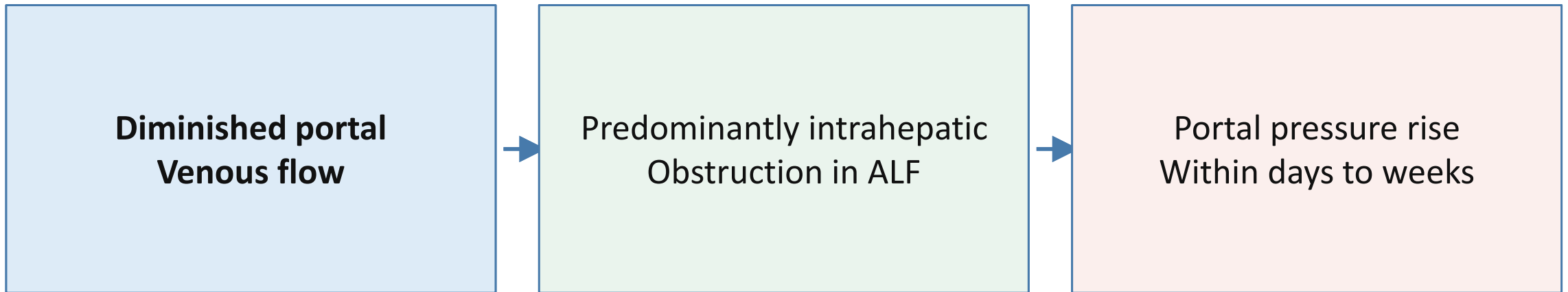
Hepatic synthetic products	Consequences of profound failure
Factors II, V, VII, IX and X	Lower functional clotting-factor availability
Factors XI and XII; fibrinogen	Further loss of hemostatic proteins
Clearance of activated factors	Loss of regulation may contribute to DIC

Coagulopathy and bleeding risk



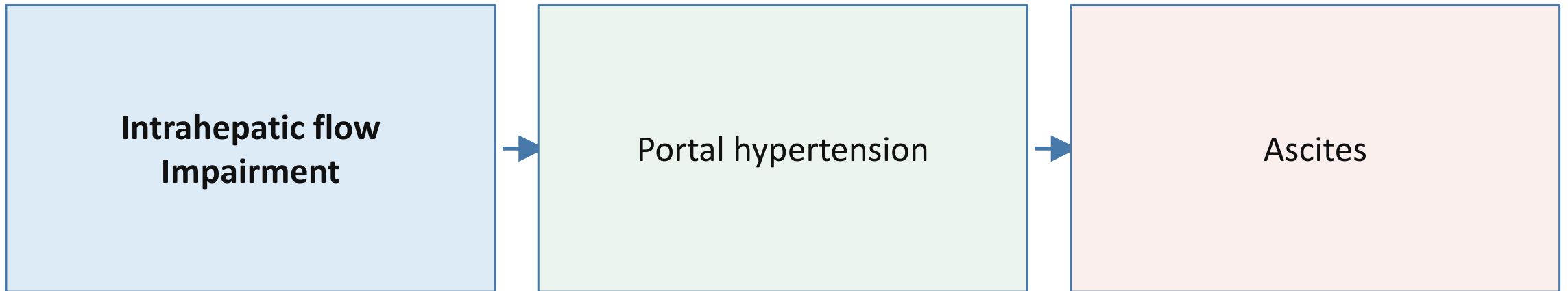
Impaired clearance of activated factors may also contribute to disseminated intravascular coagulation.

Acute portal hypertension



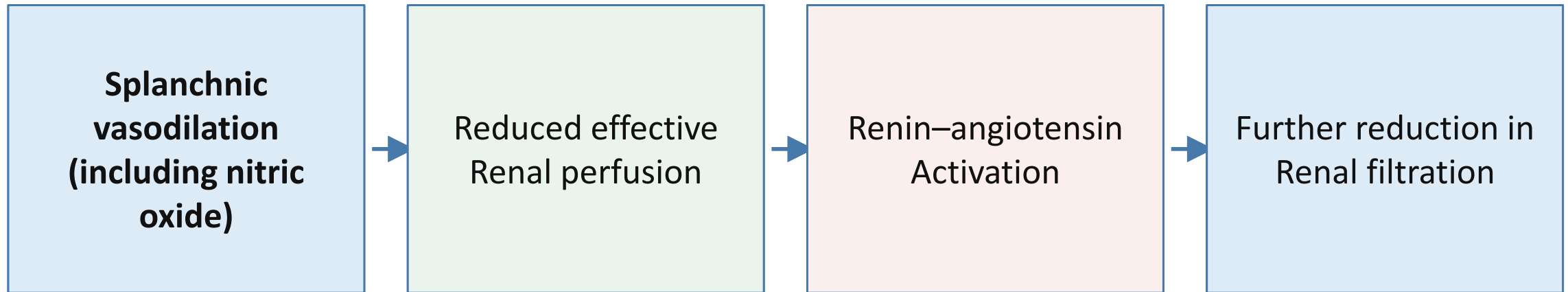
Portal hypertension is more typical of chronic disease but can complicate acute failure.

Ascites from acute portal hypertension



Ascites is the major consequence emphasized for acute portal hypertension.

Proposed pathogenesis of hepatorenal syndrome



This is a proposed hemodynamic sequence; Pathophysiology is not fully established.

Renal presentation of hepatorenal syndrome

- Urine output falls as kidney perfusion deteriorates.
- Blood urea and creatinine concentrations rise.
- The syndrome occurs without intrinsic kidney disease explaining the failure.
- Fulminant hepatic failure may precipitate this complication, although cirrhosis is the more usual setting.

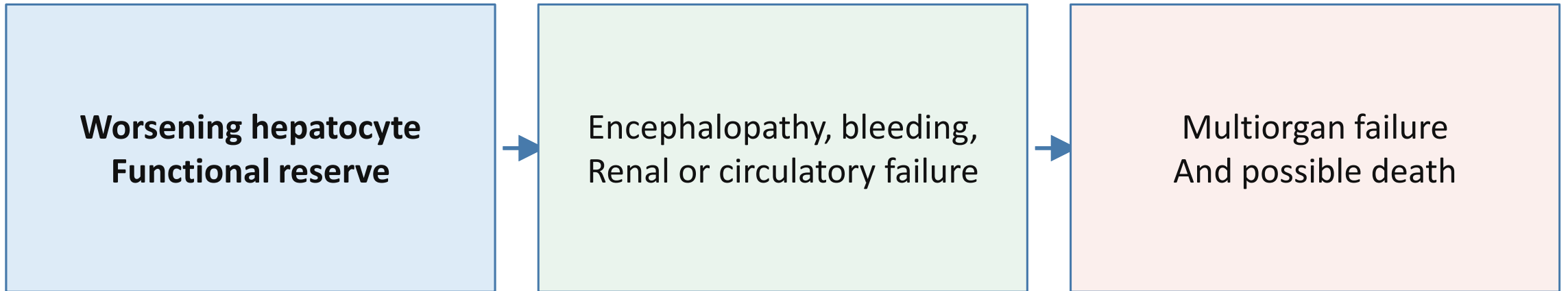
Why renal dysfunction may reverse

- The major mechanism presented is hemodynamic rather than destructive renal pathology.
- Renin–angiotensin activation aggravates perfusion defects.
- Renal function may improve when liver function is restored.
- Liver transplantation is the example of recovery given in the text.

Acute failure versus chronic failure

Characteristic	Acute liver failure	Chronic failure / cirrhosis
Time course	Within 26 weeks of initial injury	Progresses over months to years
Typical pathology	Massive necrosis or metabolic failure	Fibrous septa and regenerative nodules
Portal hypertension	Possible; often intrahepatic obstruction	Frequent; complex vascular consequences

Why early recognition is consequential



The source explicitly identifies transplantation as a possible life-saving intervention.

Case application: Rapid-onset toxic pattern

A patient develops marked aminotransferase elevation, jaundice, and deteriorating consciousness within days of an acetaminophen exposure. Later, AST/ALT begin to decline as coagulopathy worsens.

Which interpretation of the falling enzymes is unsafe?

Assuming recovery: A declining release of enzymes may accompany loss of viable hepatocyte mass.

Case application: Function without massive necrosis

A pregnant patient develops profound hepatic dysfunction. Tissue assessment reveals extensive microvesicular steatosis without the massive hepatocyte loss typical of many toxic failures.

Which pathophysiologic category fits best?

Predominant metabolic / mitochondrial hepatocyte dysfunction, as described for acute fatty liver of pregnancy.

Case application: Neurologic progression

Following severe acute hepatitis, a patient develops altered behavior, asterixis, confusion, and subsequently impaired consciousness.

Which physiological defect helps explain the CNS syndrome?

Failed hepatic ammonia detoxification; Astrocyte glutamine accumulation is one proposed edema mechanism.

The integrated pathology of acute liver failure

Primary lesion or dysfunction	Observable clinical consequence
Massive necrosis / mitochondrial failure	Rapid loss of hepatic function
Impaired bile formation and flow	Hyperbilirubinemia; jaundice and icterus
Reduced synthesis; altered coagulation clearance	Coagulopathy and hemorrhagic risk
Failed ammonia clearance	Encephalopathy and cerebral edema
Portal and systemic hemodynamic disturbance	Ascites; possible hepatorenal syndrome

Synthesis: Essential distinctions

- Acute liver failure is a clinical syndrome, not a single histologic lesion.
- Direct toxicity and immune-mediated injury often cause extensive hepatocyte necrosis.
- Mitochondrial dysfunction can produce severe failure without extensive cell death.
- The liver's loss of synthesis, excretion and detoxification explains the life-threatening phenotype.

Primary teaching source

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 18: Liver and Gallbladder — Acute Liver Failure (printed pp. 751–753).
- Supporting context: Hepatocyte and Parenchymal Responses; Scar Formation and Regression (printed pp. 749–751).
- The original textbook figures were not reproduced; all diagrams in this lecture are editable schematics.