

Clinicopathologic Syndromes of Viral Hepatitis

Clinical patterns • injury mechanisms • morphology • interpretation

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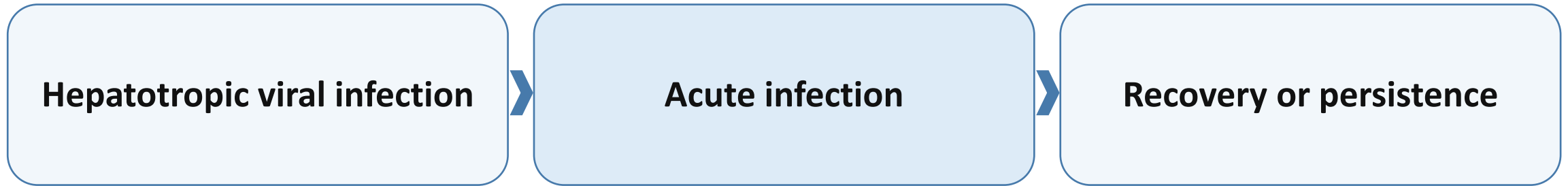
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Learning objectives

- Distinguish the five clinical syndromes of hepatotropic viral infection.
- Relate acute hepatitis to lobular inflammation, hepatocyte death, and necrosis patterns.
- Identify chronic hepatitis by portal inflammation, interface activity, and fibrosis.
- Interpret viral markers, biopsy findings, and common diagnostic mimics.

One infection — several clinicopathologic outcomes



- Acute infection can be asymptomatic, symptomatic, or complicated by liver failure.
- Persistent infection may present as chronic hepatitis or an asymptomatic reservoir.

Histology alone cannot identify the virus

- Hepatitis viruses produce overlapping patterns of hepatocellular injury.
- Autoimmune hepatitis, drug-induced injury, and Wilson disease may resemble viral hepatitis.
- Serologic and molecular tests determine the viral etiology.

Morphology identifies the injury pattern; Virologic testing identifies the agent.

Transmission and persistence: Broad viral differences

Virus	Principal transmission	Chronic infection pattern
HAV	Fecal–oral	Does not cause chronic infection
HBV	Parenteral / sexual / perinatal	Chronic infection can develop
HCV	Primarily parenteral	Frequently persists
HDV	Parenteral with HBV	HBV required for infection
HEV	Fecal–oral	Persistence mainly in immunocompromised hosts

Summary based on the viral chapters and Table 18.3.

Acute infection: Symptomatic versus asymptomatic

Asymptomatic

- Few or no clinically recognized symptoms
- Recognized by elevated aminotransferases
- Antibodies may establish previous infection

Symptomatic

- Clinically apparent hepatitis develops
- Clinical course has four named phases
- May resolve or progress to liver failure

Asymptomatic infection with recovery

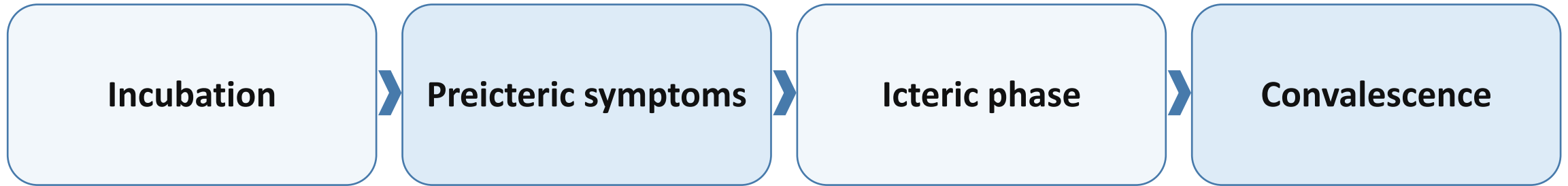
- Infection can be clinically silent despite hepatocellular injury.
- Aminotransferases may be only minimally elevated.
- Prior infection may be recognized retrospectively by antiviral antibodies.

Absence of jaundice or symptoms does not exclude prior viral hepatitis.

Serologic evidence after silent infection

- Anti-HAV antibodies can document previous HAV exposure.
- Anti-HBV antibodies may identify a prior subclinical HBV infection.
- Interpret antibody type and accompanying markers before assigning infection status.

Symptomatic acute hepatitis: Four clinical phases



- These phases describe the typical symptomatic sequence; Individual infections vary.
- The presence or absence of jaundice does not identify the virus.

Incubation is clinically silent but not inert

- Incubation precedes recognized symptoms.
- Different viruses have different incubation intervals.
- Virus transmission can occur before the patient becomes visibly ill.

Incubation intervals summary

Virus	Typical incubation interval	Clinical implication
HAV	2–6 weeks	Exposure may precede symptoms by weeks
HBV	2–26 weeks	Broad interval between exposure and illness
HCV	4–26 weeks	Most acute infections are subclinical
HDV	Similar to HBV	Requires simultaneous or preceding HBV
HEV	About 4–5 weeks	Fecal–oral exposure precedes illness

Intervals reflect Robbins Table 18.3; Avoid using them as diagnostic cutoffs.

Preicteric symptoms precede jaundice

- The preicteric phase represents symptomatic illness before visible jaundice.
- A clinical syndrome may be recognized before overt bilirubin-related findings.
- Clinical findings alone cannot reliably distinguish HAV, HBV, HCV, HDV, and HEV.

Icteric hepatitis is a clinical phenotype

- Jaundice defines the icteric phase of symptomatic acute hepatitis.
- Its timing follows the incubation and preicteric phases.
- The severity of symptoms must be evaluated separately from virologic identity.

Convalescence and recovery

- The convalescent phase follows acute symptoms.
- Recovery may be established clinically and by appropriate virologic follow-up.
- The distinction between viral clearance and persistence depends on the specific infection.

When is acute hepatitis most infectious?

Late incubation



Early symptoms



Later acute illness

- Peak infectivity near the end of the asymptomatic incubation period and early acute symptoms.
- Practical implication: Symptom-based case recognition may occur after transmission has begun.

Typical clinical trajectories vary by virus

HAV and HEV

- Acute infections dominate in immunocompetent hosts
- HAV does not cause chronic hepatitis
- HEV can be severe during pregnancy

HBV, HCV and HDV

- HBV can recover or persist
- HCV commonly progresses to persistence
- HDV modifies the course of underlying HBV

Acute liver failure is an exceptional severe outcome

- A minority of hepatotropic viral infections lead to acute liver failure.
- The morphologic substrate may be widespread or massive hepatocyte necrosis.
- Clinical deterioration reflects loss of viable functioning liver parenchyma.

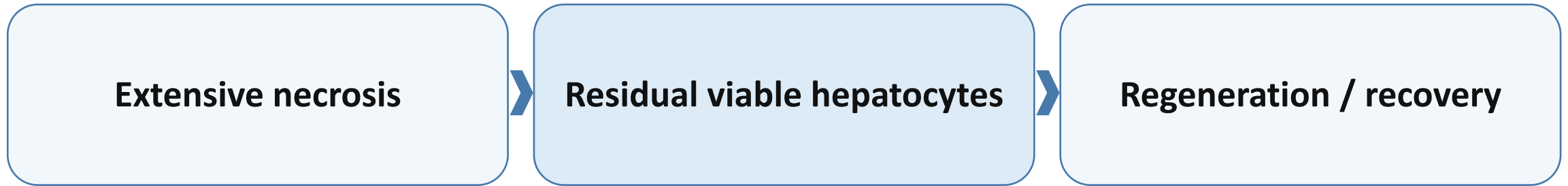
Viruses implicated in acute liver failure

- The textbook attributes a subset of acute liver failure cases to viral hepatitis.
- HAV and HEV are prominent worldwide causes of viral-associated acute failure.
- The relative contribution of HBV varies geographically.

HEV in pregnancy: Clinically important vulnerability

- HEV usually causes self-limited acute hepatitis in immunocompetent hosts.
- Pregnancy is associated with an increased risk of severe HEV-associated hepatitis.
- Severe cases may progress to liver failure.

Acute failure: Tissue loss versus recovery



- Supportive care maintains the patient while surviving hepatocytes regenerate.
- Failure to recover in time can necessitate liver transplantation.

Acute hepatitis: Gross liver appearances

Uncomplicated or inflamed liver

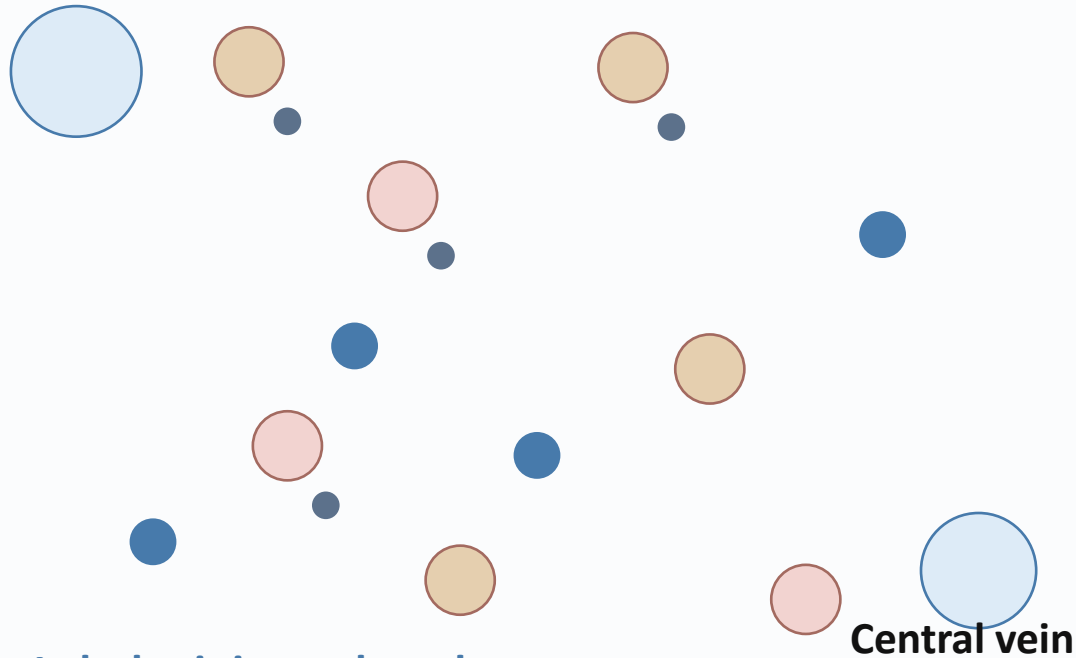
- May remain normal in size
- Can become enlarged from inflammation
- Gross appearance is not pathogen-specific

Severe liver failure

- May become reduced in size
- Extensive necrosis explains tissue collapse
- Functional failure tracks the loss of viable hepatocytes

Acute hepatitis: Lobular-predominant injury

Portal tract



Lobular injury + lymphocytes

Central vein

Original conceptual schematic — not a histologic specimen

Interpretation

- Inflammatory cells involve portal areas and lobules.
- Hepatocytes show injury, apoptosis, and necrosis.
- Pigmented macrophages scavenge cellular debris.

The acute inflammatory infiltrate

- Lymphocytes predominate in both portal and lobular compartments.
- Variable plasma cells and eosinophils may also appear.
- Inflammation by itself does not distinguish viral from autoimmune or drug-related hepatitis.

Portal and lobular compartments in acute hepatitis

Portal compartment

- Inflammation may occupy the portal tract
- Not necessarily accompanied by established fibrosis
- May coexist with lobular hepatocyte injury

Lobular compartment

- Inflammatory cells intermix with hepatocytes
- Apoptosis and necrosis can occur
- Pigmented macrophages may be scattered in injured zones

Apoptosis: Single-cell hepatocyte loss

- Viral-associated hepatocellular damage may induce apoptosis.
- An apoptotic hepatocyte represents death of an individual injured cell.
- Macrophages remove dead-cell debris from the lobule.

Necrosis: Hepatocyte death can be confluent

- Necrosis may affect clusters rather than isolated hepatocytes.
- Confluent necrosis denotes loss of groups of adjacent hepatocytes.
- Increasing continuity and extent of necrosis indicate more severe injury.

Pigmented macrophages follow cell loss

- Macrophages phagocytose material released from dead hepatocytes.
- Pigment-containing macrophages can therefore mark prior or ongoing cell injury.
- This reaction accompanies but does not identify the cause of hepatitis.

Increasing extent of hepatocyte necrosis

Single-cell injury



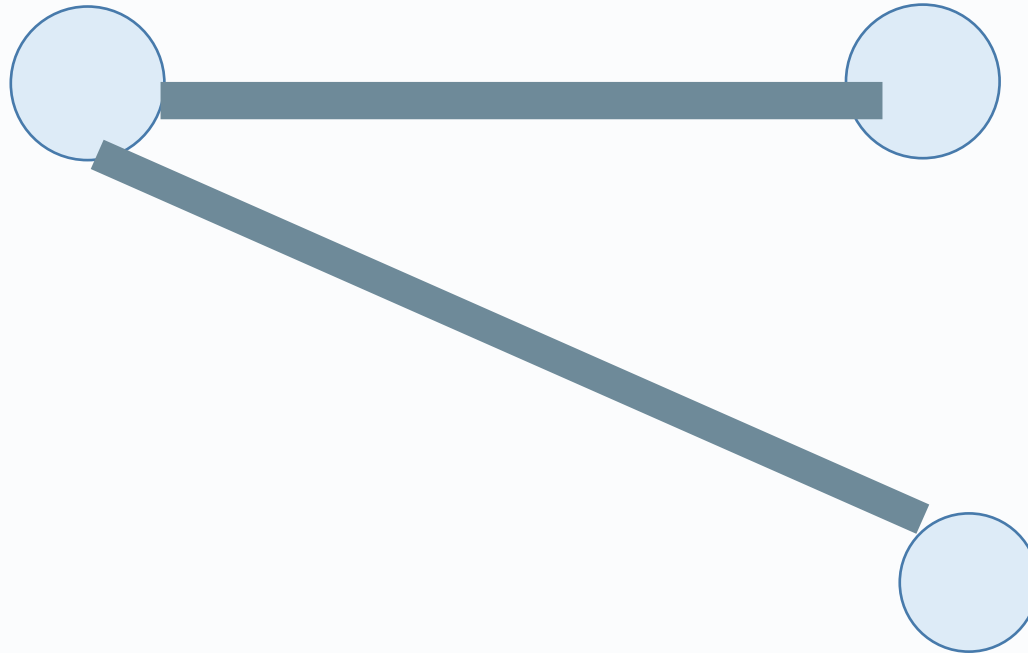
Confluent necrosis



**Bridging / panlobular
necrosis**

- Necrosis that forms bridges links vascular regions of the lobule.
- Panlobular necrosis involves an entire lobule; Massive necrosis may produce liver failure.

Bridging necrosis links vascular structures



Confluent hepatocyte necrosis links vascular regions

Original conceptual schematic — not a histologic specimen

Interpretation

- The term describes continuity of necrotic zones.
- The bridge may connect portal and/or central vascular regions.
- It is a severity pattern, not a virus-specific lesion.

Panlobular necrosis reflects extensive injury

- Panlobular or panacinar necrosis involves the whole functional lobular unit.
- It can develop when necrosis spreads beyond small isolated groups.
- Widespread necrosis threatens hepatic functional reserve.

Confluent versus bridging versus massive necrosis

Confluent / bridging

- Confluent: Groups of hepatocytes die together
- Bridging: Confluent necrosis connects vascular regions
- Severity is assessed by extent and distribution

Massive liver necrosis

- Very large areas of parenchyma are lost
- May lead to shrunken liver and liver failure
- Recovery requires sufficient remaining hepatocytes

Acute hepatitis may include cholestasis

- Cholestasis can accompany lobular hepatocellular injury.
- The textbook schematic includes cholestasis among acute injury findings.
- Interpret cholestasis alongside inflammation, cell injury, and the clinical presentation.

What acute histology can and cannot establish

Can describe

- Portal and lobular inflammation
- Apoptosis, necrosis, and necrosis distribution
- Presence of cholestatic change

Cannot reliably establish

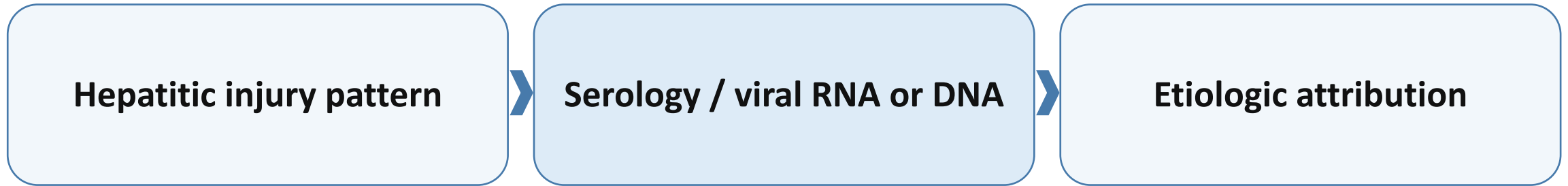
- Whether the culprit is HAV, HBV, HCV, HDV, or HEV
- Whether a similar pattern is drug-induced
- Whether autoimmunity or Wilson disease is the cause

Etiologic investigation uses serology and nucleic acids

Virus	Serologic testing highlighted by Robbins	Molecular method
HAV	Anti-HAV IgM	—
HBV	HBsAg / anti-HBc	HBV DNA PCR
HCV	Anti-HCV antibody	HCV RNA PCR
HDV	Anti-HDV IgM or IgG	HDV RNA PCR
HEV	Anti-HEV IgM or IgG	HEV RNA PCR

Marker combinations and timing require clinical interpretation.

The key diagnostic distinction in a hepatitis pattern



- Morphology assesses the tissue response and injury severity.
- Serologic and molecular testing provides evidence of the causative virus.

Acute infection may progress to persistence

- HBV and particularly HCV account for much of chronic viral hepatitis.
- Progression is not universal and differs by virus and host setting.
- The chronic syndrome may have minimal symptoms despite ongoing disease.

Chronic hepatitis: Operational clinicopathologic definition

- The textbook defines continuing or relapsing hepatic disease beyond six months.
- Clinical, biochemical, or serologic evidence may indicate chronicity.
- Morphologic fibrosis can support a chronic disease process.

Histology and longitudinal clinical evidence are complementary, not interchangeable.

Chronic hepatitis can remain clinically silent

- Persistent aminotransferase elevation may be the only recognized finding.
- Absence of symptoms does not exclude ongoing inflammation and fibrosis.
- The degree of clinical disturbance need not mirror histologic injury.

Symptoms of chronic viral hepatitis

- Fatigue is the most common symptom described in the source.
- Malaise and loss of appetite may occur.
- Occasional episodes of mild jaundice can accompany chronic disease.

Laboratory features in chronic hepatitis

- Aminotransferases may remain persistently elevated.
- Prothrombin time prolongation and hyperglobulinemia may occur.
- Hyperbilirubinemia or mild alkaline phosphatase elevations can also appear.

Immune complexes produce extrahepatic disease

Persistent
antigen



Antibody binding



Circulating
complexes

Vasculitis

Glomerulonephriti
s

Cryoglobulinemia

Extrahepatic immune-complex disease

Original conceptual schematic — not a histologic specimen

Interpretation

- Chronic HBV or HCV can generate antigen–antibody complexes.
- Extrahepatic disease may involve vessels, kidney, or circulating cryoglobulins.
- Extrahepatic manifestations do not replace virologic testing.

Vasculitis as an extrahepatic manifestation

- Circulating antigen–antibody complexes may produce vascular inflammation.
- Vasculitis can therefore accompany chronic HBV or HCV infection.
- A vascular manifestation does not automatically establish viral etiology.

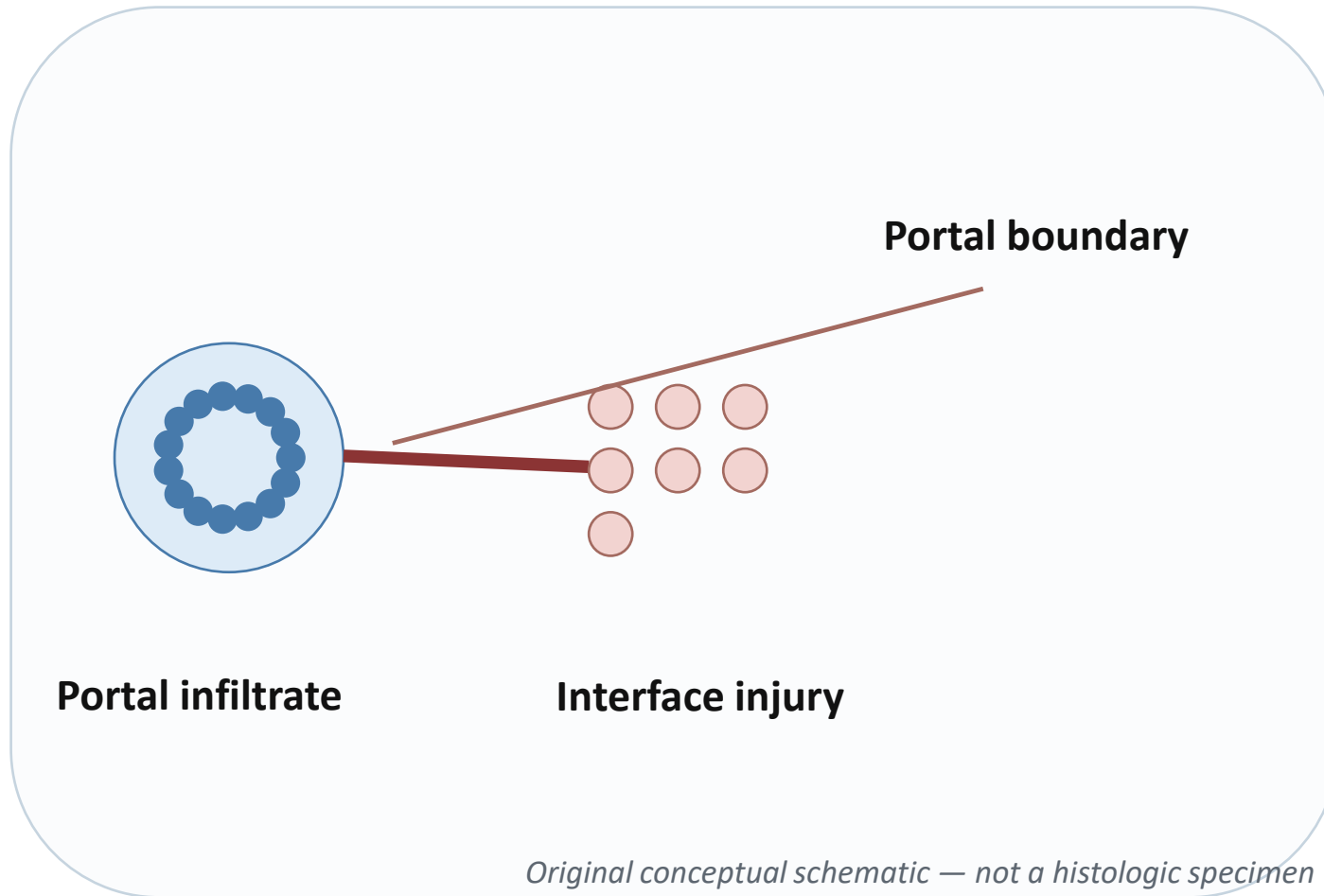
Glomerulonephritis in chronic viral hepatitis

- Immune-complex disease may involve renal glomeruli.
- Renal manifestations can be part of systemic HBV/HCV-associated disease.
- Interpret renal disease within the broader infectious and clinical context.

Cryoglobulinemia provides another systemic clue

- Cryoglobulinemia is included among immune-complex syndromes in chronic HBV/HCV.
- It reflects extrahepatic immune phenomena during ongoing infection.
- The liver and systemic manifestations may require parallel evaluation.

Chronic hepatitis: Portal inflammation and interface injury



Interpretation

- Portal lymphocytes / plasma cells expand portal tracts.
- Inflammatory cells cross the limiting plate.
- Periportal hepatocyte damage constitutes interface activity.

Portal infiltrates define the chronic pattern

- The characteristic chronic hepatitis infiltrate is portal and lymphocytic.
- Lymphoplasmacytic inflammation is another common description.
- Fibrosis accompanies the characteristic chronic histologic pattern.

Interface activity indicates active periportal injury

- Inflammation extends across the portal limiting plate.
- Adjacent periportal hepatocytes are damaged.
- Interface activity reflects inflammatory injury rather than fibrosis stage alone.

Portal inflammation versus interface activity

Portal inflammation

- Inflammatory cells occupy portal stroma
- May expand the portal tract
- Important component of chronic hepatitis

Interface activity

- Cells breach the portal–parenchymal boundary
- Periportal hepatocytes are injured
- An indicator of inflammatory activity

Lobular activity may persist in chronic disease

- Chronic hepatitis often has superimposed lobular inflammation.
- The amount of lobular injury is variable.
- Portal and lobular components should be assessed separately.

Fibrosis begins around the portal tract

- Portal fibrosis is an early structural consequence of chronic injury.
- Periportal fibrosis reflects extension beyond the portal compartment.
- Fibrosis may increase as chronic hepatocyte damage continues.

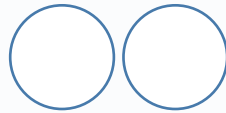
Portoportal bridging fibrosis marks progression

- Fibrous connections develop between portal tracts.
- Bridging fibrosis indicates more advanced architectural remodeling.
- Bridging fibrosis is different from bridging necrosis.

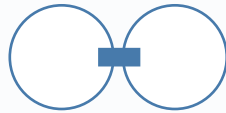
Chronic liver injury: Sequence of fibrosis



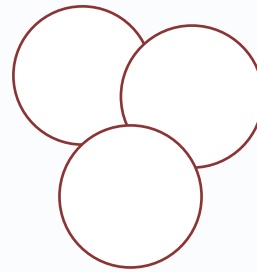
Portal



Periportal



Bridging



Cirrhosis

Portal scar expands → bridges → nodular remodeling

Original conceptual schematic — not a histologic specimen

Interpretation

- Initial portal / periportal fibrous tissue.
- Bridges eventually connect portal regions.
- Advanced remodeling culminates in cirrhosis.

Cirrhosis is the architectural endpoint

- Continuing chronic hepatitis can culminate in cirrhosis.
- Cirrhosis reflects advanced distortion of hepatic architecture by fibrosis.
- Chronic HBV/HCV also increase hepatocellular carcinoma risk.

Inflammatory grade and fibrosis stage

Grade: Activity

- Describes degree of inflammation / ongoing injury
- Includes interface and lobular inflammatory activity
- May change as inflammatory activity changes

Stage: Fibrosis

- Describes amount and distribution of scar tissue
- Progresses from portal fibrosis to bridging and cirrhosis
- Helps guide clinical management

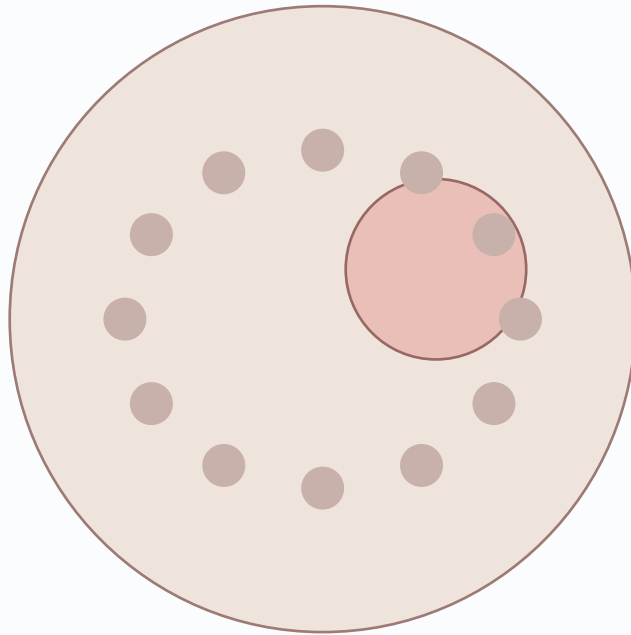
Why obtain a liver biopsy?

- Histology may support a diagnosis of chronic hepatitis.
- Biopsy can assess inflammatory activity (grade).
- Biopsy can assess fibrosis (stage) that informs management with clinical parameters.

Biopsy does not replace etiologic testing

- Acute and chronic viral hepatitis overlap with autoimmune injury.
- Drug reactions and Wilson disease can generate similar inflammatory patterns.
- Serologic and molecular testing remains crucial to assign viral etiology.

HBV: Ground-glass hepatocyte is an antigen effect



Accumulated HBsAg in endoplasmic reticulum

Original conceptual schematic — not a histologic specimen

Interpretation

- Endoplasmic reticulum contains accumulated HBsAg.
- Cytoplasm develops a finely granular, ground-glass appearance.
- HBsAg immunostaining can verify antigen accumulation.

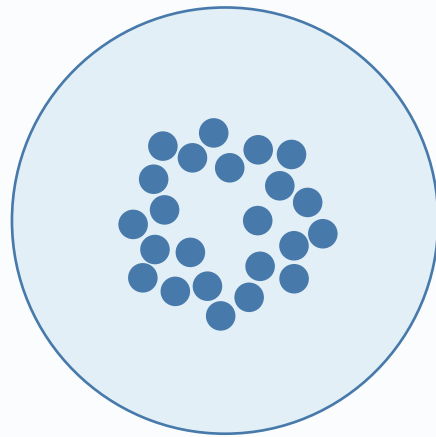
Ground-glass change and HBV infection

- The ground-glass hepatocyte is characteristic of chronic HBV.
- The cytoplasmic appearance reflects retained HBsAg in endoplasmic reticulum.
- Morphology suggests HBV; Antigen-specific staining provides confirmation.

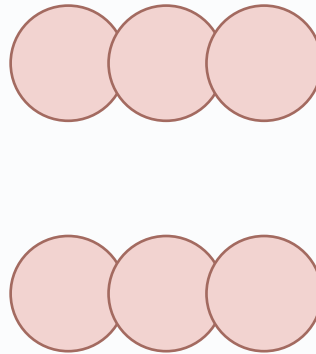
HBV immunohistochemistry: Complementary antigens

- HBsAg staining identifies hepatitis B surface antigen in tissue.
- HBcAg staining can provide additional viral antigen evidence.
- Viral antigen localization complements serologic and molecular tests.

HCV: Portal lymphoid aggregates



Lymphoid aggregate



Adjacent liver parenchyma

Original conceptual schematic — not a histologic specimen

Interpretation

- Chronic HCV often produces conspicuous portal lymphoid aggregates.
- Some aggregates organize into lymphoid follicles.
- The pattern is characteristic but not independently diagnostic.

HCV-associated steatosis

- Fat accumulation is common in chronic HCV infection.
- Steatosis can be especially pronounced with HCV genotype 3.
- Steatosis is a morphologic clue, not proof of HCV infection.

Focal bile duct injury can accompany HCV

- Chronic HCV sometimes causes bile duct injury.
- The finding may simulate a primary biliary disorder.
- description, bile duct injury is typically focal.

Characteristic morphologic clues: HBV versus HCV

Chronic HBV

- Ground-glass hepatocytes
- HBsAg accumulates in hepatocyte endoplasmic reticulum
- HBsAg / HBcAg immunostains may demonstrate viral antigens

Chronic HCV

- Portal lymphoid aggregates or follicles
- Steatosis may be prominent, especially genotype 3
- Focal bile duct injury may occur

Carrier state describes transmission without symptoms

- A carrier harbors an organism and can transmit it.
- Some carriers have no detectable liver disease.
- Others have asymptomatic, nonprogressive liver damage.

The inactive HBV carrier phenotype

- Historically called a “healthy carrier” phenotype.
- HBsAg and anti-HBe present; HBeAg absent.
- Normal aminotransferases, low or undetectable HBV DNA, and little significant hepatic injury.

“Healthy carrier” is historical terminology; Do not infer absence of transmission risk.

Do not equate HBV and HCV carrier categories

HBV

- A low-replication, asymptomatic carrier phenotype is described
- Virus may still be present and transmissible
- Requires biochemical and virologic characterization

HCV

- No equivalent “healthy carrier” state is recognized
- Asymptomatic persistence does not imply a benign inactive-carrier category
- Viral RNA testing informs infection status

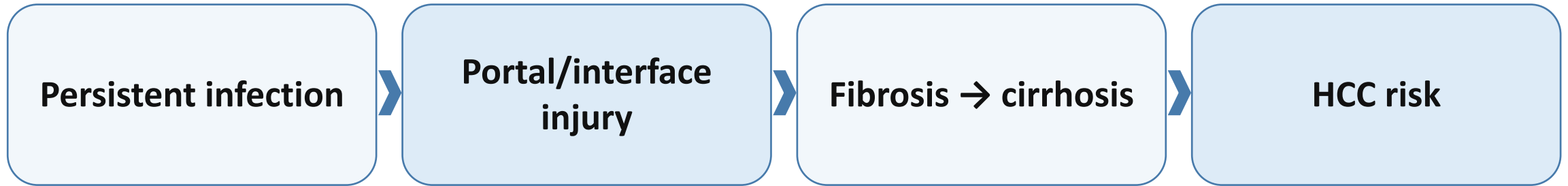
HIV changes the course of HBV and HCV

- HIV co-infection is an important comorbidity in chronic viral hepatitis.
- Untreated HIV increases severity of HBV- or HCV-associated liver disease.
- The immunologic setting must be considered when assessing progression.

Chronic HBV and HCV increase HCC risk

- Chronic HBV and HCV are associated with hepatocellular carcinoma.
- Risk is especially important in patients who develop cirrhosis.
- The histologic trajectory links persistent injury, fibrosis, and late consequences.

From viral infection to progressive liver disease



- This is a possible disease trajectory, not an inevitable outcome for every infected person.
- Serial clinical, virologic, and fibrosis assessment distinguish patients along this spectrum.

Applied case: Clinically silent infection

A person has no jaundice or apparent systemic illness. Serum transaminases are mildly elevated, and later antiviral antibodies establish prior exposure.

Discuss

- Which clinicopathologic syndrome best fits?
- Can the causative virus be diagnosed from the absence of symptoms?

Applied case: Severe acute injury

A patient with clinically acute hepatitis develops liver failure. The liver is reduced in size, with extensive confluent and panlobular hepatocyte necrosis.

Discuss

- Which morphologic pattern explains the failure?
- Why might the remaining hepatocyte mass determine recovery?

Applied case: Chronic viral hepatitis

A biopsy shows portal lymphoplasmacytic inflammation, interface activity, and portoportal bridges of fibrous tissue.

Discuss

- Which features show inflammatory activity?
- Which finding indicates advanced fibrosis stage?

Applied case: Characteristic viral clues

A biopsy shows portal lymphoid follicles, steatosis, and focal bile duct injury in a patient with evidence of chronic hepatitis.

Discuss

- Which virus has this constellation in the Robbins description?
- Why are viral serology and RNA testing still necessary?

Synthesis: Three diagnostic axes

- Clinical syndrome: Silent, symptomatic, fulminant, chronic, or carrier state.
- Etiology: Virus-specific serology and molecular tests.
- Morphology: Injury pattern, inflammatory activity, and fibrosis stage.

A complete diagnosis integrates all three rather than substituting one for another.

References and source boundaries

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 18.
- Core topic: “Clinicopathologic Syndromes of Viral Hepatitis,” printed pp. 760–762.
- Virus context: preceding HAV–HEV sections, printed pp. 756–760.
- All conceptual diagrams in this lecture are original schematics; no photomicrographs were reproduced.