

Primary Biliary Cirrhosis - PBC

Clinical Background

Primary biliary cirrhosis (PBC) is an autoimmune liver disorder characterized by chronic, progressive cholestatic disease.

Epidemiology

- Incidence – 25-27/1,000,000 in U.S.
- Age – peak onset in 40s
- Sex – M<F, 1:9

Risk Factors

- Presence of another autoimmune disorder
- Family history of PBC
 - The risk for a first-degree relative of a PBC patient is 50- to 100-fold higher than the general population

Pathophysiology

- Etiology is unknown
- Pathogenesis of PBC is believed to be caused by:
 - Defect in immune tolerance resulting in the expansion of self-mitochondrial antigen specific for T and B lymphocytes
 - Inappropriate immune response following environmental or infectious agent causes modification of mitochondrial proteins or molecular mimicry
- PBC is characterized by T-cell mediated destruction of bile duct epithelial cells resulting in loss of ducts and persistent cholestasis, which may lead to end-stage liver failure without treatment

Clinical Presentation

- Large majority of patients initially diagnosed are asymptomatic or only mildly fatigued
- Fatigue, pruritus, jaundice
- Complications
 - Osteoporosis
 - Esophageal varices
 - Hepatocellular carcinoma
- Association with other autoimmune disorders
 - CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia)
 - Sicca syndrome
 - Autoimmune thyroid disease
 - IgA deficiency
 - Chronic autoimmune hepatitis (AIH)
 - PBC and AIH have many overlapping immunologic features
 - Some patients may have serologic tests and histologic findings suggestive of AIH in addition to PBC (may be continuum of a single disease entity)
 - Addison disease
 - Systemic lupus erythematosus (SLE)
 - Autoimmune thrombocytopenia or hemolytic anemia

- Rheumatoid arthritis
- Scleroderma

Treatment

- Medical therapy
 - Ursodeoxycholic acid does not reduce the risk for mortality or liver transplantation
 - Cholestyramine for pruritis
- Liver transplantation for endstage cirrhosis

Diagnosis

- Indications for testing – chronic pruritis, jaundice; elevated liver enzymes with predominant cholestatic picture
- Laboratory testing
 - Initial testing – aminotransferases, alkaline phosphatase, bilirubin
 - Serologic testing should include other autoimmune liver antibodies to rule out AIH
 - Anti-nuclear antibodies (ANA)
 - Smooth muscle antibody (SMA)
 - Liver-kidney microsome-1 antibody (LKM1)
 - Perinuclear staining anti-neutrophil cytoplasmic antibody (pANCA)
 - PBC is strongly associated with antimitochondrial antibody (AMA), M2 type
 - However, M2 levels in PBC do not appear correlated with clinical activity or disease progression
 - Approximately 5-10% of PBC patients are AMA negative
- Histology – biopsy is not always indicated and not necessary for diagnosis if patient has positive AMA and evidence of cholestasis on liver testing, but it does allow classification of disease severity
 - Pathological lesion is chronic non-suppurative destructive cholangitis
- Imaging studies
 - If AMA negative and PBC is suspected, endoscopic retrograde cholangiopancreatography (ERCP), cholangiography or magnetic resonance cholangiopancreatography should be performed

Prognosis

- AMA with IgG3 subclass may identify patients with more severe disease risk

Differential Diagnosis

- Autoimmune hepatitis
- Biliary carcinoma
- Cholelithiasis
- Chronic hepatitis
- Nonalcoholic fatty liver disease
- Primary sclerosing cholangitis (PSC)

Monitoring

- Anti-gp210 is prognostic in PBC
 - Failure to see a decline with treatment increases risk of progression to end-stage hepatic failure

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Alanine Aminotransferase, Serum or Plasma 0020008 Method: Enzymatic	Initial testing to evaluate liver dysfunction		
Bilirubin, Direct & Total, Serum or Plasma 0020426 Method: Spectrophotometry	Initial testing to evaluate liver dysfunction		
Alkaline Phosphatase Isoenzymes 0021020 Method: Heat Inactivation/Enzymatic	Initial testing to evaluate liver dysfunction		
Autoimmune Hepatitis Panel Plus with Reflex to Titers 0055351 Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody	Rule out autoimmune hepatitis		
Mitochondrial M2 Antibody, IgG (ELISA) 0050065 Method: Enzyme-Linked Immunosorbent Assay	Aid in the diagnosis of primary biliary cirrhosis (PBC)	A negative M2 antibody result does not rule out PBC; about 5-10% of these patients are seronegative	

Additional Tests Available

Test Name and Number	Comments
Anti-Nuclear Antibodies (ANA), IgG Screen with Reflex to IFA Titer 0050080 Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody	

<p>F-Actin (Smooth Muscle) Antibody, IgG by ELISA with Reflex to Smooth Muscle Antibody, IgG Titer 0051174 Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody</p>	
<p>Liver-Kidney Microsome - 1 Antibody, IgG 0055241 Method: Enzyme-Linked Immunosorbent Assay</p>	
<p>Anti-Neutrophil Cytoplasmic Antibody, IgG 0050811 Method: Indirect Fluorescent Antibody</p>	
<p>Centromere Antibody, IgG 0050714 Method: Multi-Analyte Fluorescent Detection</p>	

Guidelines

Primary biliary cirrhosis. American Association for the Study of Liver Diseases - Private Nonprofit Research Organization. 2000 April (Revised 2009 July).

General References

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References from the ARUP Institute for Clinical and Experimental Pathology®

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Liver Disease or Hepatitis of Unknown Etiology Testing Algorithm

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