

Hepatitis E Virus

Transmission · Pathogenesis · Clinical pathology

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Learning goals

- Describe the routes and epidemiology of hepatitis E virus (HEV).
- Relate viral properties and host immunity to liver injury.
- Interpret the temporal sequence of HEV RNA, IgM, and IgG.
- Recognize severe pregnancy-associated disease and persistence during immunosuppression.

Where hepatitis E fits among hepatotropic viruses

Hepatotropic hepatitis viruses

- Hepatitis A, B, C, D, and E cause viral hepatitis.
- Different viruses produce overlapping hepatitis patterns.

Hepatitis E emphasis

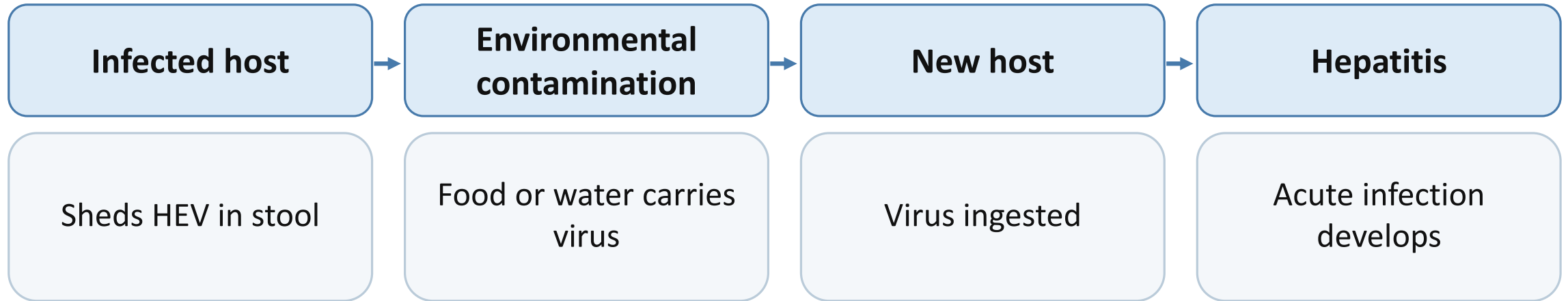
- Commonly an acute enterically transmitted infection.
- Chronicity depends strongly on immune status.

Hepatitis E: The core disease concept

Enteric infection with a strong acute-hepatitis phenotype

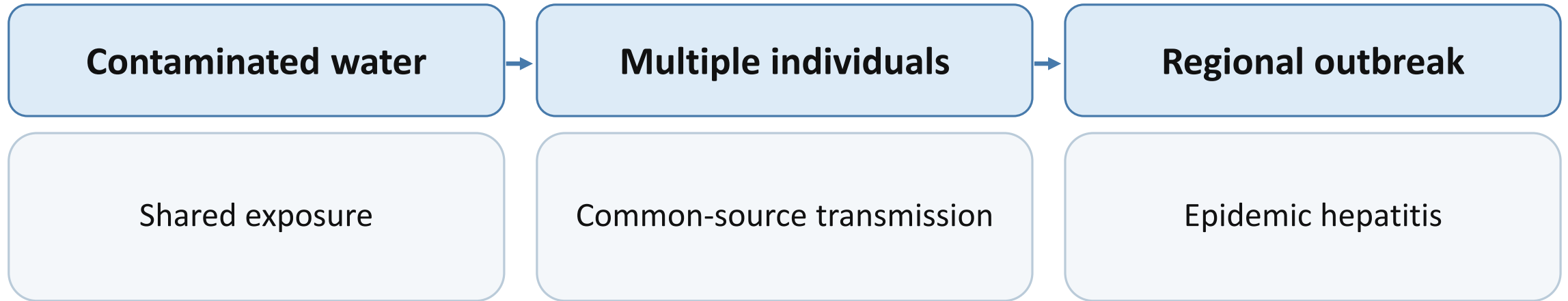
- Frequently water-borne and transmitted by the fecal–oral route.
- Most infections resolve; Clinical risk differs in pregnancy and immunosuppression.
- Clinical chemistry and serology reflect the host response to infection.

Fecal–oral transmission is the principal route



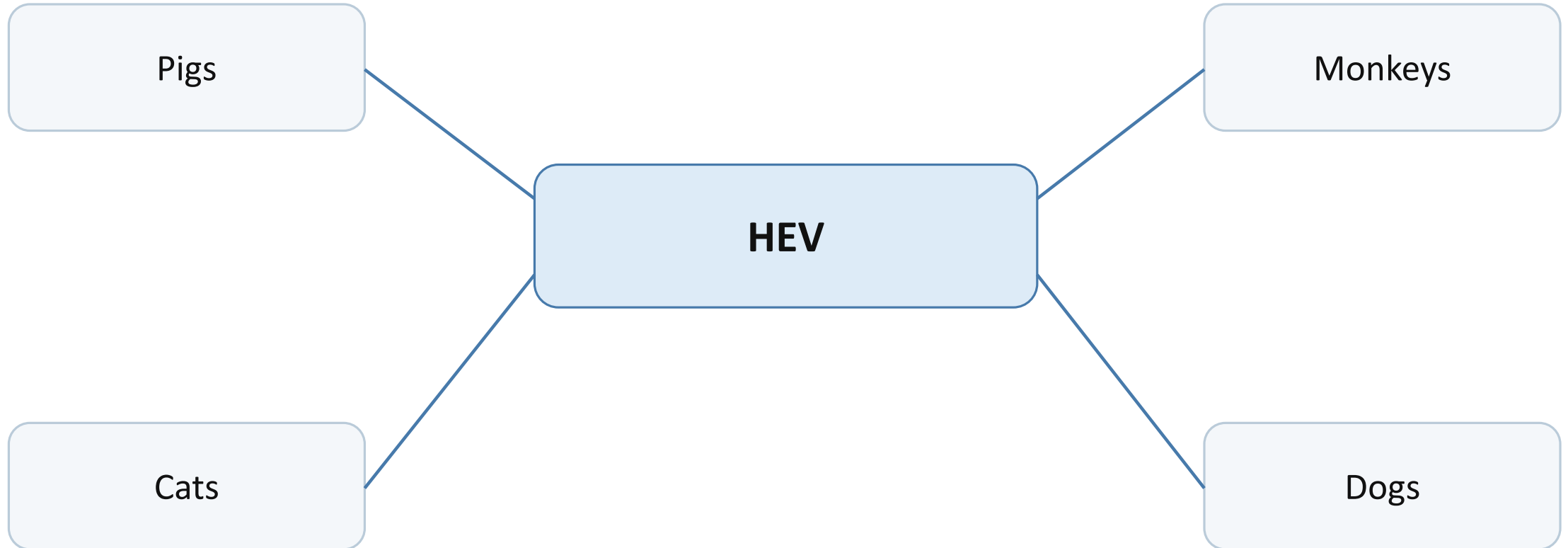
The portal of exposure is enteric, although organ-related exposures also occur.

Water-borne transmission explains epidemics



Water quality and sanitation are critical to this epidemiologic pattern.

HEV is also a zoonosis



Animal reservoirs described in the Robbins text; Reservoir status does not imply equal public-health importance.

Zoonotic exposures broaden the epidemiology

Exposure setting

- Contact with pigs or pig farming.
- Consumption of organ meat.

Epidemiologic implication

- Infection occurs outside classic water-borne epidemic settings.
- HEV may be encountered in high-income countries.

Why pig farming matters clinically

Occupational context may provide the exposure clue

- The textbook associates cases in high-income countries with pig farming.
- Relevant exposure history can direct consideration of HEV.
- Absence of travel does not exclude hepatitis E.

Food-associated exposure in high-income settings

Consumption of organ meat is a documented association

- Dietary exposure complements the water-borne epidemiologic pattern.
- Food exposure is relevant to a targeted clinical history.
- The supplied text does not quantify the risk of any individual food item.

Geographic distribution of epidemics

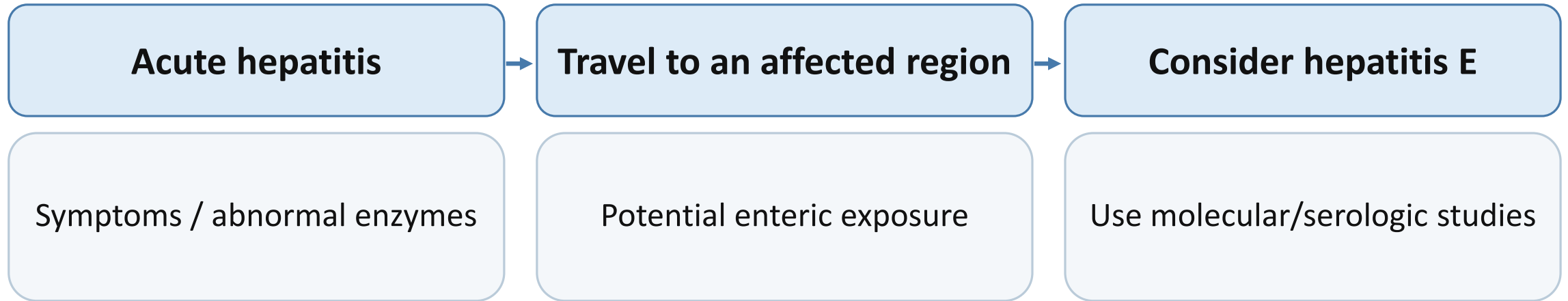
Reported epidemic settings	Teaching implication
Asia / Indian subcontinent	Endemic or outbreak-associated exposure
Sub-Saharan Africa	Epidemic hepatitis may be HEV-related
Middle East and China	Include HEV in acute hepatitis evaluation
Mexico	Reported epidemic location

Sporadic hepatitis E: The India example

More than 30% of sporadic acute hepatitis cases in India

- This is the figure reported 11th edition.
- In the stated setting, HEV exceeds hepatitis A in frequency.
- Do not generalize this proportion to every population or year.

Travel history can redirect the differential



Travel is one clue, not a requirement for HEV infection.

Two epidemiologic patterns of HEV

Water-borne epidemics

- Fecal–oral transmission.
- Clusters in endemic regions.
- Potential for common-source exposure.

Zoonotic/sporadic infection

- Associated with animals or organ-meat exposure.
- Reported in high-income nations.
- May occur without travel.

Epidemiologic assessment: Focused questions

- Was the patient exposed to potentially contaminated water?
- Was there travel or residence in an epidemic region?
- Is there occupational contact with pigs?
- Was organ meat consumed?
- Is the patient pregnant or immunosuppressed?

HEV virology: Source-described classification

Family

- Hepeviridae

Genus terminology used by Robbins

- Orthohepevirus
- Taxonomic nomenclature reproduced from the supplied edition.

HEV is described as a nonenveloped RNA virus

Positive-stranded RNA virus without a conventional envelope

- The HEV particle as unenveloped.
- This is a textbook virion-level description.
- The source does not elaborate on alternative particle forms.

Positive-strand RNA is the HEV genetic material

Positive-stranded RNA

Viral coding capacity

- Multiple open reading frames

Replication-associated proteins

- Viral protease and RNA polymerase

Original conceptual schematic; Not a scaled physical genome map.

Genome size reported

Approximately 7.3 kilobases (kb) of RNA

- The viral genetic material is a single positive-sense RNA genome.
- Genome length and coding organization are viral properties, not diagnostic thresholds.
- Do not infer sequence-level detail from this schematic.

The HEV genome contains four open reading frames

ORF 1

ORF 2

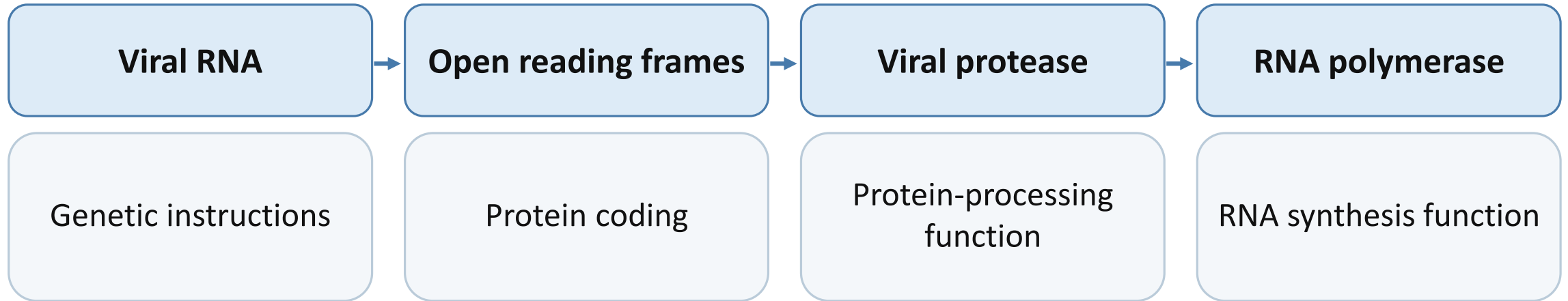
ORF 3

ORF 4

Four coding regions → multiple viral proteins

Four open reading frames are reported; Lengths and order are not depicted to scale.

Encoded proteins support replication



These are examples of proteins named in the primary text, not a complete proteome.

The virus itself is not directly cytopathic

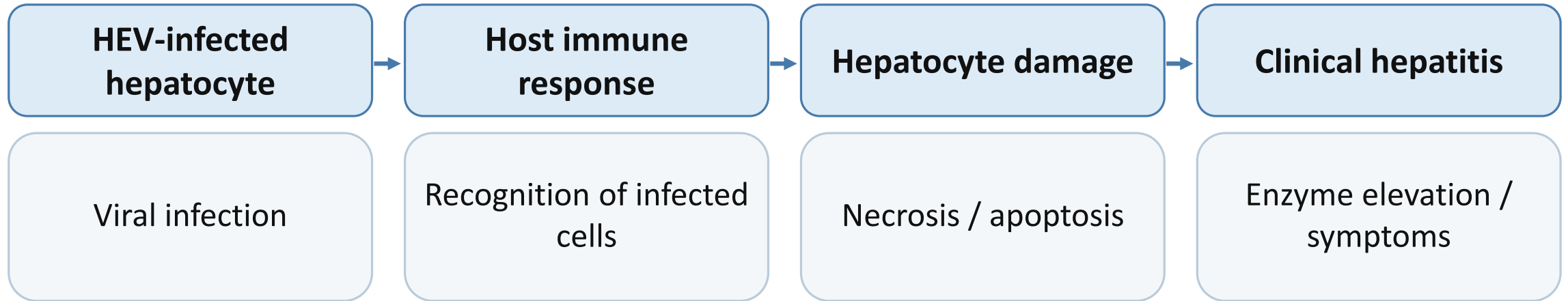
HEV infection

- Hepatocytes contain viral infection.
- HEV as noncytopathic.

Hepatic injury

- Primarily associated with the host response to infected cells.
- Pathology can therefore reflect immune-mediated injury.

The host response links infection to hepatitis



General morphological endpoints are drawn from the adjacent viral-hepatitis section.

Virologic infection and tissue injury differ

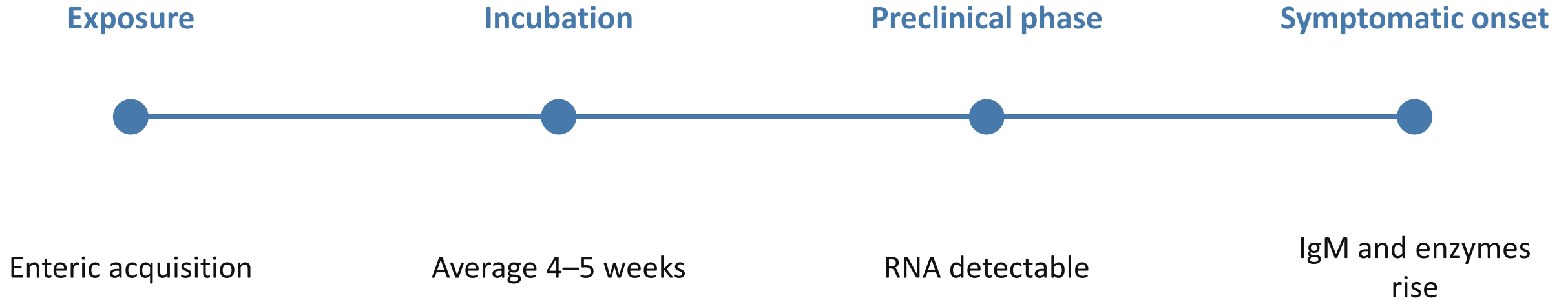
Virologic evidence

- HEV RNA in serum or stool.
- Virion shedding in stool.

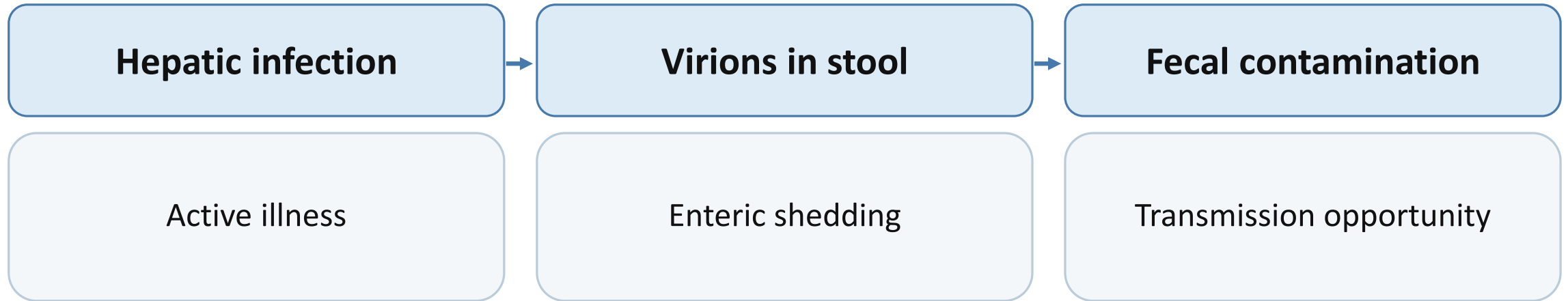
Tissue response

- Host-driven hepatocyte injury.
- Serum aminotransferase elevation.

Acute infection begins before symptoms



Virions are shed in stool during acute illness



Stool contains both diagnostically relevant viral material and a transmission hazard.

The incubation period averages 4–5 weeks

Exposure precedes the typical clinical presentation by several weeks

- The textbook gives an average incubation interval, not a fixed patient-level value.
- Incubation should be considered when taking a travel or exposure history.
- Clinical illness does not begin at the moment of infection.

HEV RNA can be detected before clinical illness

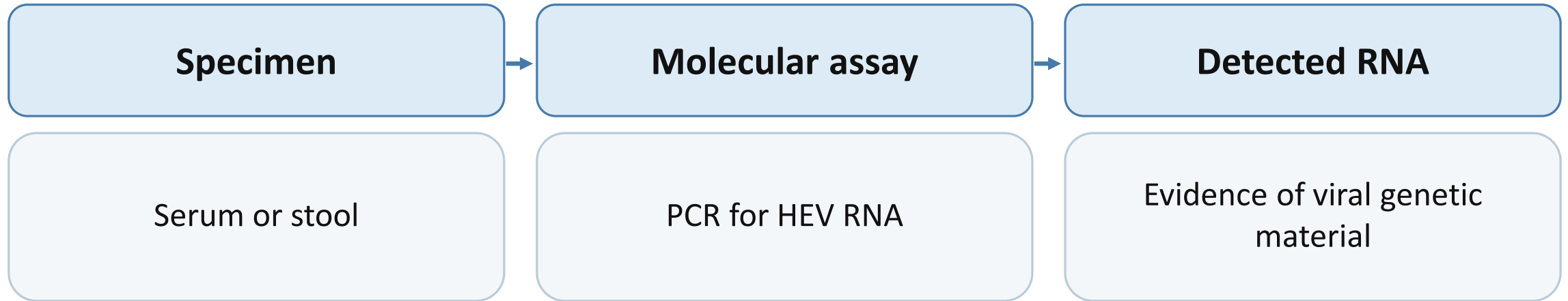
Serum

- PCR may detect HEV RNA before symptoms.

Stool

- PCR may detect HEV RNA before symptoms.
- Virions may also be detected.

PCR provides direct virologic evidence



Interpret timing, clinical context, and assay availability together.

Clinical onset aligns with three changes

Symptoms begin

Aminotransferases rise

IgM anti-HEV appears

These changes are described as virtually simultaneous at clinical onset.

These events as virtually simultaneous.

Aminotransferases reflect hepatocellular injury

Biochemistry

- Serum aminotransferase elevation accompanies illness onset.

Mechanistic explanation

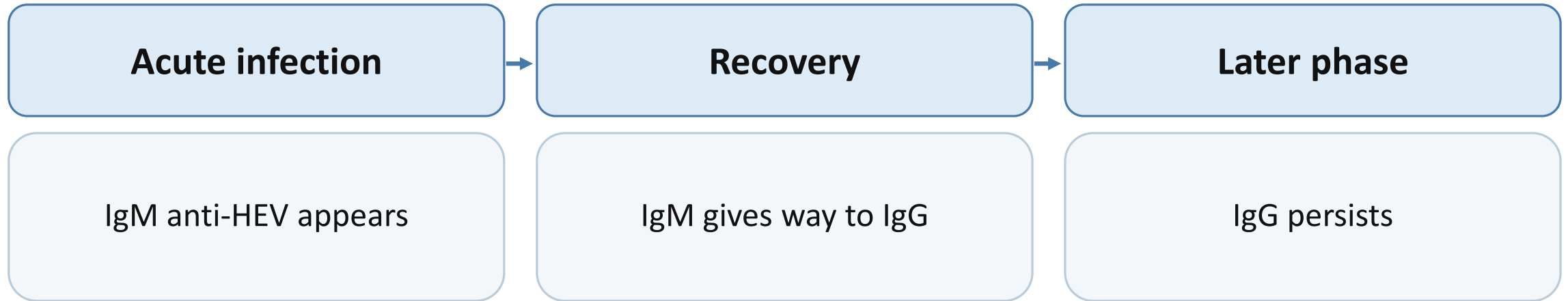
- Host-mediated hepatocyte injury drives a biochemical hepatitis phenotype.

IgM anti-HEV is an acute-phase serologic marker

IgM anti-HEV appears with clinical onset

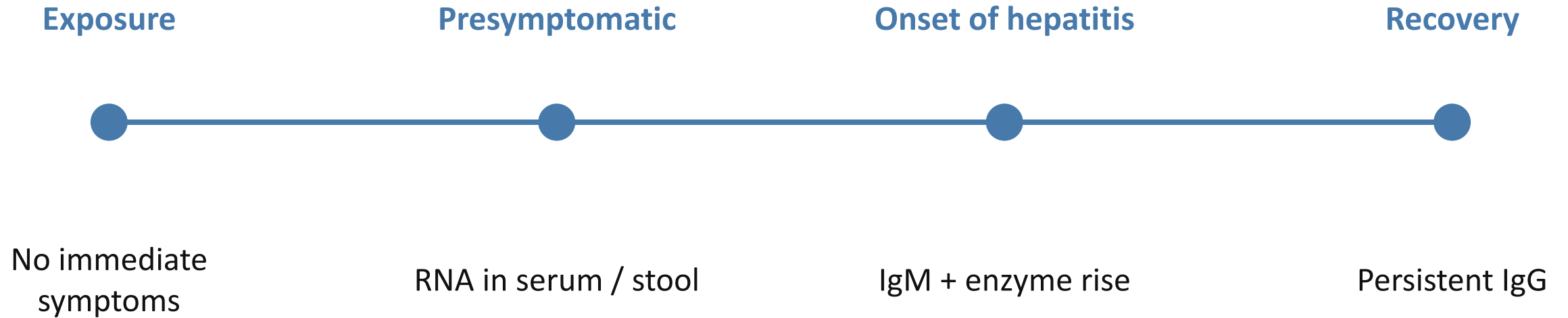
- The temporal association is central to acute infection recognition.
- Serologic data are interpreted with exposure, chemistry, and PCR.
- An antibody result alone does not describe liver-injury severity.

IgG anti-HEV persists after recovery



Persistent IgG differs conceptually from persistent viremia.

Integrated timeline of HEV markers



Usual acute hepatitis resolves in 2–4 weeks

Self-limited disease is the usual clinical course

- The onset follows the average 4–5-week incubation period.
- Most patients then recover over approximately 2–4 weeks.
- This describes typical, not universal, outcomes.

Immune status determines whether HEV persists

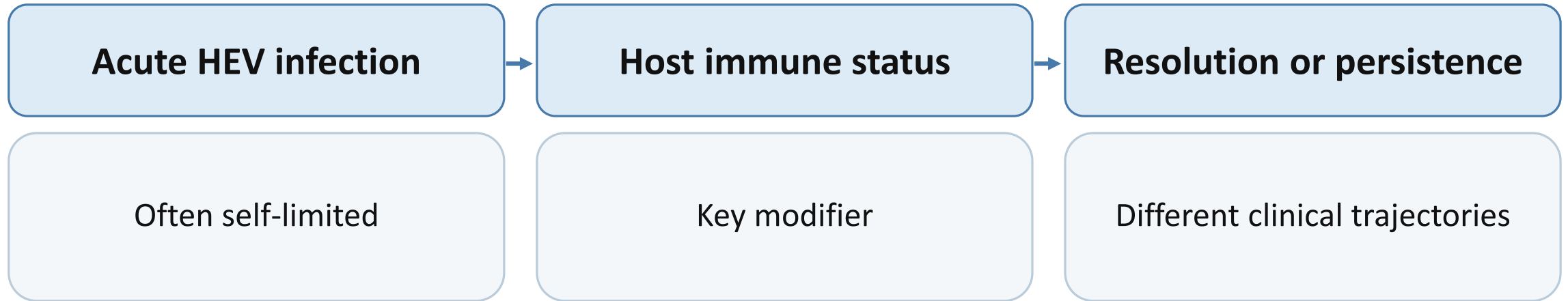
Immunocompetent host

- Persistent viremia is not observed in the Robbins description.
- Chronic liver disease from HEV is not observed.

Immunosuppressed host

- Chronic HEV infection can occur.
- Examples include AIDS and transplant recipients.

Acute disease and chronic infection are distinct



The source does not describe a persistent immunocompetent carrier state.

Pregnancy is a major severity modifier

Acute HEV can be particularly severe during pregnancy

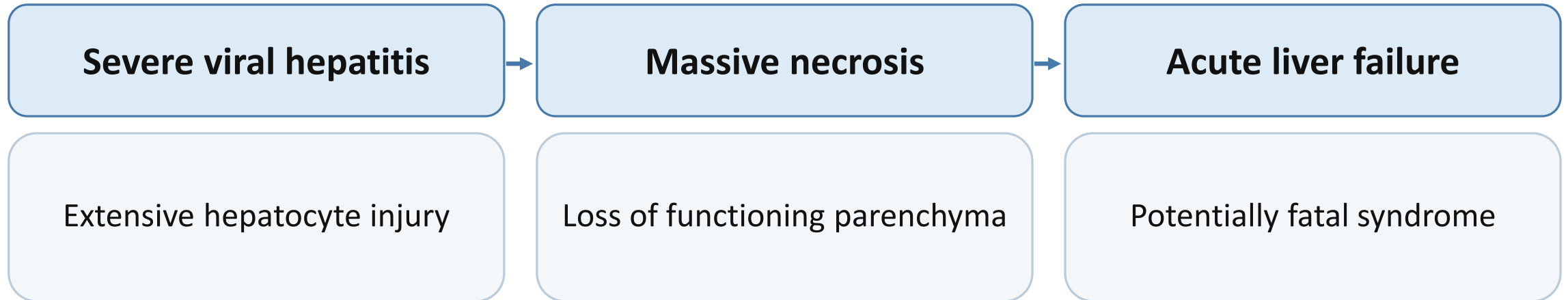
- High pregnancy-associated mortality.
- The adjacent syndrome section identifies HEV as a cause of liver failure in pregnancy.
- A pregnant patient with acute hepatitis requires careful etiologic assessment.

Pregnancy-associated mortality: Source figure

Mortality may approach 20% in pregnant females

- This is the value stated section.
- It should not be treated as a universal contemporary case-fatality rate.
- It identifies pregnancy as a high-risk clinical setting.

HEV can contribute to acute liver failure



The adjacent Robbins section specifically highlights HEV-associated liver failure in pregnancy.

The pathology of severe acute hepatitis

Milder hepatocellular injury

- Inflammatory infiltrates.
- Hepatocyte apoptosis or focal necrosis.

Severe injury

- Confluent and bridging necrosis.
- Massive necrosis can produce liver failure.

Immunosuppression permits chronic HEV

Chronic HEV infection can occur when host defense is impaired

- The source highlights recipients of transplanted organs.
- It also includes patients with AIDS.
- Persistence changes the expected acute, self-limited course.

Immunocompromised hosts: Two examples



Illustrative categories named; The source does not quantify subgroup risks.

Persistent viremia is different from IgG persistence

Persistent viral RNA

- Suggests ongoing viral genetic material detection.
- Relevant when HEV is suspected to be chronic.

Persistent IgG antibody

- Expected after recovery.
- Does not, by itself, show ongoing viral replication.

Chronic hepatitis: Context

Continuing or relapsing disease beyond 6 months and/or fibrosis

- This is the general clinicopathologic definition of chronic hepatitis.
- It is not provided as an HEV-specific PCR cutoff in this text.
- Chronic HEV is described particularly in immunosuppressed patients.

Viral-hepatitis morphology is not HEV-specific

Morphologic patterns overlap among hepatotropic viruses

- Acute hepatitis shows lobular injury and inflammation.
- Autoimmune hepatitis and drug reactions can show similar changes.
- Virologic testing is required for attribution to HEV.

Acute hepatitis: Gross appearance varies

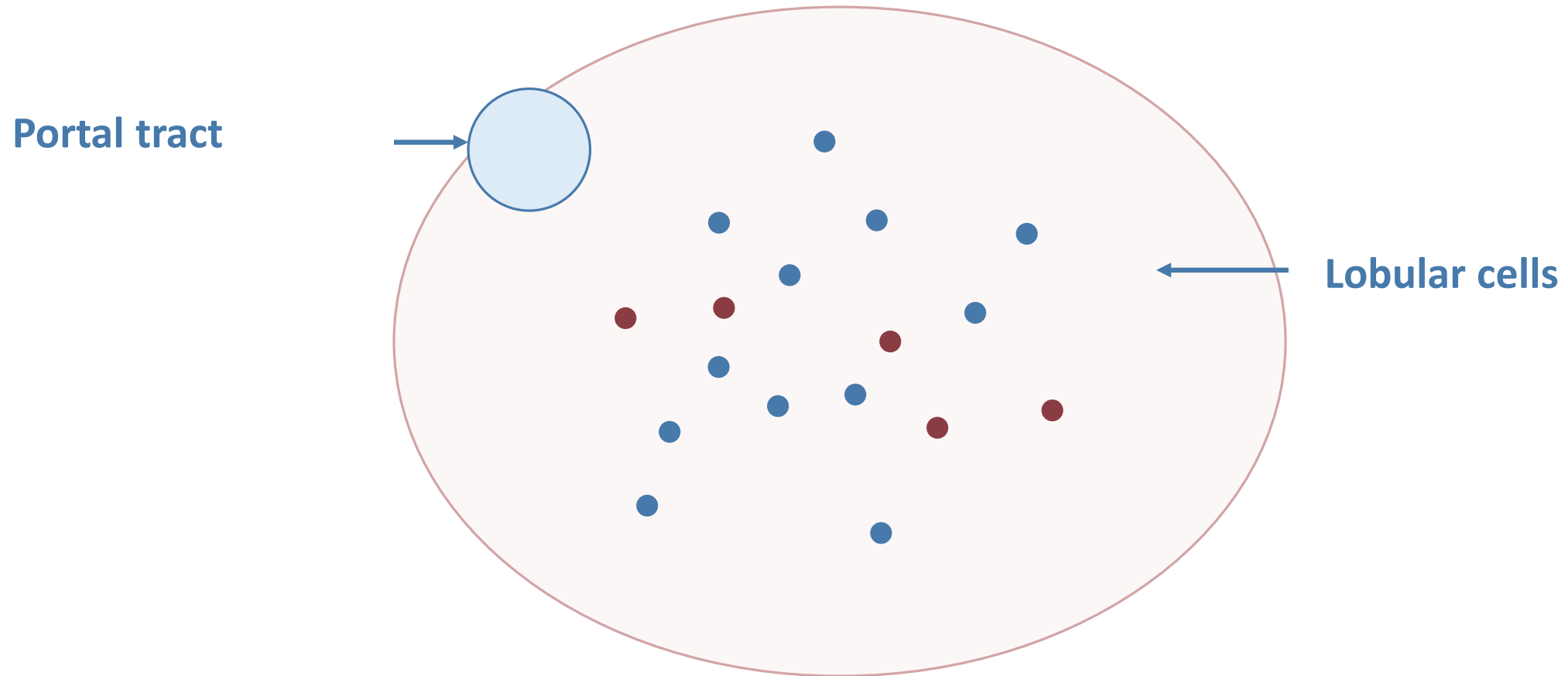
Less severe disease

- Liver may be normal-sized or enlarged.
- Inflammation can contribute to enlargement.

Acute liver failure

- Liver can be shrunken.
- Extensive parenchymal loss underlies the change.

Acute hepatitis: Inflammation is portal and lobular



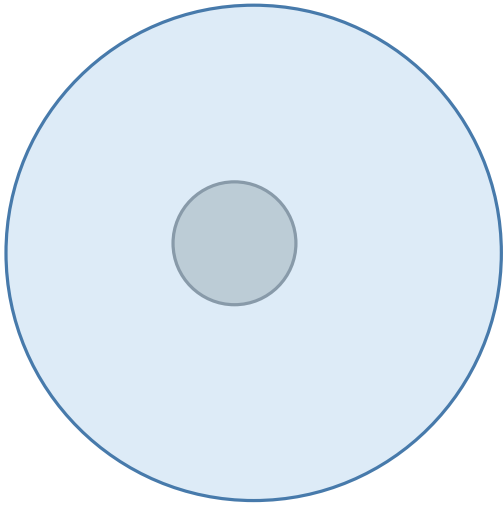
Simplified architectural schematic of generic acute viral hepatitis—not histopathologic evidence.

Lymphocytes predominate in viral hepatitis

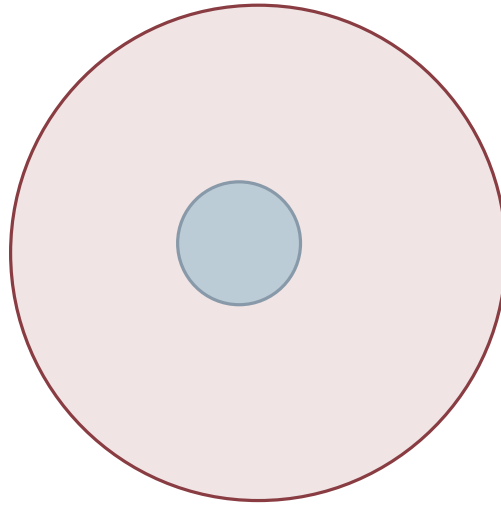
Portal and lobular infiltrates are mainly lymphocytic

- Plasma cells and eosinophils may be variably admixed.
- Inflammation accompanies hepatocyte injury.
- Cellular composition alone does not identify the hepatitis virus.

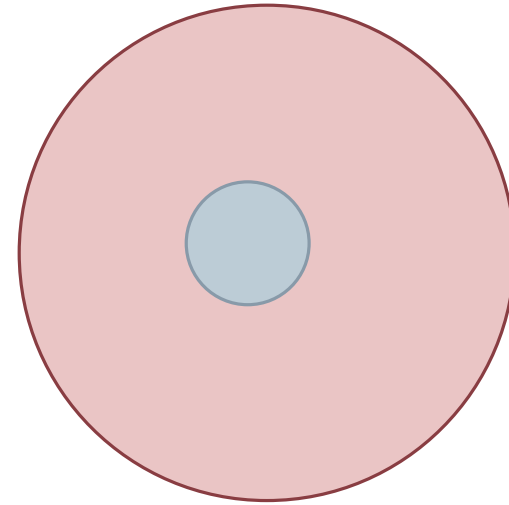
Hepatocyte injury: Necrosis and apoptosis



Injured hepatocyte



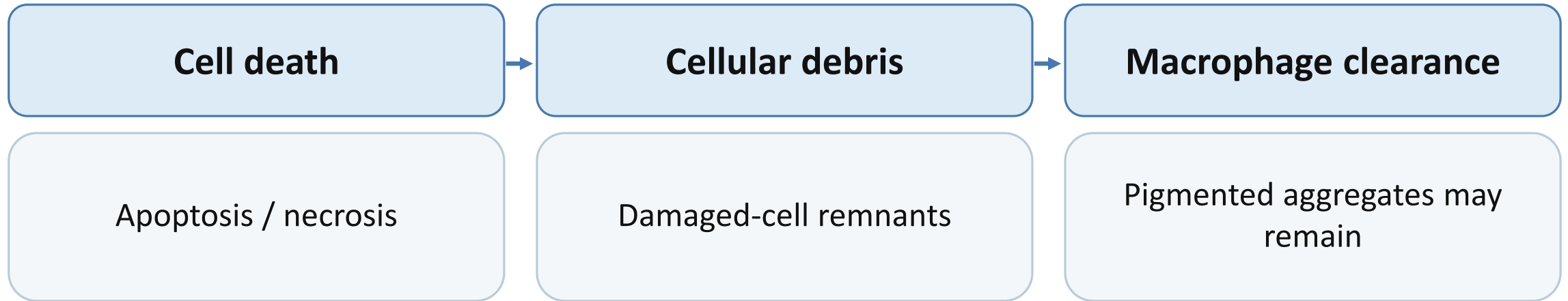
Apoptotic cell



Necrotic cell

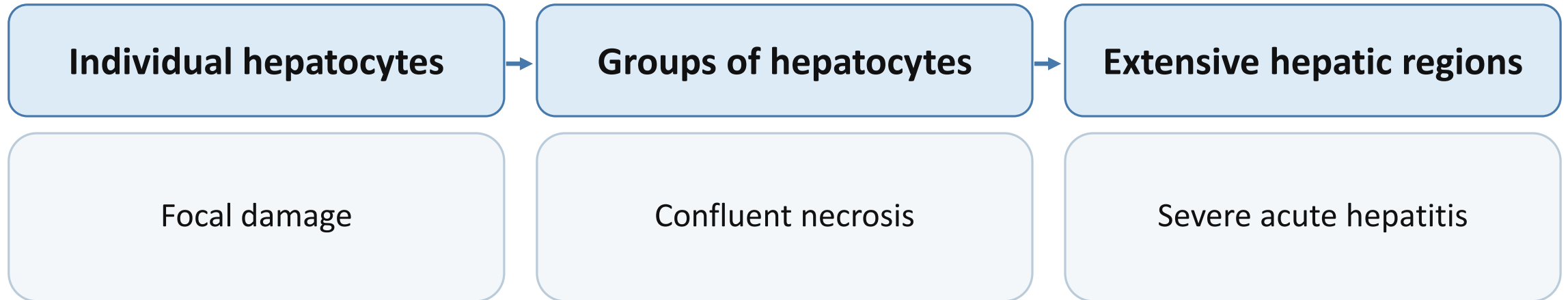
Original conceptual cells; Not an H&E photomicrograph.

Macrophages remove hepatocyte debris



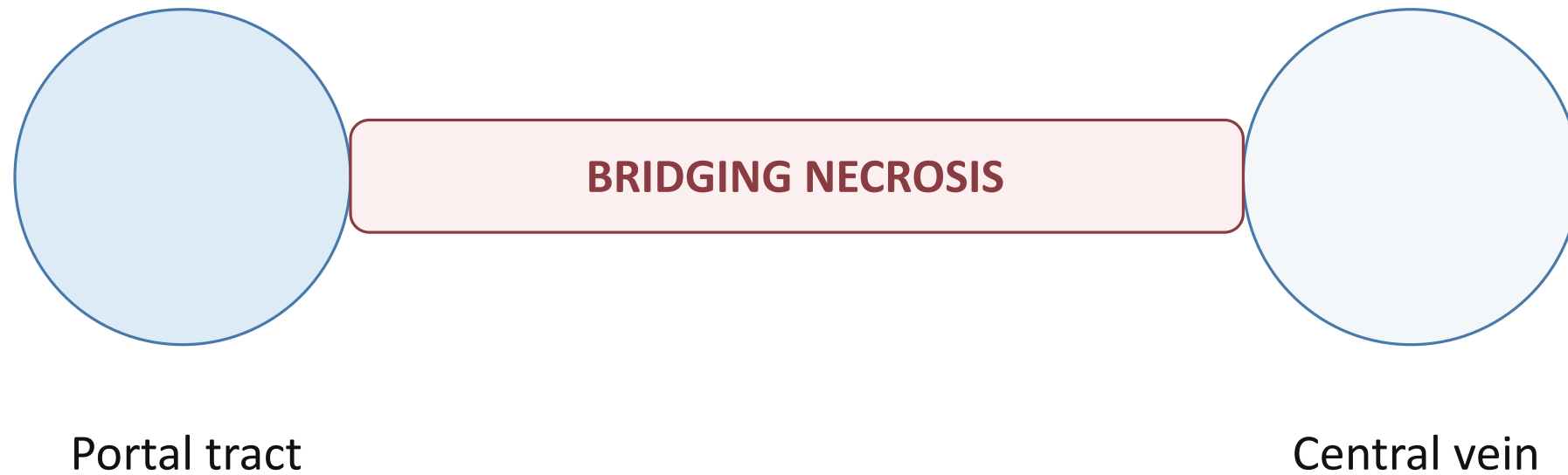
This morphologic response is shared among causes of acute hepatitis.

Confluent necrosis indicates more extensive injury



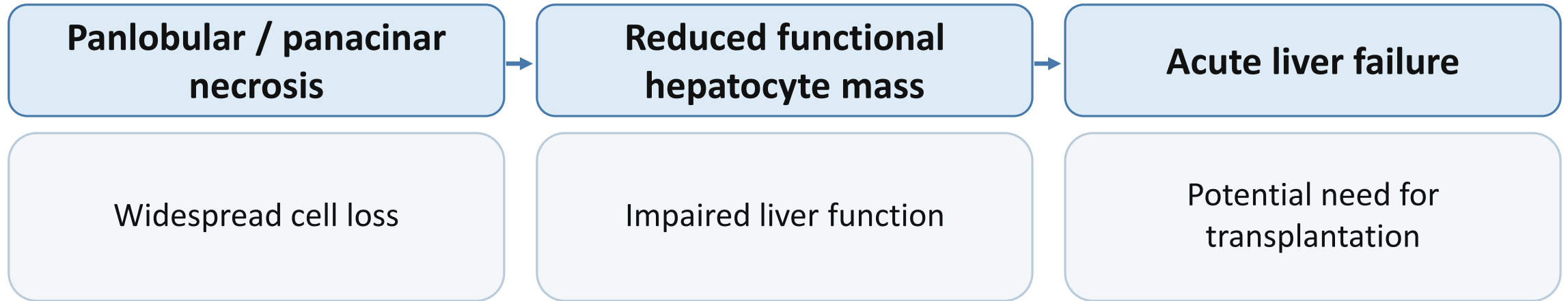
Extent matters more than a purported HEV-specific histologic sign.

Bridging necrosis connects vascular structures



Anatomical schematic of generic severe hepatitis; Not drawn to histologic scale.

Massive hepatocellular necrosis can cause failure



Acute viral hepatitis to acute liver failure through massive necrosis.

Chronic hepatitis changes the tissue architecture

Active inflammation

- Portal lymphocytes or lymphoplasmacytic cells.
- Interface activity at the limiting plate.

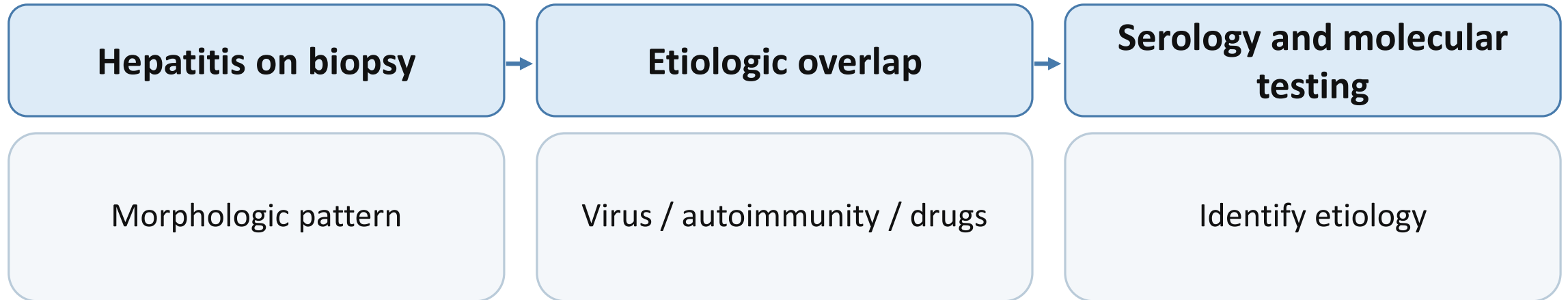
Fibrotic remodeling

- Portal / periportal fibrosis.
- Possible bridging fibrosis and cirrhosis.

Acute versus chronic morphology

Characteristic	Acute viral hepatitis	Chronic viral hepatitis
Principal pattern	Lobular inflammation / injury	Portal inflammation / fibrosis
Hepatocyte damage	Apoptosis or necrosis	Interface activity may occur
Advanced change	Confluent or massive necrosis	Bridging fibrosis / cirrhosis

The histology cannot type HEV infection



Do not call HEV on nonspecific tissue morphology alone.

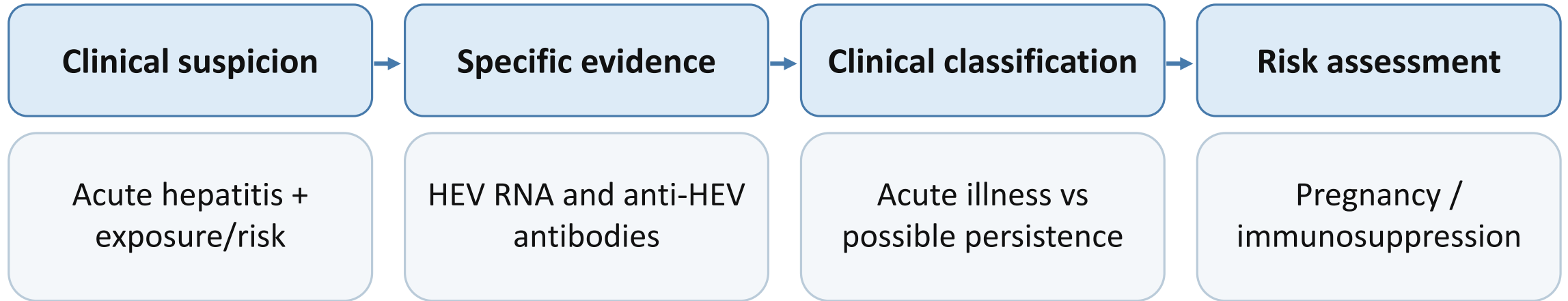
Hepatitis A versus E: Shared and distinct features

Feature	Hepatitis A	Hepatitis E
Transmission	Fecal–oral	Fecal–oral
Course in competent host	Typically self-limited	Typically self-limited
Chronic hepatitis	Not observed	In immunosuppressed hosts
High-risk theme	Acute liver failure possible	Severe disease in pregnancy

Viral-hepatitis diagnosis requires specific markers

Virus	Selected source-listed approach
HAV	IgM anti-HAV
HBV	HBsAg / anti-HBc; HBV DNA PCR
HCV	Anti-HCV; HCV RNA PCR
HDV	IgM/IgG anti-HDV; HDV RNA PCR
HEV	IgM/IgG anti-HEV; HEV RNA PCR

A source-grounded HEV testing framework



This is an educational interpretation framework, not a validated clinical guideline.

Antibody and RNA tests answer different questions

Molecular testing

- HEV RNA shows detectable viral genetic material.
- Can be positive before symptoms.

Serologic testing

- IgM accompanies the acute clinical phase.
- IgG persists during recovery.

Case: Acute hepatitis after travel

A young adult develops acute hepatitis several weeks after returning from a region where HEV epidemics occur. An exposure to unsafe water is possible.

What makes HEV a defensible diagnosis to investigate?

- Fecal–oral, water-borne exposure fits the epidemiology.
- The interval fits the average 4–5-week incubation.
- Order appropriate HEV serology and/or HEV RNA testing.

Case: Acute hepatitis in pregnancy

A pregnant patient presents with newly symptomatic acute hepatitis. An enterically transmitted hepatitis virus is under consideration.

What changes the urgency of recognizing HEV?

- Unusually severe HEV disease in pregnancy.
- HEV can lead to acute liver failure in this population.
- Etiologic assessment and clinical monitoring must account for that risk.

Case: Ongoing hepatitis after transplantation

An organ-transplant recipient has persistently abnormal liver tests after an episode of suspected viral hepatitis.

Which HEV-related deviation from the usual course matters?

- Chronic infection can occur with immunosuppression.
- Persistent HEV RNA is different from persistent IgG.
- Virologic testing is needed to establish current infection.

Clinical synthesis: Four decisive distinctions

Question	HEV-specific answer
How acquired?	Enteric / water-borne, with zoonotic associations
Why hepatocyte injury?	Predominantly host immune response
How recognize the phase?	RNA, acute IgM, recovery-phase IgG
Who develops severe/persistent disease?	Pregnancy (severity); immunosuppression (persistence)

Key learning points

- HEV commonly causes an acute fecal–oral hepatitis.
- HEV is an RNA virus, with injury attributed mainly to host response.
- RNA detection can precede symptoms; IgM rises with illness; IgG persists in recovery.
- Severe pregnancy-associated disease and chronic infection with immunosuppression are major exceptions.
- Morphology is not etiologically specific: Use appropriate molecular and serologic tests.

Reference and source boundaries

Primary textbook

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

Sections used

- Hepatitis E Virus (p. 760).
- Clinicopathologic Syndromes of Viral Hepatitis and Table 18.3 (pp. 760–761).
- Morphology of Viral Hepatitis (pp. 761–762).
- Hepatitis A Virus and Viral Hepatitis parent context (pp. 755–756).