

Autoimmune Hepatitis

Immune mechanisms · Morphology · Integrated diagnosis

Pathology lecture

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Learning objectives: Connect mechanism, biopsy and diagnosis

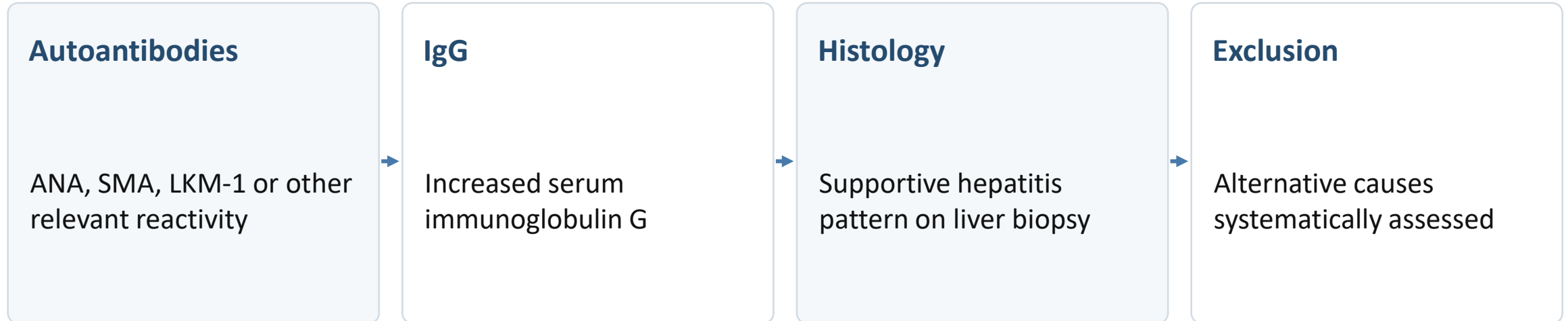
- Explain HLA association and the lymphocyte–plasma cell response.
- Recognize interface activity, plasma cells, necrosis and fibrosis.
- Integrate serology, serum IgG, biopsy and exclusion of mimics.
- Anticipate clinical course, overlap syndromes and treatment response.

Autoimmune hepatitis: The defining concept

Chronic progressive immune-associated hepatocellular inflammation

- Genetic susceptibility and autoantibodies are common.
- Immunosuppressive treatment often induces remission.
- Untreated disease may progress to cirrhosis or death.

Four complementary diagnostic evidence streams

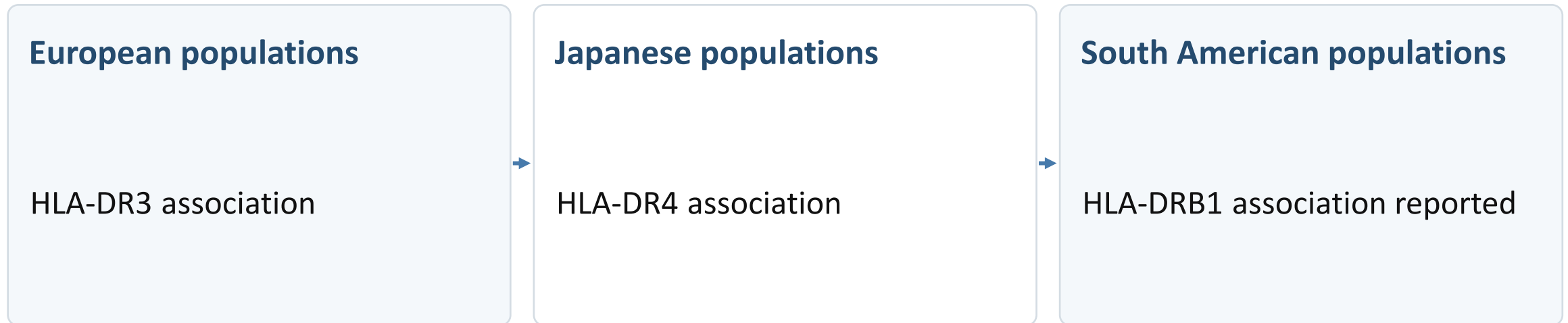


No single stream independently establishes the diagnosis.

Female predominance and population distribution

- Women account for approximately 78% of cases summary.
- HLA associations vary across populations; Susceptibility is not uniform.
- AIH can occur across a wide range of clinical ages and presentations.

Genetic predisposition: HLA associations



Association indicates susceptibility, not a stand-alone diagnostic test.

Proposed triggers versus established uncertainty

Proposed triggers

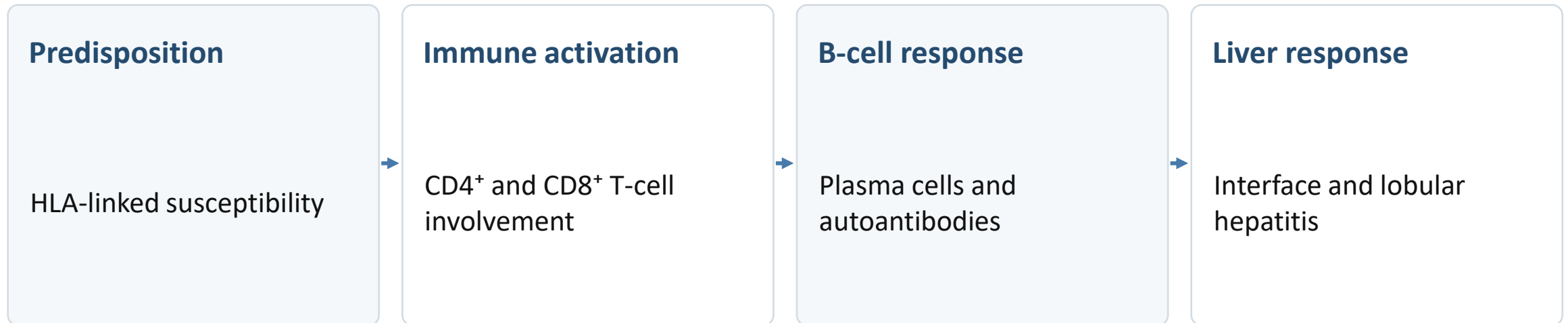
Viral infection
Drugs or toxins
Vaccination

What remains uncertain

Target autoantigens are not defined in the source.
The initiating loss of tolerance is not established.

Temporal associations should not be interpreted as demonstrated causality.

Conceptual sequence of hepatocellular immune injury



Exact causal links between these elements remain incompletely understood.

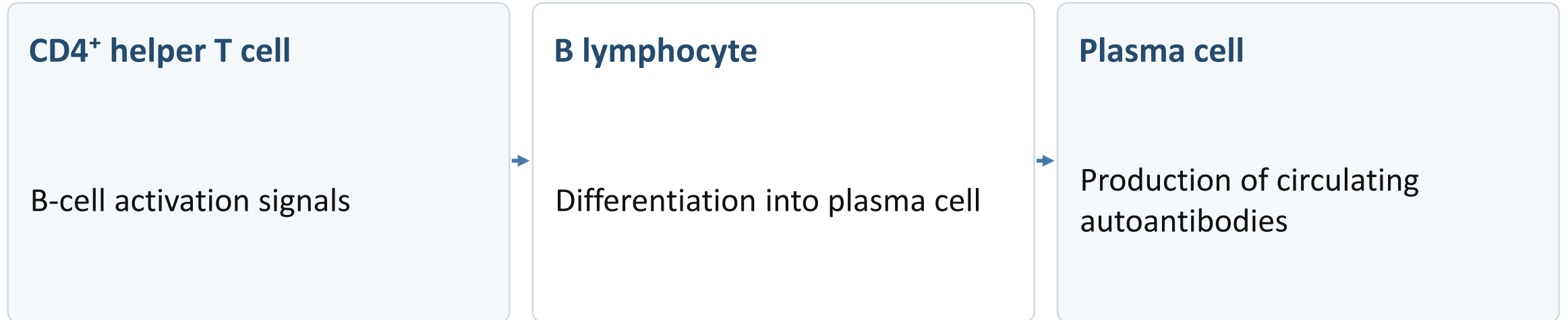
CD4⁺ helper T cells: Coordinating the response

- The hepatic infiltrate is predominantly enriched in CD4⁺ helper T cells.
- Helper T-cell activity supports B-lymphocyte activation.
- Activated B cells differentiate into antibody-secreting plasma cells.
- Cellular composition does not by itself prove the mechanism of injury.

CD8⁺ cytotoxic T cells: Localization at the interface

- CD8⁺ T cells are identified at the portal–parenchymal interface.
- Their location corresponds to zones of interface hepatocyte injury.
- The precise contribution of cytotoxicity to tissue injury is not fully defined.

Plasma cells and autoantibody production



Serologic detectability is not equivalent to direct antibody-mediated cytotoxicity.

Autoantibodies are diagnostic clues—not severity meters

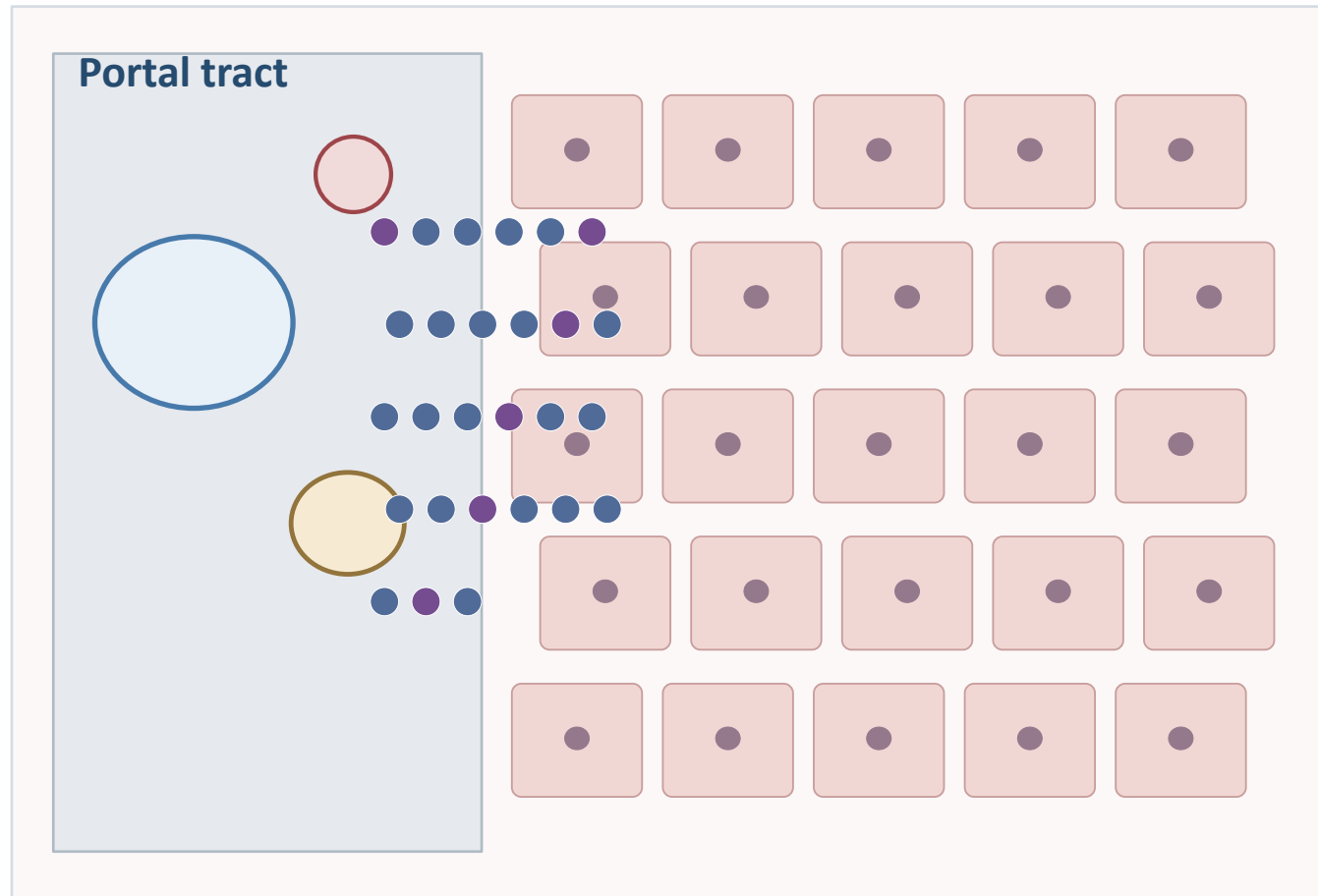
Antibody positivity supports an immune-associated phenotype

- Measured titers correlate poorly with disease severity or outcome.
- Autoantibodies can also accompany chronic viral hepatitis and steatohepatitis.
- A small subset has seronegative autoimmune hepatitis.

Drug-associated autoimmune hepatitis-like injury

- Minocycline, nitrofurantoin and α -methyldopa are textbook examples.
- Drugs may induce both autoantibodies and hepatocellular injury.
- The phenotype can imitate idiopathic autoimmune hepatitis.
- Recovery after withdrawal of the culprit drug supports a drug-related process.

Portal–lobular architecture: Where interface injury occurs

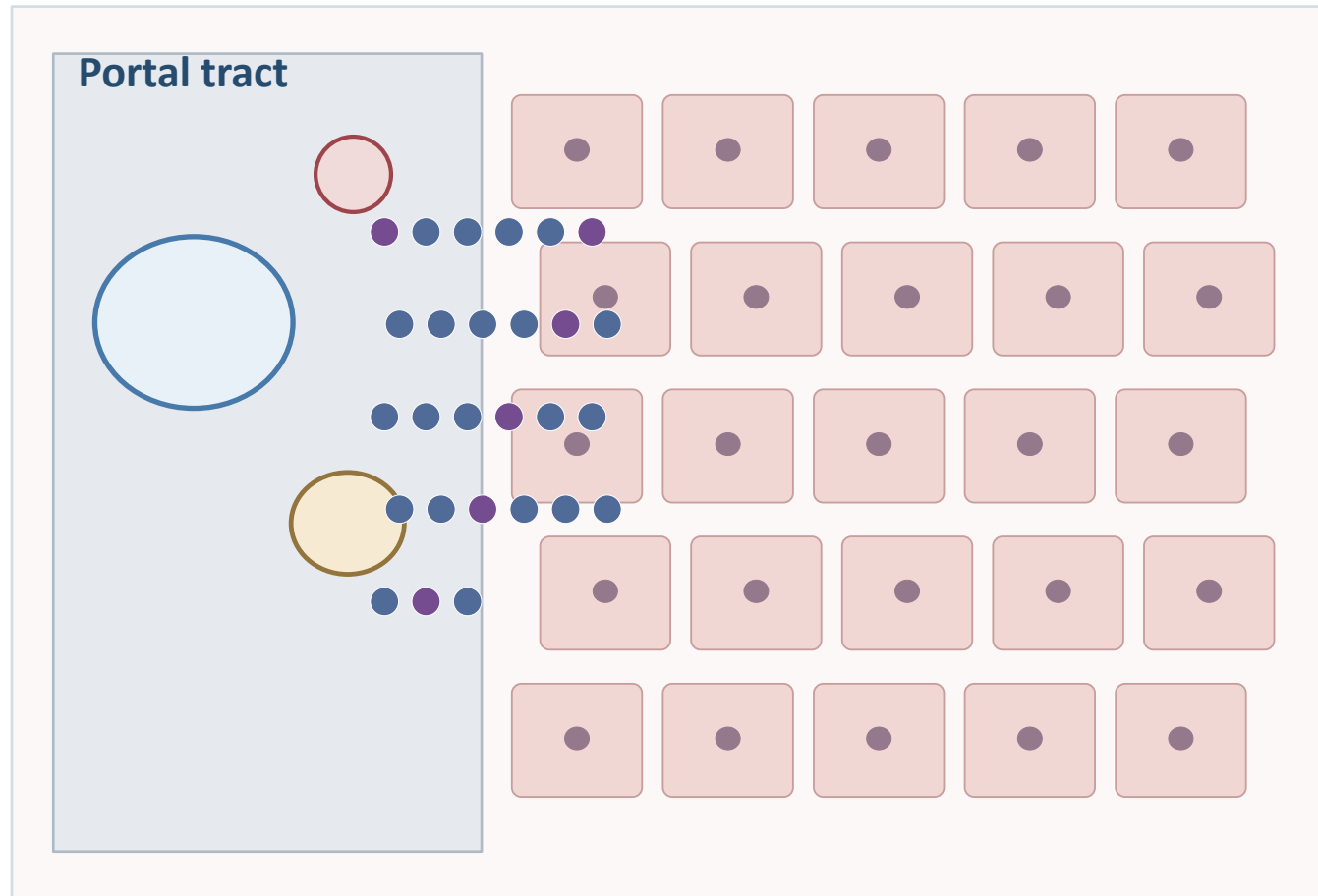


Anatomic orientation

A portal tract lies adjacent to periportal hepatocyte plates. Interface activity involves inflammatory cells extending into hepatocytes at the junction.

Schematic — not a histologic specimen

The microscopic signature: Interface hepatitis

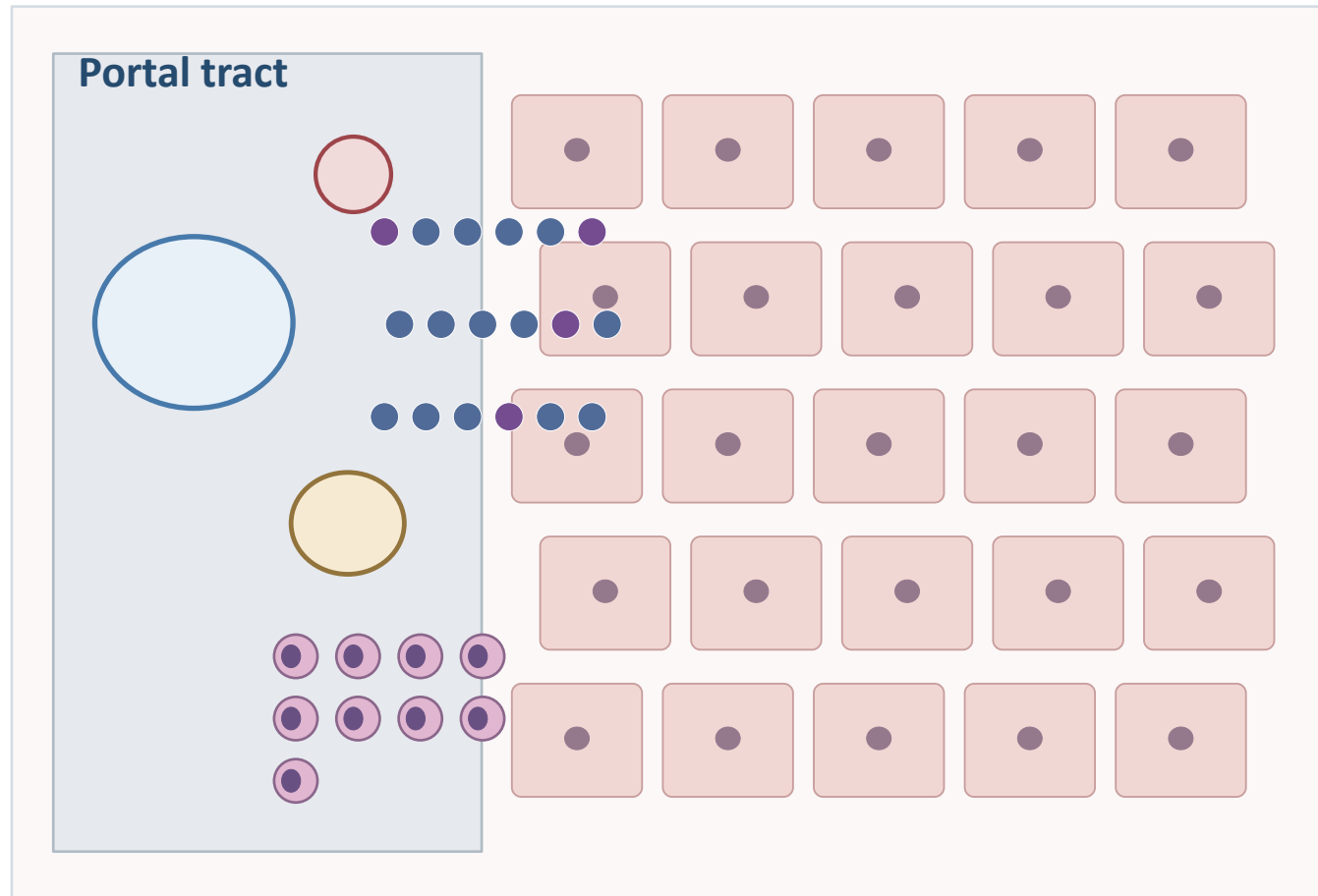


Interpretive point

Interface inflammation is characteristic in AIH but is not specific. Similar activity occurs in several other hepatitis etiologies.

Schematic — not a histologic specimen

Plasma-cell-rich inflammation: An important clue



Microscopic pattern

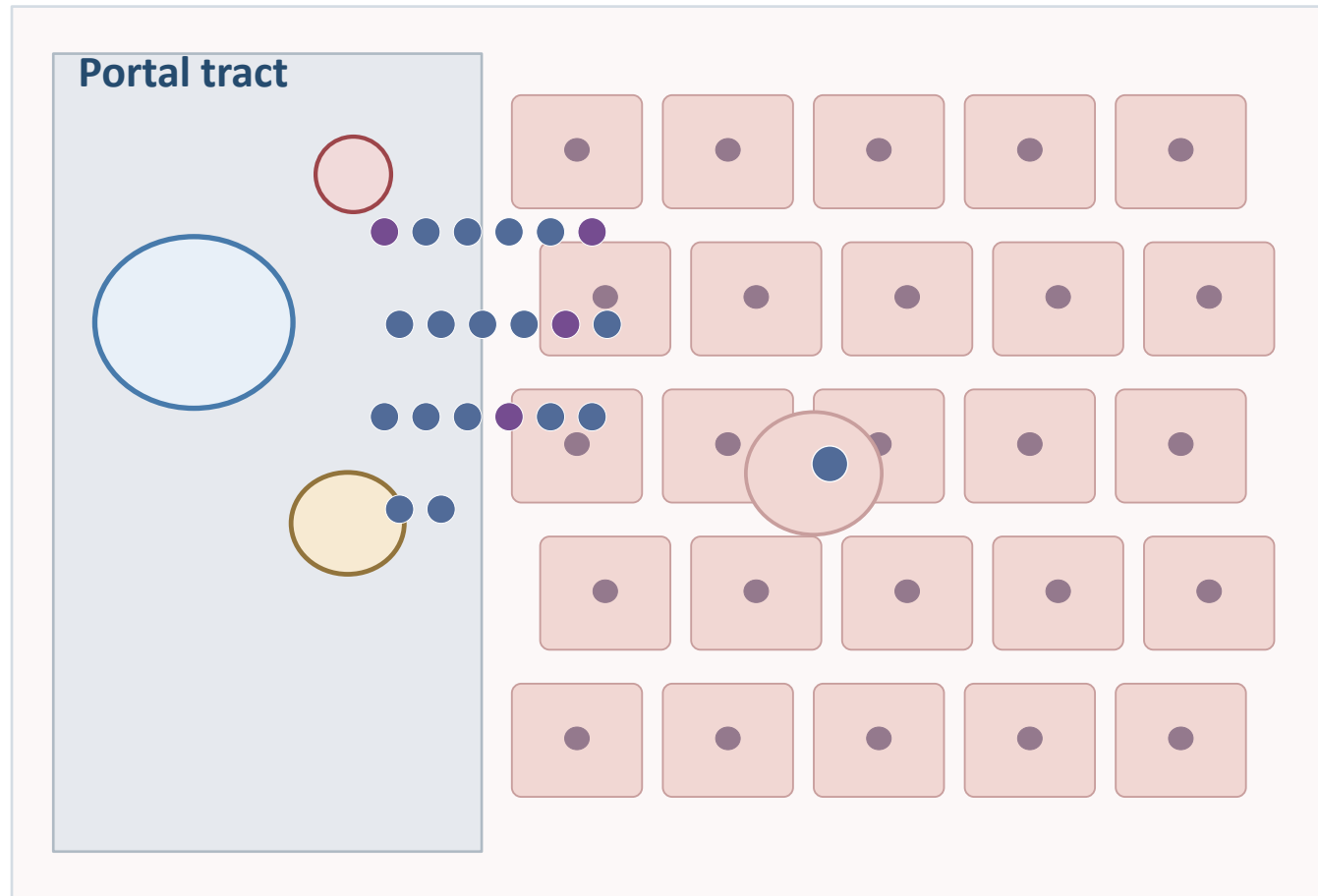
Plasma cells may occur in conspicuous clusters. Assess their density together with the overall pattern and clinical findings.

Schematic — not a histologic specimen

Plasma cells: Significance and limitations

- Numerous clustered plasma cells are typical of AIH.
- The inflammatory infiltrate also includes lymphocytes.
- Plasma-cell prominence strengthens suspicion but does not establish etiology.
- Pattern recognition requires assessment of portal and lobular compartments.

Emperipolesis: An inflammatory cell within a hepatocyte

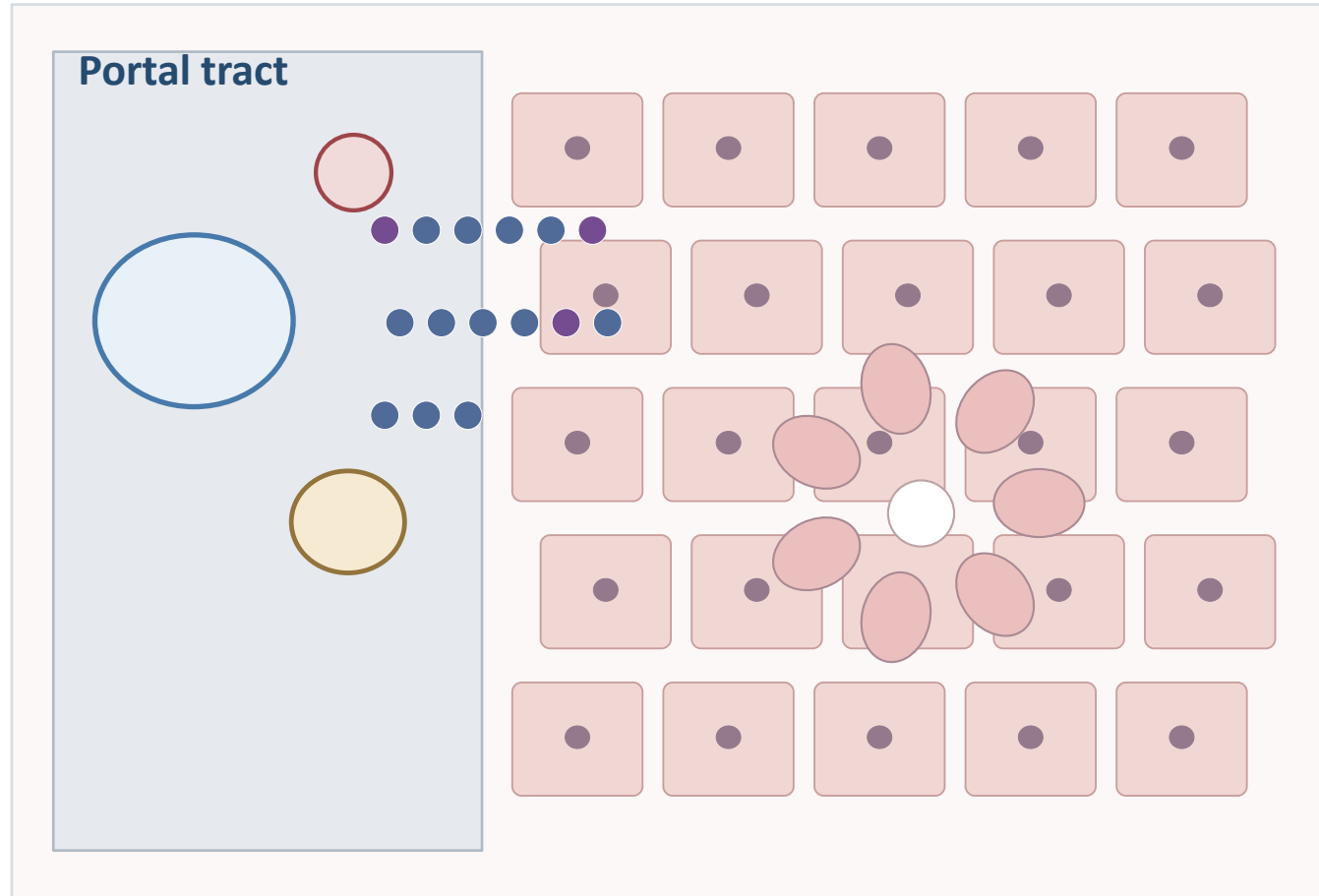


Definition

Lymphocytes or plasma cells may lie within the hepatocyte cytoplasm. This finding is not pathognomonic and should not be required in isolation.

Schematic — not a histologic specimen

Hepatocyte rosettes: An architectural regenerative pattern



Morphologic relationship

Hepatocytes may form a circular arrangement around a dilated canaliculus. this is described as a regenerative response.

Schematic — not a histologic specimen

Confluent necrosis: Severity spans several zones

Perivenular

Groups of hepatocytes lost near central venules



Panacinar

Extensive involvement of an entire acinus



Bridging

Confluent injury connects vascular landmarks

Necrosis distribution helps characterize severity and pattern.

Perivenular confluent necrosis

- Groups of injured hepatocytes can be centered on perivenular regions.
- This pattern demonstrates that injury is not restricted to portal interfaces.
- Assess the remaining lobular architecture for associated inflammation.

Panacinar necrosis

- Confluent hepatocyte death can extend across an entire acinus.
- Extensive hepatocellular loss corresponds to severe active injury.
- Acute clinical presentation may occur despite underlying chronic disease.

Bridging necrosis is not bridging fibrosis

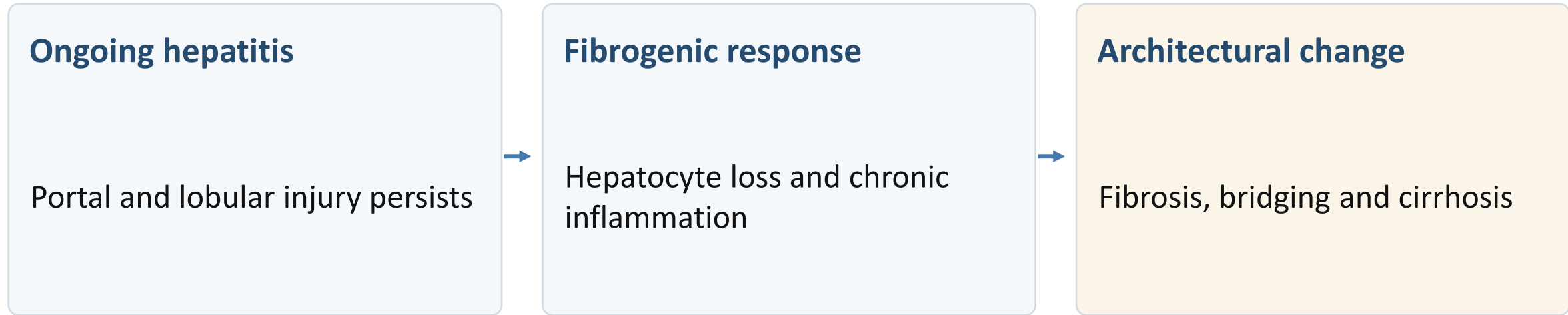
Bridging necrosis

Confluent hepatocyte loss connects vascular structures.
It reflects active and potentially severe injury.

Bridging fibrosis

Collagenous septa link architectural landmarks.
It indicates chronic remodeling rather than simply active cell loss.

Persistent autoimmune injury can culminate in cirrhosis



Fibrosis may already be present before overt symptoms appear.

Fibrosis at the first biopsy may reveal delayed recognition

- Most cases already show some fibrosis when first examined.
- Fibrosis may increase with continuing disease activity.
- Asymptomatic or apparently acute disease may coexist with advanced scarring.

Burnt-out cirrhosis: Little activity does not exclude AIH

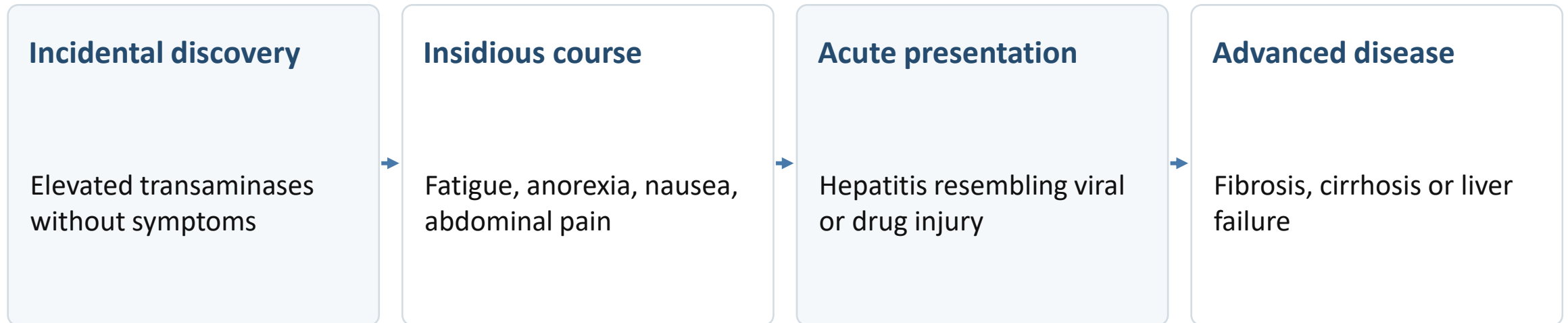
Advanced scarring may remain after active inflammation becomes limited

- Subclinical autoimmune injury can precede recognition for years.
- A biopsy with cirrhosis and little hepatitis may obscure the original etiology.
- Interpret tissue changes in the context of history and serology.

Liver biopsy: Active injury versus accumulated damage

Feature	What it describes	Interpretive consequence
Interface hepatitis	Active hepatocyte injury at the border	Indicates ongoing inflammation
Lobular activity	Parenchymal necroinflammation	Can dominate acute presentations
Confluent necrosis	Contiguous hepatocyte loss	Indicates substantial injury
Fibrosis / cirrhosis	Architectural scar formation	Reflects cumulative disease

Clinical spectrum: One disease, several entry points



Asymptomatic autoimmune hepatitis

- Transaminase elevation may be found during routine testing.
- Absence of symptoms does not reliably exclude fibrosis.
- Histologic assessment may reveal substantial longstanding injury.

Insidious symptoms and their pathologic context

- Fatigue, anorexia, nausea and abdominal pain are common nonspecific symptoms.
- These manifestations overlap with many inflammatory liver diseases.
- Laboratory, serologic and tissue evaluation are necessary for attribution.

Acute autoimmune hepatitis

- Initial symptoms and laboratory abnormalities may resemble acute viral hepatitis.
- Drug-induced liver injury is another major clinical mimic.
- Underlying fibrosis may demonstrate pre-existing, unrecognized chronic disease.

Acute liver failure is within the disease spectrum

An apparently acute attack can represent severe AIH

- Confluent, panacinar or bridging necrosis may accompany severe activity.
- The source recognizes acute liver failure as a possible presentation.
- Prompt etiologic discrimination is clinically consequential.

Clinical acuity does not equal histologic chronicity

Abrupt presentation

Symptoms develop rapidly.
Hepatocellular injury may be extensive.
Other acute hepatitises require exclusion.

Pre-existing disease

Fibrosis can be present on the first biopsy.
Cirrhosis may already be established.
The clinical onset is not necessarily disease onset.

Associated autoimmune diseases

- Type 1 diabetes mellitus can coexist with AIH.
- Autoimmune thyroiditis is another recognized association.
- Celiac disease (celiac sprue) is also described.
- Comorbidity raises suspicion but does not constitute diagnostic proof.

Overlap with autoimmune cholestatic diseases

AIH–PBC overlap

Combines hepatitic features of AIH with unequivocal evidence of primary biliary cholangitis.

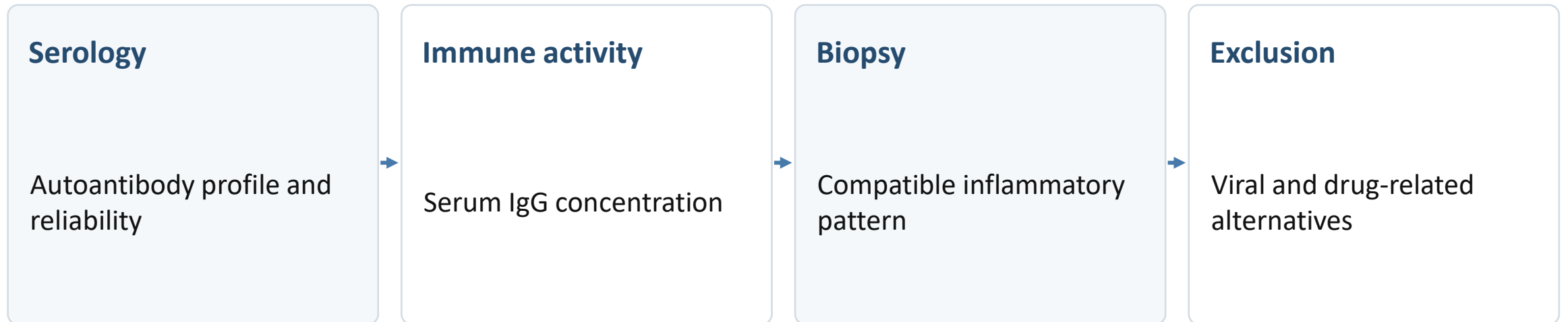
AIH–PSC overlap

Combines AIH with evidence of primary sclerosing cholangitis.
The source notes PSC overlap particularly in children.

Overlap diagnosis requires two established components

- Serologic, biochemical and/or histologic evidence must substantiate both diseases.
- An isolated AMA or nonspecific cholestasis is not sufficient by itself.
- The second component may only become apparent months or years later.

Four diagnostic pillars must be interpreted together



A composite assessment is more robust than any isolated positive test.

Type 1 autoimmune hepatitis: Typical serologic profile

Antibody	Interpretation in context
ANA	Common in type 1 AIH; not disease-specific
Anti-smooth muscle (SMA/ASMA)	Common in type 1 AIH; used in scoring
Anti-SLA/LP	Additional autoantibody that can support AIH
AMA	Occasionally detected; more characteristic of PBC

Anti-SLA/LP: An additional supportive autoantibody

- Anti-soluble liver antigen/liver-pancreas antibodies may occur in AIH.
- In the original simplified system, positive SLA contributes 2 antibody points.
- The total autoantibody domain is capped at 2 points.
- Other liver diseases still require independent assessment.

Type 2 autoimmune hepatitis: Defining antibodies

Marker	Relevant interpretation
Anti-LKM-1	Recognizes CYP2D6; characteristic of type 2 disease
Anti-liver cytosol-1 (LC1)	Another characteristic antibody in type 2 disease
Clinical setting	Type 2 AIH is described more often in children
Morphology and natural history	Broadly similar to type 1 AIH

Type 1 versus type 2 autoimmune hepatitis

Type 1

More common subtype.
ANA and/or SMA are typical.
Anti-SLA/LP may occur.

Type 2

More frequent in children.
Anti-LKM-1 and anti-LC1 are characteristic.
Other clinical and histologic findings broadly overlap.

Subtype assignment rests on the antibody phenotype, not unique tissue morphology.

Serum IgG: Useful but not a stand-alone diagnosis

Increased serum IgG provides independent diagnostic support

- Hypergammaglobulinemia often accompanies autoimmune hepatitis.
- In the simplified score, IgG contributes 0, 1 or 2 points.
- A total diagnosis still requires evaluation of morphology and mimics.

Seronegative autoimmune hepatitis

- A small subset of cases lacks detectable conventional autoantibodies.
- A negative screening panel therefore cannot absolutely exclude AIH.
- Serum IgG, histologic activity and exclusion of other causes remain important.

A positive autoantibody is not specific to AIH

Supports AIH when concordant

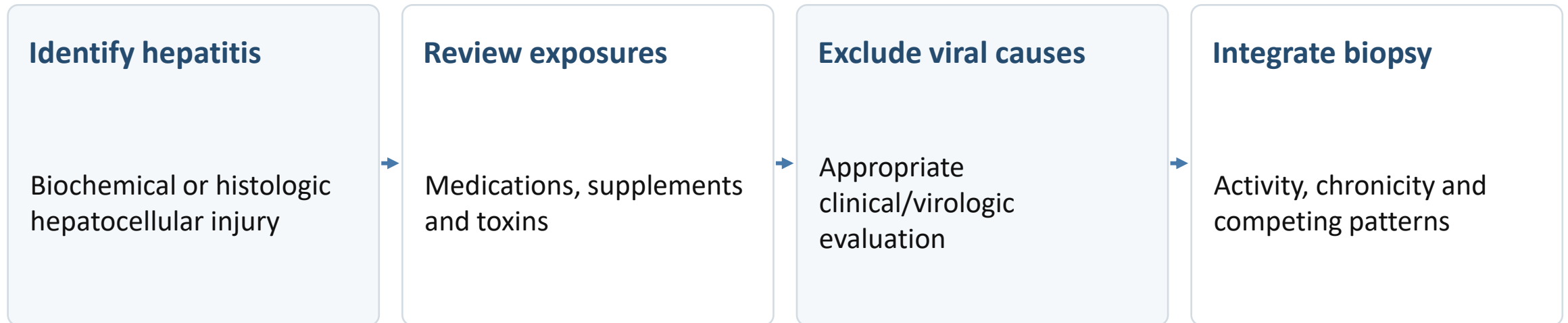
Raised IgG
Compatible biopsy
Competing causes excluded

Potentially misleading alone

Steatohepatitis
Chronic hepatitis B
Chronic hepatitis C

Antibody titers also have limited correlation with severity and outcome.

A disciplined exclusion strategy



When drug injury resembles autoimmune hepatitis

- Ask about minocycline, nitrofurantoin and α -methyldopa exposure.
- An autoimmune-like drug reaction can include circulating autoantibodies.
- Drug discontinuation typically leads to clinical recovery in the source.
- The exposure–response relationship is essential to interpretation.

Histology supports diagnosis but is not pathognomonic

- Interface activity, lobular hepatitis and plasma cells form a supportive pattern.
- Acute and chronic hepatitis of other causes can look similar.
- Severe necrosis, rosettes or emperipolesis cannot replace clinical correlation.
- Histology should also assess fibrosis and alternative disease features.

Simplified AIH score: Antibody and IgG domains

Domain	Finding	Points
Autoantibodies	ANA or SMA $\geq 1:40$	1
Autoantibodies	ANA/SMA $\geq 1:80$; LKM $\geq 1:40$; or SLA positive	2 (max)
Serum IgG	Above upper limit of normal	1
Serum IgG	$>1.10 \times$ upper limit of normal	2

Simplified AIH score: Tissue and viral-exclusion domains

Domain	Finding	Points
Histology	Likely/typical for AIH	2
Histology	Possible/compatible with AIH	1
Histology	Unlikely/atypical for AIH	0
Exclusion of viral hepatitis	No viral hepatitis identified	2

2022 histologic consensus: Likely versus possible AIH

Likely AIH (2 points)

Lymphocytic/lymphoplasmacytic portal or lobular inflammation.
More than mild interface or lobular activity.
No convincing features of another liver disorder.

Possible AIH (1 point)

Mild interface or lobular inflammatory activity; OR
Supportive hepatitis features coexist with findings suggesting another disease.

Diagnostic score thresholds

Probable AIH ≥ 6 points · Definite AIH ≥ 7 points

- Original simplified score has a maximum of 8 points.
- Autoantibody domain contributes no more than 2 points in total.
- Clinical judgment remains necessary if the score is discordant.

Simplified scoring: Hennes et al. 2008; Histology updated 11e.

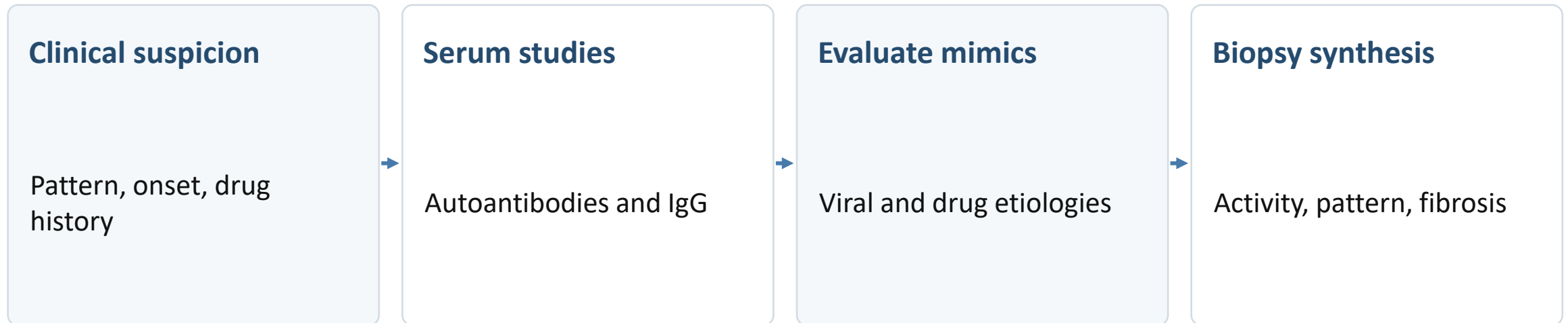
Common diagnostic scoring pitfalls

- Do not add multiple autoantibody points beyond the domain maximum of 2.
- Distinguish 1-point from 2-point IgG thresholds precisely.
- Do not label every interface hepatitis specimen as typical AIH.
- Treat missing viral exclusion as a genuine evidentiary gap.

Differential diagnosis: Interpret the entire pattern

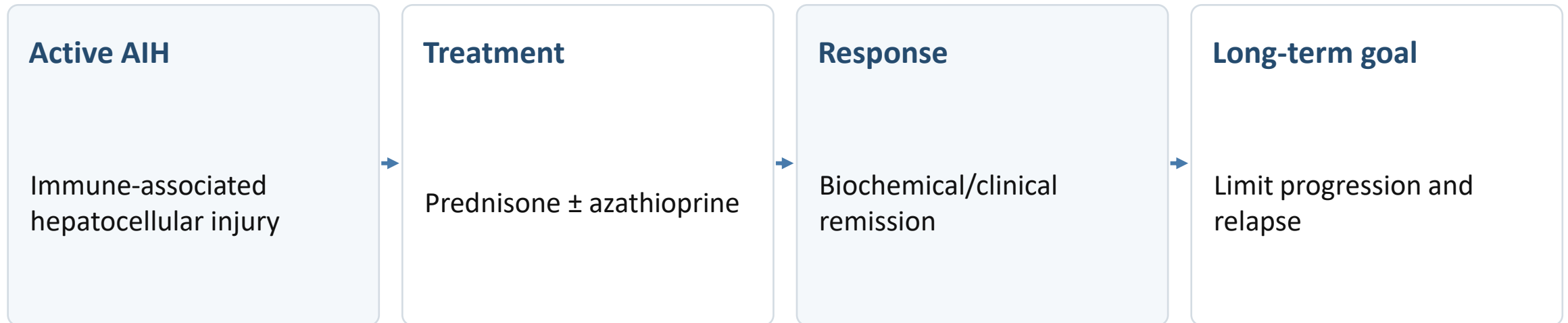
Alternative	Why it may mimic AIH	Discriminator
Viral hepatitis	Active portal/lobular hepatitis; antibodies may occur	Virologic evaluation
Drug-induced liver injury	Autoimmune-like serology and hepatocellular injury	Medication history; withdrawal
Steatohepatitis	Chronic injury and nonspecific autoantibodies	Competing morphologic pattern
PBC / PSC overlap	Mixed hepatitic and cholestatic features	Independent evidence of both

Integrated diagnostic workflow for suspected AIH



Use a simplified score as an aid, not a substitute for synthesis.

Immunosuppressive therapy targets ongoing activity



Therapeutic details are summarized from the textbook, not individualized prescribing.

Treatment response: An important aspect of disease behavior

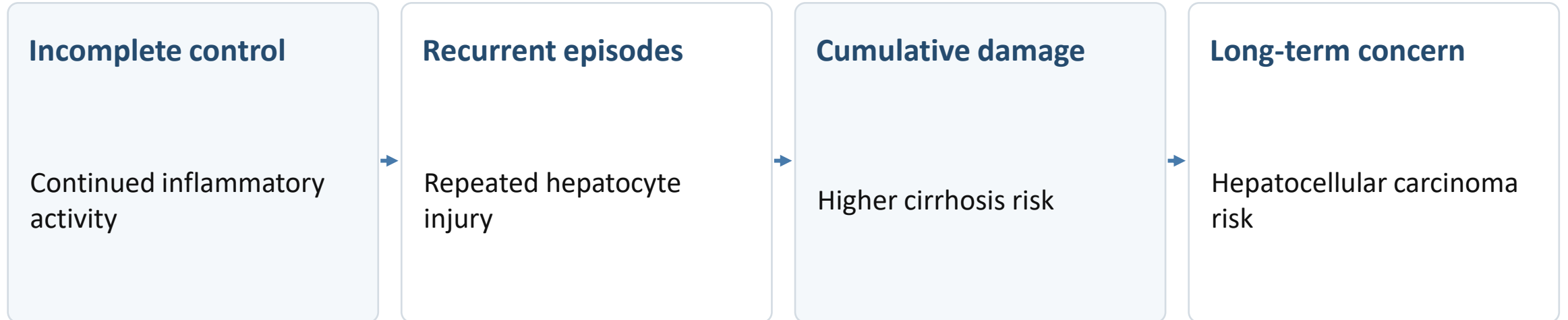
Remission occurs in approximately 80–90% with standard therapy

- Prednisone, with or without azathioprine, as first-line therapy.
- Remission generally occurs within 12 months in responding patients.
- Treatment response is supportive context, not proof of initial diagnosis.

Steroid intolerance and alternatives

- The source notes other immunosuppressants when glucocorticoids are not tolerated.
- Selection depends on a specialist assessment and patient-specific factors.
- An unfavorable drug effect must be distinguished from ongoing autoimmune activity.

Why incomplete response and relapse matter



Advanced AIH: Cirrhosis and hepatocellular carcinoma

- Cirrhosis can be present even at first diagnosis.
- Incomplete response or multiple relapses increases progression risk.
- Hepatocellular carcinoma is a recognized long-term concern in this group.

Liver transplantation: Textbook outcome figures

- Liver transplantation may be necessary in patients with advanced cirrhosis.
- Approximately 75% survival at 10 years after transplant.
- Disease recurrence is reported in approximately 20% of recipients.
- These are textbook summary figures; They are not individual prognostic estimates.

Case 1: Applying the simplified AIH score

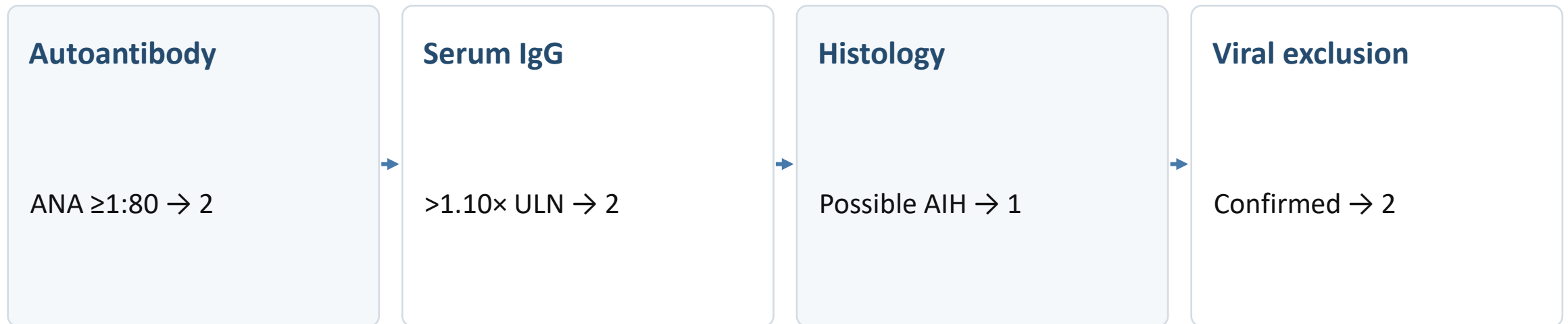
Case vignette

Illustrative scenario: ANA 1:160, IgG 1.3× upper limit of normal, viral hepatitis excluded, and biopsy judged “possible AIH” under updated histologic categories.

Task

Compute the score.
What diagnostic category does it support?

Case 1: Transparent point allocation



Total: 7 points — definite AIH by the simplified score.

Case 2: The medication-history trap

Case vignette

Illustrative scenario: Hepatocellular injury, increased IgG and positive ANA emerge during nitrofurantoin therapy. The biopsy shows interface hepatitis and plasma cells.

Task

What competing diagnosis must be addressed before labeling idiopathic AIH?

Case 2: Interpretation before disease labeling

- Nitrofurantoin is a documented trigger of autoimmune-like drug liver injury.
- The serology and biopsy do not by themselves establish idiopathic AIH.
- Drug exposure timing and clinical course after withdrawal are essential.

Case 3: Cholestatic overlap versus incidental markers

Case vignette

Illustrative scenario: A patient with AIH has an antimitochondrial antibody detected and a persistent cholestatic biochemical pattern.

Task

What additional evidence would justify diagnosing an AIH–PBC overlap syndrome?

Case 3: Do not infer overlap from one marker

- Overlap requires unequivocal evidence supporting each disease component.
- Biochemical and serologic findings must be assessed alongside morphology.
- Longitudinal reassessment may reveal a second component later.

Recognition checklist: AIH on a liver biopsy

Evaluate	What to document
Inflammation	Portal and lobular distribution; interface activity
Cell composition	Lymphocytes and prominence/clustered plasma cells
Hepatocyte injury	Apoptotic/confluent necrosis; extent and topography
Regeneration	Rosettes if present; not obligatory
Chronicity	Fibrosis / cirrhosis; activity may be low in burnt-out stage
Competing pattern	Evidence that favors viral, drug or cholestatic disease

Integrated synthesis: Four indispensable ideas

AIH is diagnosed by convergence—not a single antibody or biopsy sign

- T-cell and plasma-cell responses produce characteristic hepatitis patterns.
- Presentations range from incidental elevation to acute liver failure.
- Exclude viral and drug injury; Use IgG, serology and histology together.
- Control of immune activity changes the natural history.

Selected references

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Lohse AW, Sebode M, Bhathal PS, et al. Consensus recommendations for histological criteria of autoimmune hepatitis. *Liver Int*. 2022;42:1058–1069.