

DIAGNOSIS OF AUTOIMMUNE HEPATITIS

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INTRODUCTION

- **Autoimmune hepatitis is a chronic, inflammatory disease**
- **Characterized by circulating autoantibodies and elevated serum globulin**
- **Start as acute hepatitis and progress to chronic liver disease and cirrhosis**

SUBTYPES OF AIH

- **The most common type 1 AIH (AIH-1) ((ANA) and (SMA)**
- **The less common type 2 AIH (AIH-2) (anti-LKMI and anti-LCI antibodies)**
- **AIH-3 (antibodies against soluble liver antigen/liver pancreas (anti-SLA/LP)**

DIAGNOSTIC EVALUATION

- **Patterns of clinical presentation**
- **Associated extrahepatic disorders**
- **Laboratory features**
- **Imaging**
- **Histology**

PATTERNS OF CLINICAL PRESENTATION

Autoimmune hepatitis has a variety of clinical phenotypes

- **Asymptomatic patients**
- **Acute hepatitis**
- **Chronic hepatitis**
- **Cirrhosis**

Table 3. Presentation of AIH in adults, children, and early adulthood.

	Adult		Paediatric	
	Definition	Prevalence	Definition	Prevalence
Asymptomatic AIH	Absence of symptoms, only elevated liver biochemistry ^{7,72}	6-23% ^{52,55,58,59,72}	Absence of symptoms, only elevated liver biochemistry	12-18% ⁵⁵
Chronic AIH	>6 months from onset of elevated liver biochemistry or symptoms ^{# 7,72}	48-68% ^{58,65}	>6 months from onset of elevated liver biochemistry or symptoms	33-52% ^{61,62}
Acute AIH	<30 days from onset of symptoms ^{* 67,72}	10-26% ^{51,55,58}		19-58% ^{55,57,61}
Acute exacerbation of chronic AIH	Acute injury developing in patients with underlying (often unrecognised) chronic disease	About one-third of patients with AIH have cirrhosis at diagnosis ^{7,50,57,71,72}		
Acute severe AIH	Acute presentation with jaundice and coagulation disturbance (INR ≥ 1.5 and <2), but without encephalopathy ^{66,67}			
ACLF	Acute injury developing in patients with (often unrecognised) cirrhosis and extrahepatic organ failure ⁶⁸		Acute injury developing in patients with (often unrecognised) cirrhosis with extrahepatic organ failure ⁶⁸	26% ⁶¹
ALF	Hepatic necrosis with encephalopathy within 8 weeks from onset ^{53,69}		Elevated ALT and INR >1.5 and encephalopathy or elevated ALT and INR >2 regardless the presence of encephalopathy ⁷⁰	3.6-12.5% ^{56,61-63} with 3-fold higher risk in LKM1-related AIH ⁵⁷

No definition of presentation:^{51,55}.

ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; INR, international normalised ratio; LKM1, liver kidney microsomal type 1 antibodies.

*Jaundice, fatigue, drowsiness, fever.

[#]Manifestation of advanced fibrosis or cirrhosis, symptoms related to chronic liver disease, e.g. pruritus, malaise, jaundice, fatigue, arthralgias and abdominal pain/discomfort.

Extrahepatic disorders associated with autoimmune hepatitis

Extrahepatic diseases		Frequency among patients with AIH (%)
Pulmonary disorders	Fibrosing alveolitis	<1
	Pulmonary fibrosis	<1
	Sarcoidosis	<1
	Asthma	1 to 4
Hematological disorders	Immune thrombocytopenia	<1
	Autoimmune hemolytic anemia	<1
	Pernicious anemia	1
	Antiphospholipid syndrome	1
Neurologic disorders	Multiple sclerosis	<1
	Mononeuritis multiplex	<1
Miscellaneous	Primary amenorrhea	4
	Glomerulonephritis	1
	Cryoglobulinemia	<1
	Uveitis	<1
	Polyglandular autoimmune syndrome	<1
Endocrine disorders	Autoimmune thyroiditis	8 to 23
	Diabetes (type 1)	1 to 10
Gastrointestinal disorders	IBD (ulcerative colitis)	2 to 8
	Celiac disease +/- IgA deficiency	1 to 6
Connective tissue disorders	Rheumatoid arthritis	2 to 4
	Sjögren's disease	1 to 7
	Mixed connective tissue disease	1 to 2.5
	Systemic lupus erythematosus	1 to 2.6
	Systemic sclerosis/CREST	<1
	Polymyalgia rheumatica	<1
	Polymyositis	<1
	Dermatomyositis	<1
Skin disorders	Psoriasis	3
	Vitiligo	1 to 2
	Pyoderma gangrenosum	<1
	Acne	<1
	Urticaria	<1
	Lichen planus	<1
	Erythema nodosum	<1
	Dermatitis herpetiformis	<1

AIH: autoimmune hepatitis; CREST: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; IBD: inflammatory bowel disease.

LABORATORY FEATURES

- **Liver biochemical and function tests**
- **Gamma globulins**
- **Autoantibodies**

LIVER BIOCHEMICAL AND FUNCTION TESTS

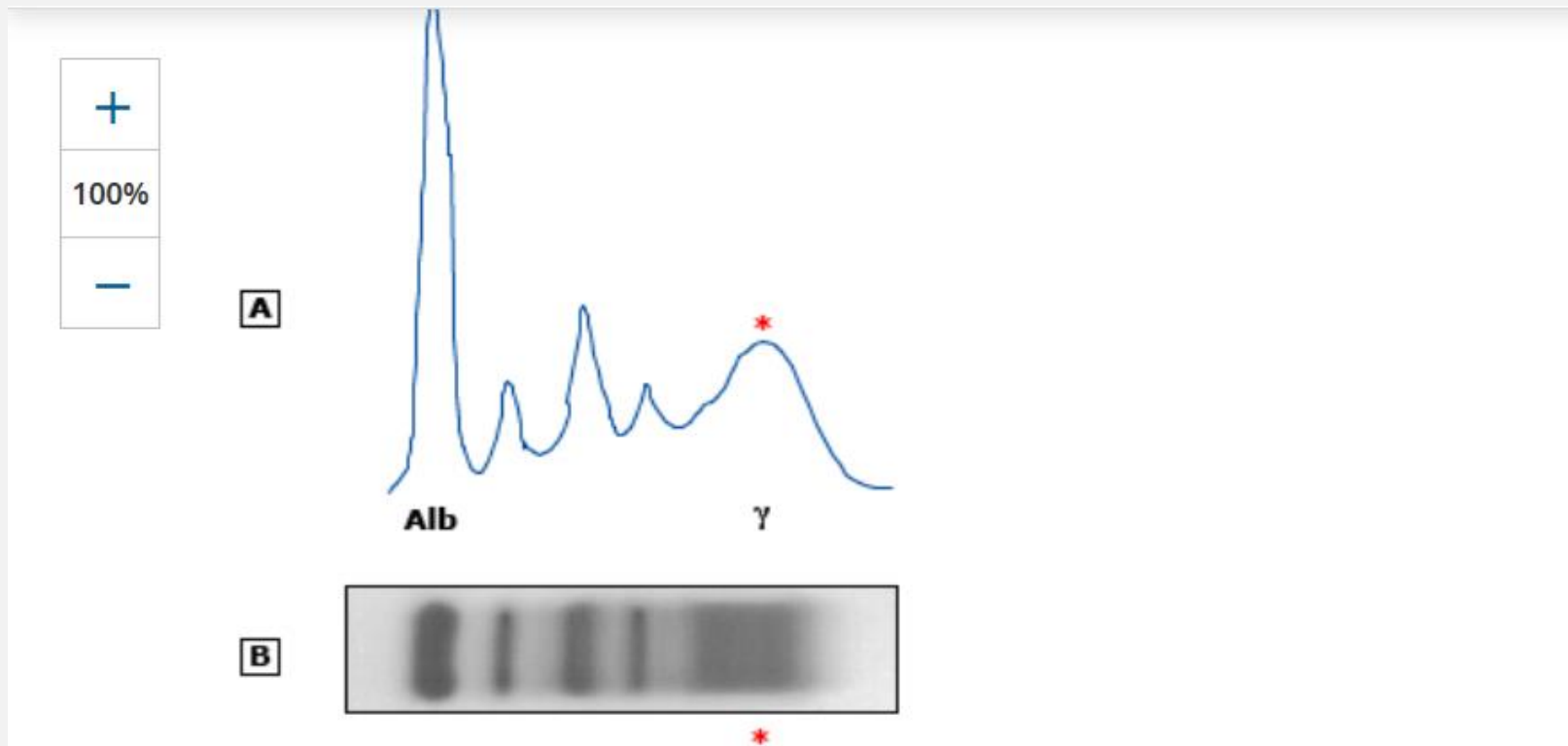
Acute presentations

- ALT and AST may exceed 10 to 20 times the upper limit)
- Ratio of alkaline phosphatase to AST (or ALT) is often $<1:5$, and in some cases is $<1:10$

Chronic symptoms or those with cirrhosis

- AST and ALT elevations are less profound, (1.5 to 5 times the upper limit)
- The ratio of alkaline phosphatase to AST (or ALT) is lower and approaches 1:2

GAMMA GLOBULINS



AUTOANTIBODIES

- **Antinuclear antibodies** (the most common circulating autoantibodies in autoimmune hepatitis, and may be the only autoantibody present)
- **Anti-smooth muscle antibodies** (are more specific than ANA for autoimmune hepatitis)
- **Anti-actin antibodies** (are more specific than ANA for type I autoimmune hepatitis)

AUTOANTIBODIES

- **Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)**

(Found in approximately 10 to 30 percent of adult patients with type I AIH)

- **Anti-neutrophil cytoplasmic antibodies**

((p-ANCA) have been identified in patients with type I AIH)

- **Anti-mitochondrial antibodies** (can occur in type I)

AUTOANTIBODIES

- **Anti-DNA antibodies**
- **Anti-liver-kidney microsomal-1 antibodies** –(anti-LKM-1) occur mostly in patients with type 2 disease
- **Anti-liver-kidney microsomal-3 antibodies** – (anti-LKM-3) are found rarely in patients with type 2 disease
- **Anti-liver cytosol antibody-1 (ALC-1)** is a marker of type 2 autoimmune hepatitis

Classification of autoantibodies in autoimmune hepatitis

Antibody	Disease subtype	Additional features
Antinuclear antibody (ANA)	Type 1	Most common antibodies in type 1 disease
Antismooth muscle antibody (ASMA)	Type 1	ASMA titers of 1:320 or greater generally reflect the presence of AAA
Antiactin antibody (AAA)	Type 1	Not routinely measured in North American laboratories
Antimitochondrial antibody (AMA)	Type 1	More specific for primary biliary cholangitis
Atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	Type 1	Also found in patients with primary sclerosing cholangitis
Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)	Type 1 and type 2	More common in children with type 2 disease
Anti-DNA antibodies (single stranded DNA [ssDNA] and double-stranded DNA [dsDNA])	Type 1 and type 2	Anti-dsDNA antibody is commonly associated with systemic lupus erythematosus
Anti-liver kidney microsomal-1 antibody (ALKM-1)	Type 2	Occurs mostly in type 2 disease
Anti-liver cytosol-1 antibody (ALC-1)	Type 2	May occur in conjunction with ALKM-1
Anti-liver kidney microsomal-3 antibody (ALKM-3)	Type 2	Rarely present

Figure 2. Stepwise approach to elevated aminotransferases

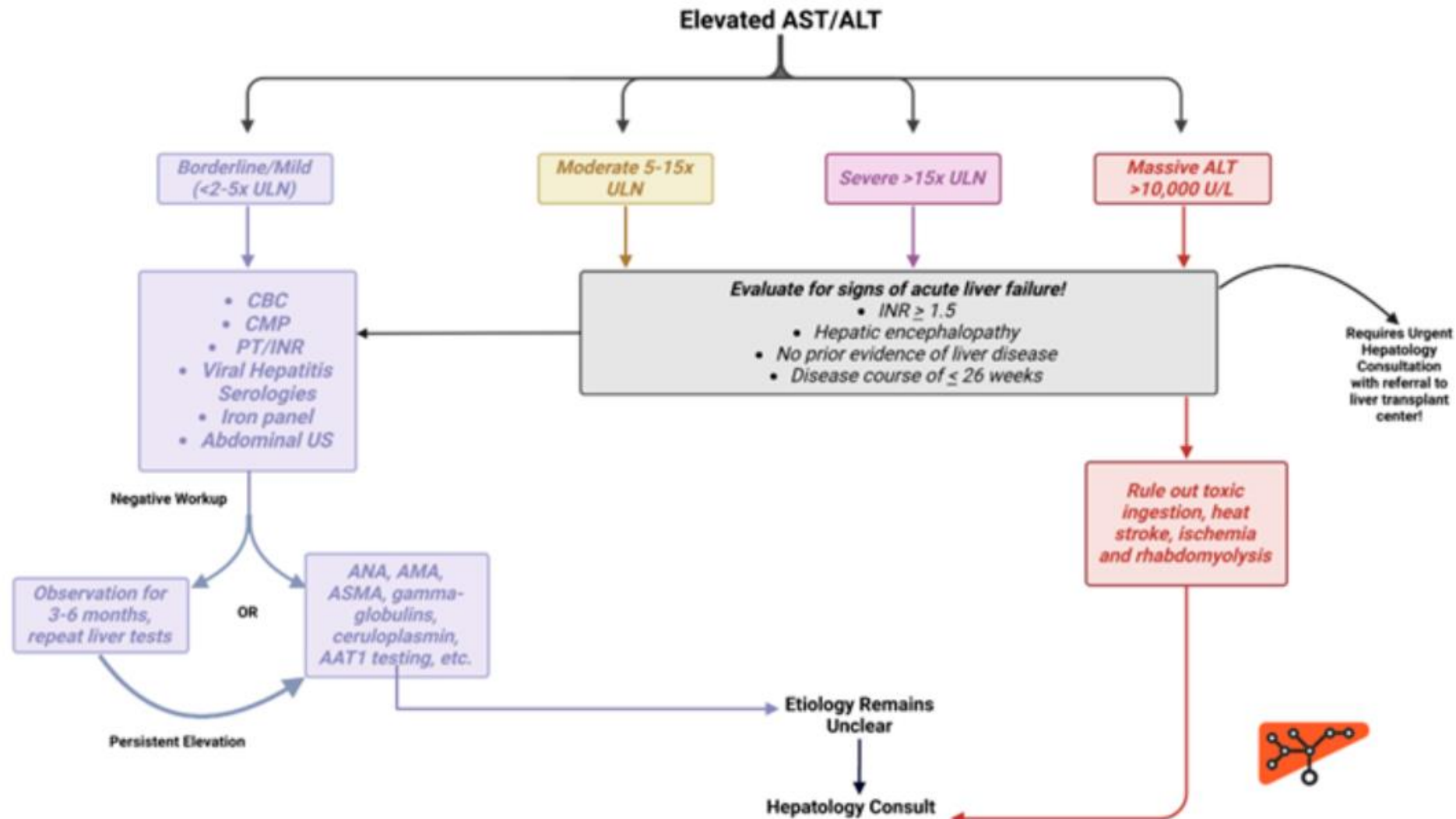
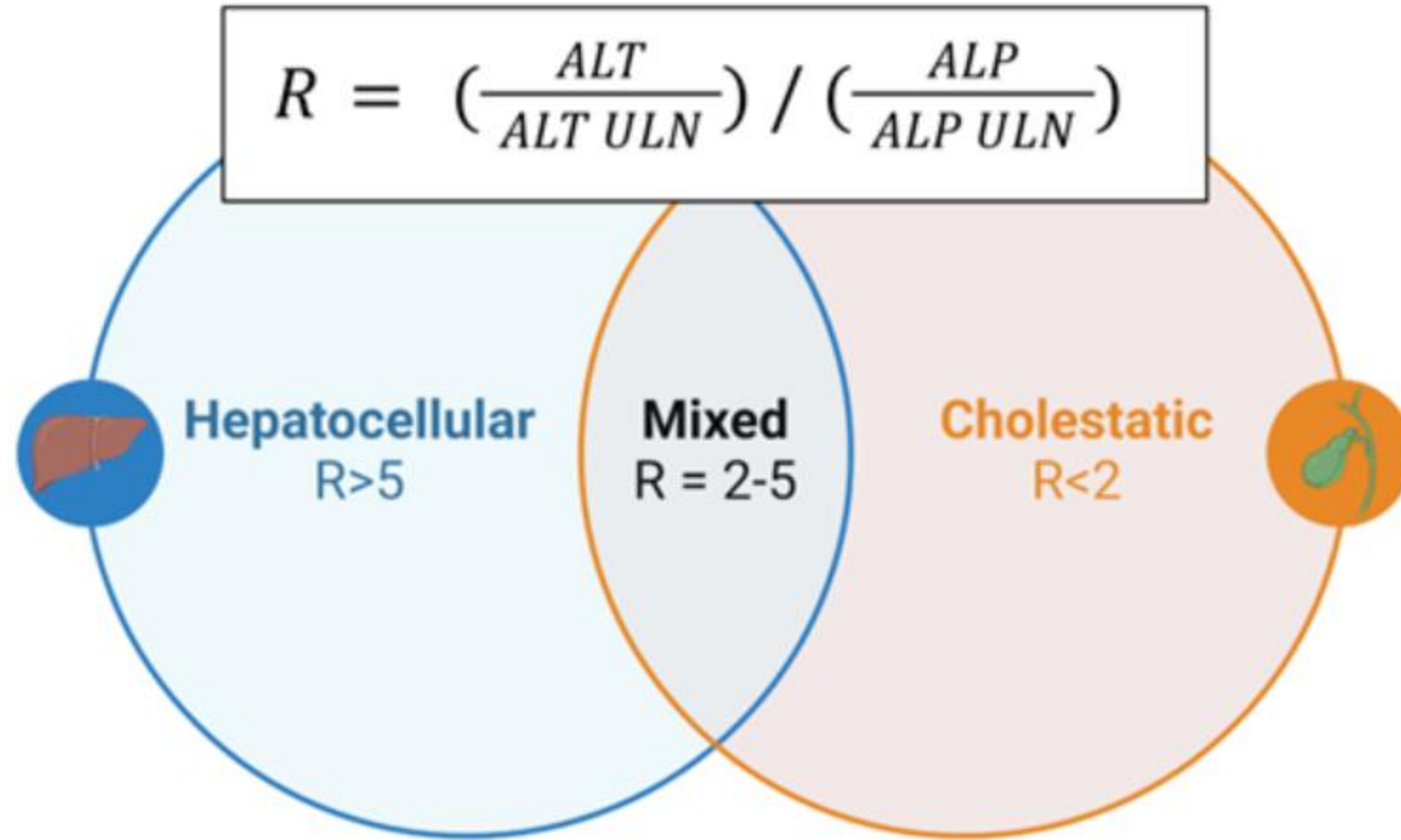
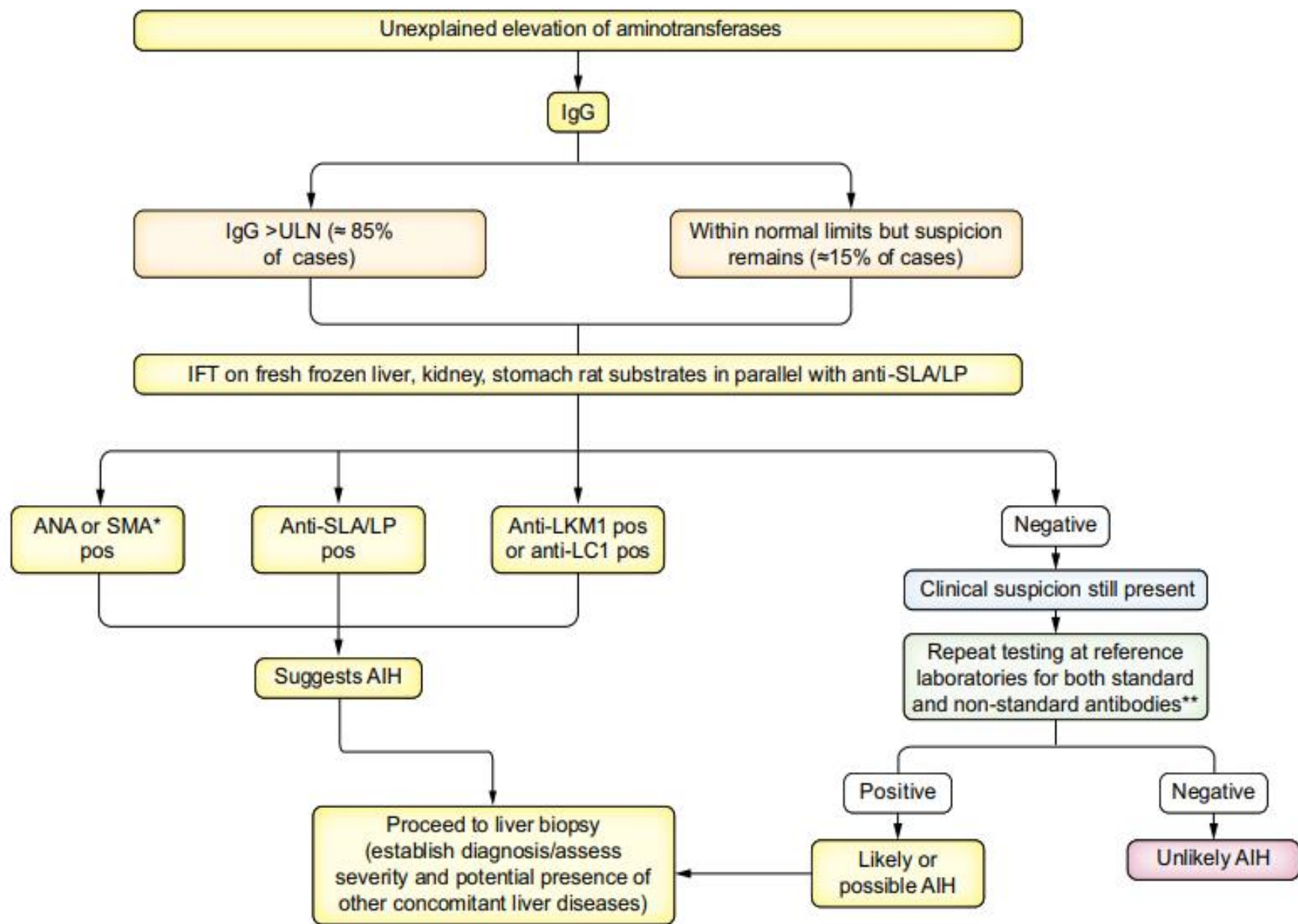


Figure 1. R-value and the different patterns of liver injury.





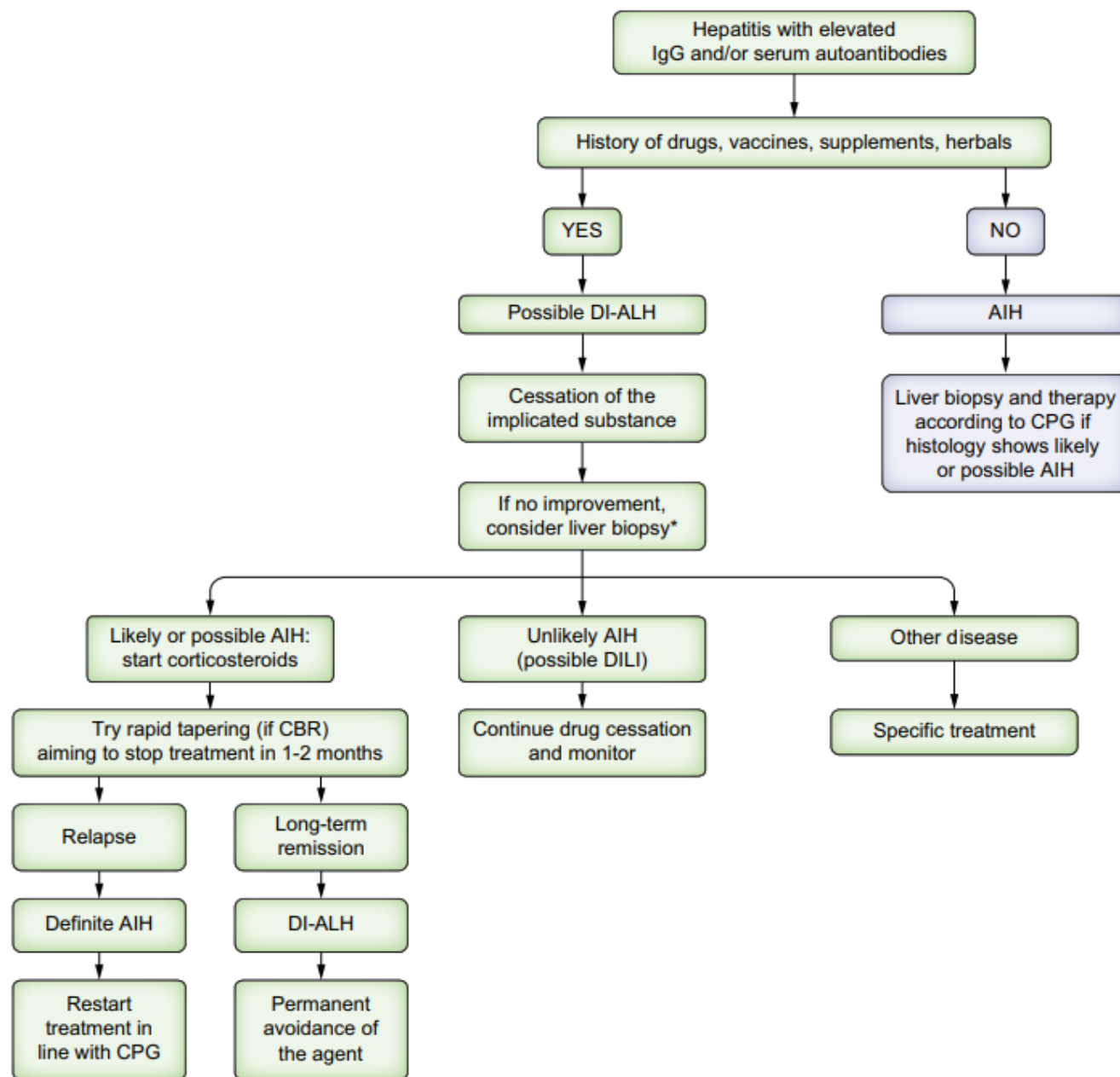


Fig. 2. Suggested algorithm for the differential diagnosis of DI-ALH and AIH. *The period of time to perform a liver biopsy depends on clinical judgement and varies according to the severity of ALT elevation. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; CBR, complete biochemical response; CPG, clinical practice guidelines; DI-ALH, drug-induced – autoimmune-like hepatitis; DILI, drug-induced liver injury; IgG, immunoglobulin G.

Table 3. — Revised scoring system for diagnosing AIH as developed in 1999

Criterion	Score
Female sex	+ 2
AF/AST (or ALT) ratio < 1.5 1.5-3.0 > 3.0	+ 2 0 - 2
Serum globulin or IgG above upper limit > 2.0 1.5-2.0 1.0-1.5 < 1.0	+ 3 + 2 + 1 0
ANA, SMA or anti-LKM1 > 1:80 1:80 1:40 < 1:40	+ 3 + 2 + 1 0
AMA positive	- 4
Viral hepatitis markers Positive Negative	- 3 + 3
Medication use Positive Negative	- 4 + 1
Alcohol intake < 25 g daily > 60 g daily	+ 2 - 2
Histology Interface hepatitis Lymphoplasmacytic infiltration Rosettes None of the above Biliary changes Other features	+ 3 + 1 + 1 - 5 - 3 - 3
Other autoimmune disease in patient or first-grade relative	+ 2

Table 1. — **Original diagnostic scoring system for AIH as developed in 1993**

Criterion	Score
Sex	
Female	+ 2
Male	0
AF/AST (or ALT) ratio	
> 3.0	- 2
< 3.0	+ 2
Serum globulin, γ -globulin or IgG above upper limit	
> 2.0	+ 3
1.5-2.0	+ 2
1.0-1.5	+ 1
< 1.0	0
ANA, SMA or anti-LKM1	
> 1:80	+ 3
1:80	+ 2
1:40	+ 1
< 1:40	0
AMA	
Positive	- 2
Negative	0
Viral markers	
Positive IgM HAV, HBsAg or IgM anti-HBc	- 3
Positive anti-HCV on ELISA	- 2
Positive anti-HCV on PCR	- 3
Positive test indicating active infection by any other virus	- 3
Seronegativity for all of the above	+ 3
Recent use of hepatotoxic medication or parenteral blood products	
Positive	- 2
Negative	+ 1
Mean alcohol intake in men	
< 35 g daily	+ 2
35-50 g daily	0
50-80 g daily	- 2
> 80 g daily	- 1
Mean alcohol intake in women	
< 25 g daily	+ 2
25-40 g daily	0
40-60 g daily	- 2
> 60 g daily	- 1
Other autoimmune disease in patient or first-grade relative	+ 1

Table 4. Proposed scoring system for the diagnosis of AIH and the AIH/PSC variant in the paediatric age group.⁸⁰

Characteristic	Cut-off	AIH points	AIH/PSC points
ANA and/or SMA*	≥1:20**	1	1
	≥1:80	2	2
Anti-LKM1* or	≥1:10**	1	1
	≥1:80	2	1
Anti-LC1	Positive**	2	1
Anti-SLA/LP	Positive**	2	2
pANNA	Positive	1	2
IgG	>ULN	1	1
	>1.2x ULN	2	2
Liver histology***	Compatible	1	1
	Typical	2	2
Absence of viral hepatitis (A, B, E, EBV), MASH, Wilson, and drug exposure	Yes	2	2
Extrahepatic autoimmunity	Yes	1	1
Family history of autoimmune disease	Yes	1	1
Cholangiography	Normal	2	-2
	Abnormal	-2	2

Score ≥7: Probable AIH; ≥8: Definite AIH. Score ≥7: Probable AIH/PSC; ≥8: Definite AIH/PSC.

AIH, autoimmune hepatitis; AIH/PSC, autoimmune hepatitis – primary sclerosing cholangitis; ANA, antinuclear antibody; anti-LC-1, anti-liver cytosol type 1; anti-LKM-1, anti-liver kidney microsomal antibody type 1; anti-SLA/LP, anti-soluble liver antigen/liver pancreas; EBV, Epstein-Barr virus; IAHPG, International Autoimmune Hepatitis Pathology Group; IgG, immunoglobulin G; MASH, metabolic dysfunction-associated steatohepatitis; pANNA, peripheral antinuclear neutrophil antibodies; SMA, smooth muscle antibodies; ULN, upper limit of normal.

*Antibodies measured by immunofluorescence assay on a composite rodent substrate (kidney, liver, stomach).

**Addition of points achieved for ANA, SMA, anti-LKM-1, anti-LC-1, and anti-SLA/LP autoantibodies cannot exceed a maximum of 2 points.

***Substitution of the histological component with the 2022 IAHPG criteria is expected to increase the sensitivity of AIH diagnosis also in children, as the new criteria are applicable in atypical cases with acute onset and predominantly lobular pattern of inflammation.⁹

DIAGNOSTIC SCORING SYSTEMS

Clinical feature	Points
ANA or SMA • $\geq 1:40$ • ANA or SMA $\geq 1:80$ or LKM1 $\geq 1:40$ or SLA-positive	+1 +2
Serum IgG • >upper limit of normal • >1.1 times upper limit of normal	+1 +2
Histologic findings • Compatible with AIH • Typical of AIH	+1 +2
Hepatitis viral markers • Negative	+2
Aggregate score without treatment • Definite AIH • Probable AIH	≥ 7 ≥ 6

AUTOANTIBODY NEGATIVE AUTOIMMUNE HEPATITIS

- Approximately 20 percent of patients who present with all the features of autoimmune hepatitis lack circulating ANA, ASMA, or anti-LKM-I antibodies
- These patients are usually regarded as having autoantibody negative autoimmune hepatitis or cryptogenic chronic hepatitis
- A therapeutic response to anti-inflammatory therapy may be the only indication that autoimmune hepatitis is the underlying disease in these patients

ATYPICAL AUTOANTIBODIES

- **Anti-soluble liver antigen/liver pancreas antigen (anti-SLA/LP)**
- **Atypical perinuclear anti neutrophil cytoplasmic antibodies (p-ANCA)**
- **Anti-actin antibodies**
- **Anti- α -actinin antibodies**
- **Anti-liver cytosol I (anti-LCI) antibodies**
- **Anti-asialo glycoprotein receptor antibodies (anti-ASGPR)**
- **Double-strand DNA (ds DNA) antibodies**

COMMON FEATURES IN HISTOLOGY

- **Interface hepatitis (70-80 % of patients)**
- **Plasma cell infiltration (66 %)**
- **Emperipolesis (65 %)**
- **Lobular hepatitis (47 %)**
- **Hepatocytic rosettes (33 %)**
- **Centrilobular necrosis (29 %)**

DIFFERENTIAL DIAGNOSIS

- **Primary biliary cholangitis**
- **Overlap syndromes**
- **Viral hepatitis**
- **Drug-induced liver injury**
- **Metabolic dysfunction-associated steatohepatitis**
- **Systemic lupus erythematosus (SLE)-associated liver disease**
- **Iron overload**
- **NAFLD**
- **NASH**
- **Celiac**

**THANK
YOU
FOR
YOUR
ATTENTION**

