

Hepatitis C virus

Virology • chronic liver injury • diagnosis • treatment targets

Virology and immune escape

Clinicopathologic progression and hepatic morphology

Diagnostic interpretation and antiviral principles

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Learning objectives

Explain why HCV commonly persists after acute infection.

Interpret HCV RNA, anti-HCV and aminotransferase findings.

Recognize hepatic and extrahepatic manifestations.

Connect viral proteins to direct-acting antiviral targets.

The central clinicopathologic paradox

Acute infection is usually clinically silent.

Persistent viremia can lead to progressive inflammation and fibrosis.

A clinically well patient may nevertheless have significant liver injury.



Where HCV fits among hepatotropic viruses

Hepatitis viruses A–E are major hepatotropic pathogens.

HCV and HBV account for much chronic viral hepatitis.

Overlapping histology makes virologic testing indispensable.

Feature	HCV	Other hepatitis viruses
Genome	Single-stranded RNA	HBV: Partially dsDNA
Chronic infection	Common	HAV: None
Etiology on biopsy	Not specific	Serology / RNA needed

The population burden is substantial

The textbook estimates approximately 50–60 million infections worldwide.

It describes approximately 2.4 million chronic infections in the United States.

These are textbook figures, not a separately verified current surveillance update.

Worldwide

50–60 million

United States

2.4 million

Transmission

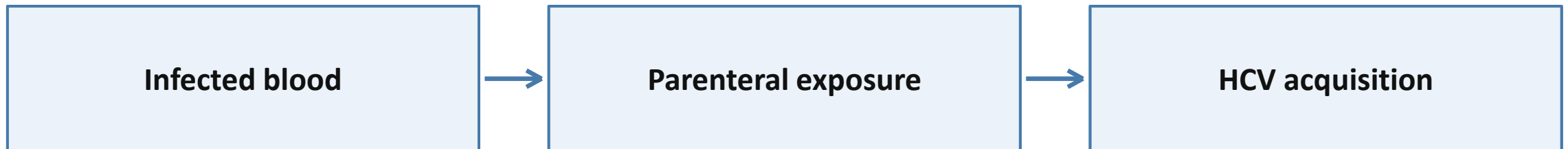
Parenteral

Transmission is principally blood-borne

Parenteral exposure is the principal route.

Injection drug use and sharps injury provide direct access to blood.

Careful exposure history informs testing but cannot exclude infection.



Injection-associated transmission

Sharing injection equipment allows contaminated blood transfer.

Multiple blood exposures can occur within an injection network.

Transmission risk is linked to contact with infected blood—not to symptoms.



Other clinically important exposure settings

Needlestick injury is an occupational exposure.

Sexual and perinatal transmission can occur.

Epidemiologic histories may identify repeated contacts with infected persons.

Healthcare / sharps



Sexual contact



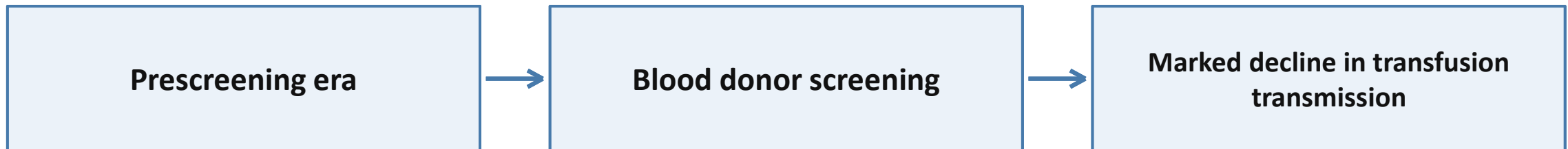
Perinatal exposure

Blood screening changed the transmission landscape

Donor screening greatly reduced transfusion-related HCV.

The textbook contrasts high infection incidence in the mid-1980s with much lower later figures.

Historic exposure histories remain relevant when assessing longstanding infection.



No identified exposure does not exclude HCV

No identifiable risk factor in about one-third of affected people.

Risk assessment alone is therefore insufficient to rule out infection.

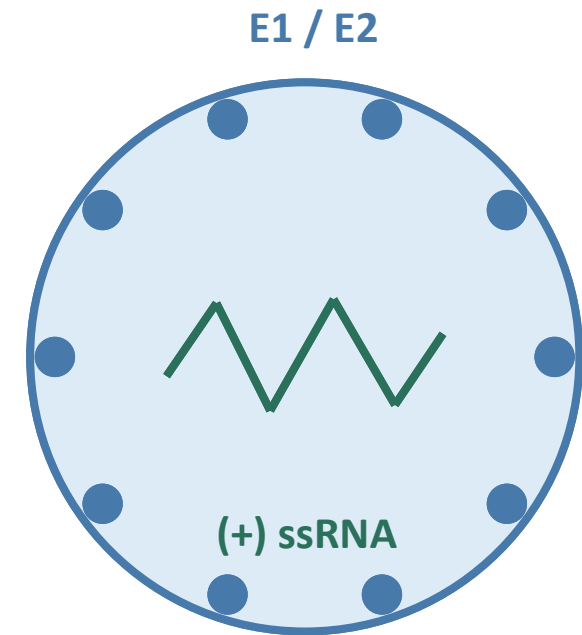
Serologic and molecular testing are needed when clinically indicated.

HCV is an enveloped positive-sense RNA virus

HCV belongs to the Flaviviridae family.

It contains single-stranded RNA with a single open reading frame.

The genomic RNA encodes a polyprotein processed into functional products.



The RNA genome encodes one polyprotein

A single open reading frame is translated into a precursor polyprotein.

Proteolytic processing generates envelope and nonstructural functions.

This arrangement makes viral proteases essential replication components.

Single translated polyprotein → viral proteolytic processing

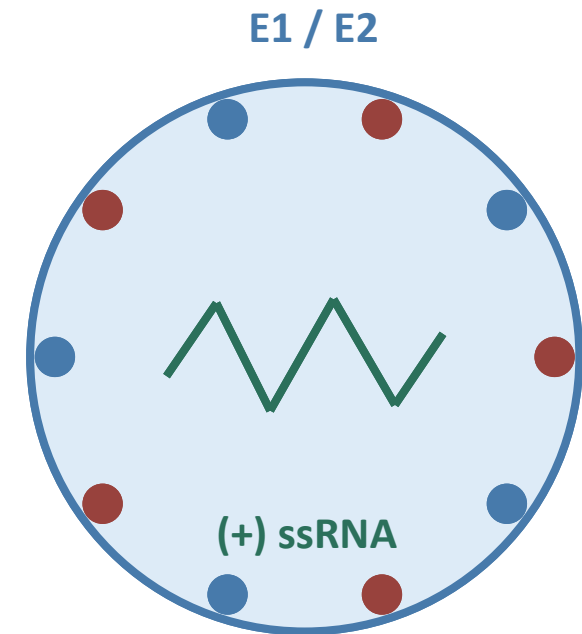
E1	E2	P7	NS2	NS3/4A	NS5A	NS5B
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E1 and E2 are envelope proteins

E1 and E2 are located at the viral envelope.

Anti-E2 antibodies may neutralize circulating virus.

Variation in E2 epitopes enables immune escape.



Nonstructural proteins have distinct tasks

NS3/4A: Viral protease and antagonist of antiviral signaling.

NS5A: Component of the replication complex.

NS5B: Viral RNA-dependent RNA polymerase.

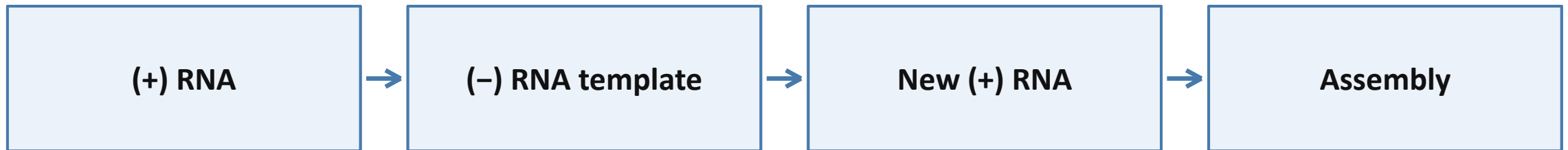
Viral protein	Principal role	Antiviral target
NS3/4A	Protease	Protease inhibitors
NS5A	Replication complex	NS5A inhibitors
NS5B	RNA synthesis	Polymerase inhibitors

HCV replication occurs without DNA integration

The viral RNA is translated and replicated in the infected hepatocyte.

Replication uses a negative-strand RNA intermediate.

HCV has no integrated viral DNA intermediate in its replication cycle.

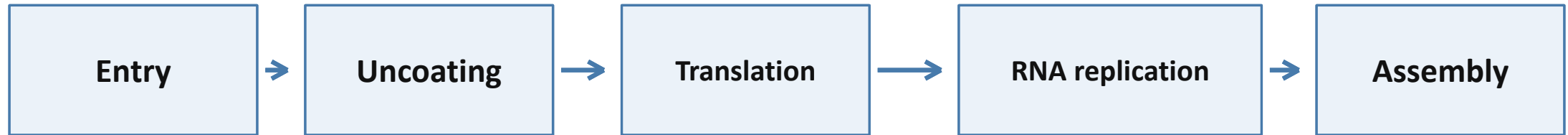


The HCV life cycle has separable targets

Entry is followed by endocytosis and uncoating.

RNA translation and polyprotein cleavage supply replication proteins.

Viral RNA replication precedes assembly and release.



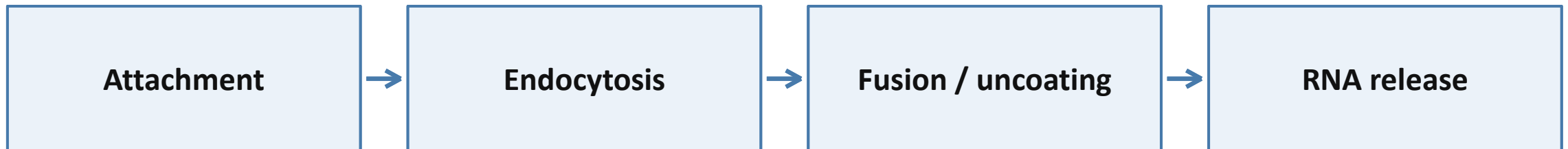
Original mechanism schematic; Drug targets are proteins acting during these stages

Entry begins at the hepatocyte surface

Envelope-associated virus binds host cell receptors.

Endocytosis internalizes the particle.

Uncoating releases positive-sense RNA for translation.



Translation creates the viral protein toolkit

Positive-sense viral RNA functions as a translation template.

A precursor polyprotein is processed by proteases.

Mature viral products can support replication and virion production.

Single translated polyprotein → viral proteolytic processing

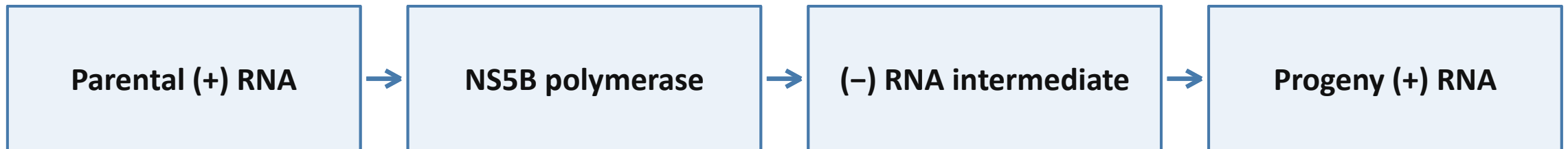
E1	E2	P7	NS2	NS3/4A	NS5A	NS5B
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RNA synthesis requires a negative-strand template

NS5B synthesizes complementary negative-strand RNA.

The negative strand templates new positive-strand genomes.

RNA-dependent polymerase function is an effective drug target.

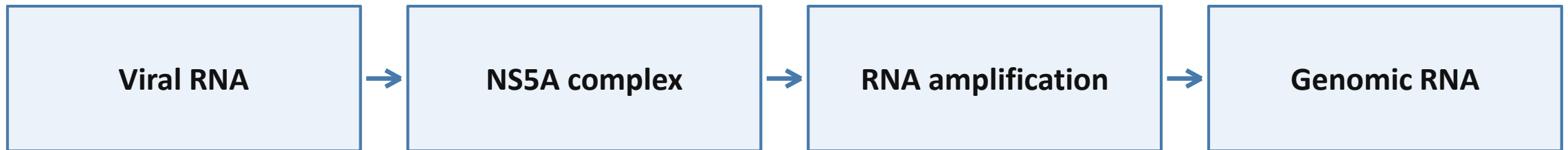


The replication complex coordinates RNA production

NS5A participates in the replication complex.

RNA synthesis is associated with intracellular membrane structures.

Interrupting NS5A impairs successful viral replication.

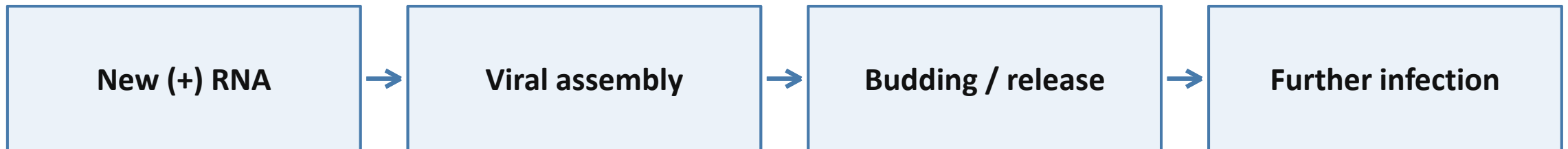


Assembly closes the replicative cycle

New RNA genomes are packaged into particles.

Envelope acquisition and maturation precede release.

Released HCV particles enable continuing infection of other cells.

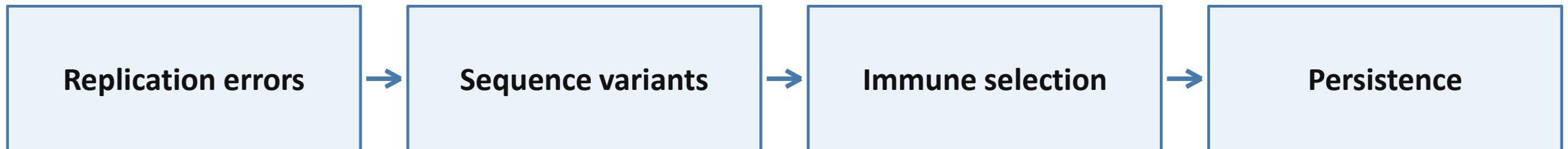


The polymerase generates substantial diversity

HCV RNA polymerase has low copying fidelity.

Replication continuously generates genetic variants.

Genetic diversity gives the virus opportunities to evade host pressure.



Genotypes and quasispecies are not identical

Seven genotypes with multiple subtypes.

Within an infected individual, related variants form quasispecies.

Evolution within the host is relevant to persistent infection.

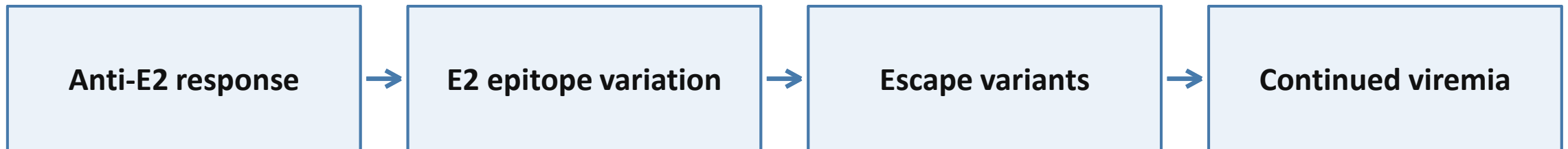
Level	Definition	Clinical relevance
Genotype	Major viral lineage	Population diversity
Subtype	Subdivision of genotype	Further classification
Quasispecies	Within-host variant swarm	Immune escape potential

Variation of E2 supports antibody escape

Neutralizing antibodies may target the E2 envelope protein.

Emerging variants can have altered E2 epitopes.

Antibody recognition may fail to eliminate the evolving viral population.



NS3/4A also undermines host antiviral defense

NS3/4A protease impairs interferon-mediated cellular responses.

This acts alongside adaptive antibody escape.

Multiple avoidance mechanisms make spontaneous clearance difficult.

Innate signaling inhibited



Adaptive recognition evaded



HCV can persist

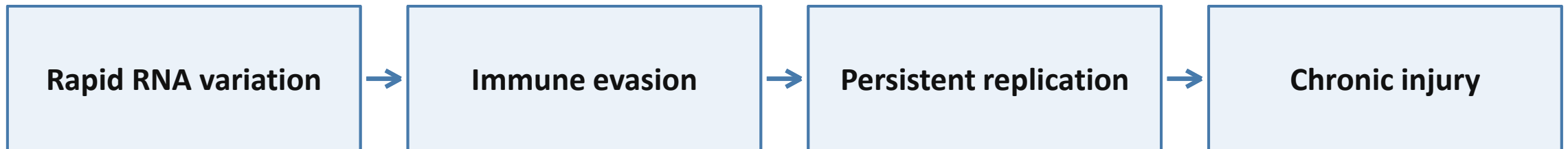
Persistence is an interaction, not one mutation

Ongoing replication supplies new variants.

Host immune pressure selects surviving viral populations.

Interferon antagonism further weakens control.

Persistent infection sustains hepatic immune injury.

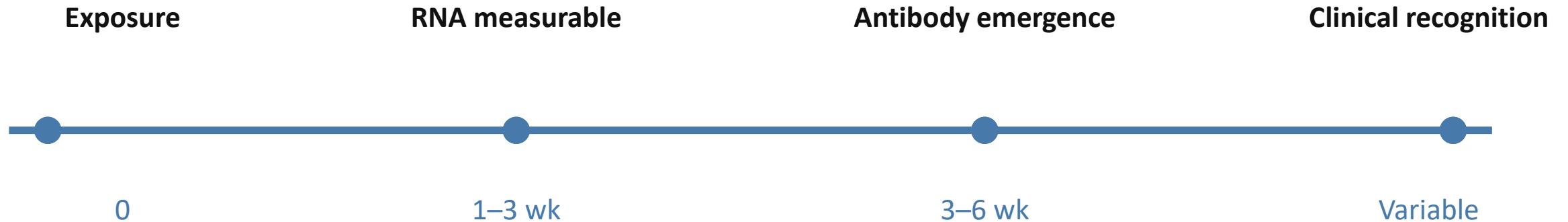


The incubation period is variable

A 4–26 week incubation interval.

The cited mean incubation is approximately 9 weeks.

The absence of symptoms in the incubation phase does not imply absence of infection.



Qualitative event sequence (not a measured biomarker curve)

HCV RNA is an early marker of infection

HCV RNA may be detected 1–3 weeks after infection.

RNA detection identifies ongoing viral replication.

It can become positive before antibodies have developed.



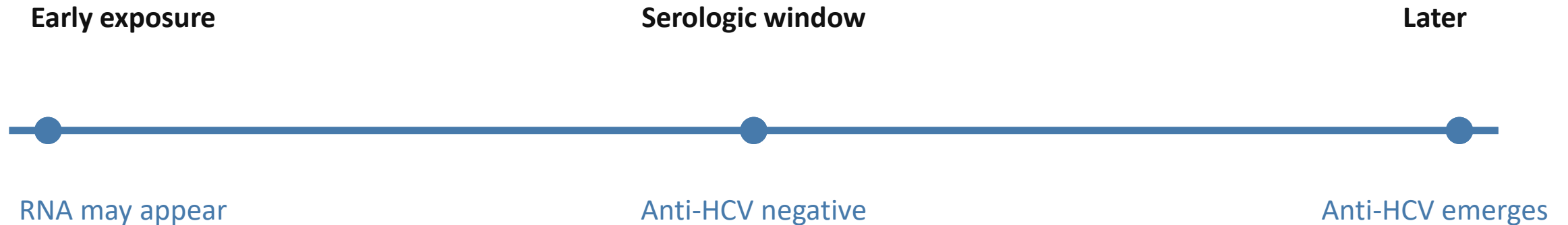
Qualitative event sequence (not a measured biomarker curve)

Anti-HCV antibodies arise after a window period

Emergence 3–6 weeks after infection.

Antibody testing may therefore be negative early after exposure.

A negative antibody result cannot alone exclude very recent HCV.



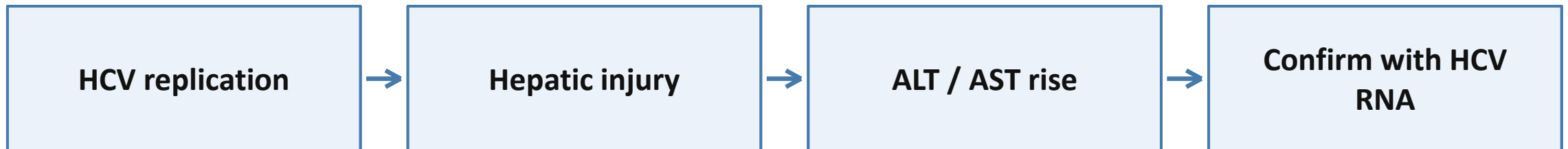
Qualitative event sequence (not a measured biomarker curve)

Aminotransferases may increase with early viremia

A rise in aminotransferases may accompany detectable HCV RNA.

Enzyme elevation reflects hepatocyte injury, not direct viral identity.

The biochemical pattern must be interpreted with virologic testing.



Interpreting the two major HCV laboratory markers

Anti-HCV indicates an immune response to HCV exposure.

HCV RNA indicates detectable circulating viral nucleic acid.

The two tests answer different questions and may disagree.

Marker	Interpretation
Anti-HCV antibody	Immune response to exposure
HCV RNA	Viremia at sampling

RNA positive with negative anti-HCV

Consider very early infection before seroconversion.

The antibody result may also be negative with immunosuppression.

An RNA result directly identifies current viremia.

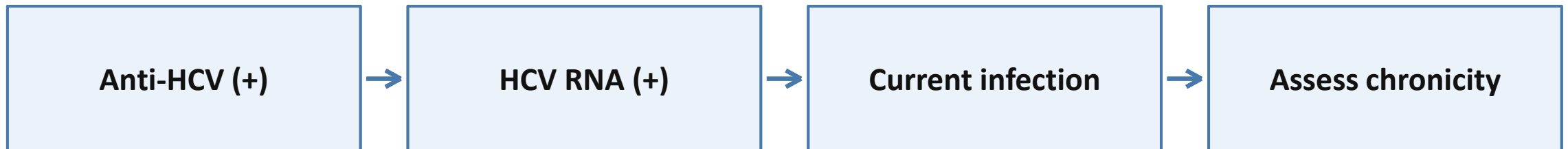
Anti-HCV	HCV RNA	Interpretation
Negative	Positive	Early / impaired antibody response
Negative	Negative	No evidence in sample; Window still possible

Anti-HCV and RNA both positive

Antibodies document exposure and an immune response.

Detected RNA supports ongoing HCV infection.

Chronicity requires appropriate longitudinal context, not one isolated antibody result.



Anti-HCV positive but RNA undetectable

This can occur after spontaneous clearance or successful treatment.

Antibody positivity does not establish current replication.

The antibody may remain detectable, or may wane over time.

Finding	Implication
Anti-HCV positive	Prior immune exposure
HCV RNA undetectable	No circulating RNA detected
Clinical history	Differentiate cure and past spontaneous clearance

Serology alone cannot reliably date infection

The timing of exposure may be unknown.

Anti-HCV can persist after virus elimination.

RNA persistence over time establishes continuing infection.

Acute hepatitis C is usually asymptomatic

Approximately 85% of acute infections are asymptomatic.

Severe acute hepatitis is unusual.

Mild disease at presentation does not predict a harmless long-term course.

Acute clinical course

~85% asymptomatic

Severe acute hepatitis

Rare

Long-term risk

Persistence

Chronic infection is the characteristic outcome

Progression to chronic infection in 80–90% of cases.

Persistent RNA after several months indicates chronic infection.

Chronicity is biologically compatible with few or no symptoms.

Chronic infection

80–90%

Key marker

Persistent HCV RNA

Clinical phenotype

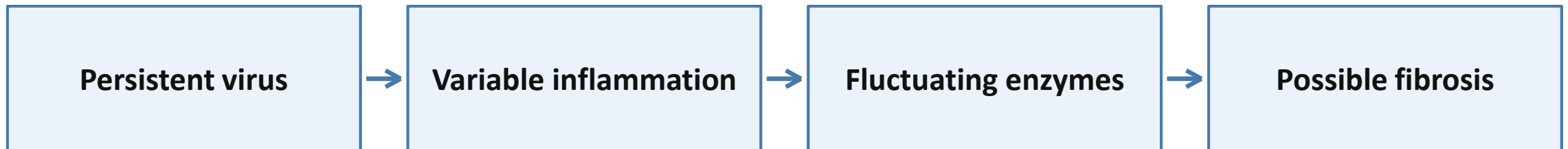
Often silent

Aminotransferases fluctuate during chronic HCV

ALT and AST may rise intermittently rather than remain continuously high.

Periods of normal aminotransferases do not exclude ongoing liver injury.

HCV RNA and the broader liver assessment are therefore important.



Normal enzymes are not proof of a healthy liver

HCV-associated damage can progress despite normal transaminases.

Biochemical activity and cumulative fibrosis are different dimensions.

Assessment of chronic infection should not rely on ALT alone.

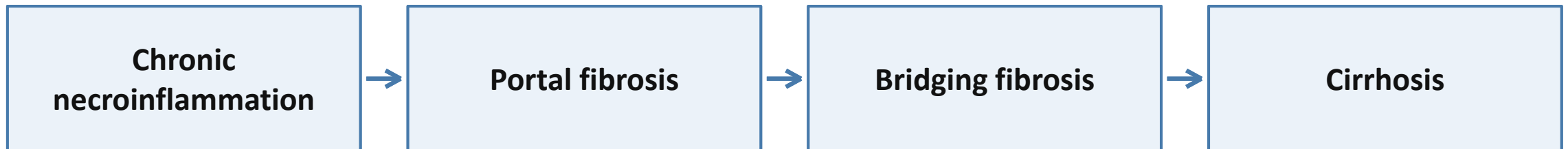
Measurement	What it primarily reflects
ALT / AST	Current hepatocyte injury
HCV RNA	Detectable viremia
Fibrosis assessment	Accumulated architectural damage

Cirrhosis can develop after decades

Cirrhosis in roughly one-fifth of chronic infections over 20–30 years.

Fibrosis accumulates through sustained inflammation and wound healing.

Progression is heterogeneous among patients.

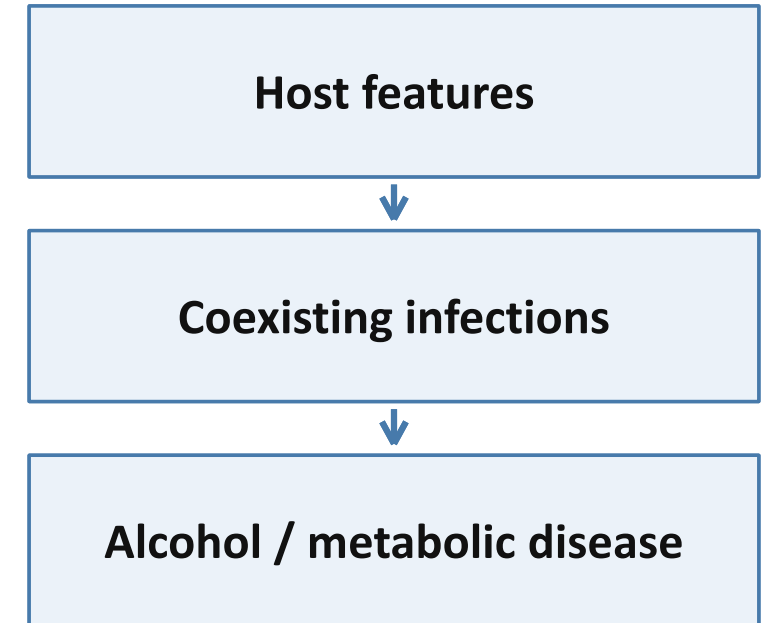


Progression depends on host and exposure factors

The textbook associates older age and male sex with progression.

Alcohol use and immunosuppressive therapy are important modifiers.

HBV/HIV coinfection and insulin resistance-associated disease also matter.

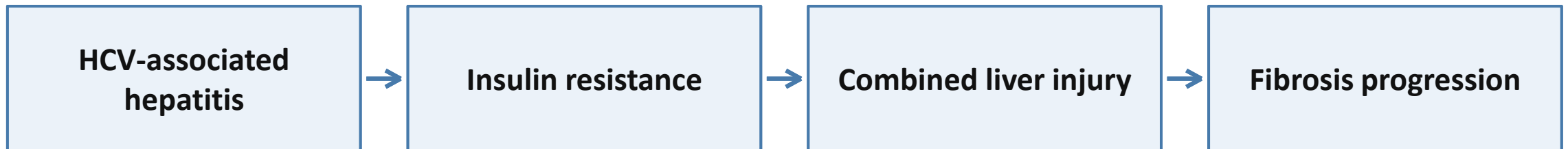


Metabolic disease can compound HCV injury

Obesity, type 2 diabetes and metabolic syndrome are linked to progression.

Steatosis may coexist with viral inflammatory injury.

Risk interpretation should consider viral and metabolic insults together.



Coinfections modify chronic hepatitis

HBV and HIV coinfection are linked to more severe liver disease.

Untreated HIV exacerbates HCV-related liver injury.

Interpret chronic hepatitis within the patient’s complete infectious context.

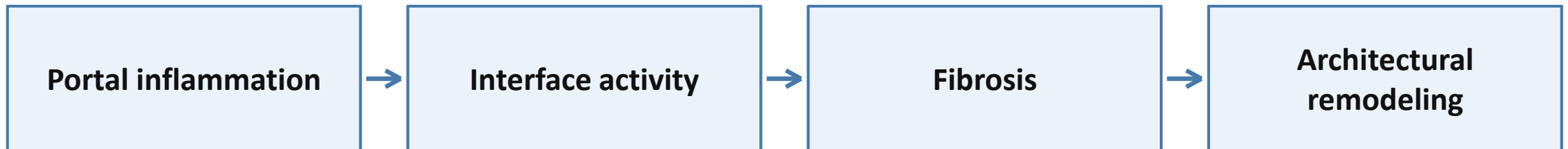
Context	Pathology implication
HCV alone	Chronic inflammatory injury
HBV with HCV	Additional hepatotropic infection
HIV with HCV	Potential acceleration of liver disease

A chronic hepatitis pattern has three components

Portal chronic inflammatory infiltrates are characteristic.

Interface activity reflects injury at the limiting plate.

Fibrosis evolves from portal expansion to bridging and cirrhosis.

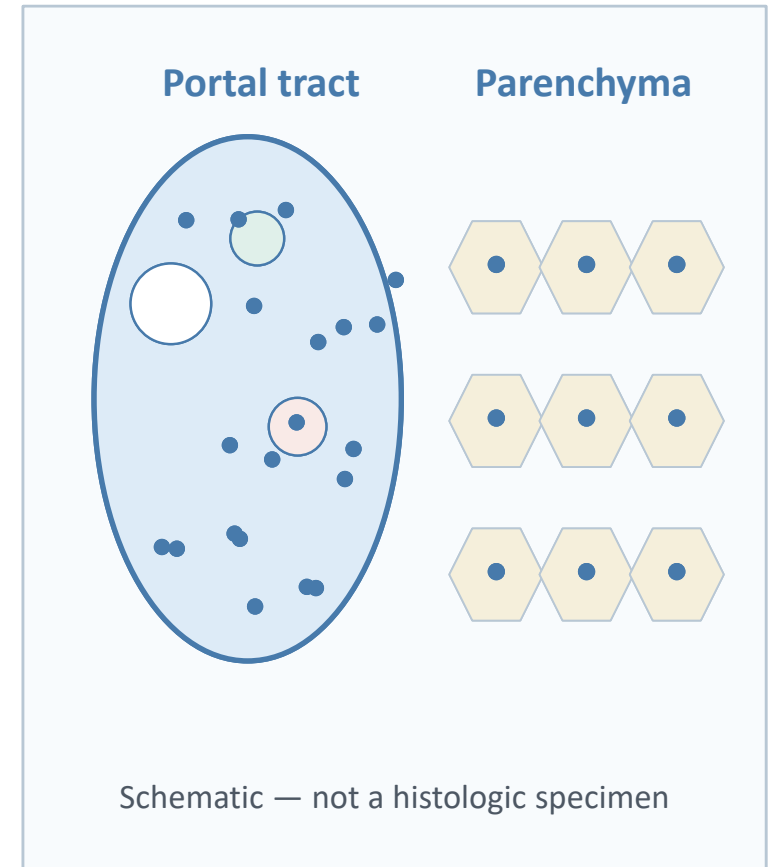


Portal inflammation is a central lesion

Lymphocytes, sometimes with plasma cells, accumulate in portal tracts.

The portal compartment becomes expanded by inflammatory cells.

Portal inflammation is common but is not uniquely diagnostic of HCV.

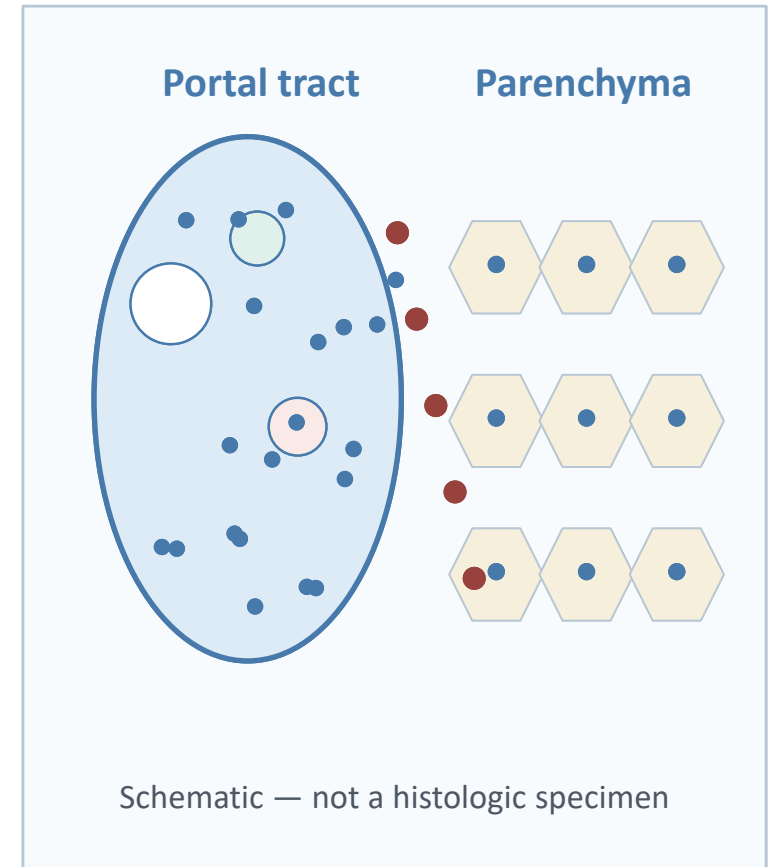


Interface activity injures periportal hepatocytes

Inflammatory cells cross the portal-parenchymal boundary.

Periportal hepatocytes undergo inflammatory injury.

Interface hepatitis reflects active damage, not simply the presence of lymphocytes.

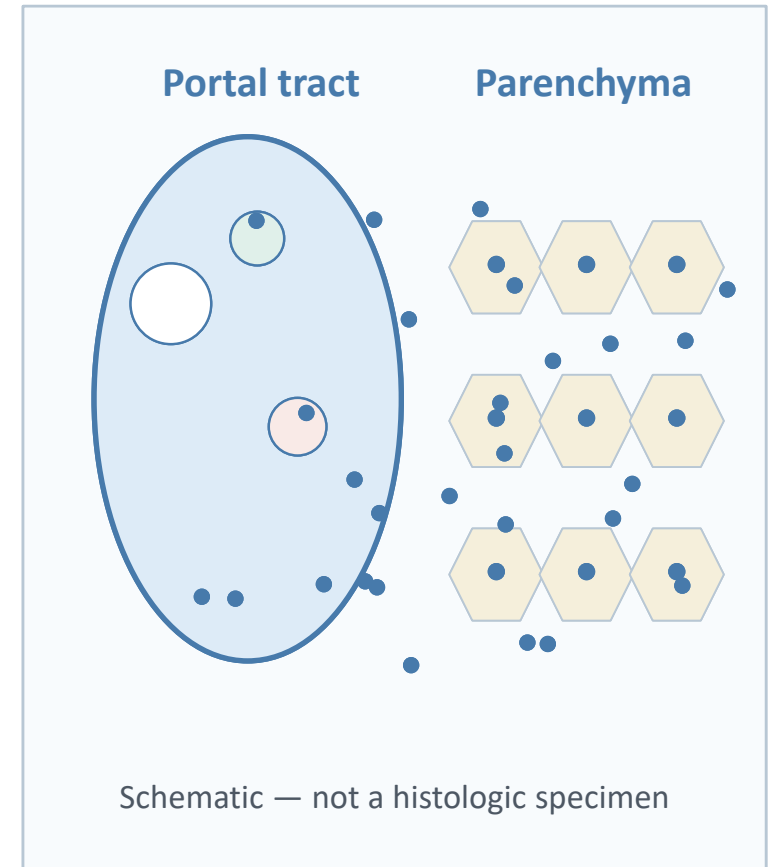


Lobular inflammation accompanies portal injury

Inflammation may involve the lobular parenchyma.

Injured hepatocytes may undergo apoptosis or necrosis.

Macrophages remove cellular debris after hepatocyte death.

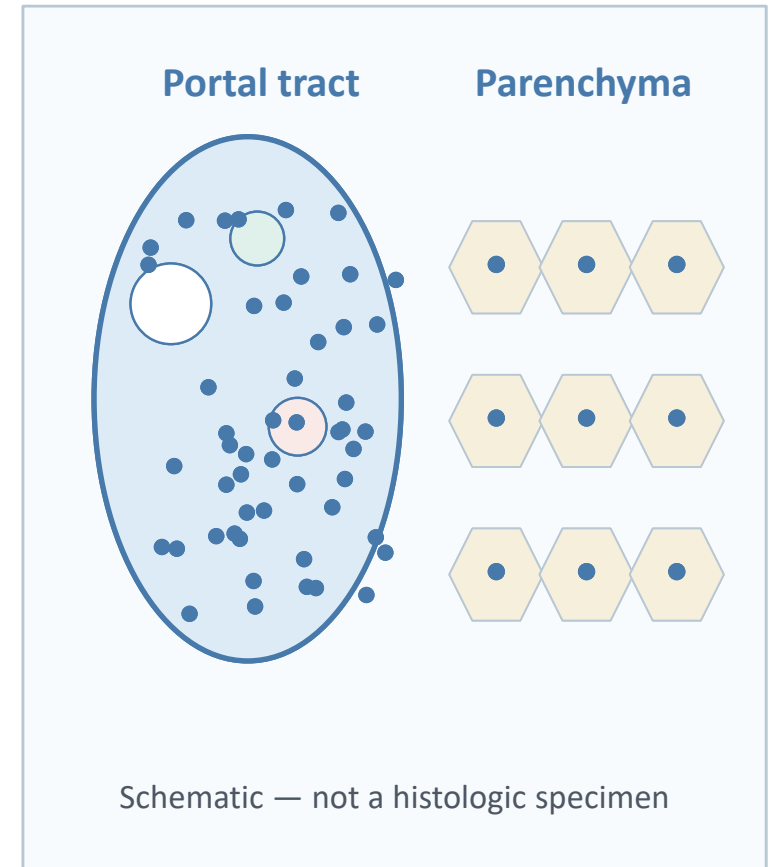


HCV can produce prominent portal lymphoid follicles

Lymphoid aggregates or follicles are characteristic supportive features.

They occur within portal tracts on chronic hepatitis specimens.

These findings favor HCV in context but are not specific enough to establish etiology.

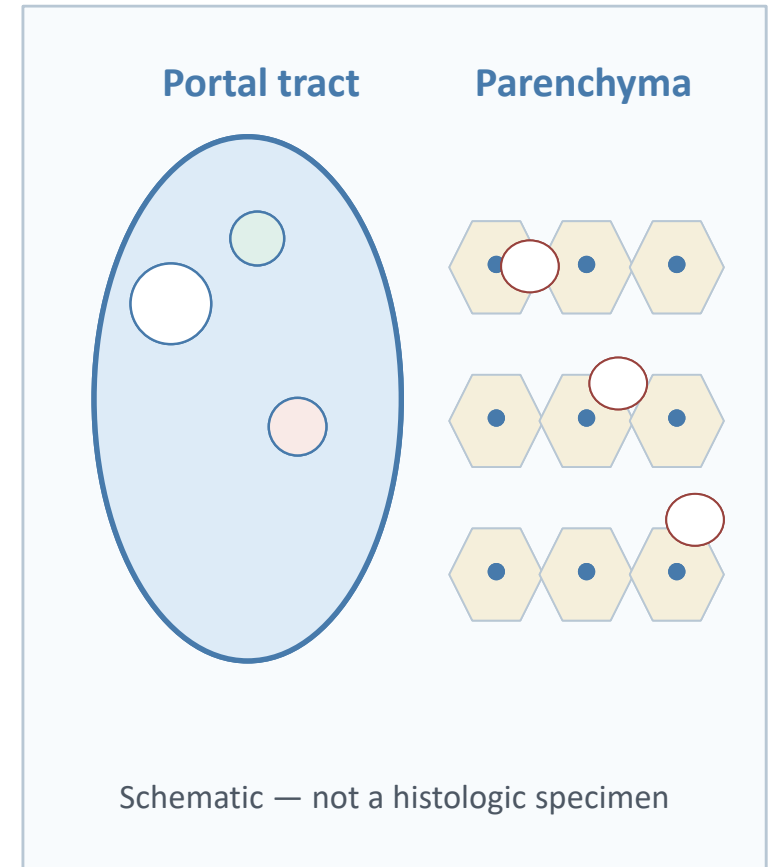


Steatosis is a frequent accompanying feature

Hepatocellular fat accumulation is common with chronic HCV.

Particularly marked steatosis with genotype 3.

Steatosis does not by itself discriminate viral from metabolic liver disease.

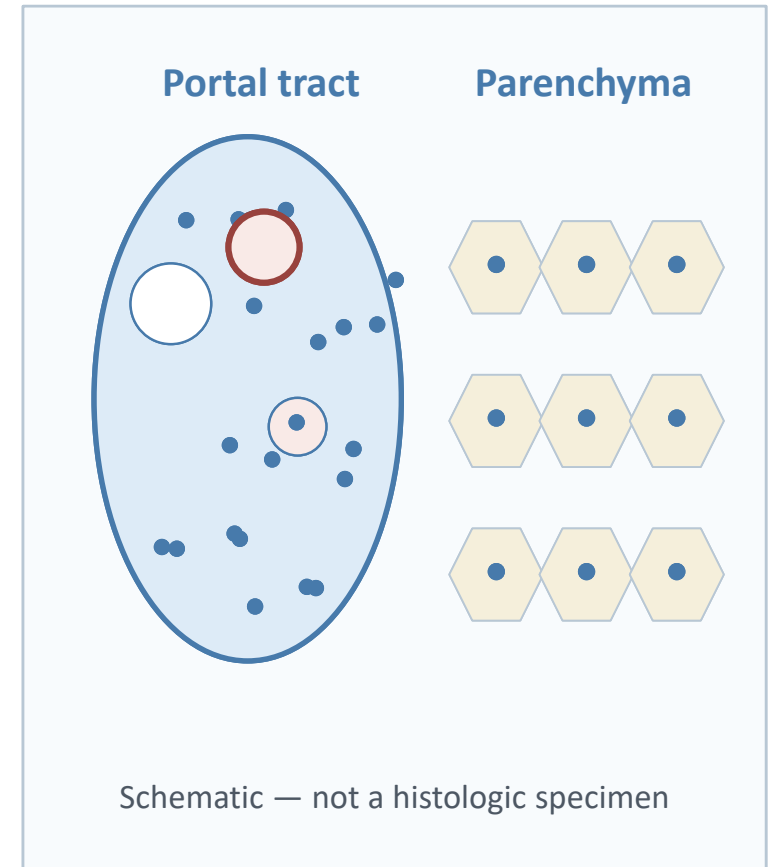


Focal bile duct injury may create a diagnostic pitfall

Chronic HCV may injure small portal bile ducts.

The finding can resemble a biliary disorder.

Its usually focal distribution and the broader inflammatory pattern aid interpretation.



Acute and chronic patterns are histologically different

Acute hepatitis usually has lobular and portal inflammatory injury.

Chronic hepatitis has sustained portal inflammation with fibrosis.

Morphologic overlap with nonviral diseases necessitates clinical correlation.

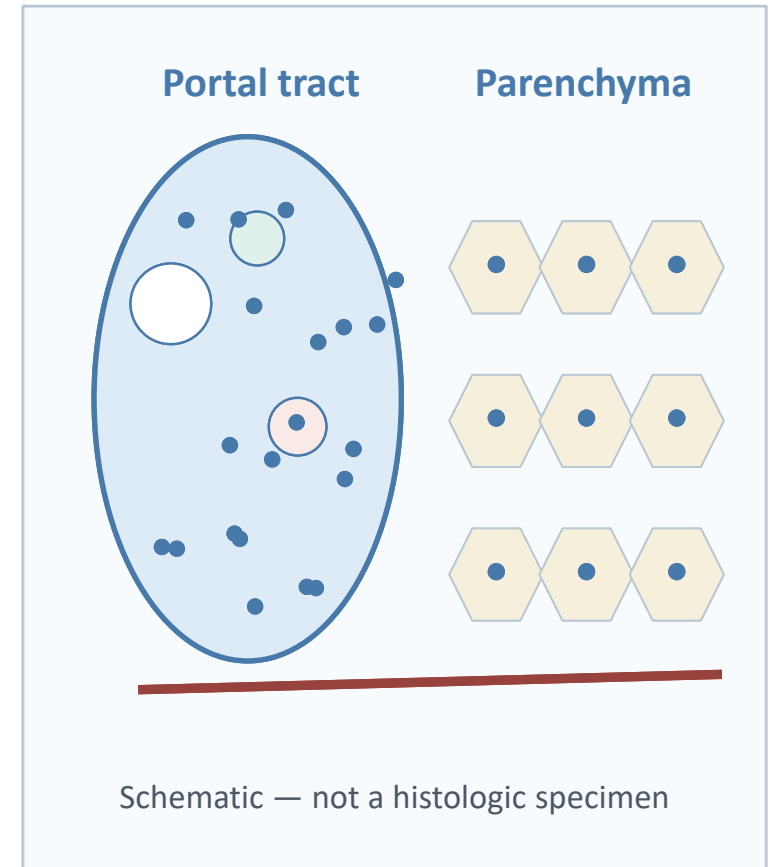
Feature	Acute viral hepatitis	Chronic hepatitis
Inflammation	Portal and lobular	Portal dominant $\pm$ lobular
Hepatocyte injury	Apoptosis / necrosis	Interface activity
Fibrosis	Not defining	Major chronic feature

Fibrosis begins in the portal compartment

Persistent injury stimulates fibrogenesis.

Portal and periportal fibrosis precede large bridging scars.

Fibrosis stage measures accumulated matrix deposition.

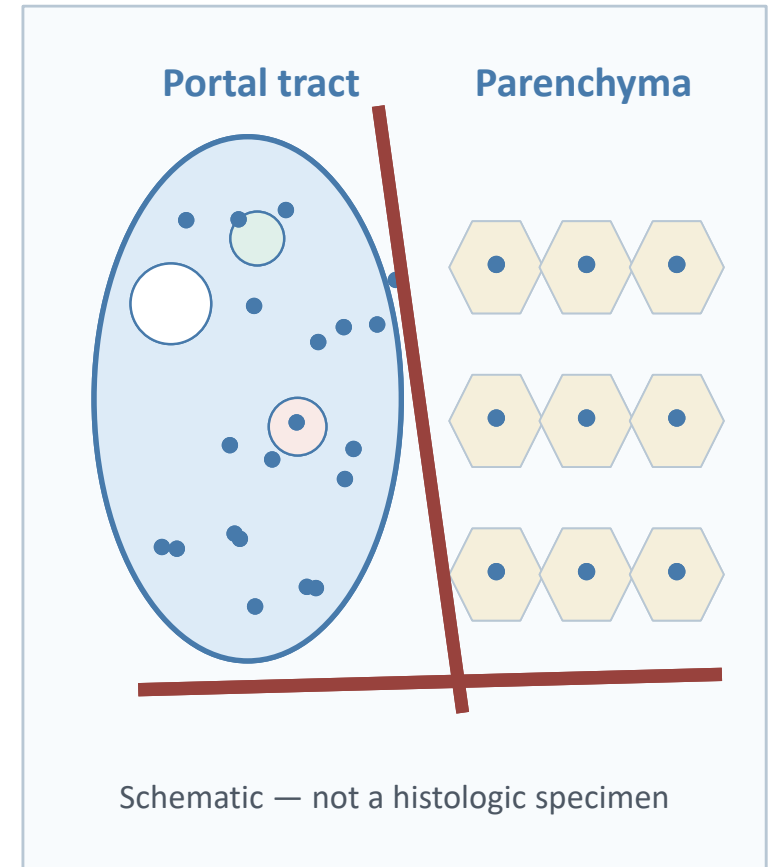


Bridging fibrosis links vascular compartments

Fibrous septa may connect portal tracts.

Bridges distort hepatic architecture as disease advances.

Bridging fibrosis should not be confused with bridging necrosis of severe acute injury.

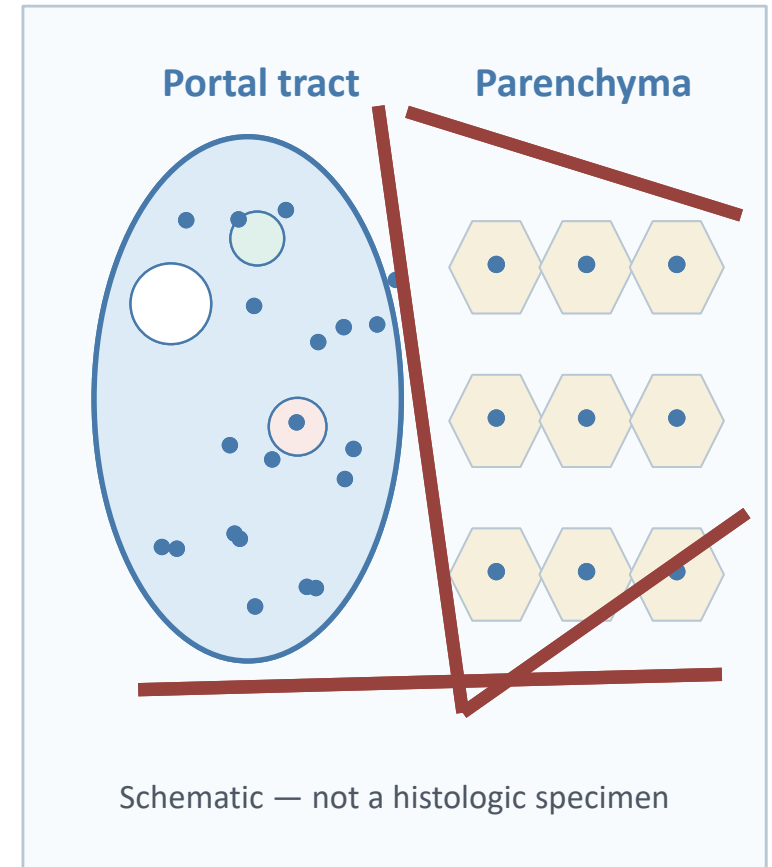


Cirrhosis is the end-stage architectural pattern

Fibrous septa surround regenerative hepatocyte nodules.

Normal lobular architecture is remodeled.

Cirrhosis creates clinical complications and increases the risk of hepatocellular carcinoma.



Histologic grade and stage answer different questions

Grade describes the activity of inflammatory hepatocellular injury.

Stage describes the severity of fibrosis.

A patient can have modest current activity but advanced accumulated scarring.

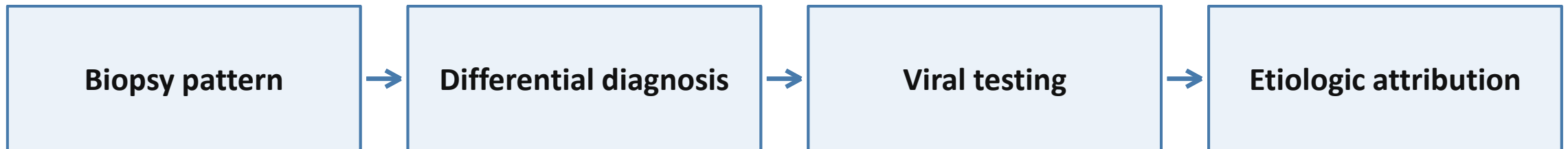
Dimension	Histologic question
Grade	How active is hepatocyte injury?
Stage	How much fibrosis has accumulated?
Viral markers	Is HCV presently detectable?

Biopsy is not an etiologic molecular test

HCV-associated lymphoid follicles, steatosis and duct injury are clues.

Chronic hepatitis has overlapping patterns across multiple causes.

Specific diagnosis requires anti-HCV and HCV RNA testing in context.



Chronic hepatitis may remain clinically subtle

Fatigue is a common symptom when chronic hepatitis is symptomatic.

Malaise, decreased appetite and episodic mild jaundice can occur.

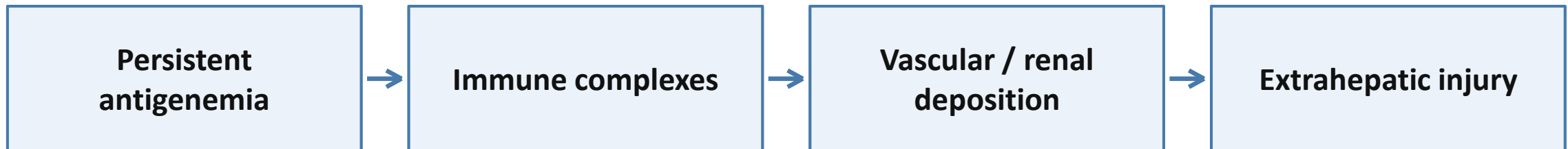
Laboratory evidence may precede any subjective illness.

Immune complexes contribute to extrahepatic disease

Persistent antigen exposure can support circulating immune complexes.

The textbook associates chronic HCV with vasculitis, glomerulonephritis and cryoglobulinemia.

Hepatic and systemic manifestations may coexist.

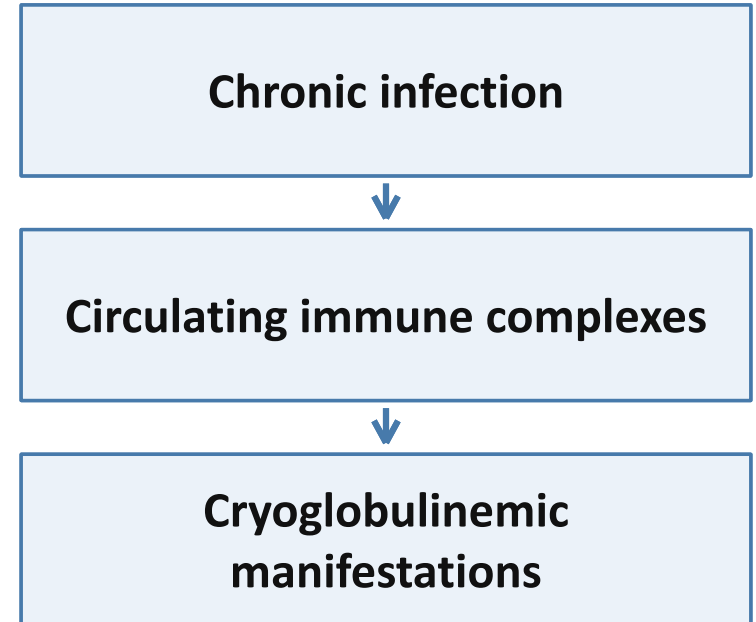


Cryoglobulinemia is a classic HCV association

Immune complex disease may manifest as cryoglobulinemia.

Systemic involvement can occur despite mild hepatic symptoms.

Recognition of extrahepatic manifestations should prompt appropriate virologic evaluation.

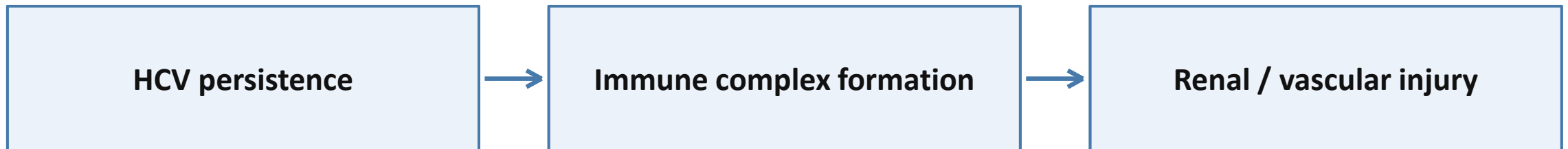


Glomerulonephritis and vasculitis are possible

Immune complexes may involve glomerular and vascular structures.

The mechanism differs from direct hepatocyte injury.

The clinical evaluation must look beyond the liver in selected patients.

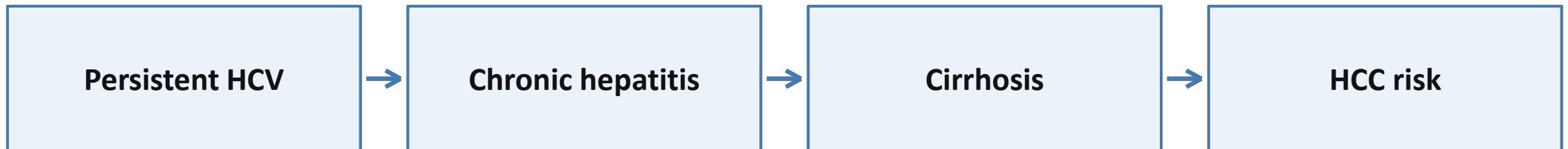


Cirrhosis links chronic HCV to liver cancer

Individuals with HCV-related cirrhosis have increased HCC risk.

The textbook attributes a substantial fraction of U.S. Liver cancers to HCV.

HCC risk is an important long-term consideration even when symptoms are limited.



A “healthy carrier” state is not recognized for HCV

In HBV, selected asymptomatic low-replication states are described.

The textbook does not recognize a comparable healthy-carrier category for HCV.

RNA-positive patients may still develop injury despite normal enzymes.

HBV context	HCV context
Defined low-replication carrier descriptions	No equivalent healthy-carrier state
HBV serologic categories	RNA detection for current HCV

HCV and HBV leave different diagnostic clues

HBV may produce ground-glass hepatocytes with viral antigen.

HCV often has portal lymphoid follicles and steatosis.

Neither morphological comparison replaces serologic or molecular confirmation.

Feature	Chronic HBV	Chronic HCV
Ground-glass hepatocytes	Characteristic HBV pattern	Not a defining feature
Portal lymphoid follicles	May occur	Characteristic association
Steatosis	Variable	Common; Genotype 3 notable

The differential of chronic hepatitis is broad

Autoimmune hepatitis can resemble chronic viral hepatitis.

Drug- or toxin-induced injury may cause overlapping inflammation.

Wilson disease and other liver diseases may show similar hepatitic patterns.

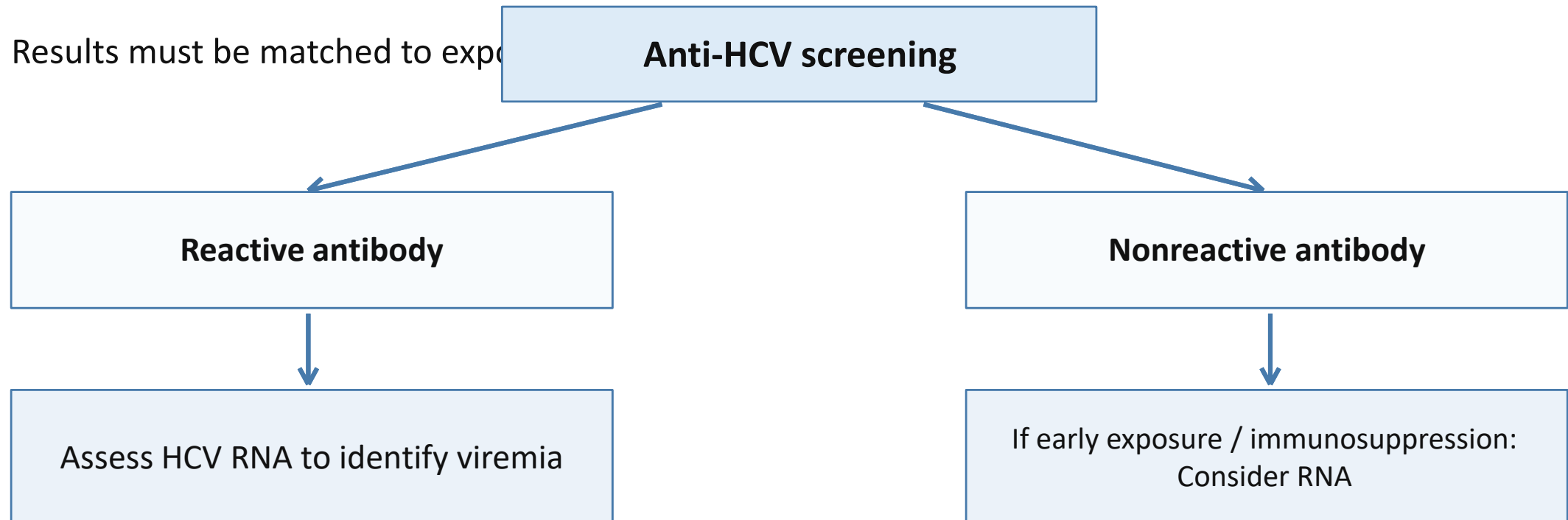
Possible etiology	Why morphology may overlap
HCV	Chronic portal and interface injury
Autoimmune hepatitis	Lymphoplasmacytic inflammation
Drug / toxin	Hepatitic injury patterns
Wilson disease	Chronic hepatitis-like injury

A coherent testing strategy separates exposure and viremia

Anti-HCV is used for screening in the source text.

Detectable HCV RNA establishes current viral nucleic acid in blood.

Results must be matched to exposure



Early infection and immunosuppression are screening pitfalls

Early infection may precede measurable anti-HCV.

Immunosuppression can blunt an antibody response.

When suspicion remains, HCV RNA offers direct virologic assessment.



Direct-acting therapy exploits specific viral functions

Three principal antiviral target classes.

NS3/4A protease and NS5A replication functions are drug targets.

NS5B polymerase inhibitors block viral RNA synthesis.

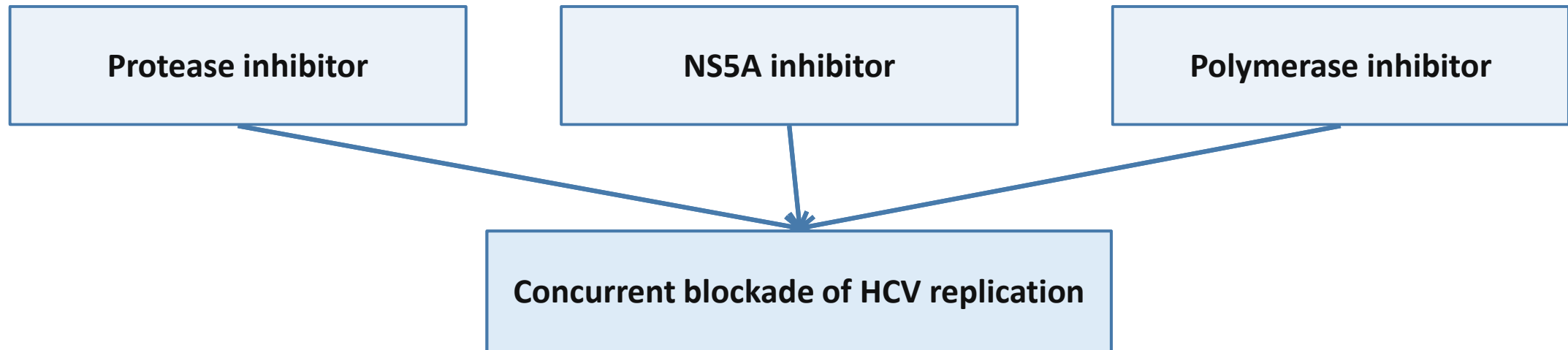
Target	Functional consequence of inhibition
NS3/4A	Impaired protein processing
NS5A	Disrupted replication complex
NS5B	Inhibited viral RNA synthesis

Combination therapy counters antiviral resistance

Distinct drug targets reduce the chance that one escape variant dominates.

Combination regimens rather than monotherapy.

Targeting multiple essential stages supports durable viral suppression.

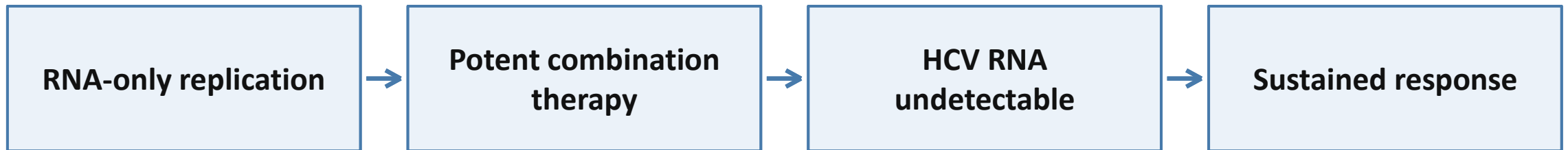


HCV can be cured because it does not integrate

HCV replicates as RNA and does not integrate into the host genome.

Prolonged inhibition can eliminate detectable replicating virus.

This biological property distinguishes HCV treatment from HIV suppression.



Viral response is evaluated using HCV RNA

Successful therapy is assessed through absence of detectable viral RNA.

Anti-HCV antibody may remain positive after virologic cure.

The textbook associates sustained viral response with a very high probability of cure.

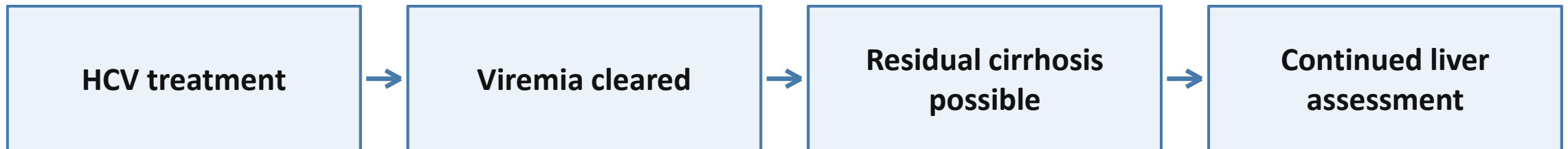
After treatment	What it means
HCV RNA undetectable	Virologic response
Anti-HCV still positive	Prior exposure; Not treatment failure
Advanced fibrosis present	Separate ongoing liver risk assessment

Eliminating HCV does not erase established cirrhosis

Virus eradication interrupts the replicative driver of injury.

Existing advanced fibrosis may remain clinically relevant.

Long-term care still depends on structural liver damage and other risk factors.



Teaching case: Antibodies negative after exposure

Hypothetical: A patient presents after a recent blood exposure.

Anti-HCV is negative, but ALT is elevated.

Question: Which virologic test best assesses early current infection?

Interpretation: HCV RNA testing can detect infection before seroconversion.

Teaching case: Normal ALT but HCV RNA detected

Hypothetical: An asymptomatic person has normal aminotransferases.

Both anti-HCV and HCV RNA are positive.

Question: Does normal ALT establish absence of liver disease?

Interpretation: No. Ongoing viremia and accumulated fibrosis require separate assessment.

Teaching case: Portal lymphoid aggregates

Hypothetical: Chronic hepatitis biopsy shows lymphoid follicles and steatosis.

No viral serology is supplied.

Question: Is the histology alone sufficient to diagnose HCV?

Interpretation: No. These clues are supportive, not pathognomonic; Confirm with virologic testing.

Teaching case: Antibody persists after treatment

Hypothetical: HCV RNA is undetectable after successful therapy.

Anti-HCV remains positive.

Question: Does persistent antibody establish ongoing infection?

Interpretation: No. Detectable RNA, not persistent antibody, indicates current viremia.

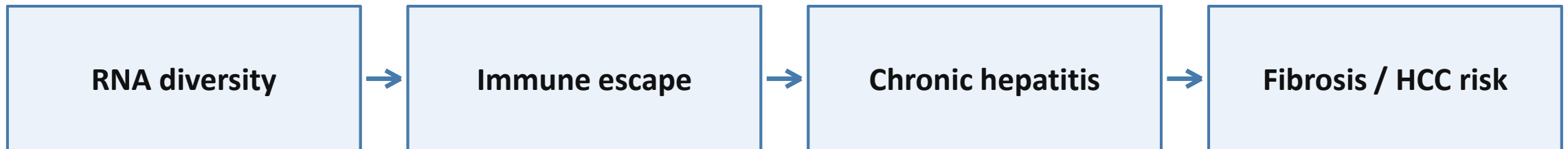
One integrated model of HCV pathobiology

An error-prone RNA virus evades immune elimination.

Persistent replication promotes chronic necroinflammatory injury.

Portal fibrosis may progress to cirrhosis and HCC.

Direct-acting therapy interrupts essential replication functions.



Five distinctions to retain

Antibody exposure $\neq$ RNA-confirmed current infection.

Normal ALT $\neq$ absence of fibrosis.

Portal lymphoid follicles suggest HCV but are not diagnostic.

Histologic grade $\neq$ fibrosis stage.

HCV cure $\neq$ immediate elimination of established cirrhosis.

Primary sources and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).

Chapter 18, “Hepatitis C Virus,” pp. 758–760.

Supporting parent section: “Viral Hepatitis,” pp. 755–756.

Morphology and associated syndromes: pp. 760–762.