

Autoimmune Liver Disease

Indications for Ordering

Differential evaluation of autoimmune liver disease (ALD) after exclusion of viral and drug-induced hepatitis, alcoholism, and specific hereditary risk factors

Test Description

Autoimmune Liver Disease Evaluation with Reflex to Smooth Muscle Antibody (SMA), IgG by IFA

- Semiquantitative enzyme-linked immunosorbent assay/semiquantitative indirect fluorescent antibody
- Components
 - F-Actin (Smooth Muscle) Antibody, IgG
 - Liver-Kidney Microsome – 1 Antibody, IgG
 - Mitochondrial M2 Antibody, IgG (ELISA)
 - Smooth Muscle Antibody, IgG Titer

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR-3) with Reflex to ANCA Titer

- Semiquantitative indirect fluorescent antibody/semiquantitative multiplex bead assay

Tests to Consider

Primary tests

[Autoimmune Liver Disease Evaluation with Reflex to Smooth Muscle Antibody \(SMA\), IgG by IFA 2007210](#)

- Recommended first-line panel for evaluation of ALD
 - Negative results do not rule out disease

[ANCA-Associated Vasculitis Profile \(ANCA/MPO/PR-3\) with Reflex to ANCA Titer 2006480](#)

- Initial test for evaluation of ALD in conjunction with autoimmune liver disease evaluation with reflex to SMA

Related tests

- [Antinuclear Antibody \(ANA\) with HEp-2 Substrate, IgG by IFA 3000082](#)
- [F-Actin and Mitochondrial M2 Antibodies, IgG by ELISA with Reflex to Smooth Muscle Antibody \(SMA\), IgG by IFA 2007209](#)
- [F-Actin \(Smooth Muscle\) Antibody, IgG by ELISA with Reflex to Smooth Muscle Antibody, IgG Titer 0051174](#)
- [Liver Cytosolic Antigen Type 1 \(LC-1\) Antibody, IgG 2010711](#)
- [Liver-Kidney Microsome Antibody, IgG 0099270](#)
- [Liver-Kidney Microsome – 1 Antibody, IgG 0055241](#)
- [Mitochondrial M2 Antibody, IgG \(ELISA\) 0050065](#)
- [Smooth Muscle Antibody, IgG Titer 0051244](#)
- [Soluble Liver Antigen Antibody, IgG 0055235](#)

Disease Overview

Prevalence

ALD – 5% of all liver diseases

- Autoimmune hepatitis (AIH)
 - 15-25/100,000 inhabitants in Europe (EASL, 2015)
- Primary biliary cholangitis (PBC)
 - 1.9-40.2/100,000 in European populations (EASL, 2017; Bowlus, 2014)

Incidence

- AIH
 - 0.85-1.9/100,000 per year for adults of white northern European ancestry (Czaja, 2015)
- Primary sclerosing cholangitis (PSC)
 - 0.3-5.8/100,000 per year in European populations (EASL, 2017)

Physiology

ALD

- Etiology – antibodies directed against the liver
- Chronic course with slow progression – may resemble other chronic liver diseases (eg, alcoholic cirrhosis, chronic viral hepatitis)
- Laboratory findings may include
 - Hypergammaglobulinemia (elevated total protein, decreased albumin, and decreased anion gap)
 - Elevated liver enzymes in the absence of chronic or drug-induced hepatitis

AIH – two main types, AIH types 1 and 2

- A variant of type 1, referred to as type 3, has been described
- AIH type 1 – most common
 - Female preponderance (70-80% of cases)
 - Seen in all ethnic groups, with a predominance in Caucasians
 - Affects individuals of all ages, but less common in children
 - Associated autoimmune diseases
 - Thyroiditis
 - Rheumatoid arthritis
- AIH type 2 – usually presents in childhood; rare in adults
 - Clinical features vary widely
 - Arthralgias
 - Anorexia, fatigue, jaundice, lethargy, malaise
 - Hepatomegaly, nausea, upper abdominal pain
 - Progression to cirrhosis and liver failure possible
 - Antibody-negative disease
 - Same presentation and histology as antibody-positive AIH
 - Diagnosis of exclusion
 - No other etiology found for liver disease/cirrhosis – key to this diagnosis
 - Overlap syndrome (AIH present with one of the following)
 - Autoimmune cholangitis
 - Antimitochondrial antibodies (AMA)-negative PSC
 - Autoimmune sclerosing cholangitis
 - IgG4 cholangitis
 - PBC
 - PSC
 - Laboratory tests – several antibodies may be present, depending on AIH type (see table)

PBC

- Female preponderance (~90% of cases)
- Age – primarily >40 years
- Clinical features
 - Most patients are asymptomatic or only mildly fatigued at time of diagnosis
 - Chronic pruritus, hyperpigmentation
 - Jaundice, hepatomegaly, splenomegaly, upper abdominal pain
 - Progression to cirrhosis and liver failure possible
 - Many overlapping features with AIH
 - Associated with other autoimmune disorders (eg, CREST syndrome, rheumatoid arthritis)
- Laboratory tests
 - AMA – specific for PBC
 - Some patients with PBC may be negative for AMA but positive for GP210 or SP100 antibodies

PSC

- Male preponderance
- Age – ~40 years at time of diagnosis
- Strongly associated with inflammatory bowel disease (IBD) – 75-90%
- Clinical features – mimic those of PBC
 - Clinical course varies widely
 - Asymptomatic patients – 20-40%
 - Fatigue, jaundice, pruritus, upper abdominal pain
 - Progression to cirrhosis and liver failure possible
 - Increased risk for
 - Cholangiocarcinoma
 - Colorectal cancer if PSC is concurrent with ulcerative colitis (compared to patients with only ulcerative colitis)
- Laboratory tests
 - Predominant – Atypical p-ANCA, ANA, +/- SLA

Diagnostic/prognostic issues

- May be difficult to diagnose AIH initially as symptoms may mimic those of chronic hepatitis
- No single diagnostic test for AIH
- Antibody testing may be helpful in diagnosing/distinguishing ALD subtype after more common etiologies of hepatitis have been ruled out (see table)
 - Titers may be lower early in disease
 - Low titers in children likely reflect disease
- Liver biopsy may be appropriate in certain patients
 - Should be performed when diagnosis is still unclear
 - Considered “gold standard”

Test Interpretation

Clinical sensitivity – ~85-90% for AMA

Results

See table

Limitations

- Negative antibody testing does not rule out ALD
- All interpretation of antibody patterns must be done in conjunction with clinical presentation
 - There may be overlap between diseases and antibodies detected
 - No single test shows absolute specificity

References

- Bowlus CL, Gershwin E. The diagnosis of primary biliary cirrhosis. *Autoimmun Rev.* 2014; 13(4-5): 441-4
- Czaja AJ. Diagnosis and management of autoimmune hepatitis. *Clin Liver Dis.* 2015; 19(1): 57-79
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol.* 2015 Oct;63(4):971-1004
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol.* 2017; 67(1): 145-172

Associated Autoantibody Profile										
Disease	ANA Pattern	ANCA Pattern	SMA	F-actin	AMA (M2)	GP210	SP-100	LKM-1	LC-1	SLA
AIH-1	Homogenous pattern most common		+	+	-	-	-	-	-	+/-
AIH-2	-	Rare	-	-	-	-	-	+	+	-
PSC	+	Atypical p-ANCA	+/-	-	-	-	-	-	-	+/-
PBC	Nuclear dot or nuclear envelope pattern on HEp-2 cell substrate	-	-	-	+	+	+	-	-	-
AIH, autoimmune hepatitis type 1 or 2; AMA, antimitochondrial antibody; ANA, antinuclear antibody; GP210, glycoprotein-210; LC-1, liver cytosolic antigen type 1; LKM-1, liver-kidney microsomal-1 (cytochrome P450 2D6); M2, mitochondrial antigen 2 (PDH-E2); p-ANCA, perinuclear antineutrophil cytoplasmic antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody										