

Hepatitis D Virus

Viral dependence · clinical patterns · liver injury

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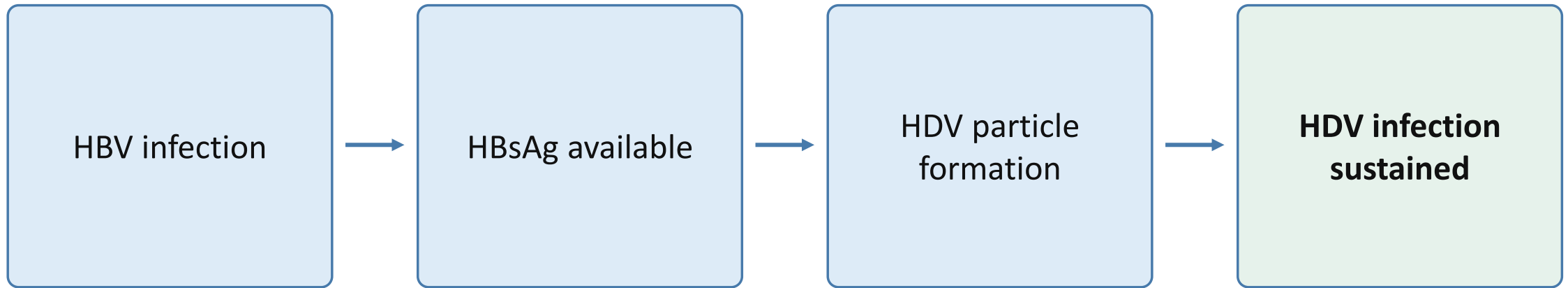
Learning objectives

- Explain why HDV requires hepatitis B virus.
- Contrast simultaneous HBV–HDV infection with HDV superinfection.
- Interpret source-described viral markers and hepatic injury patterns.
- Connect clinical course with cirrhosis and HCC risk.

HDV is an HBV-dependent RNA virus

- HDV is also called the delta agent.
- It requires hepatitis B virus for its life cycle.
- HBV dependence distinguishes it from autonomous hepatitis viruses.

HDV dependence: The causal chain



Dependency is on HBV envelope antigen for the HDV life cycle.

HDV and HBV are distinct viruses

Hepatitis B virus

Partially double-stranded DNA genome

Makes multiple viral proteins

HBV supplies surface antigen

Reverse transcription in replication

Hepatitis D virus

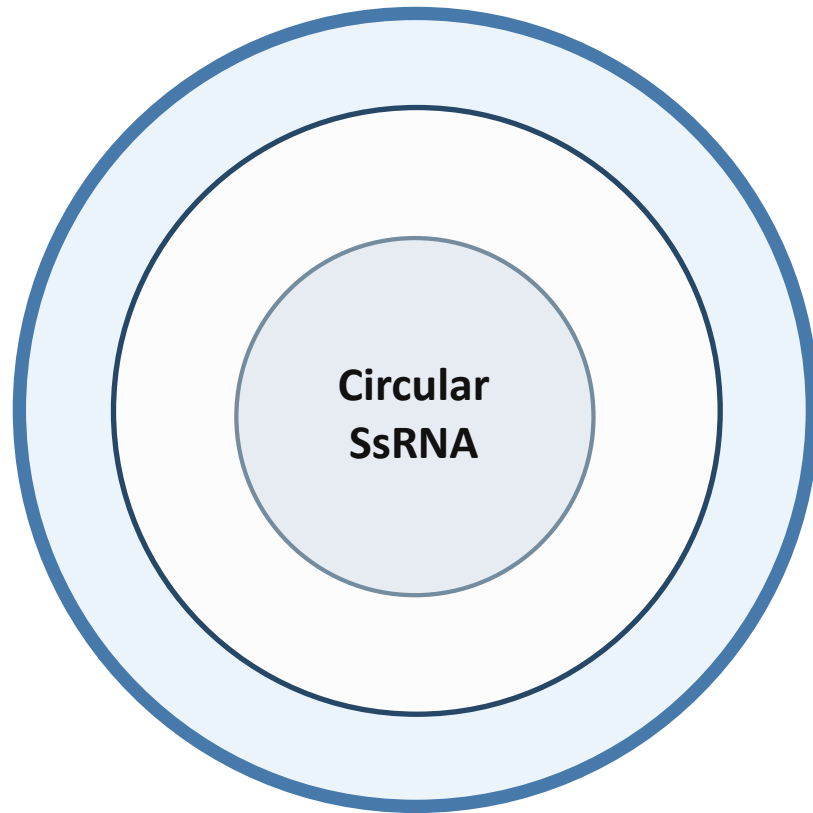
Circular single-stranded RNA genome

Encodes delta antigen (HDAg)

HDV uses the HBV-derived coat

Host RNA polymerase supports RNA synthesis

HDV particle: Envelope and interior



HBsAg-containing outer coat

Delta antigen (HDAg) assembly

Circular single-stranded RNA

The viral particle is approximately 35 nm

- HDV as a 35-nm, double-shelled particle.
- An external coat surrounds an internal polypeptide assembly.
- The interior contains delta antigen and the RNA genome.

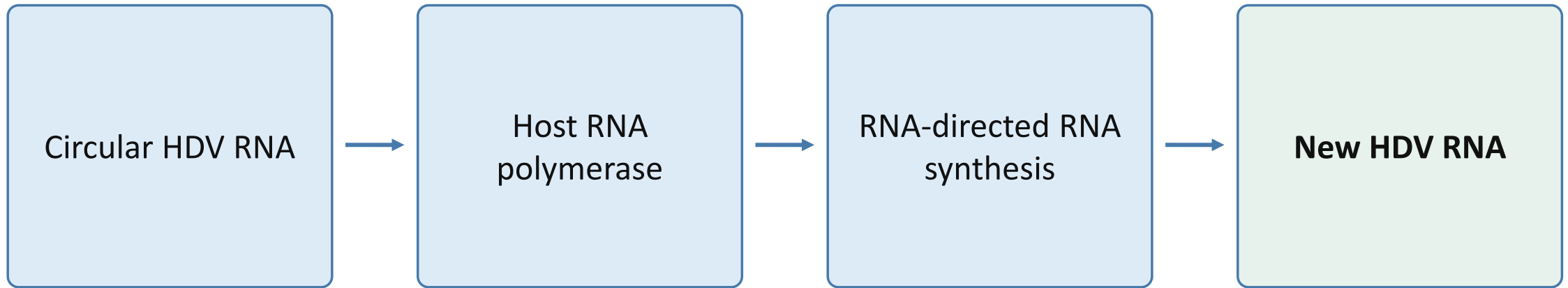
HBsAg enables HDV particle assembly

- The HDV external coat contains hepatitis B surface antigen.
- The surface protein supply is why HBV infection matters.
- HDV cannot complete its infectious life cycle independently.

HDV has very limited coding capacity

- Delta antigen (HDAg) is the only protein produced by HDV.
- The genome is circular, single-stranded RNA.
- Host and HBV products therefore contribute essential functions.

RNA replication uses host machinery



Replication description is mechanistic; Not a full molecular pathway.

HDV replication versus HBV replication

HDV RNA replication

Circular single-stranded RNA

RNA-directed RNA synthesis

Uses a host RNA polymerase

Depends on HBV for its coat

HBV DNA replication

Partially double-stranded DNA

Reverse transcription via RNA intermediate

Encodes a viral polymerase

Produces its own surface proteins

Hepatocyte injury has unresolved mechanisms

- The basis of HDV-associated disease flares is not well understood.
- Direct viral cytopathic injury has been proposed.
- Enhanced cytotoxic responses of the host have also been proposed.

Two proposed mechanisms of flares

Direct cytopathic hypothesis

Hepatocytes may be injured by HDV-related processes

Discussed as a proposed mechanism

Not established as the sole cause

Enhanced host response

Immune-mediated killing may increase

Discussed as a proposed mechanism

Not established as the sole cause

HDV transmission is predominantly parenteral

- Exposure to infected blood is the central route.
- Intravenous drug use is a described transmission setting.
- Multiple blood transfusions are another described setting.

Exposure history: Important clues

Shared injection equipment

Parenteral exposure is central to the HDV transmission pattern.

Blood transfusion history

Repeated transfusion exposure is listed as a risk setting.

Reported geographical concentration

- High prevalence is described in the Amazon basin and central Africa.
- The Middle East and Mediterranean basin are also highlighted.
- Lower frequency in Southeast Asia and China.

Epidemiology: Interpret estimates carefully

Fraction among HBV-infected

The textbook estimates that approximately 5% have HDV co-infection.

Estimated global burden

The textbook estimates approximately 15 million persons with HDV.

Two sequences of infection

Coinfection

HBV and HDV acquired together

Acute hepatitis may resolve

Usually both viruses clear

Chronicity less typical

Superinfection

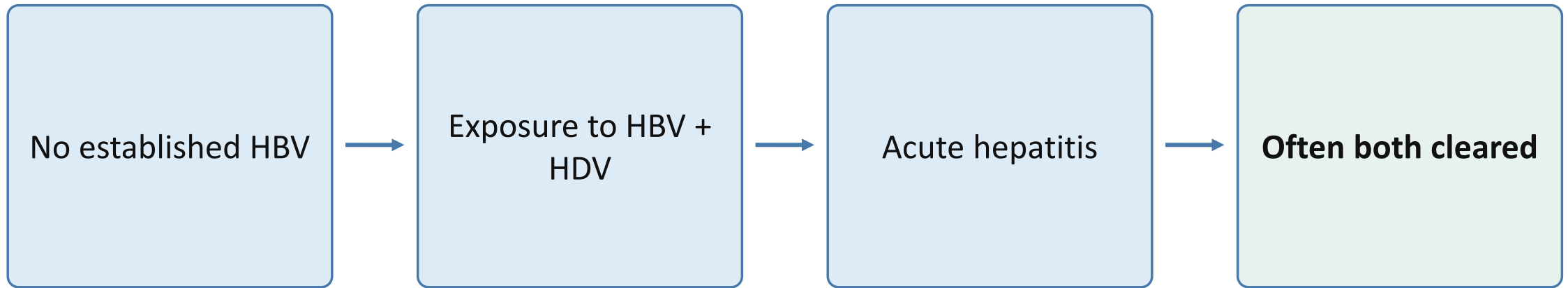
HDV acquired after established HBV

Severe acute or exacerbated hepatitis

Chronic HDV is frequent

Chronicity >80% (Robbins)

Coinfection: Simultaneous acquisition



This is coinfection, not superinfection.

Coinfection resembles acute hepatitis B

- Acute disease can be clinically indistinguishable from hepatitis B.
- Exposure introduces both HBV and HDV.
- Clinical features alone cannot establish the viral combination.

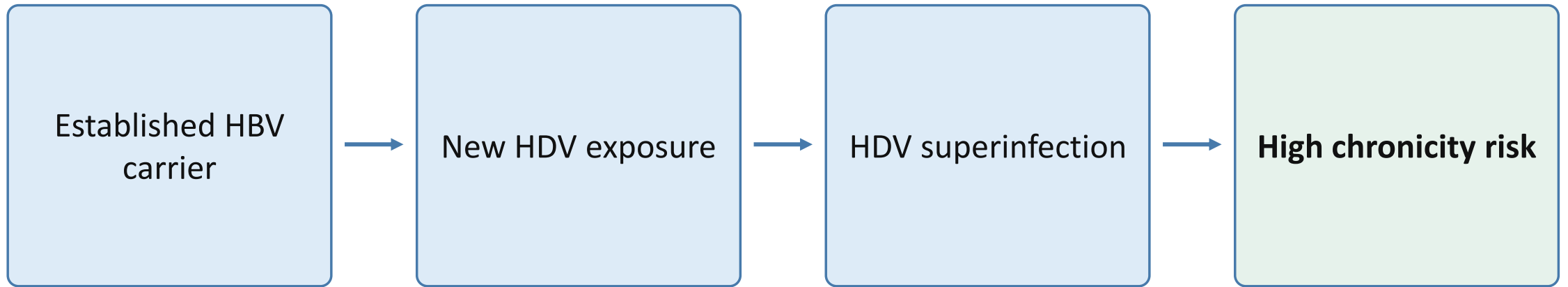
Coinfection is commonly self-limited

- Acute hepatitis may resolve after the simultaneous infection.
- Clearance of both viruses usually follows.
- The usual outcome contrasts with HDV superinfection.

Coinfection can still be dangerous

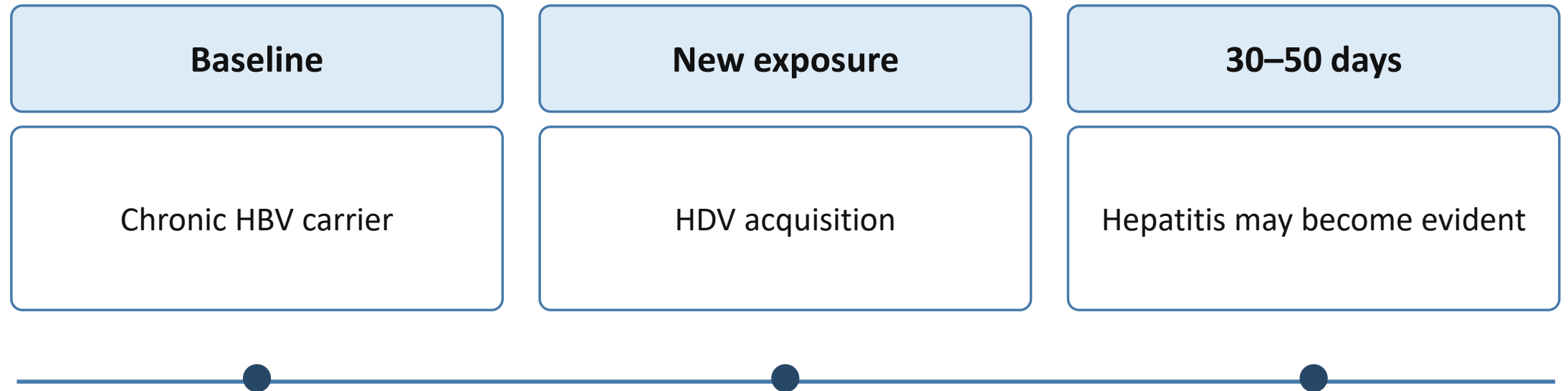
- A higher rate of acute hepatic failure in intravenous drug users.
- That complication is a risk, not the usual course of all coinfections.
- Severity and likelihood of chronicity are different outcome dimensions.

Superinfection: Two-stage acquisition



The host has HBV before acquiring HDV.

Superinfection: Clinical onset



Interval is reported for superinfection, not a universal incubation range.

Previously silent HBV may become symptomatic

- A carrier with no symptoms may develop severe acute hepatitis.
- The new clinical event follows acquisition of HDV.
- Recognize an abrupt shift in illness rather than assuming stable HBV.

Established chronic hepatitis may worsen

- HDV can exacerbate a pre-existing chronic hepatitis B illness.
- This is another clinical presentation of superinfection.
- A disease flare does not by itself determine which virus is replicating.

Superinfection frequently becomes chronic

- Chronic HDV infection follows >80% of superinfections.
- This is a distinctive contrast with usual coinfection outcomes.
- Persistent infection creates a setting for progressive liver injury.

Superinfection: Possible two-phase pattern

Early / active HDV phase

HDV replication active

HBV replication suppressed

Serum transaminases high

Later / chronic phase

HDV replication decreases

HBV replication increases

Transaminases fluctuate

Schematic disease-course pattern; Individual courses vary.

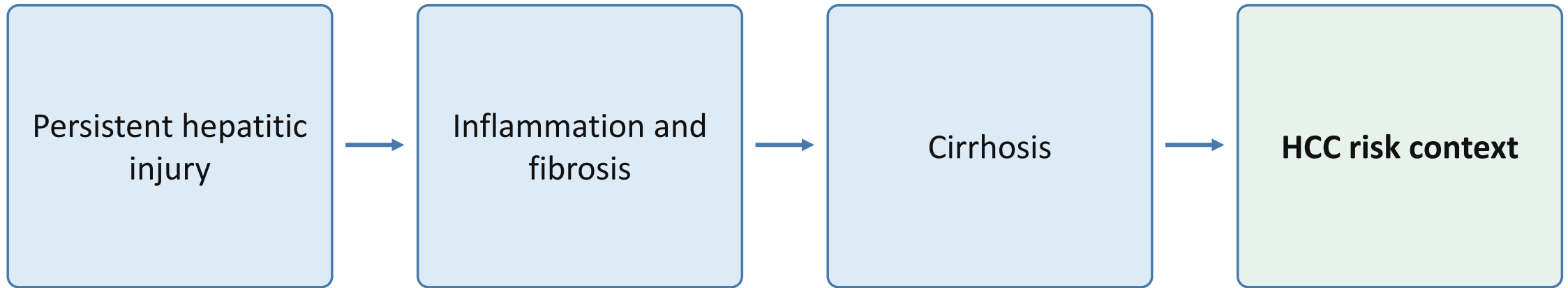
HBV and HDV activity need not move together

- The proposed phases can show opposing viral replication patterns.
- High aminotransferases do not uniquely quantify either viral activity.
- The phase model describes possibilities, not an immutable sequence.

Chronic HBV–HDV infection carries risks

- HBV–HDV coinfection is associated with progression to cirrhosis.
- Risk of hepatocellular carcinoma is increased.
- Risk is clinically important even without distinctive histology.

Progression: Infection to clinical consequences



Progression is possible, not an inevitable individual outcome.

Symptoms do not establish HDV etiology

- Acute HDV coinfection may resemble acute HBV infection.
- A chronic HBV carrier may experience a severe flare after HDV exposure.
- Serologic and molecular evidence is needed to identify infection.

Serologic windows in hepatitis D

Before / early symptoms	Recent exposure	Chronic delta hepatitis
HDV RNA detectable	IgM anti-HDV	HBsAg present
Blood and liver	May appear late; Transient	Anti-HDV persists

Distinct detection contexts; Not a required chronological sequence.

HDV RNA: An early direct marker

- HDV RNA can be detected in blood and liver just before illness.
- Detection also occurs in the early days of symptomatic disease.
- Its presence is direct molecular evidence of HDV.

IgM anti-HDV: Recent exposure marker

- Robbins calls IgM anti-HDV the most reliable indicator of recent exposure.
- Its appearance may be late.
- The detectable interval is frequently short-lived.

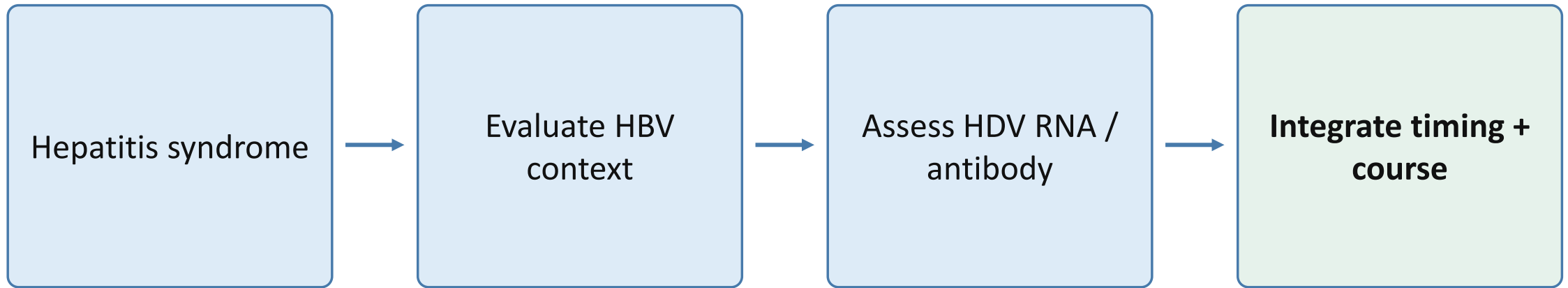
Chronic delta hepatitis: Persistent markers

- HBsAg remains present in serum.
- Anti-HDV antibodies can persist for months or longer.
- Persistent antibody is not identical to a viral replication measurement.

Interpret the markers by their target

Marker	Main information
HBsAg	HBV surface-antigen presence; Necessary context
HDV RNA	Direct evidence of HDV genetic material
IgM anti-HDV	Recent HDV exposure; Late or transient
Persistent anti-HDV	History/persistence of antibody response

A conceptual diagnostic reasoning path



Educational logic; Not a formal diagnostic protocol.

Diagnostic pitfall: A negative IgM window

- IgM anti-HDV may not appear promptly after exposure.
- It may also disappear after a short interval.
- A single antibody result must be interpreted in temporal context.

HDV must be distinguished from other injury

Common hepatitic findings

Portal or lobular lymphocytes

Necrosis or apoptosis

Fibrosis in chronic hepatitis

Etiologic confirmation

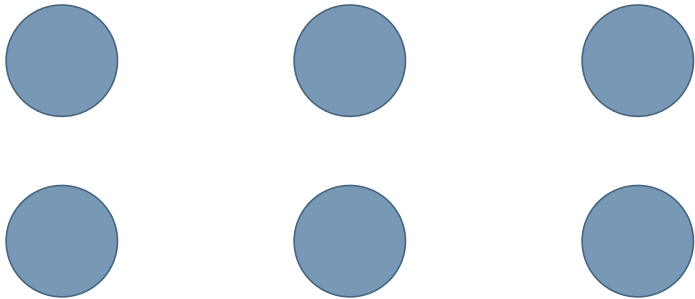
Serology and molecular tests

Context of HBV and HDV markers

Etiology cannot be read from fibrosis alone

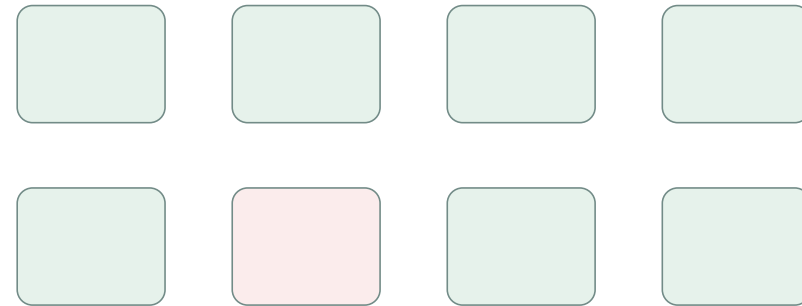
Acute viral hepatitis: Common pattern

Portal compartment



Blue circles = lymphocytes

Hepatocyte lobule



Pale green = hepatocytes; Pink = injury

Lobular inflammation + hepatocyte injury

Schematic only — common hepatitis pattern; No HDV-specific morphology.

Acute hepatitis: Portal and lobular inflammation

- Lymphocytes predominate in the inflammatory infiltrate.
- Plasma cells and eosinophils may be variably present.
- HDV cannot be diagnosed from these shared findings alone.

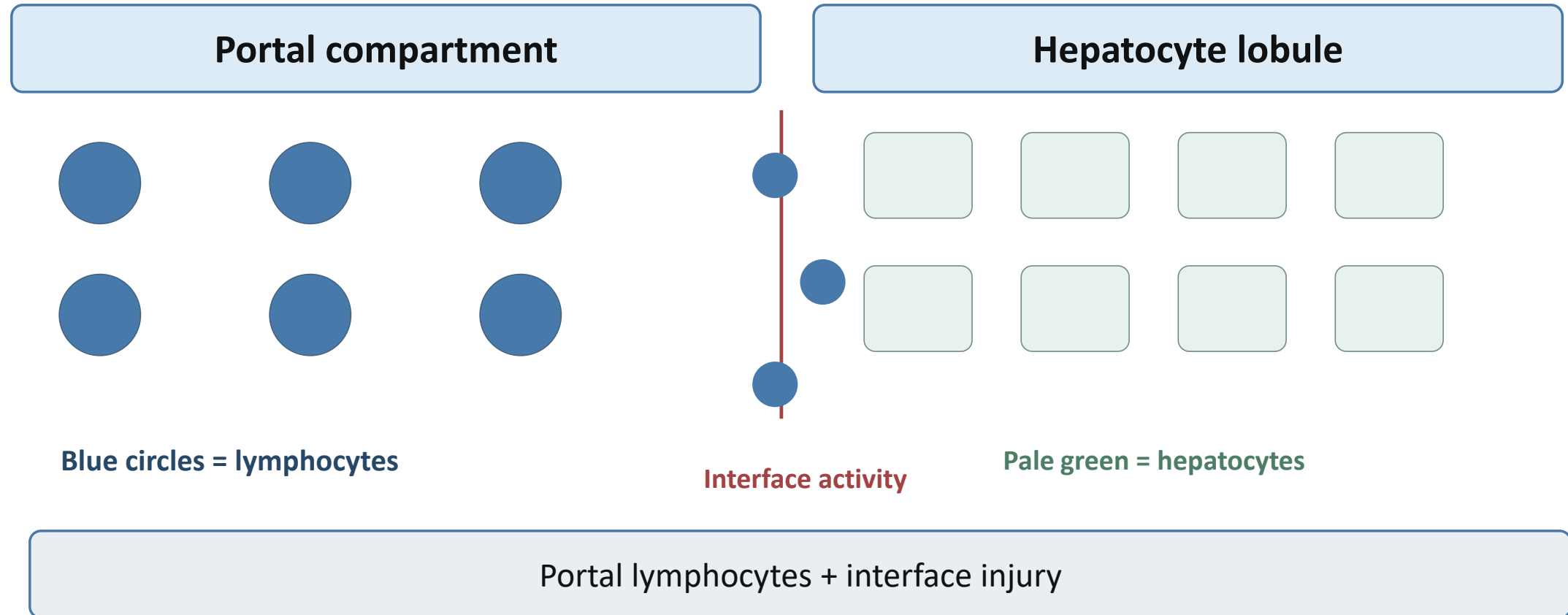
Hepatocyte death: Apoptosis and necrosis

- Hepatocyte injury may produce necrosis or apoptosis.
- Pigmented macrophages scavenge cellular debris.
- These changes establish injury rather than the viral subtype.

Severe acute hepatitis: Confluent necrosis

- Necrosis may involve groups of adjacent hepatocytes.
- Severe cases can show bridging or panlobular necrosis.
- Massive necrosis may accompany acute liver failure.

Chronic viral hepatitis: Common pattern



Schematic only — common hepatitis pattern; No HDV-specific morphology.

Chronic hepatitis: Portal inflammation

- Portal lymphocytic or lymphoplasmacytic infiltration is characteristic.
- Inflammation may breach the limiting plate.
- Periportal hepatocyte injury is termed interface activity.

Fibrosis progression in chronic injury

Portal and periportal fibrosis



Portoportal bridging fibrosis



Architectural remodeling



Cirrhosis

Histology is rarely virus-specific

- Viral hepatitis patterns overlap with autoimmune hepatitis.
- Drug reactions and Wilson disease can also resemble hepatitis.
- Serology and molecular studies help establish etiology.

Do not confuse HBV morphology with HDV

HBV-associated feature	HDV diagnostic implication
HBsAg-filled ER can make ground-glass hepatocytes	This points to HBV, not uniquely to HDV
HBsAg or HBcAg immunostains support HBV	HDV remains a separate diagnostic question
Chronic inflammation and fibrosis may coexist	Morphology alone cannot identify HDV

Biopsy: Grade and stage are different

- Inflammatory activity represents disease grade.
- Fibrosis extent represents disease stage.
- Morphology characterizes injury but does not replace etiologic testing.

HBV vaccination prevents HDV infection

- HDV depends on HBV for its life cycle.
- Preventing HBV infection also prevents HDV infection.
- This is a direct clinical consequence of the dependency mechanism.

Therapeutic evidence: Respect source limits

- Interferon-based treatment with limited clearance.
- It also discusses viral entry and replication as therapeutic targets.
- Specific regimens and current approvals require separate verification.

Case 1: Simultaneous viral exposure

Clinical scenario

A person develops acute hepatitis after a single exposure event involving HBV and HDV. Clinical features resemble acute hepatitis B.

Question: Coinfection or superinfection? What is the usual outcome?

Case 1: Interpretation

- This is HBV–HDV coinfection because both were acquired together.
- Acute hepatitis may be indistinguishable from acute HBV.
- Usual recovery with clearance of both viruses.

Case 2: HBV carrier with acute hepatitis

Clinical scenario

An asymptomatic chronic HBsAg-positive carrier has a new parenteral exposure. Severe hepatitis develops about 40 days later.

Question: Which HDV acquisition pattern best fits?

Case 2: Interpretation

- New HDV exposure in an established HBV carrier is superinfection.
- Onset about 30–50 days after the inoculum.
- Superinfection is associated with a high likelihood of chronic HDV.

Case 3: Fluctuating laboratory activity

Clinical scenario

A person with chronic HBV–HDV has an early severe flare with high transaminases. Later aminotransferase levels fluctuate.

Question: Can this correspond to the possible two-phase course?

Case 3: Interpretation

- The early phase may have active HDV and suppressed HBV replication.
- In a later phase, HDV may decrease as HBV replication increases.
- This model is possible, not required for all patients.

Final synthesis: Four discriminating ideas

Question	Core answer
What makes HDV different?	An RNA virus dependent on HBV
Why is superinfection important?	Persistent chronic HDV is common
What establishes etiology?	HBV context plus HDV serology / RNA
Why follow long term?	Fibrosis, cirrhosis, HCC risk

Core references and source limitations

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Hepatitis D Virus and adjacent Hepatitis B Virus sections.
- General viral hepatitis syndromes, morphology, and Table 18.3.
- Original chapter PDF and authentic licensed tissue images were unavailable.