

HEPATITIS B VIRUS

Viral biology • immune-mediated injury • serology • chronic liver disease

Dr Abu Suraih Sakhri

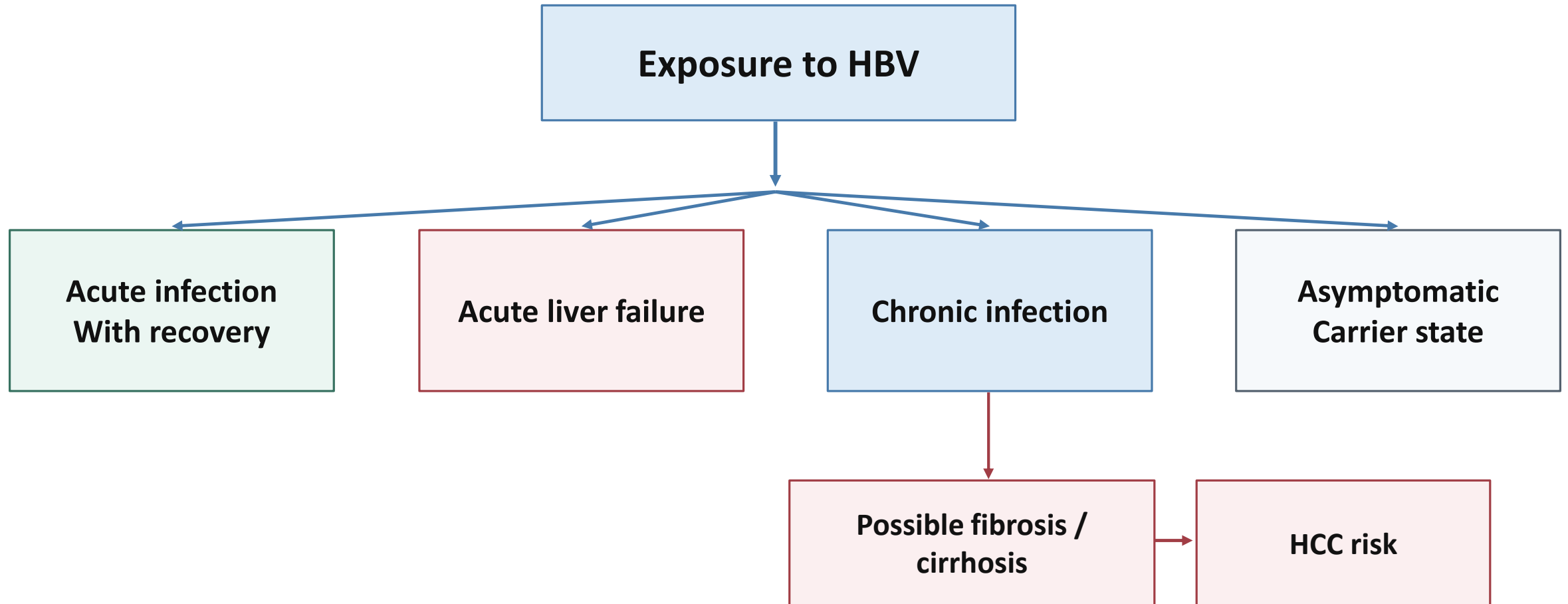
MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning objectives

- Explain HBV structure, genome, entry, and replication through an RNA intermediate.
- Relate antiviral immunity to hepatocyte injury, clearance, and chronic infection.
- Interpret HBsAg, anti-HBs, anti-HBc, HBeAg, and serum HBV DNA in clinical context.
- Recognize major histologic patterns and long-term complications of HBV infection.

HBV produces several distinct clinical outcomes



Multiple outcomes depend on age at infection, host immunity and comorbidities.

HBV is a DNA hepatotropic virus

- HBV belongs to the family Hepadnaviridae.
- The virion carries partially double-stranded circular DNA.
- Replication proceeds through reverse transcription of an RNA intermediate.
- Long-term liver injury depends strongly on the host antiviral immune response.

Central paradox

A DNA virus that uses reverse transcriptase during replication.

Burden of chronic hepatitis B

WHO estimates reported (data year: 2022)

254 million people living with chronic HBV infection

The same source reports approximately 1.2 million new infections and 1.1 million HBV-related deaths annually.

Geography and transmission are linked

- HBV prevalence varies substantially across world regions.
- High-prevalence settings include parts of Africa, Asia, and the Western Pacific.
- Perinatal acquisition is an important driver of chronic infection in high-prevalence regions.
- Prevalence and transmission patterns should not be generalized from one region to another.

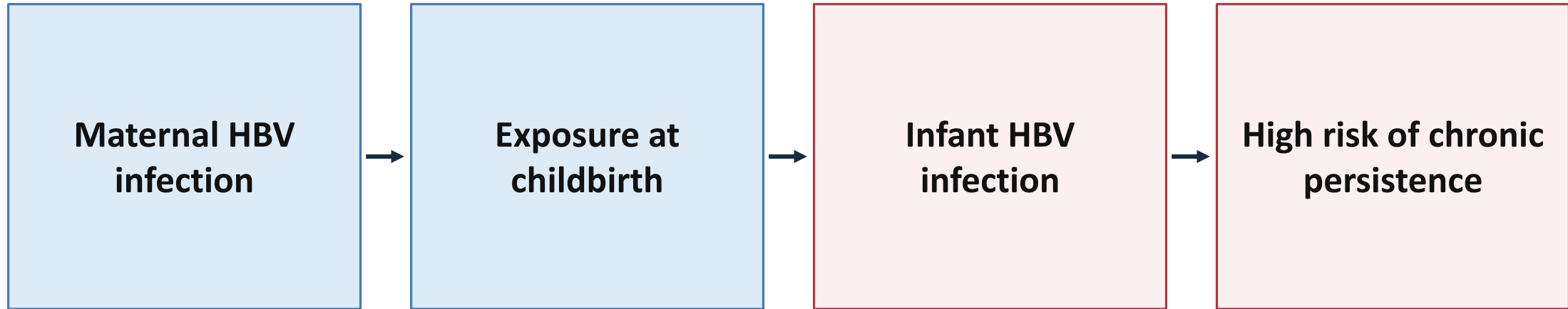
HBV transmission occurs through infected body fluids

Exposure category	Mechanism / examples
Parenteral	Blood exposure; Needle or syringe sharing
Sexual	Unprotected sexual contact
Perinatal	Transmission from an infected mother at birth
Horizontal in children	Minor breaks in skin or mucosa; Close bodily contact
Transfusion-related	Markedly reduced by donor screening

Blood-donor screening reduces transfusion-associated HBV

- Screening donated blood for HBsAg helps identify infectious donations.
- Exclusion of paid blood donors is another measure described in the source.
- Transfusion transmission has been sharply curtailed where these measures are implemented.
- Other parenteral exposures remain important routes of HBV spread.

Transmission at birth changes the natural history



The very young host has a much greater risk of persistent HBV infection than an infected adult.

Childhood horizontal transmission is also possible

- Transmission does not require a recognized needlestick exposure.
- Minor breaks in skin or mucous membranes may permit viral entry.
- Close household or childhood contact contributes in some high-prevalence settings.
- Route of acquisition and age at infection both influence downstream disease burden.

Age is a major determinant of HBV persistence

Perinatal infection

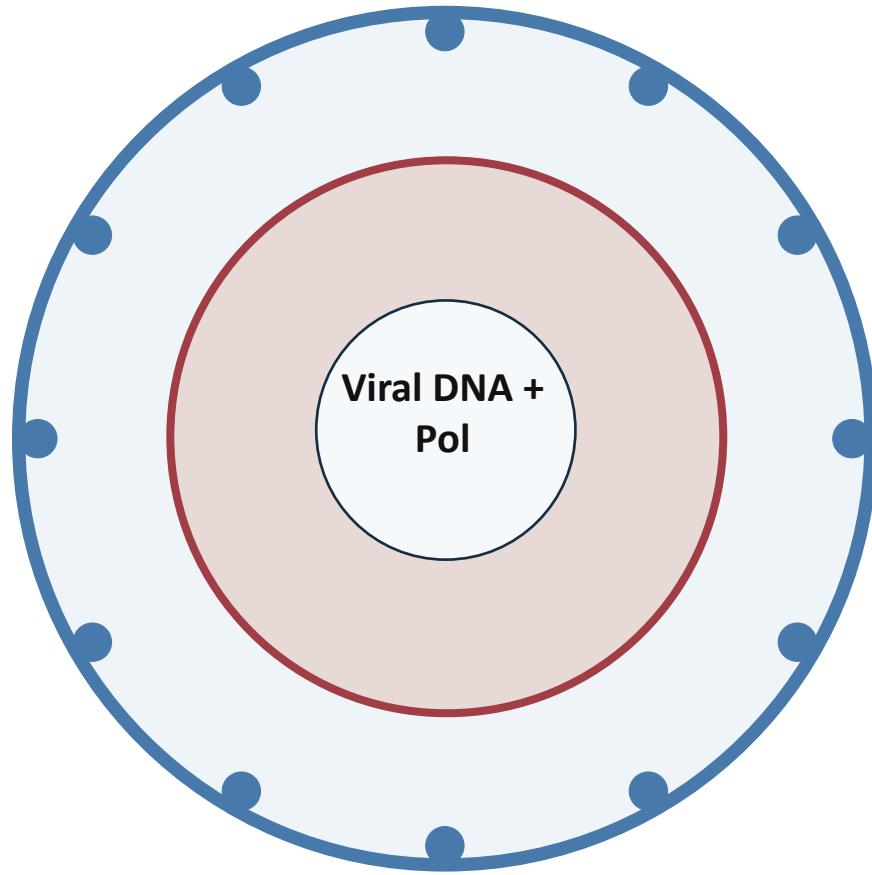
- Approximately 90% may develop chronic infection.
- Prolonged viral persistence increases lifetime complication risk.
- Prevention around childbirth is therefore crucial.

Adult-acquired infection

- Most cases resolve spontaneously.
- Chronic infection develops in a minority.
- Acute symptoms may be absent despite infection.

Figures refer to the textbook population estimates, not an individual patient's prediction.

HBV virion architecture



HBsAg-bearing envelope

Host-derived lipid envelope contains viral surface glycoproteins.

HBcAg nucleocapsid

Partially double-stranded circular viral DNA and polymerase are enclosed by the core.

The HBV genome encodes several functional products

Gene product	Main role
HBsAg	Envelope proteins: Large, middle, and small
HBcAg	Core/nucleocapsid protein; Virion assembly
HBeAg	Product of precore/core transcript; Replication-associated serum marker
HBV polymerase	DNA polymerase and reverse transcriptase activities
HBx	Transcriptional effects; Implicated in HBV-related HCC

Three related proteins comprise HBsAg

Large HBsAg

- Part of the viral envelope.
- Usually associated with complete virions.
- Participates in hepatocyte entry.

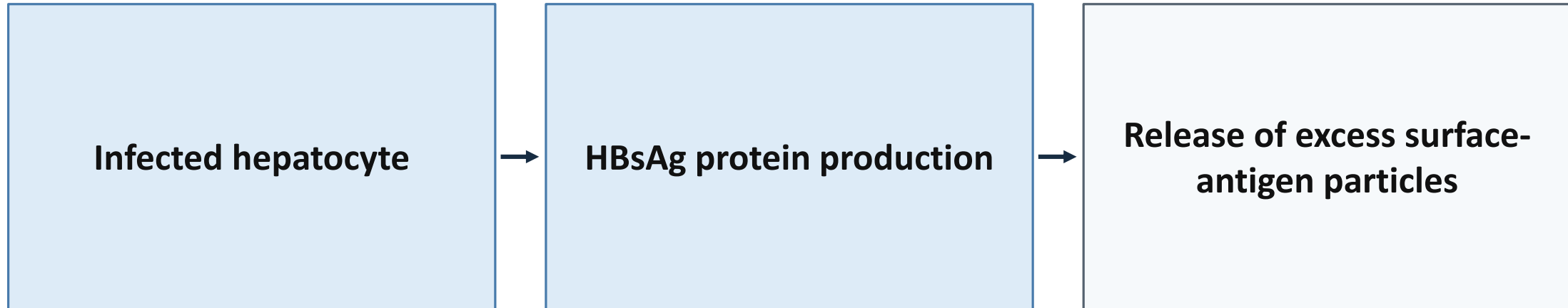
Middle HBsAg

- Related envelope glycoprotein.
- Encoded by the same viral surface region.
- Contributes to the HBV surface-antigen family.

Small HBsAg

- Abundantly released from infected cells.
- Can be present without viral core material.
- Contributes to noninfectious envelope particles.

HBsAg is not synonymous with an intact virion



Noninfectious envelope particles lack a viral core; Serum HBsAg does not directly quantify intact infectious virions.

HBcAg and HBeAg are related but distinct

HBcAg

- Nucleocapsid protein.
- Participates in assembly of complete virions.
- Can be identified by tissue immunostaining.

HBeAg

- Produced from a longer precore/core transcript.
- Serum marker associated with ongoing replication.
- May be absent in replication-competent mutants.

HBV polymerase performs reverse transcription

One enzyme complex carries two crucial enzymatic activities

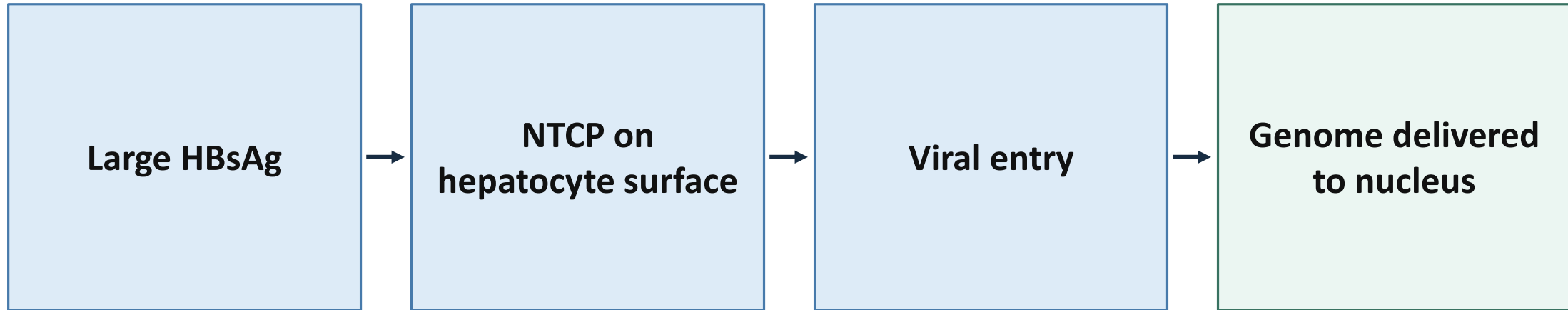
DNA polymerase activity + reverse transcriptase activity

Reverse transcriptase activity enables viral DNA production from an RNA intermediate.

HBx may contribute to HBV-associated carcinogenesis

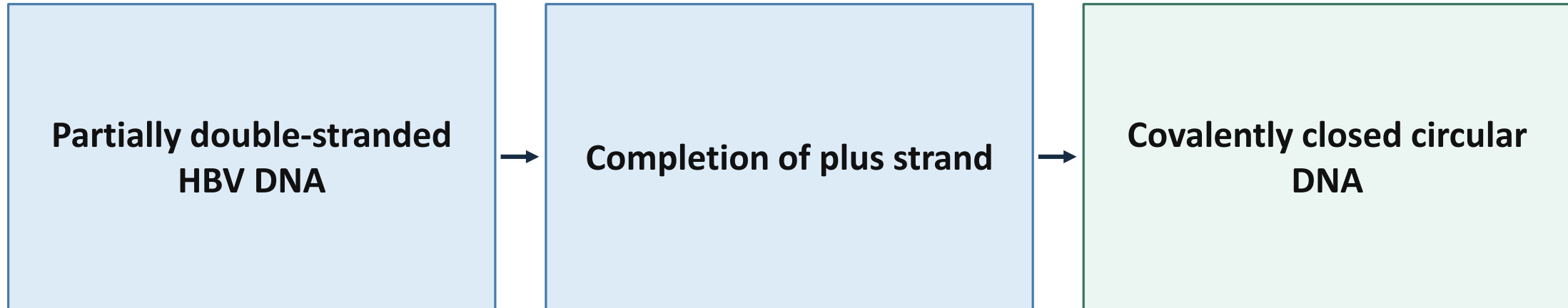
- HBx is not essential for the core replication process.
- It may activate transcription of viral and selected host genes.
- Its activity has been implicated in HBV-associated hepatocellular carcinoma.
- The mechanism should not be reduced to a single HBx-driven event.

HBV enters hepatocytes through NTCP



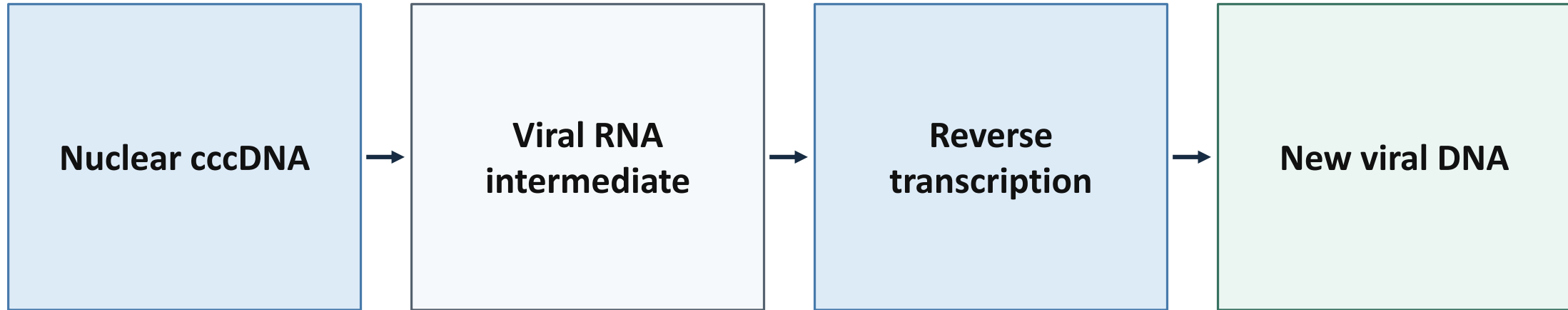
NTCP: Sodium taurocholate cotransporting polypeptide, a hepatocyte bile-salt transporter.

The nuclear genome forms cccDNA



CccDNA is a nuclear viral DNA form that supports subsequent transcription.

Reverse transcription makes HBV biologically distinctive



This simplified cycle displays molecular directionality, not all steps in particle assembly.

HBV replication spans nuclear and cytoplasmic events

Nuclear phase

- Genome reaches the hepatocyte nucleus.
- Plus strand is completed.
- CccDNA is established.

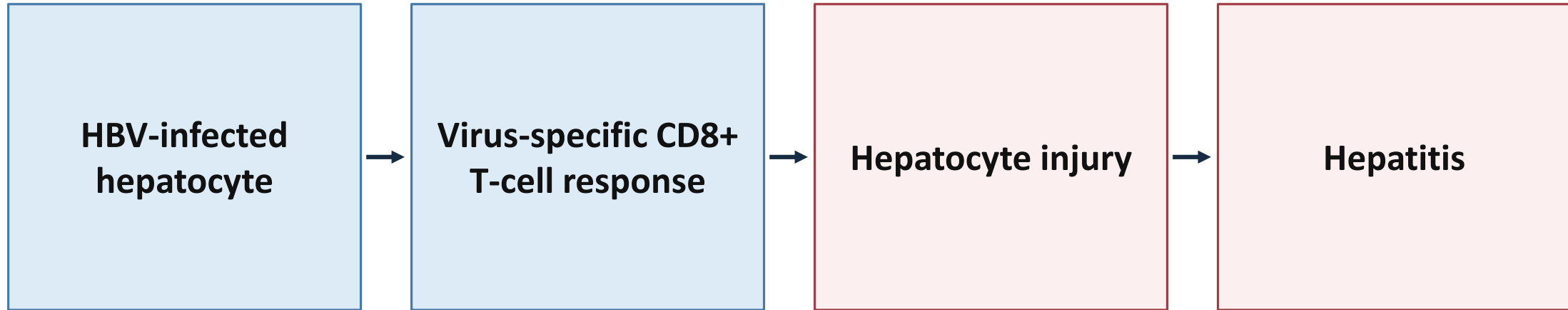
RNA-mediated replication

- Viral transcription yields an RNA intermediate.
- Reverse transcription regenerates viral DNA.
- New viral particles may be assembled and released.

Viral persistence is not just continued protein secretion

- The cccDNA form is established in infected hepatocyte nuclei.
- HBsAg may be produced abundantly without intact viral core particles.
- Measures of antigen production and HBV DNA replication provide different information.
- Persistent infection may not be eliminated readily by antiviral therapy.

Immune responses dominate hepatocyte injury

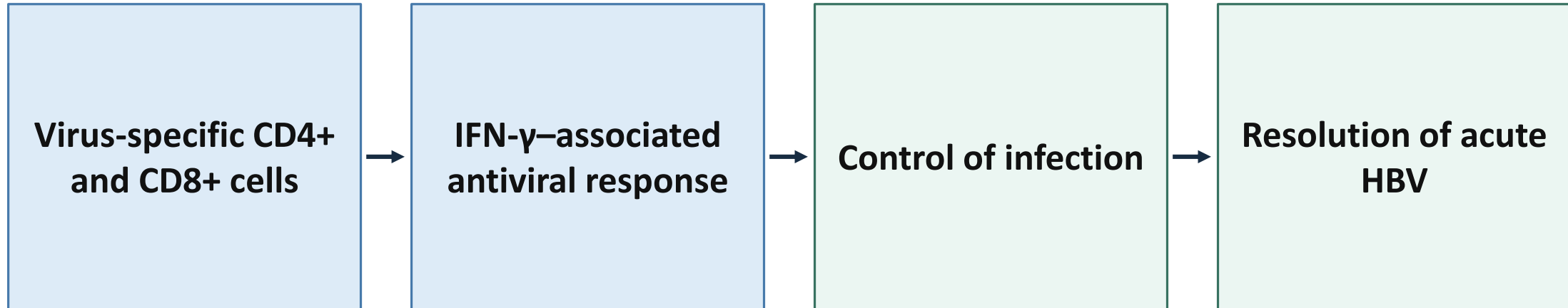


The principal tissue damage is immunologically mediated; The source also allows cytopathic effects with very high viral replication.

CD8+ T cells target HBV-infected hepatocytes

- Cytotoxic CD8+ T cells are major effectors of hepatocyte damage.
- Virus-specific recognition couples infection to necroinflammatory injury.
- The magnitude and character of host immunity shape the clinical course.
- A viral infection can therefore produce severe injury without direct viral lysis as the dominant mechanism.

Effective T-cell immunity favors viral clearance



The textbook associates a strong virus-specific interferon- γ -producing response with resolution.

Different immune responses lead to different outcomes

Effective antiviral response

- Stronger virus-specific T-cell activity.
- Greater likelihood of control and recovery.
- Anti-HBs may appear after clearance.

Persistent infection

- Insufficient durable elimination of infection.
- HBsAg and viral DNA may persist.
- Repeated immune-mediated injury may lead to fibrosis.

High viral protein production can also alter cells

- High-level replication and abundant viral proteins can produce cytopathic changes.
- Nevertheless, most hepatocyte injury is attributed to the host immune attack.
- Ground-glass change exemplifies an HBV-related intracellular protein accumulation pattern.
- Distinguish intracellular antigen accumulation from mechanisms of necroinflammatory injury.

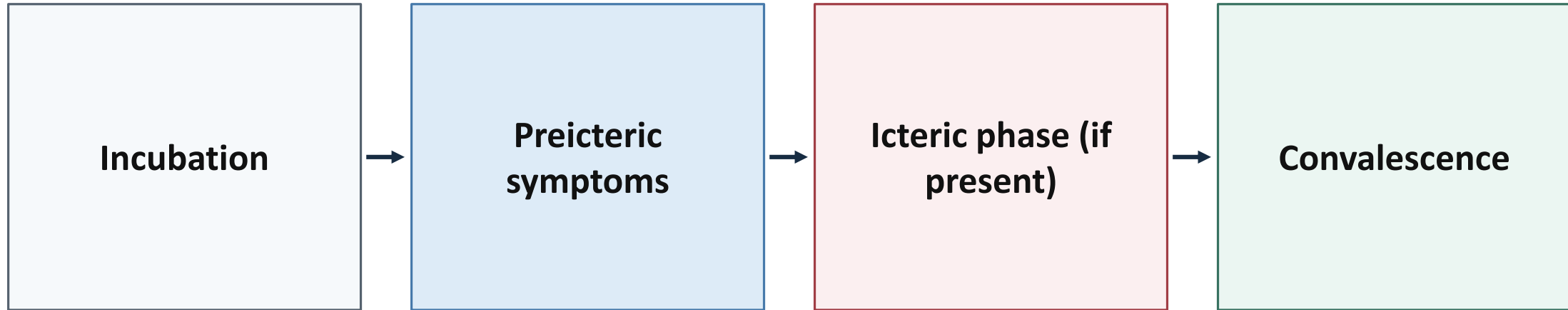
HBV has a prolonged incubation period

Interval reported in the source

Approximately 4–26 weeks

HBsAg can become detectable before symptoms; Infectivity is not restricted to the icteric phase.

Acute viral hepatitis has recognizable clinical phases



Not all individuals enter a clinically apparent icteric phase.

Most acute adult HBV infections are mild or subclinical

- Nearly two-thirds of acute adult infections are reported as mild or subclinical.
- Clinical silence does not exclude viral replication or transmission.
- The remaining symptomatic presentations often resemble other causes of acute hepatitis.
- Serology and molecular testing establish the etiology.

Acute symptoms reflect a hepatitic syndrome

- Constitutional symptoms include anorexia and fever.
- Jaundice may develop as liver dysfunction becomes apparent.
- Right upper-quadrant pain can accompany acute hepatic inflammation.
- The symptom complex is not specific for HBV versus another hepatotropic virus.

HBV can produce immune-complex disease outside the liver



Clinical examples include glomerulonephritis and polyarteritis nodosa.

Acute liver failure is an uncommon severe outcome

- Acute liver failure in approximately 0.1%–0.5% of acutely infected individuals.
- Severe hepatocyte necrosis can develop over a short clinical interval.
- Extensive loss of hepatocyte function may be life-threatening.
- Acute liver failure is distinct from slowly progressive chronic HBV-associated cirrhosis.

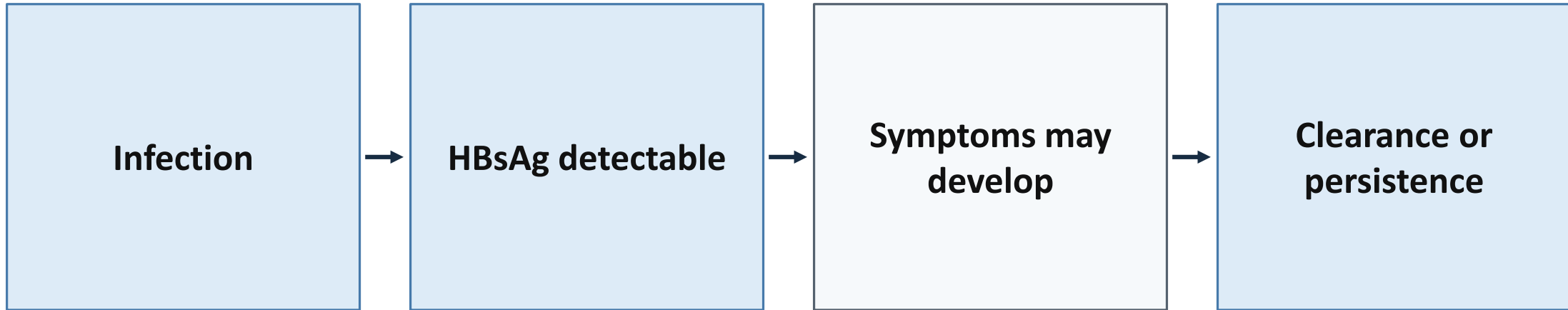
Most adult HBV infections resolve without treatment

- A self-limited course is the usual adult outcome.
- HBsAg disappears as infection resolves.
- Protective anti-HBs typically becomes detectable after antigen clearance.
- The proportion progressing to chronic HBV is much higher after perinatal acquisition.

HBV serology measures different biological events

Marker	Principal information
HBsAg	Current HBV surface-antigen expression
Anti-HBs	Antibody linked to recovery or vaccine-induced protection
IgM anti-HBc	Recent infection; Useful during serologic window
HBeAg	Often indicates active replication
Anti-HBe	Often accompanies declining replicative activity
HBV DNA	Direct evidence of viral genomic material in serum

HBsAg is an early marker of HBV infection



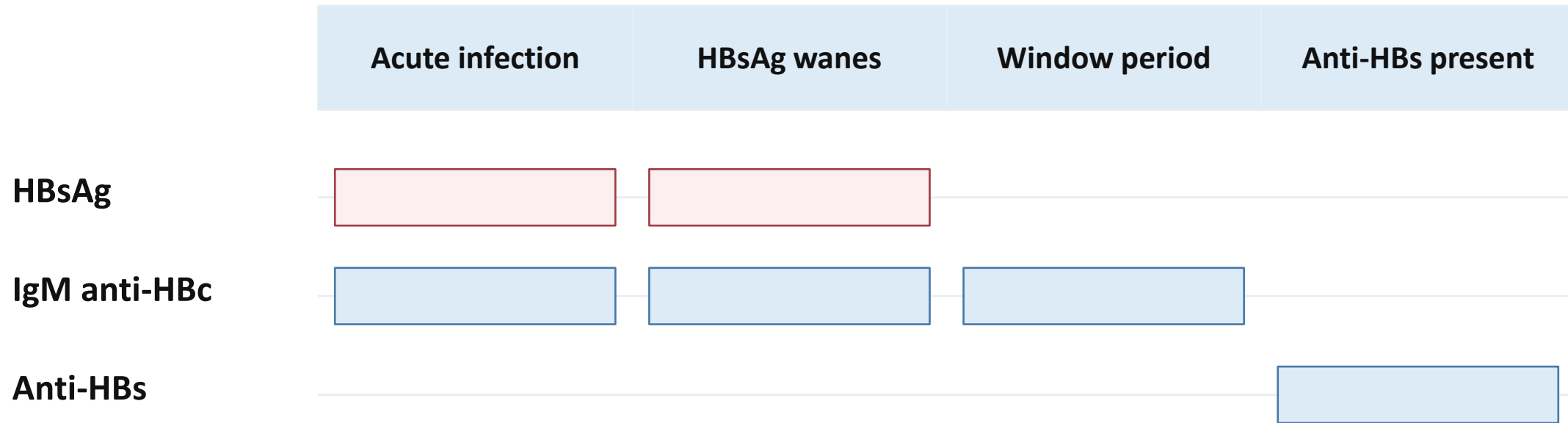
HBsAg precedes symptomatic disease and usually disappears after recovery.

Anti-HBs indicates a protective antibody response

- Anti-HBs typically appears after disappearance of HBsAg during recovery.
- Anti-HBs may persist long-term and confer protection.
- Vaccination with HBsAg seeks to generate this protective antibody.
- Absence of anti-HBs in a patient with persistent HBsAg is compatible with chronic infection.

The serologic window is bridged by IgM anti-HBc

Qualitative serologic sequence — schematic; Not a quantitative concentration curve



The marker positions are schematic; Timing varies among individuals.

HBeAg is associated with viral replication

- HBeAg usually appears soon after HBsAg during productive infection.
- Its persistence supports continued replication and infectivity.
- Sustained HBeAg may indicate a higher likelihood of chronic disease.
- HBeAg is an indirect marker and has an important mutational exception.

HBeAg-negative HBV may still replicate

Conventional interpretation

- HBeAg often accompanies HBV DNA positivity.
- Persistent HBeAg is evidence of viral replication.
- Seroconversion to anti-HBe may accompany waning infection.

Replication-competent variants

- Mutations can prevent HBeAg expression.
- HBV DNA may remain detectable despite absent HBeAg.
- Do not equate HBeAg negativity with no viral activity.

HBV DNA provides direct evidence of ongoing viral presence

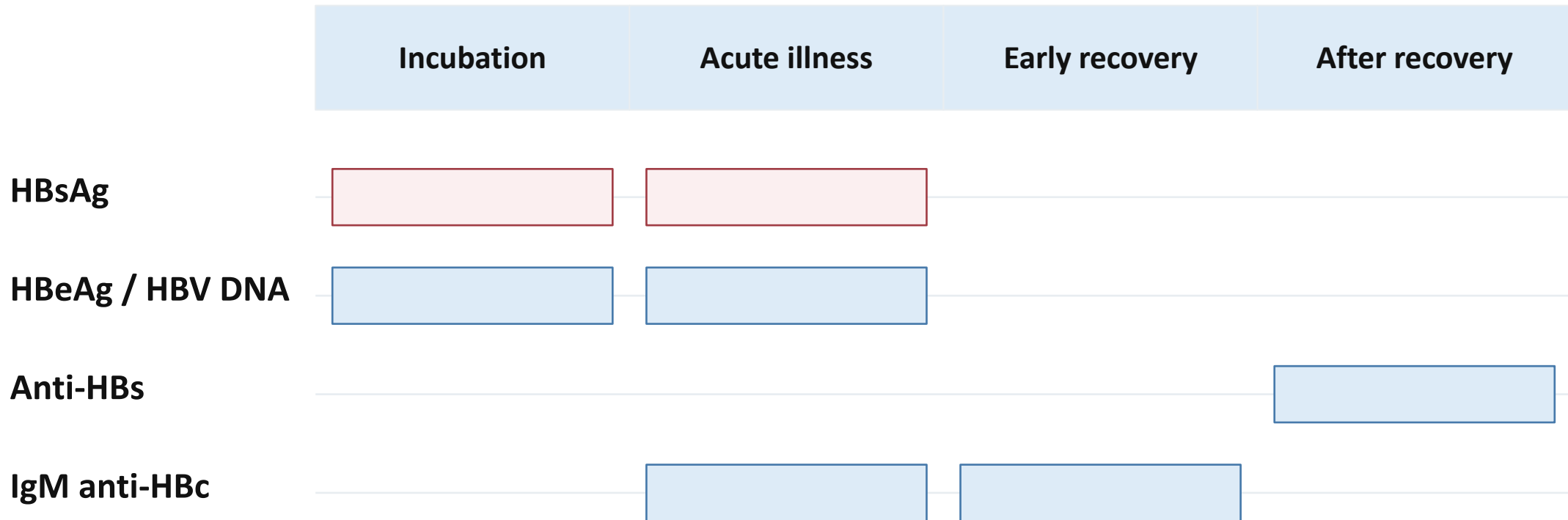
- Detectable serum HBV DNA reflects viral genomic material in circulation.
- HBV DNA helps clarify the significance of HBeAg-negative infection.
- Antigen expression, viral replication, and hepatocyte injury are related but distinct phenomena.
- Interpret HBV DNA alongside antigen markers and aminotransferase results.

Anti-HBe is not equivalent to complete virologic clearance

- Anti-HBe may emerge as acute infection wanes.
- During chronic HBV, anti-HBe may be absent or appear late.
- HBeAg-negative replication-competent viruses complicate interpretation.
- Persistent HBsAg or HBV DNA prevents a conclusion of resolved infection.

How acute HBV markers change over time

Qualitative serologic sequence — schematic; Not a quantitative concentration curve



Schematic natural history only; Markers need not follow an identical course in every patient.

Representative HBV serologic patterns

Pattern	HBsAg	Anti-HBs	Anti-HBc	Interpretation
Resolved infection	–	+	+	Prior natural infection
Post-vaccine	–	+	–	Vaccine-type response
Recent acute infection	+	–	IgM +	Recent infection
Persistent infection	+	Usually –	Often +	Evaluate for chronic HBV

Didactic patterns only; Full laboratory interpretation depends on the complete test panel and clinical context.

A single HBV marker rarely tells the whole story

Practical interpretation principle

**Integrate HBsAg + antibodies + HBV DNA + clinical
context**

In particular, neither absent HBeAg nor isolated anti-HBc should be interpreted without the other markers.

Chronic hepatitis is defined by persistence and injury

- The adjacent Robbins section describes continuing or relapsing liver disease beyond 6 months and/or morphologic fibrosis.
- Persistent HBsAg characterizes ongoing HBV infection.
- Chronic HBV may have variable aminotransferase elevations or little clinical disturbance.
- Biochemical findings alone do not fully establish disease activity or fibrosis.

Chronic HBV may remain clinically quiet

- Some patients have few or no symptoms despite continuing infection.
- Others report fatigue, malaise, appetite loss, or intermittent mild jaundice.
- Aminotransferases can fluctuate during chronic disease.
- Infection and liver injury must be assessed independently.

An asymptomatic carrier state has specific features

Parameter	Classical low-activity HBV carrier pattern
Symptoms	Absent
HBsAg	Present
HBeAg	Absent
Anti-HBe	Present
HBV DNA	Low or undetectable
Aminotransferases	Normal
Biopsy	No significant inflammatory injury

The historical phrase “healthy carrier”; It does not mean the patient is incapable of transmission.

HBV carrier status is not synonymous with no transmission

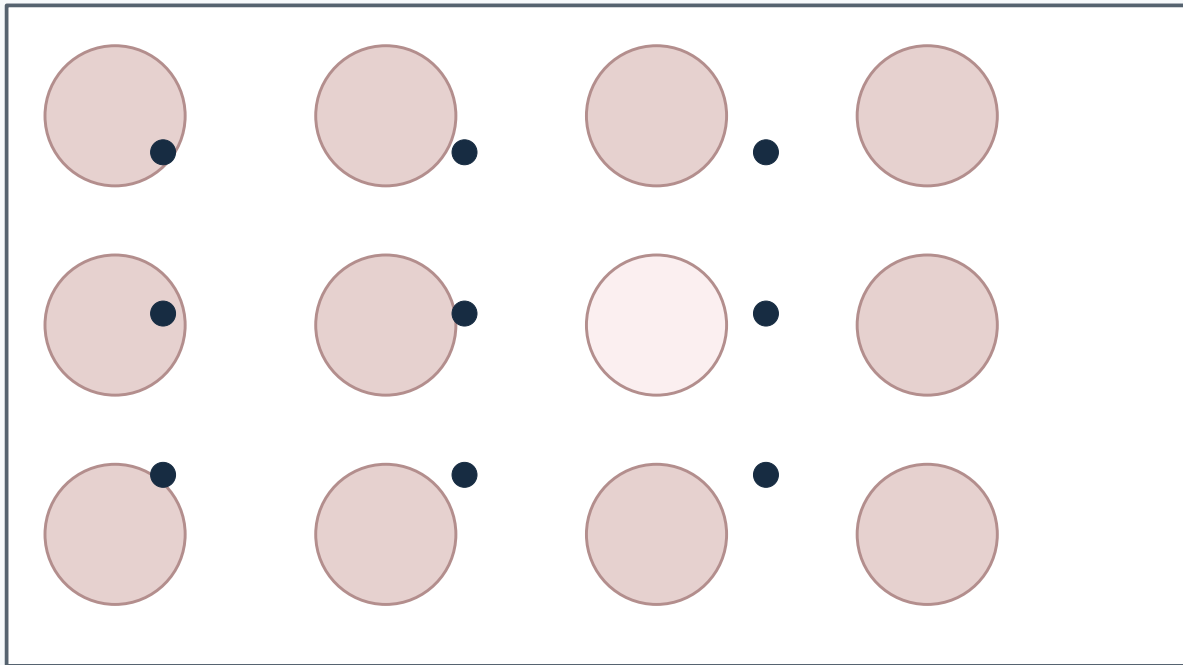
- The term “carrier” denotes harboring an organism capable of transmission.
- Patients without symptoms can still act as an infection reservoir.
- A low-activity pattern is distinct from a claim that the infection has been eradicated.
- Activity may need reassessment over time as viral and host factors change.

HBV differs from enterically transmitted hepatitis viruses

HAV	HBV	HCV
• Primarily fecal–oral transmission. • Does not produce chronic hepatitis. • Often resolves after acute infection.	• Blood, sexual, and perinatal transmission. • Can persist chronically. • Associated with cirrhosis and HCC.	• Predominantly parenteral transmission. • A high frequency of chronic infection. • May progress to cirrhosis and HCC.

Contextual comparison from the adjacent Robbins hepatitis sections.

Acute viral hepatitis shows a lobular injury pattern



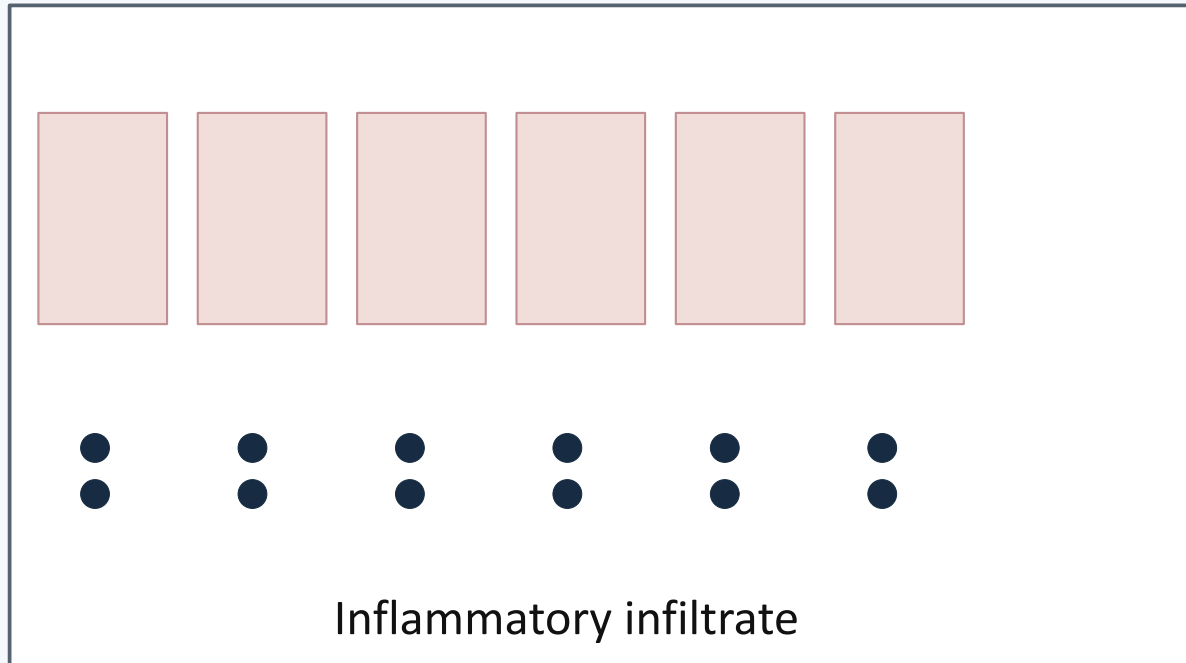
Focal damaged hepatocyte

SCHEMATIC — not a histologic specimen

Acute hepatic pattern

- Portal and lobular lymphocytic inflammation.
- Hepatocyte apoptosis and necrosis.
- Macrophages clear injured-cell debris.

Necroinflammation is a cellular immune response



SCHEMATIC — not a histologic specimen

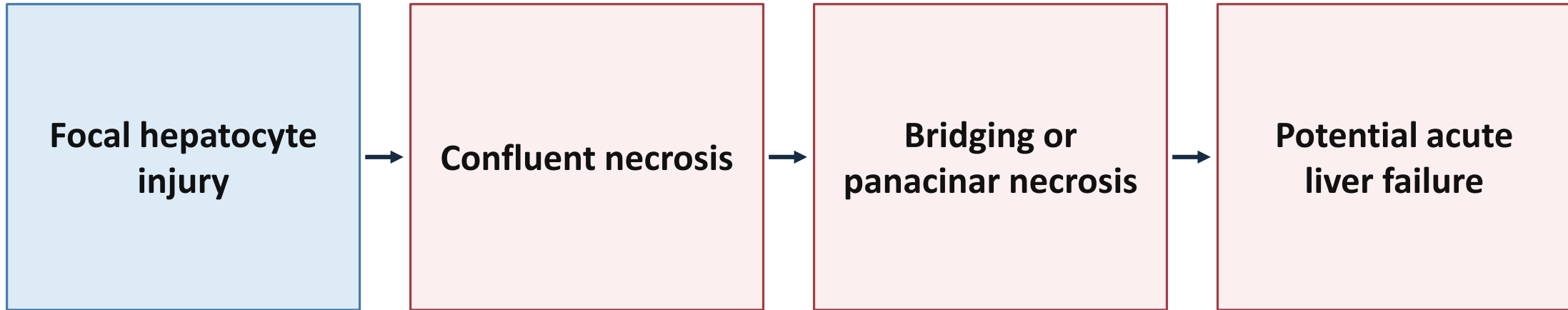
Microscopic interpretation

- T cells predominate in viral hepatitis infiltrates.
- Plasma cells and eosinophils may be variable.
- The inflammatory pattern is not exclusive to HBV.

Apoptosis and necrosis can coexist

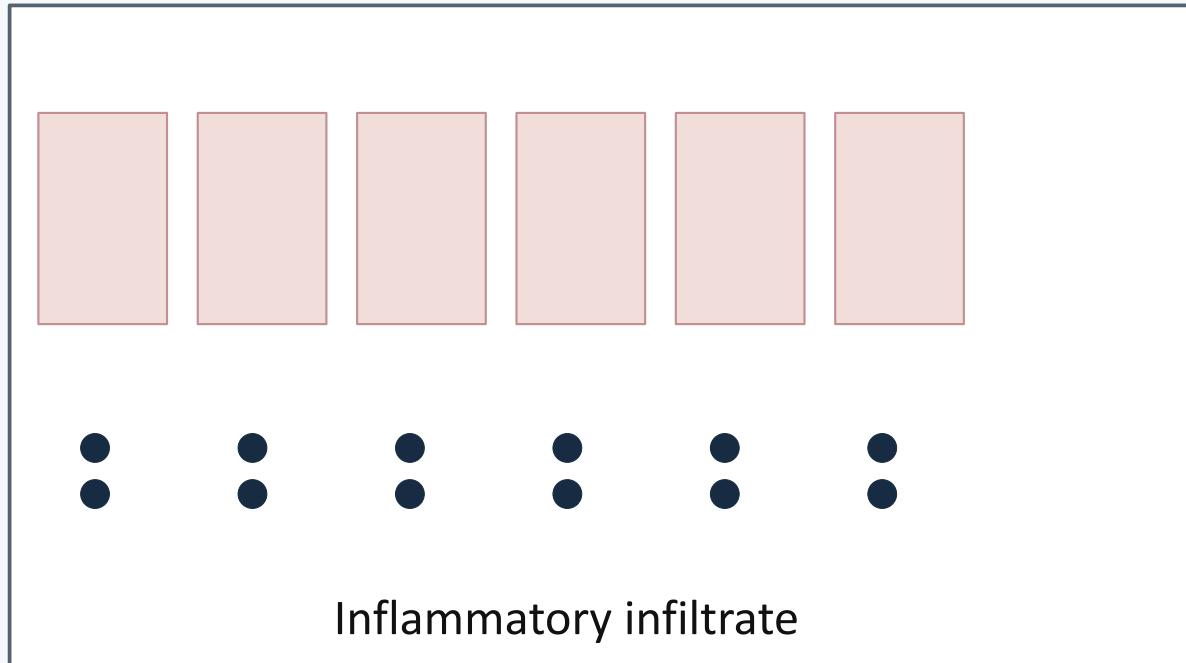
- In acute viral hepatitis, individual damaged hepatocytes may undergo apoptosis.
- Dead-cell debris can be removed by pigmented macrophages.
- Necrosis may affect individual cells or larger parenchymal areas.
- Severity of cell loss—not merely the presence of inflammation—matters clinically.

Confluent and bridging necrosis indicate severe injury



These are possible patterns of increasing extent of injury, not mandatory sequential stages.

Chronic hepatitis is centered on portal inflammation

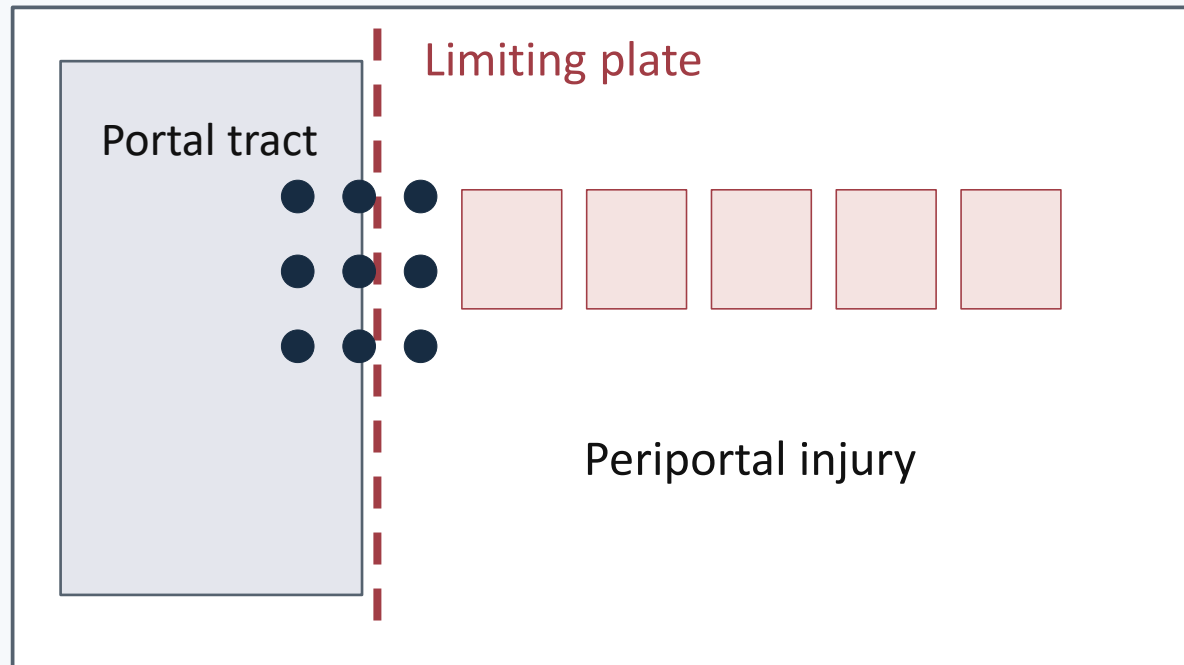


SCHEMATIC — not a histologic specimen

Chronic hepatic pattern

- Portal lymphocytic / lymphoplasmacytic infiltrate.
- Variable accompanying lobular inflammation.
- Fibrosis emerges with cumulative tissue injury.

Interface hepatitis injures periportal hepatocytes

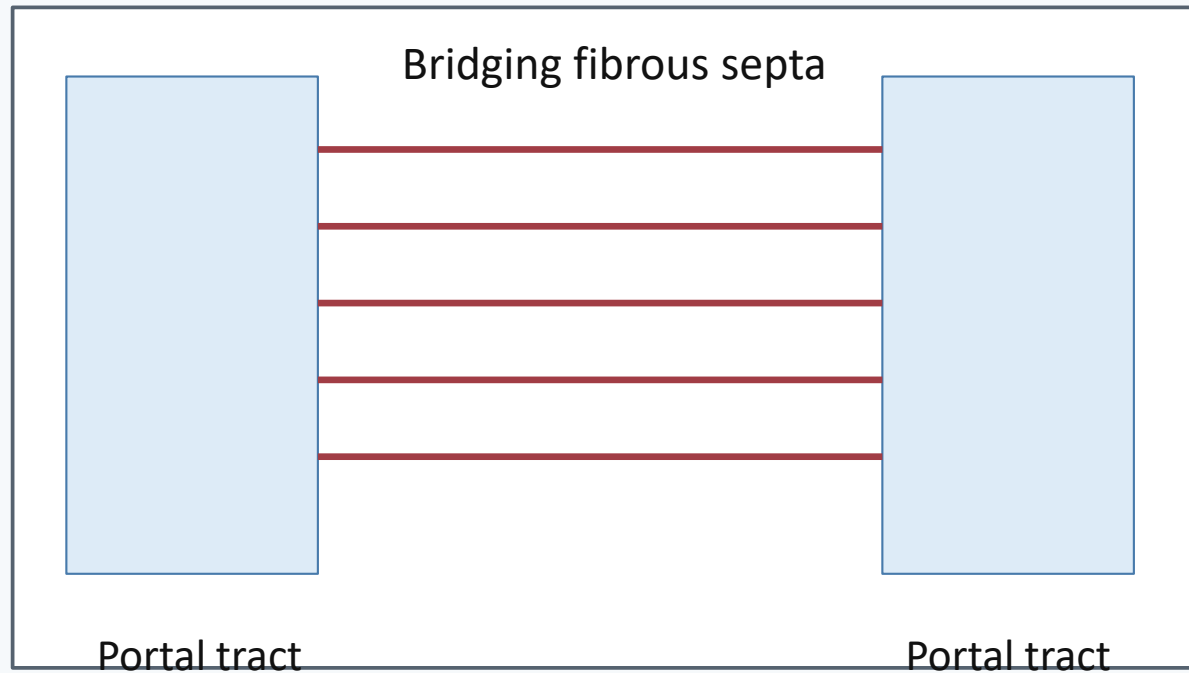


SCHEMATIC — not a histologic specimen

Interface activity

- Inflammatory cells cross the limiting plate.
- Periportal hepatocytes become damaged.
- Activity signifies ongoing immune-mediated injury.

Fibrosis bridges portal tracts as disease advances

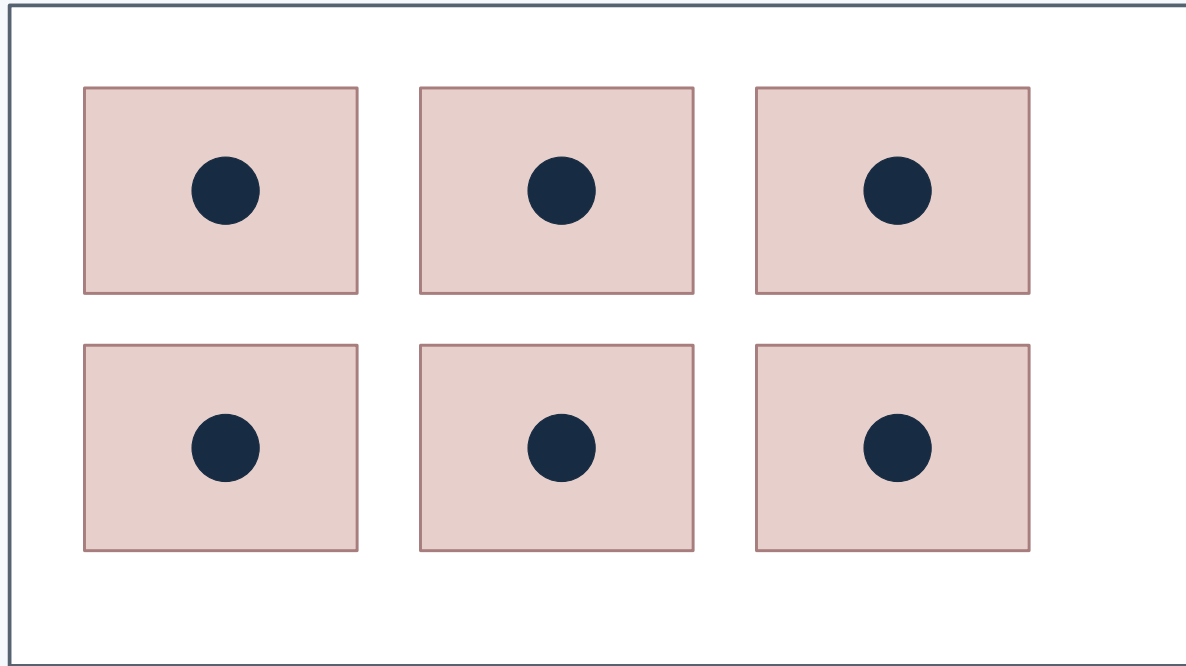


SCHEMATIC — not a histologic specimen

Fibrosis progression

- Initial portal / periportal fibrosis.
- Portoportal bridging fibrosis.
- Advanced architectural remodeling: Cirrhosis.

Ground-glass hepatocytes are a distinctive HBV clue



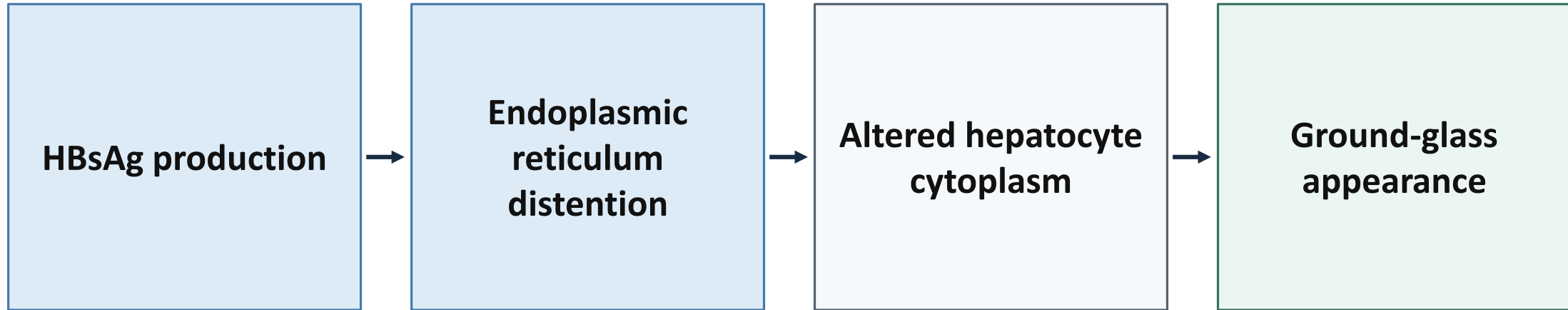
Ground-glass cytoplasm

SCHEMATIC — not a histologic specimen

HBV-associated change

- Smooth endoplasmic reticulum expands with HBsAg.
- Cytoplasm appears homogeneous or ground-glass.
- It is a clue, not a stand-alone serologic diagnosis.

The ground-glass appearance reflects HBsAg accumulation



Mechanistic explanation from the adjacent Robbins morphology section.

Immunostains can demonstrate HBV antigens in tissue

HBsAg staining

- Identifies viral surface antigen in hepatocytes.
- Supports the interpretation of ground-glass cells.
- Must be related to tissue pattern and serology.

HBcAg staining

- Detects nucleocapsid antigen in tissue.
- Provides complementary evidence of HBV infection.
- Does not by itself measure fibrosis severity.

Morphology cannot reliably type every viral hepatitis

- Acute and chronic hepatitis patterns overlap among hepatotropic viruses.
- Autoimmune hepatitis, drug injury, and Wilson disease can produce similar injury.
- Ground-glass change raises suspicion of HBV but is not the complete diagnostic workup.
- Viral serology and molecular studies are essential for etiologic attribution.

Biopsy separates inflammatory grade from fibrosis stage

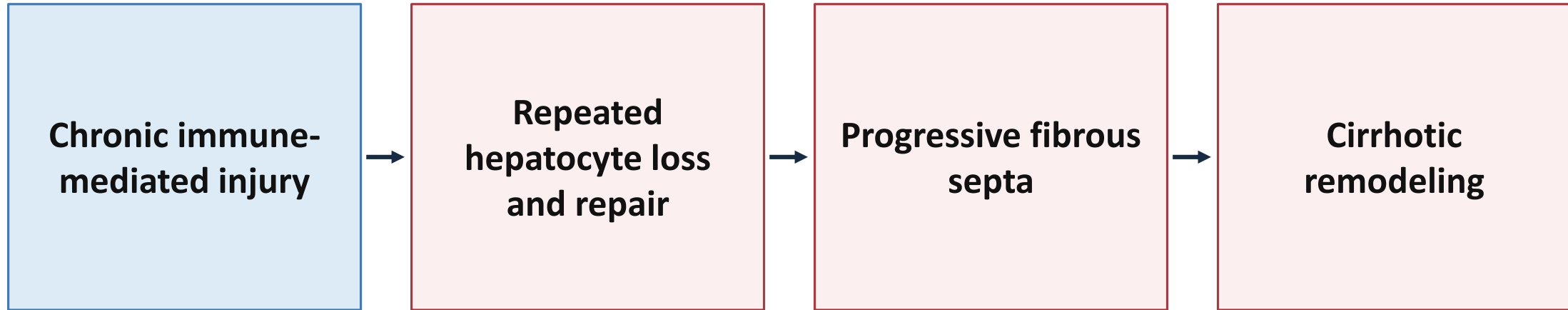
Activity / grade

- Extent and distribution of inflammation.
- Severity of hepatocyte injury and interface activity.
- Describes the current necroinflammatory process.

Fibrosis / stage

- Extent of collagenous architectural change.
- Bridging fibrosis and cirrhosis.
- Describes cumulative structural disease.

HBV-related cirrhosis arises from progressive fibrosis

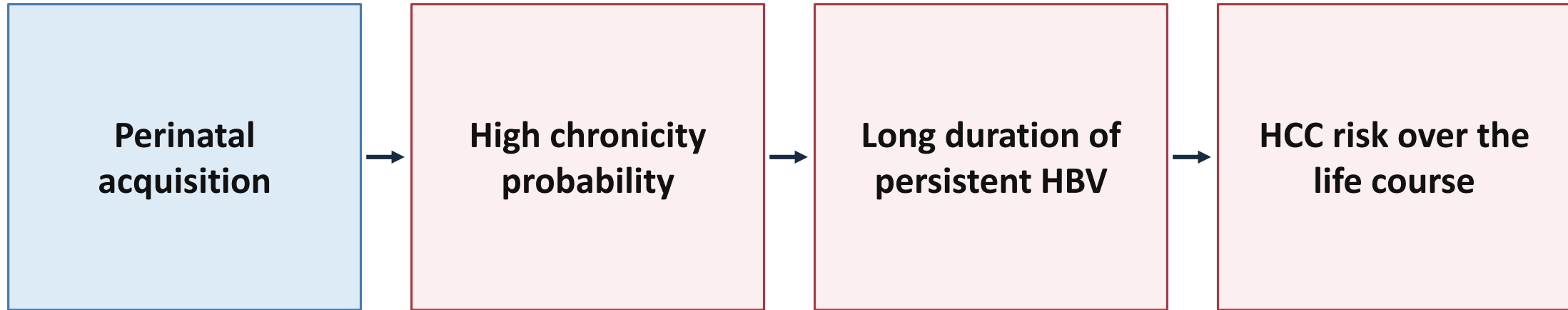


Cirrhosis is a possible endpoint of chronic hepatitis, not an inevitable result.

Chronic HBV increases hepatocellular carcinoma risk

- The Robbins source identifies HCC as a major long-term complication.
- Risk is particularly important in people infected at birth who remain chronically infected.
- Cirrhosis contributes to risk, but HBV-related carcinogenesis also has viral molecular components.
- HBx is implicated in altered host gene transcription associated with HCC.

Perinatal infection amplifies lifetime HCC risk



This is a risk pathway, not a statement that all chronically infected individuals develop cancer.

Hepatitis D depends on HBV

Important related virus

HDV requires HBV for its infectious life cycle

HBV vaccination also prevents HDV infection by preventing the required HBV infection.

HDV co-infection differs from superinfection

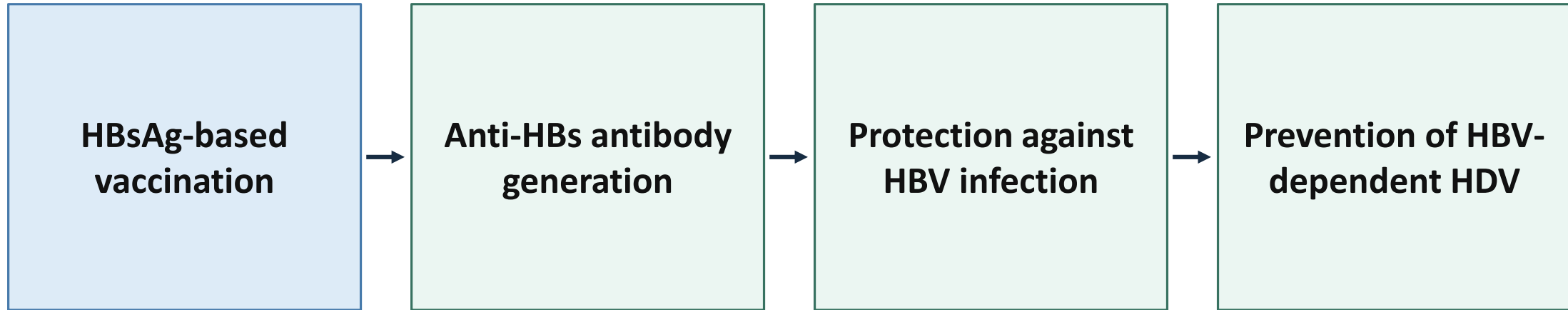
HBV–HDV co-infection

- Both viruses acquired in the same exposure.
- Acute hepatitis may resemble HBV alone.
- Clearance of both viruses is possible.

HDV superinfection

- HDV acquired in a patient with established HBV.
- May sharply exacerbate chronic hepatitis.
- Persistent delta infection and progression are more likely.

Vaccination induces an anti-HBs response



High vaccine effectiveness in infants, children, and adolescents.

Prevention targets acquisition before chronicity begins

- HBV vaccination establishes protective anti-HBs immunity.
- Prevention of perinatal infection is especially important because chronicity risk is greatest at birth.
- Blood screening and reduction of needle-sharing exposures interrupt parenteral spread.
- Reducing HBV acquisition also reduces downstream risks of cirrhosis and HCC.

Antiviral therapy suppresses replication and progression

- Interferon and antiviral reverse-transcriptase inhibitors among therapeutic approaches.
- Examples given include entecavir and tenofovir.
- Treatment can slow disease progression and reduce liver damage.
- Lowering progression risk is not equivalent to guaranteed complete eradication.

Antiviral treatment reduces—but does not abolish—risk

Important benefits

- Reduced viral replication.
- Less ongoing liver damage and slower progression.
- Lower risk of cirrhosis and hepatocellular carcinoma.

Persistent challenges

- Complete cure remains difficult.
- Established fibrosis may not disappear immediately.
- Long-term clinical assessment remains relevant.

Case: Silent infection detected through screening

Clinical vignette

An adult without jaundice has a positive serum HBsAg result during health screening.

Can asymptomatic status exclude current HBV infection?

Reasoning

No. HBV may be subclinical or associated with a low-activity carrier state; Interpret HBsAg with other serologic markers, HBV DNA and liver tests.

Case: Antibodies during the serologic window

Clinical vignette

A patient recovering from an acute hepatitic illness has lost detectable HBsAg, but anti-HBs is not yet detected.

Which antibody may establish recent HBV infection?

Reasoning

IgM anti-HBc is useful in the window after HBsAg loss and before the appearance of anti-HBs.

Case: HBeAg-negative but HBV DNA-positive

Clinical vignette

A patient has detectable HBV DNA but no detectable HBeAg.

Does absent HBeAg rule out ongoing viral replication?

Reasoning

No. Replication-competent HBV variants may lack HBeAg expression; HBV DNA should guide evaluation of replication.

Case: Hepatocyte cytoplasmic ground-glass change

Clinical vignette

Liver biopsy shows hepatocytes with unusually homogeneous, finely granular cytoplasm in a chronic hepatitis pattern.

What HBV-associated mechanism should be considered?

Reasoning

Accumulation of HBsAg in expanded endoplasmic reticulum. Serology and/or HBV antigen immunostaining are needed for confirmation.

Integrating the HBV diagnostic and pathology evidence

Clinical question	Most informative evidence
Current infection?	HBsAg with appropriate clinical context
Evidence of replication?	Serum HBV DNA; HBeAg as an imperfect indirect marker
Recent acquisition?	IgM anti-HBc in appropriate setting
Immune protection?	Anti-HBs
Extent of liver injury?	Clinical/laboratory assessment; Biopsy when indicated
Fibrosis/cirrhosis?	Fibrosis assessment and histologic stage when biopsied

The four essential HBV distinctions

- Current antigen expression is different from evidence of active viral replication.
- Immune-mediated hepatocyte injury is different from intracellular viral protein accumulation.
- Inflammatory activity (grade) is different from accumulated fibrosis (stage).
- Prevention of infection is different from treatment-mediated control of persistent infection.

References

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
Chapter 18: Liver and Gallbladder.

Relevant sections

Hepatitis B Virus (pp. 756–758); Clinicopathologic Syndromes of Viral Hepatitis (pp. 760–762); Hepatitis D Virus (p. 760).