

Viral Hepatitis

Hepatotropic viruses, liver injury, and clinicopathologic patterns

A pathology-centered overview

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Learning goals

- Differentiate hepatotropic from systemic viral causes of hepatitis.
- Compare the five classical hepatotropic viruses by transmission and persistence.
- Explain the host-response basis of hepatocyte injury.
- Recognize acute and chronic morphologic patterns and their diagnostic limitations.

Emphasis: Mechanisms, morphology, and clinical interpretation.

What “viral hepatitis” denotes

Narrow clinical usage

- Inflammation and hepatocellular injury associated with infection by hepatotropic viruses.
- Classical agents: Hepatitis A, B, C, D, and E.

Broader biologic usage

- Liver involvement during systemic viral infections.
- Examples include EBV, CMV, HSV, adenovirus, yellow fever virus, and SARS-CoV-2.

Two routes to a viral hepatitis syndrome



- Systemic viruses can also affect the liver, frequently as part of multisystem disease.
- A hepatitic phenotype does not, by itself, identify the infectious agent.

The five classical hepatotropic viruses

Virus	Genome or dependency	Core distinguishing feature
HAV	Positive-strand RNA	Acute, self-limited; No chronic carrier state
HBV	Partially double-stranded DNA	Acute or chronic; Can persist
HCV	Single-stranded RNA	Strong propensity for chronic infection
HDV	Circular single-stranded RNA	Requires HBV for infection
HEV	Positive-strand RNA	Usually acute; Chronicity with immunosuppression

Nonhepatotropic viruses are not rare exceptions

- Epstein–Barr virus and cytomegalovirus can be associated with hepatitis.
- Herpes simplex virus, adenovirus, and yellow fever virus may produce liver injury.
- SARS-CoV-2 infection can involve the liver, generally mildly or subclinically.
- Assess whether hepatitis is the primary syndrome or a manifestation of systemic infection.

Clinical context narrows the etiologic differential.

Enteric versus parenteral viral hepatitis

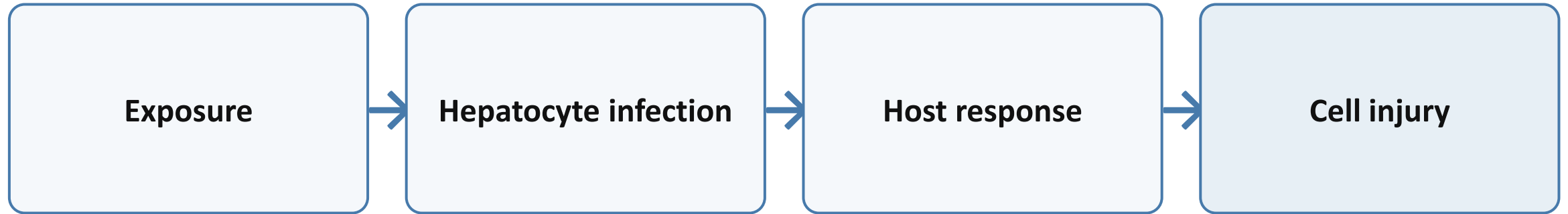
Pattern	Classical agents	Exposure clue
Enteric / fecal–oral	HAV, HEV	Contaminated food, water, sanitation
Blood and body-fluid exposure	HBV, HCV, HDV	Needles, blood exposure; Sexual/perinatal exposure for HBV
HBV-dependent transmission	HDV	Exposure in the setting of HBV infection

Why agent identification matters

Similar liver injury can arise from viruses with very different natural histories.

- HAV usually resolves without chronic infection.
- HBV and HCV can produce persistent disease and fibrosis.
- HDV can markedly worsen the course of HBV infection.
- HEV can be particularly severe during pregnancy.

From exposure to hepatocellular injury



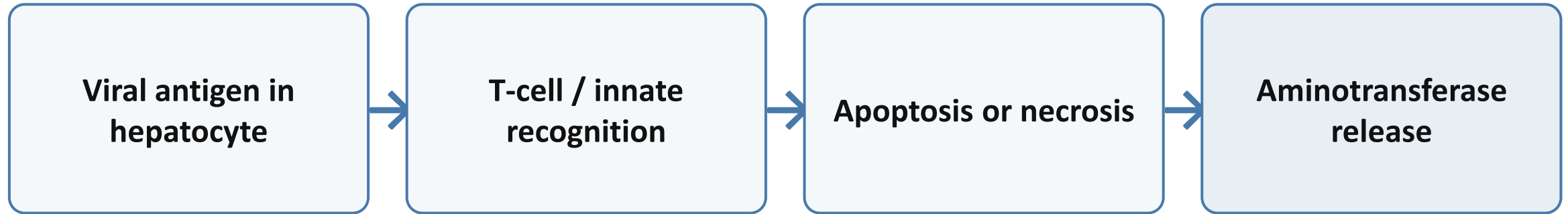
- Clinical hepatitis reflects both viral infection and host-mediated tissue responses.
- The balance between control and persistence shapes the outcome.

Hepatocyte injury is often immune mediated

- HAV is not considered directly cytopathic account.
- Cytotoxic T cells and natural killer cells damage infected hepatocytes in HAV.
- HBV injury is predominantly associated with cytotoxic CD8⁺ T-cell activity.
- HEV-associated damage is also attributed largely to the host response.

Inflammation is not simply a measure of direct viral cell destruction.

A host-response model of liver injury



- The liver inflammatory infiltrate in viral hepatitis is predominantly lymphocytic.
- Microscopic injury and biochemical hepatitis represent linked phenomena.

Successful clearance versus persistence

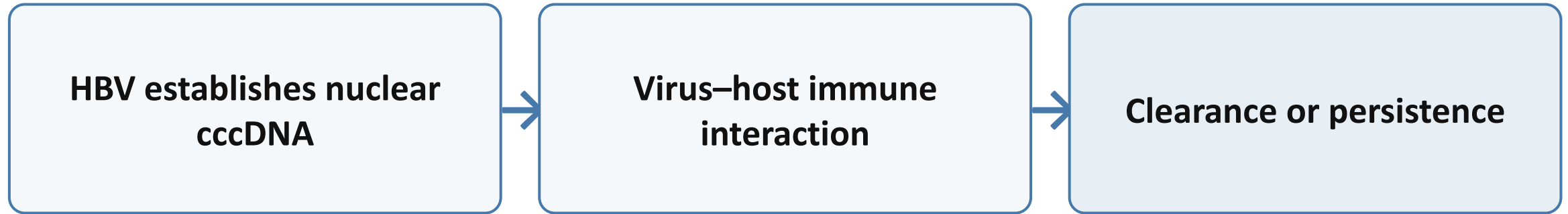
Effective antiviral response

- Virus-specific cellular immunity suppresses and removes infected cells.
- Resolution may be followed by durable antiviral antibody responses.

Incomplete viral control

- Persistent infection sustains hepatocyte injury and inflammation.
- Ongoing activity can lead to fibrogenesis and eventual cirrhosis.

Why hepatitis B can become chronic



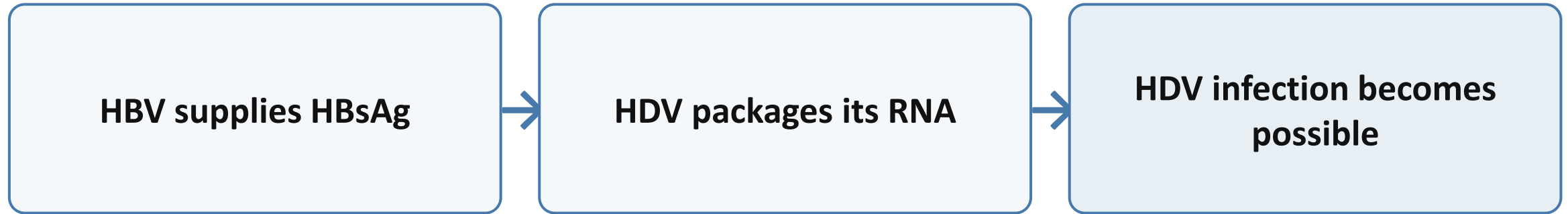
- HBV replication uses reverse transcription of an RNA intermediate.
- Strong virus-specific CD4⁺ and CD8⁺ responses favor resolution.
- Persistence is influenced by the age at infection and immune status.

HCV persistence is facilitated by viral diversity

- HCV RNA polymerase has low replication fidelity.
- Genetically diverse quasispecies emerge during infection.
- Envelope-epitope variation permits escape from some neutralizing responses.
- NS3/4A also interferes with host antiviral signaling.

These mechanisms help explain why chronic infection is frequent.

HDV depends on an existing HBV system



- HDV is a defective RNA virus requiring HBV-derived envelope proteins.
- Consequently, HDV should be considered in persons with HBV infection.

Transmission biology has clinical consequences

- HAV and HEV are often linked to fecal contamination of food or water.
- HBV can spread by blood exposure, sexual contact, and during childbirth.
- HCV and HDV are predominantly associated with parenteral exposure.
- Transmission route directs prevention and exposure assessment.

A common histologic injury pattern can conceal different epidemiologic mechanisms.

Risk patterns that redirect investigation

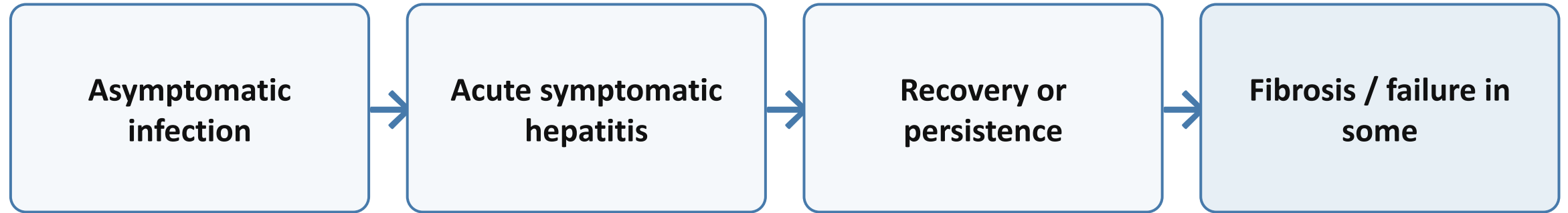
Clinical history	Agent group to consider	Reasoning
Food or water outbreak	HAV / HEV	Enteric transmission
Blood / needle exposure	HBV / HCV / HDV	Parenteral transmission
Known chronic HBV with sudden worsening	HDV among other causes	Superinfection can exacerbate disease
Systemic febrile illness	Nonhepatotropic viruses	Liver involvement may be secondary

Pathogenesis cannot be inferred from ALT alone

An elevated aminotransferase concentration describes hepatocyte injury—not its cause.

- Different hepatotropic viruses can produce comparable hepatitic inflammation.
- Autoimmune disease and drug injury can reproduce this phenotype.
- Etiologic diagnosis requires virus-specific testing.

The clinicopathologic spectrum



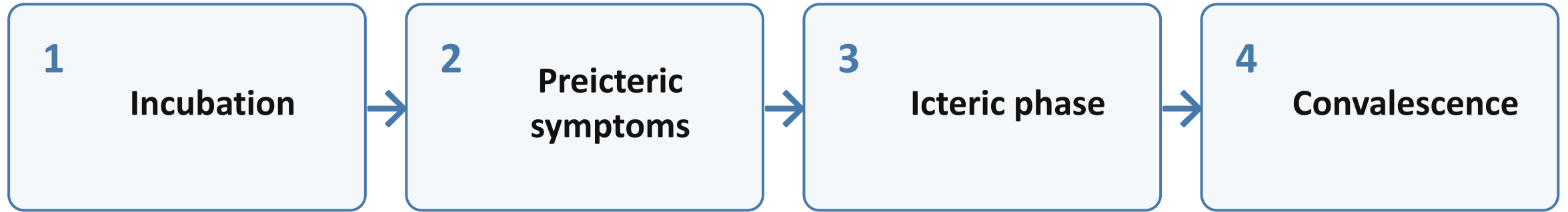
- Not every patient follows every step.
- Acute liver failure is an uncommon but severe alternative pathway.

Asymptomatic hepatitis may still be detectable

- Many acute infections are clinically silent.
- Mild aminotransferase elevations may be the only clue during infection.
- After recovery, virus-specific antibodies may indicate previous exposure.
- Symptom-based case finding alone misses a substantial fraction of infections.

Examples include subclinical HAV and HBV infection.

Four phases of symptomatic acute hepatitis



- Constitutional symptoms can precede recognizable jaundice.
- Incubation length varies across the viral agents.

Preicteric symptoms are nonspecific

- Fatigue, malaise, anorexia, and nausea can dominate presentation.
- The early syndrome may resemble other systemic infections.
- The absence of jaundice does not exclude acute viral hepatitis.
- Exposure history and appropriate viral testing improve etiologic assessment.

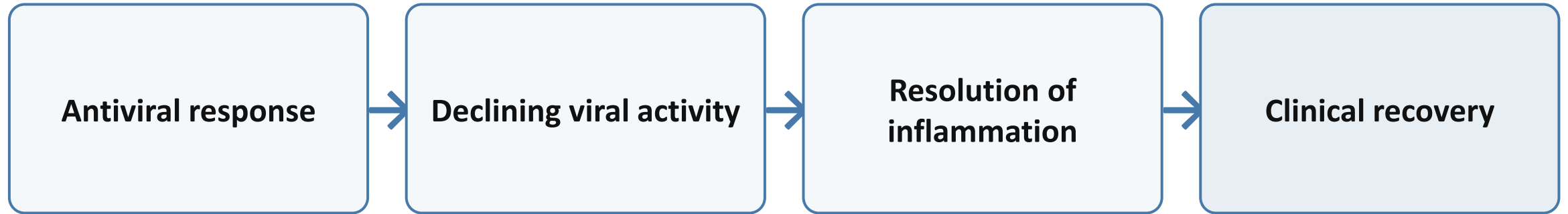
The preicteric phase is not unique to one hepatitis virus.

Jaundice reflects impaired bilirubin handling

- Hepatocellular dysfunction may impair bilirubin uptake, processing, or excretion.
- Jaundice emerges in only a subset of acute viral infections.
- Prominent jaundice does not alone establish the specific virus.
- Clinical correlation includes bilirubin and tests of hepatic synthetic function.

Mechanistic linkage is hepatocellular dysfunction, not a virus-specific visual sign.

Convalescence after acute infection



- HAV infection usually resolves without chronic persistence.
- Most immunocompetent people clear acute HEV infection.

Acute hepatitis versus acute liver failure

Acute hepatitis

- Hepatocyte injury and inflammation of variable clinical severity.
- May resolve without permanent loss of liver architecture.

Acute liver failure

- Severe hepatic dysfunction following extensive hepatocyte loss.
- Massive necrosis can accompany a shrunken liver.
- Requires urgent specialist assessment.

Acute liver failure: Viral etiologies

- Hepatotropic viral infection accounts for a subset of acute liver failure.
- HAV and HEV contribute importantly to cases worldwide.
- Severe HEV hepatitis is particularly concerning during pregnancy.
- Extensive hepatic necrosis can overwhelm regenerative capacity.

Outcome depends on the balance between residual parenchyma and injury severity.

Persistence versus recovery

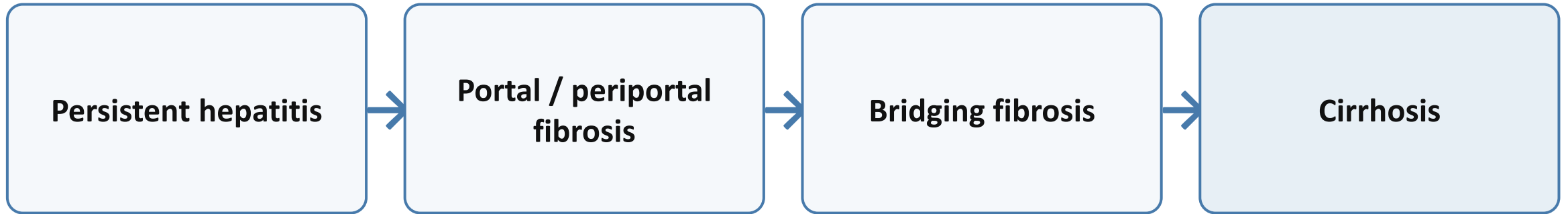
Outcome	Biologic feature	Long-term significance
Recovery	Virus controlled; Liver injury subsides	No ongoing virus-driven inflammation
Chronic infection	Persistent / relapsing hepatitis	Fibrosis, cirrhosis and complications
Asymptomatic carriage (HBV context)	Virus detectable without symptoms	Transmission still possible

Chronic hepatitis: Interpret chronicity correctly

- The Robbins description includes continuing or relapsing disease beyond 6 months.
- Morphologic fibrosis also indicates a chronic pathologic process.
- Persistent serum aminotransferase elevations may be the sole clinical clue.
- Chronic viral hepatitis requires etiologic and activity assessment.

Histologic chronicity and virologic persistence are related, but not identical constructs.

The route from chronic injury to cirrhosis



- Fibrosis reflects repeated injury and repair rather than a single acute episode.
- Portal–portal bridges distort hepatic architecture as disease advances.

Carrier status requires careful language

A carrier may be asymptomatic

- The person harbors and can transmit the infectious agent.
- Absence of symptoms does not necessarily mean absence of tissue injury.

Virologic activity varies

- Some HBV carriers have low or undetectable HBV DNA and little inflammation.
- A comparable “healthy carrier” category is not recognized for HCV.

Clinical appearance underestimates chronic disease

Minimal symptoms do not exclude persistent hepatitis or fibrosis.

- Fatigue may be the dominant symptom of chronic hepatitis.
- Laboratory tests, viral assays, and fibrosis assessment provide complementary information.
- Cirrhosis and hepatocellular carcinoma are major long-term concerns in HBV/HCV.

Hepatitis A: The archetype of self-limited infection

- Nonenveloped positive-strand RNA virus transmitted primarily fecal–orally.
- Immune-mediated hepatocyte injury follows infection.
- IgM anti-HAV appears with acute symptomatic disease.
- Chronic hepatitis and a persistent carrier state do not occur.

The HAV-specific lecture examines its epidemiology and diagnosis in depth.

Hepatitis A serology: What the antibody class means

Marker	Interpretation	Temporal pattern
IgM anti-HAV	Recent or acute HAV infection	Appears near symptom onset
IgG anti-HAV	Previous exposure or immunity	Appears during recovery; Persists
Total anti-HAV	Prior or current exposure	Must be interpreted with IgM

Hepatitis B: Multiple clinical trajectories

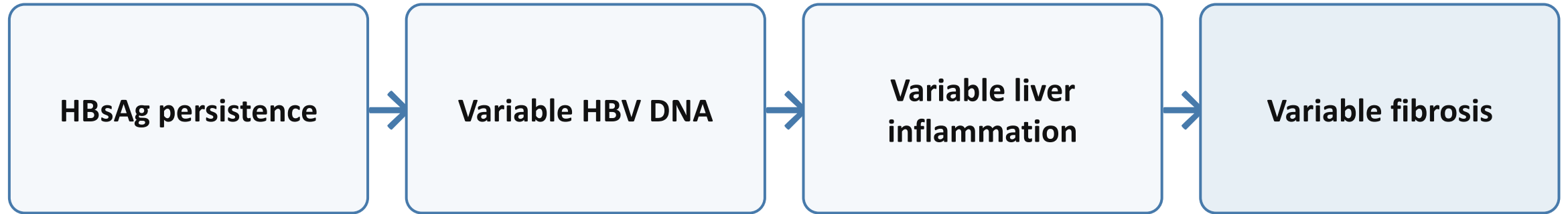
- HBV is a partially double-stranded DNA hepadnavirus.
- Outcomes include recovery, acute liver failure, chronic hepatitis, or asymptomatic carriage.
- An age-dependent host response influences chronicity.
- Sustained infection increases risk of cirrhosis and hepatocellular carcinoma.

HBV is an important example of host–virus outcome heterogeneity.

Hepatitis B marker categories

Marker	What it primarily indicates	Important nuance
HBsAg	Current HBV infection	Can occur in acute or chronic infection
IgM anti-HBc	Recent infection	Helpful during serologic window
Anti-HBs	Protective antibody response	Seen after recovery or vaccination
HBV DNA	Viral replication / viremia	Needed when HBeAg is misleading

HBV persistence is not equivalent to severe symptoms



- Some chronic infections are clinically silent.
- Serology, viral DNA, aminotransferases, and liver assessment answer different questions.

Hepatitis C: Persistence is a central problem

- Enveloped RNA virus of the Flaviviridae family.
- Acute infection is often minimally symptomatic or clinically silent.
- Rapid viral variation enables immune escape.
- Untreated persistent infection may progress to fibrosis and cirrhosis.

HCV-related chronic disease is not reliably excluded by normal symptoms.

Hepatitis C tests answer distinct questions

Test	Main inference	Limitation
Anti-HCV antibody	Exposure to HCV	Does not alone prove current viremia
HCV RNA	Current viral RNA detected	Interpreted with clinical context
Hepatic fibrosis assessment	Chronic injury burden	Cannot identify HCV without etiologic testing

Hepatitis D: Two biologically different settings

- Coinfection: HBV and HDV acquired together.
- Superinfection: HDV acquired by someone already infected with HBV.
- Superinfection is more likely to persist and exacerbate existing hepatitis.
- Diagnosis incorporates HDV-specific antibodies and HDV RNA.

Every HDV diagnosis requires an HBV context.

HBV–HDV coinfection versus HDV superinfection

Coinfection

- Simultaneous acquisition of HBV and HDV.
- May resemble acute HBV hepatitis.
- Clearance of both agents often follows.

Superinfection

- HDV acquired in pre-existing chronic HBV infection.
- Can trigger severe flare of liver injury.
- Persistent HDV infection is much more common.

Hepatitis E: Usually acute, with important exceptions

- Enterically transmitted positive-strand RNA virus; Zoonotic reservoirs are described.
- Typical infection is self-limited in immunocompetent individuals.
- Severe disease may occur during pregnancy.
- Chronic HEV infection can occur with immunosuppression.

HEV should not be simplistically described as always nonchronic.

A–E: Rapid comparison of persistence

Virus	Usual tendency	Important caveat
HAV	Acute and self-limited	No chronic hepatitis / carrier state
HBV	Recovery or persistence	Chronicity strongly shaped by age and immunity
HCV	High chronicity tendency	Acute infection may be clinically silent
HDV	Depends on HBV	Superinfection often persists
HEV	Acute and self-limited	Chronicity in immunosuppressed hosts

Viral hepatitis is a pattern, not a unique histology

Acute and chronic morphologic changes overlap with other hepatitic disorders.

- Viral hepatitis, autoimmune hepatitis, and drug injury can look similar.
- Wilson disease can also produce an overlapping hepatitic pattern.
- Serologic and molecular results provide necessary etiologic specificity.

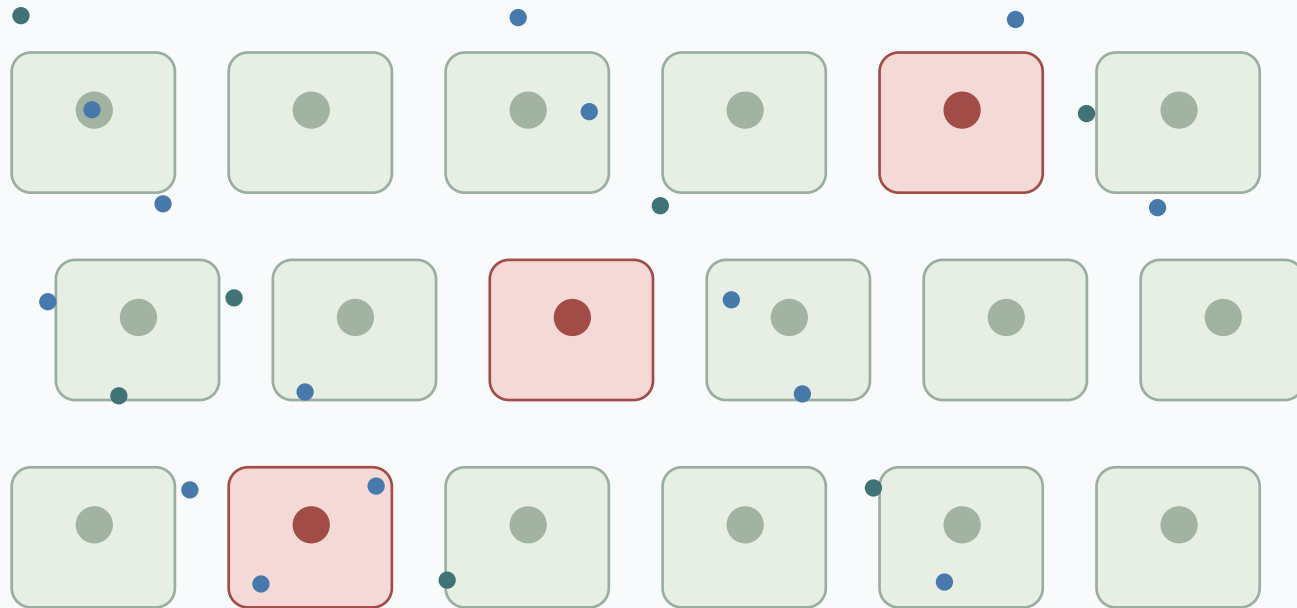
Gross appearance in acute viral hepatitis

- Liver size may be normal despite clinical hepatitis.
- Inflammation can produce hepatomegaly.
- Acute liver failure with massive necrosis can produce a shrunken liver.
- Gross size alone is not sufficient to establish diagnosis or severity.

Schematic depictions below are not source photomicrographs.

Acute hepatitis: Lobular injury schematic

ORIGINAL SCHEMATIC — NOT A HISTOLOGIC SPECIMEN



Lymphocytes

Injured hepatocyte

Characteristic components

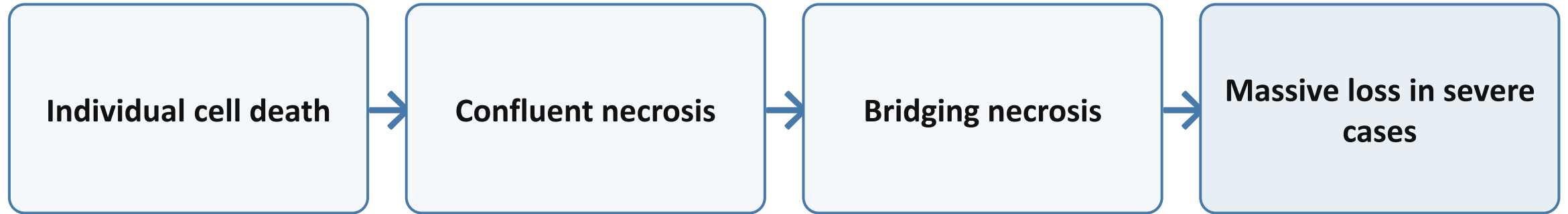
- Predominantly lymphocytic inflammatory infiltrate in portal tracts and lobules
- Hepatocyte apoptosis and necrosis occur with variable severity.
- Macrophages may remove necrotic cell debris.

Acute injury: Apoptosis and necrosis

- Damaged hepatocytes may undergo apoptosis or necrosis.
- Apoptotic hepatocytes can appear as condensed eosinophilic bodies.
- Pigmented macrophages may scavenge necrotic material.
- Tissue injury is accompanied by portal and lobular inflammatory cells.

The distribution and severity of injury matter more than a single cell.

Severe acute injury: Anatomic extension



- Bridging necrosis connects vascular structures.
- Panlobular / panacinar necrosis affects an entire lobular unit.
- Massive necrosis can produce life-threatening hepatic failure.

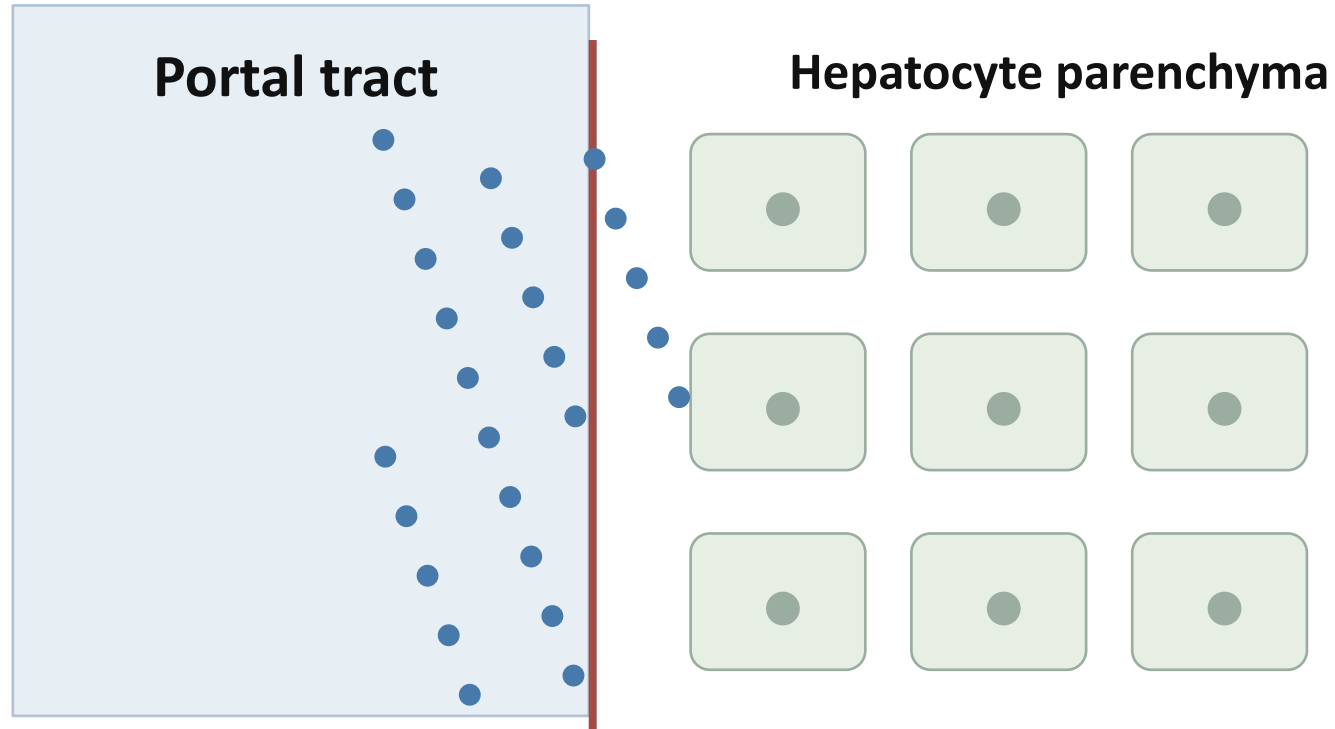
Chronic viral hepatitis: Defining morphology

- Portal lymphocytic or lymphoplasmacytic inflammation.
- Inflammatory cells may cross the limiting plate into periportal parenchyma.
- Portal and periportal fibrosis reflects ongoing injury.
- Lobular inflammation may coexist with interface activity.

Fibrosis is the distinctive chronic consequence to recognize.

Interface hepatitis: Site of inflammatory damage

ORIGINAL SCHEMATIC — NOT A HISTOLOGIC SPECIMEN



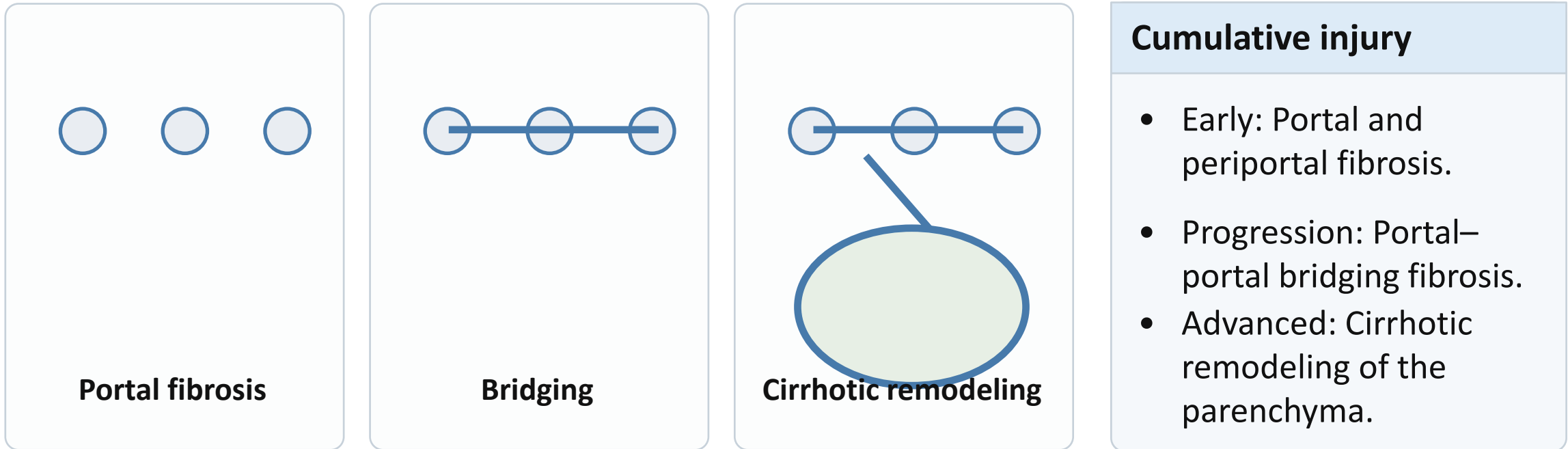
Inflammation crossing interface →

Why this matters

- Inflammatory cells cross the hepatocyte–portal tract interface.
- Periportal hepatocyte injury accompanies the inflammatory front.
- The finding is not specific for viral etiology.

Fibrosis progression is architectural

ORIGINAL SCHEMATIC — NOT A HISTOLOGIC SPECIMEN



Conceptual stages — shapes do not reproduce a biopsy field

Acute versus chronic biopsy patterns

Feature	Acute hepatitis	Chronic hepatitis
Inflammatory distribution	Lobular $\pm$ portal	Portal $\pm$ interface and lobular
Hepatocyte injury	Apoptosis and necrosis	Variable ongoing injury
Fibrosis	Not defining	Defining feature / disease stage
Advanced injury	Confluent or bridging necrosis	Bridging fibrosis to cirrhosis

HBV: Ground-glass hepatocytes

- Accumulated HBsAg expands hepatocyte endoplasmic reticulum.
- This can impart a ground-glass appearance to the cytoplasm.
- HBsAg and HBcAg immunostains help document HBV infection.
- Other inflammatory features may overlap with chronic hepatitis of other causes.

Ground-glass morphology is a supportive finding, not a standalone serologic diagnosis.

HCV: Recognizable but nonexclusive clues

- Lymphoid aggregates or follicles may be prominent in portal tracts.
- Steatosis is common, particularly with genotype 3 infection.
- Focal bile duct injury can mimic a primary biliary process.
- Morphology requires virologic correlation.

Avoid treating a suggestive pattern as etiologically pathognomonic.

Activity and stage are different biopsy questions

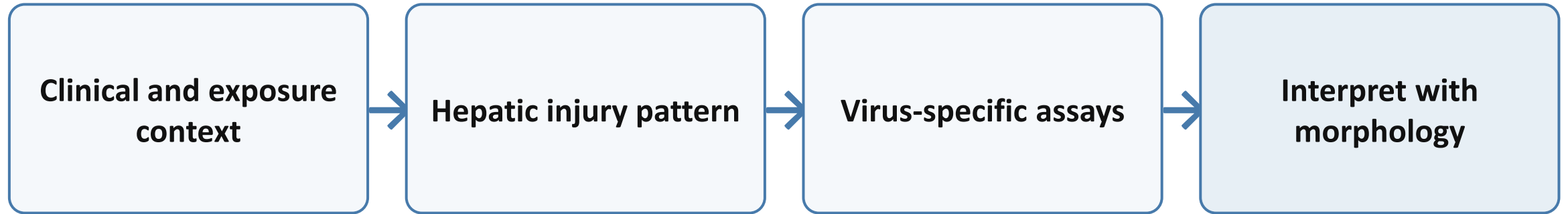
Activity / grade

- How much ongoing inflammatory hepatocyte injury is present?
- Depends on inflammation and necroinflammatory activity.

Fibrosis / stage

- How much scarring and architectural remodeling has accrued?
- Portal fibrosis may progress to bridges and cirrhosis.

Etiologic diagnostic approach to hepatitic injury



- Biopsy does not reliably distinguish all viruses.
- Serologic and molecular studies distinguish current infection from prior exposure.

Test choice must match the diagnostic question

Question	Typical test class	Example
Recent infection?	Virus-specific IgM	IgM anti-HAV / anti-HEV
Current HBV?	Antigen + viral nucleic acid	HBsAg; HBV DNA
Current HCV?	Viral nucleic acid	HCV RNA
Possible HDV?	Antibody + viral nucleic acid	Anti-HDV; HDV RNA

Why an antibody result may not equal active infection

- IgG to a virus may persist after the infection resolves.
- Anti-HCV indicates exposure; HCV RNA addresses current viremia.
- HBV surface antigen and anti-HBs have different meanings.
- Interpret antigen, antibody, and nucleic acid markers together.

Avoid equating “antibody-positive” with transmissible current infection.

Why liver biopsy remains useful

Biopsy can evaluate

- Inflammatory activity and interface injury.
- Distribution and severity of fibrosis.
- Competing or coexisting causes of hepatic injury.

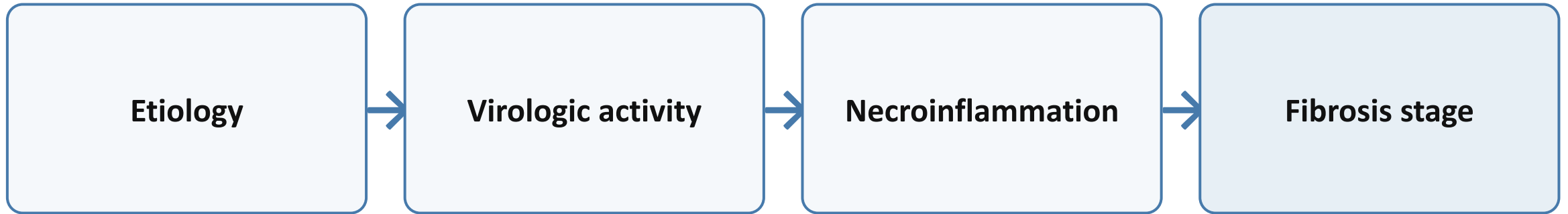
Biopsy alone cannot reliably

- Determine which hepatotropic virus is present.
- Establish current viremia.
- Replace targeted serologic and molecular testing.

Diagnostic pitfalls in viral hepatitis

Pitfall	Why it fails	More defensible approach
Diagnosing virus from morphology	Patterns overlap	Add virus-specific assays
Equating absent jaundice with no hepatitis	Many infections are subclinical	Use risk and laboratory evidence
Equating seropositivity with viremia	Antibodies may persist	Test antigen / RNA / DNA
Equating low symptoms with mild fibrosis	Chronic damage may be silent	Assess liver disease burden

Chronic disease: One integrated assessment



- These axes are complementary, not interchangeable.
- A patient may have few symptoms despite substantial structural disease.

Case: Acute hepatitis after contaminated water

ILLUSTRATIVE CLINICAL SCENARIO

An adult presents with anorexia, fatigue, and jaundice several weeks after a shared water exposure.

What etiologic group and laboratory test class should be prioritized?

Discussion answer in presenter notes

Case: Hepatitis with established HBV infection

ILLUSTRATIVE CLINICAL SCENARIO

A person known to have chronic HBV develops an abrupt severe flare after a new parenteral exposure.

What additional hepatotropic infection is especially relevant?

Discussion answer in presenter notes

Case: Silent infection and portal fibrosis

ILLUSTRATIVE CLINICAL SCENARIO

A patient has few symptoms but persistent viral markers; Biopsy shows portal inflammation, interface activity, and bridging fibrosis.

Is this an acute-only process, and what should be reported from the biopsy?

Discussion answer in presenter notes

Three diagnostic contrasts worth remembering

Comparison	The discriminating concept	Practical consequence
HAV vs HCV	Self-limited vs high persistence tendency	Different chronic follow-up implications
HBV vs HDV	HBV independent; HDV depends on HBV	Evaluate HDV in HBV context
Acute vs chronic pattern	Necroinflammation vs fibrosis	Morphology estimates duration / accumulated damage

Integrative synthesis

The etiologic virus and the tissue injury pattern answer different diagnostic questions.

- The five hepatotropic viruses share a hepatitic phenotype.
- Transmission and molecular tests identify the agent.
- Host response determines cellular injury and the course.
- Biopsy establishes activity and structural damage but is rarely agent-specific.

References and source boundary

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 18, pp. 755–762.

Primary heading: “Viral Hepatitis” (pp. 755–756).

Supporting context: individual hepatitis viruses and clinicopathologic syndromes (pp. 756–762).

Original diagrams in this lecture are editable schematics, not diagnostic specimen images.