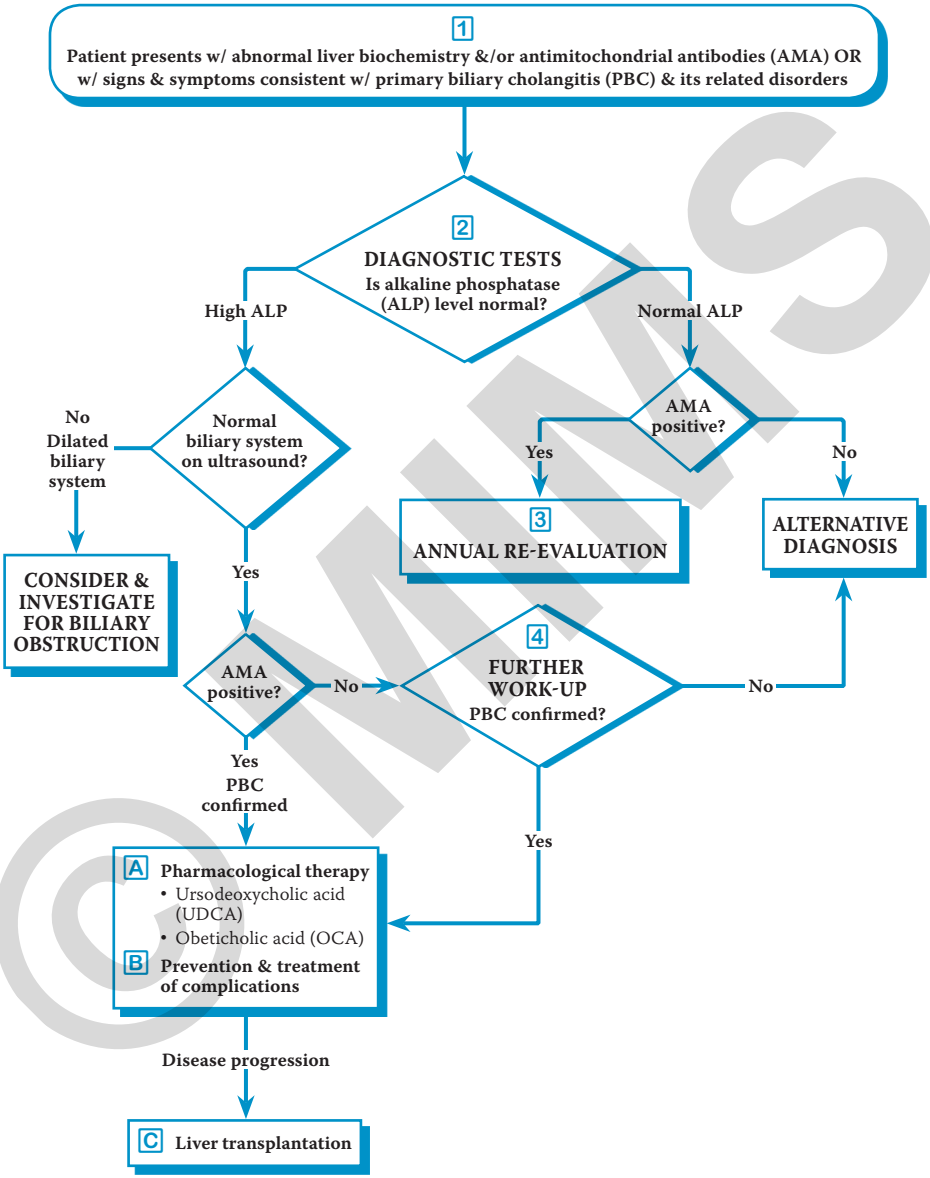
Primary Biliary Cholangitis (1 of 8)



1 INITIAL PRESENTATION OF A PATIENT W/ PRIMARY BILIARY CHOLANGITIS (PBC)

- PBC is an autoimmune disease of a chronic & progressive nature, characterized by destruction of small to medium bile ducts, leading to cholestasis & frequently, end-stage liver disease
  - Diagnostic features of PBC are the chronic biochemical cholestasis, presence of antimitochondrial antibodies (AMA) & the characteristic liver biopsy findings
- Suggested to have environmental &/or genetic factors affecting its development
- PBC is more common in Northern Europeans & the majority of the patients are middle-aged women
  - Men w/ the disease are more likely to develop hepatocellular carcinoma (HCC)
- At present, the diagnosis is most often made in an asymptomatic patient who presents w/ abnormal lab results (eg abnormal liver biochemistry profile &/or the presence of AMA) on a routine checkup or as part of workup for an associated illness

Symptoms of PBC

Fatigue

- The most common symptom seen in 50-78% of patients
- Associated w/ depression, obsessive-compulsive disorder & sleep disturbances
- Symptom does not correlate w/ severity of liver disease

Pruritus

- Prevalence rate is 20-70% in patients w/ PBC
- A circadian rhythm may be noted w/ worse symptoms at night
- May be so severe as to cause severe emotional disturbance
- May be present even in patients w/ good liver function
- Declines in severity w/ time from diagnosis

Jaundice

- Present in 10-60% of patients due to cholestasis

Right Upper Quadrant Pain

- Occurs in 8-17% of patients

Physical Exam

- In the early stages of disease, findings may be normal
- Abnormal findings increase as the disease progresses

Portal Hypertension

- Patients may present initially w/ variceal hemorrhage secondary to portal hypertension, which may be of a cirrhotic or non-cirrhotic nature
- Anemia may develop from occult bleeding of varices

Stigmata of Liver Disease

- The following may be present: Spider nevi, palmar erythema, muscle wasting, peripheral edema, parotid gland enlargement, gynecomastia, testicular atrophy, Dupuytren contracture

Signs of Malabsorption of Fat-Soluble Vitamins

- Results from insufficient biliary secretion of bile acids
- Neurological impairment & electromyograph changes secondary to vitamin E malabsorption
- Rarely, night blindness & osteomalacia are present in PBC patients

Other Possible Findings in Patients w/ PBC

- Xanthomata
  - Cholesterol deposits in the skin, they often occur around the eyes but may also be found on the palms, buttocks & heels
  - May be associated w/ hypercholesterolemia & hyperlipidemia that occur w/ PBC
- Hyperpigmentation, splenomegaly, hematemesis, melena, abdominal fullness
- Urinary tract infections
  - Usually asymptomatic but recurrent
  - Etiologic agents are usually Gram-negative organisms, ie *Enterobacteriaceae*
  - Cross reactivity between antigens on the bacterial wall & cell mitochondria is postulated to be the cause

Signs of Metabolic Bone Disease

- A patient w/ PBC may present w/ osteoporosis while remaining asymptomatic from the liver disease
  - An elevated ALP level in a patient w/ osteoporosis should alert a physician of the possibility of PBC
- PBC patients may have associated pancreatic insufficiency & celiac disease which may aggravate vitamin D malabsorption, contributing to osteoporosis
- Decreased osteoblastic activity & increased osteoclastic activity lead to development of osteoporosis in PBC patients

1 INITIAL PRESENTATION OF A PATIENT W/ PRIMARY BILIARY CHOLANGITIS (PBC) (CONT'D)

Disorders Associated w/ PBC

- Sicca syndrome
  - Symptoms include xerophthalmia, xerostomia, dental caries, dysphagia, dyspareunia & tracheobronchitis
  - Investigate symptoms by direct questioning
  - Sicca symptoms are present in about ¾ of PBC patients
- Thyroid dysfunction
  - Thyroid disease is also of autoimmune origin
  - Symptoms usually precede diagnosis of PBC
- CREST syndrome
  - (C-calcinosis cutis, R-Raynaud's phenomena, E-esophageal dysmotility, S-sclerodactyly, T-telangiectasia)
  - Complete form is rarely seen in PBC patients
  - Raynaud's syndrome by itself is seen more often & is more problematic for patients who live in cold climates
- Rheumatoid factor is detected in 25% of PBC patients
  - Symptomatic arthritis is less common
- Celiac disease & inflammatory bowel disease (IBD) occur rarely

2 DIAGNOSTIC TESTS

- At least 2 of the following criteria should be present for the diagnosis of PBC: Biochemical cholestasis w/ elevated ALP, presence of AMA, & the characteristic liver biopsy findings

Serum Chemistry

Alkaline Phosphatase (ALP)

- High ALP of hepatic origin signifying intrahepatic cholestasis is the most common biochemical abnormality in PBC
  - >1.5 times the upper limit of normal (ULN) for >24 weeks
- Response to therapy may be seen with an ALP level <2x ULN w/ treatment

Gamma-Glutamyl Transpeptidase (GGT)

- Levels are determined to confirm hepatic origin of high ALP levels

Bilirubin

- Elevated bilirubin levels occur late in the course of disease
- High bilirubin levels signify disease progression & are used as a predictor of prognosis

Cholesterol

- Total serum cholesterol levels may go up as a result of chronic cholestasis
- The high-density lipoprotein (HDL) fraction is increased, which is the reason why PBC patients do not have a higher risk for atherosclerosis

Imaging Studies

Hepatobiliary Ultrasound (US)

- US of the liver & biliary tract should be done to differentiate intrahepatic versus extrahepatic cholestasis
- Bile ducts appear normal in patients w/ PBC
- A dilated biliary system characterizes biliary obstruction & is not consistent w/ PBC
- PBC patients may have nonspecific findings on US, eg increased echogenicity of liver parenchyma & portal lymphadenopathy
- Portal hypertension may be present, as evidenced by a nodular liver appearance, ascites & intra-abdominal varices

Transient Elastography

- Accurate in diagnosing advanced fibrosis in PBC patients
- May be used in assessing prognosis & response to therapy
  - Also used to risk-stratify patients: Liver stiffness progression is a predictor of poor outcome

Antimitochondrial Antibodies (AMA)

- The presence of AMA in the serum, often in high titers (≥1:40), is the hallmark of PBC
- AMA, which target different mitochondrial enzymes, are found in up to 95% of PBC patients
- The simplest test for detection of AMA is immunofluorescence, but newer tests eg enzyme-linked immunosorbent assay (ELISA) & immunoblotting are more specific & sensitive
- Sensitivity & specificity of AMA for PBC is >95%
- Patients w/ an elevated ALP & normal hepatobiliary US should undergo serum testing for AMA

2 DIAGNOSTIC TESTS (CONT'D)

Liver Biopsy

- Findings on liver biopsy for PBC are very specific, especially in non-cirrhotic patients: Nonsuppurative destructive cholangitis & interlobular destruction of the bile ducts
- A liver biopsy is essential in the following patients to confirm or rule out PBC:
  - Low-titer (<1:40) or negative AMA
  - Transaminases [alanine aminotransferase (ALT) & aspartate aminotransferase (AST)] are prominently increased
  - Patient w/ a history of taking potentially hepatotoxic drugs
- In contrast, a patient positive for AMA w/ a titer ≥1:40 plus typical symptoms & biochemical derangements may not require a liver biopsy to make the diagnosis of PBC
  - However, the liver biopsy may provide additional information about the stage of the illness & the patient's prognosis
- For biopsy findings to provide a precise evaluation of bile duct damage, it is very important that the specimen has an adequate number (at least 10-15) of portal tracts
- Not to be used to monitor patient's response to therapy

Differential Diagnoses

- Alternative diagnoses include primary sclerosing cholangitis, obstructive jaundice, drug-induced liver injury, autoimmune hepatitis (AIH), hyperthyroidism, bone lesions, sarcoidosis

3 ANNUAL RE-EVALUATION FOR CERTAIN PATIENTS

- Patients positive for AMA, but have a normal ALP level, should have their liver biochemistry rechecked yearly
- A small study has shown that most AMA-positive asymptomatic individuals w/ normal ALP eventually develop evidence of cholestasis &/or cholestatic symptoms after several years

4 FURTHER WORKUP FOR AMA-NEGATIVE PATIENTS W/ CLINICAL SUSPICION OF PBC

- Certain patients may have clinical, biochemical & histologic evidence of PBC but consistently test negative for AMA
  - Further workup should be considered in patients negative for AMA but with high ALP & normal biliary US
- These patients most likely do have PBC but have an antibody profile more consistent w/ AIH, a variant known as PBC/AIH overlap
  - In patients w/ PBC/AIH overlap, the predominant histological pattern of injury should be targeted for treatment
- Patients w/ the above characteristics should undergo further tests

Antinuclear Antibodies (ANA) &/or Smooth Muscle Antibodies (SMA)

- AMA-negative patients clinically suspicious for PBC should be tested for ANA & SMA
  - Nearly half of PBC patients may be positive for ANA & SMA
- High titers of ANA &/or SMA are more common in AIH, but may be present in AMA-negative patients w/ a high clinical suspicion of PBC
  - In these patients, a thorough review of liver biochemistry & biopsy findings is imperative in making a correct diagnosis; patients w/ AIH have a serum ALT level of >5x ULN

Immunoglobulins (Ig)

- Testing for the immunoglobulin pattern is probably only needed in unconvincing cases
- A high level of IgM is usual in PBC
- IgA levels are usually normal but PBC has been found in patients who are IgA deficient
- In AMA-negative PBC, however, the IgG fraction is more likely to be elevated than the IgM fraction
  - AIH has serum IgG levels >2x ULN

Imaging

- Magnetic resonance cholangiopancreatography (MRCP) can be performed in patients w/ unexplained cholestasis
- Endoscopic US, an alternative to MRCP, can be used in evaluating distal biliary disease

Liver Biopsy

- May be done in patients w/ unexplained intrahepatic cholestasis after serologic screening & additional imaging
- Considered in ruling out concomitant AIH in PBC patients w/ highly elevated ALT &/or IgG
- Not required in diagnosing AMA-negative PBC if other criteria, eg cholestatic liver tests & PBC-specific autoantibodies (sp100 or gp210), are met

A PHARMACOLOGICAL THERAPY

- All PBC patients w/ abnormal liver biochemistry are possible candidates for specific therapy
- Treatment goals are to prevent end-stage liver disease & to manage PBC-associated symptoms affecting patient's quality of life

Ursodeoxycholic Acid (UDCA)

- Patients w/ abnormal liver biochemistry (regardless of histologic stage) & confirmed PBC should be given UDCA
- Chief medication used to deter disease progression
- **Action:** Increases the rate of transport of intracellular bile acids across the liver cell & into the canaliculus, thus reducing hydrophobic bile acid levels inside hepatic cells
  - May have anti-inflammatory, choleretic, cytoprotective & immunomodulatory effects
- Results in significant improvement in biochemical markers of cholestasis (ALP, GGT, bilirubin, AST, ALT); decreased serum LDL cholesterol; decreased AMA titers
- UDCA therapy results in a significant increase in survival after up to 4 years of treatment, thus delaying the need for liver transplantation
  - The biggest benefit is seen in those w/ the most severe disease
- UDCA also protects PBC patients from developing hepatoma
- UDCA use may have little effect on symptoms
  - The drug may delay development of portal hypertension
  - Treatment reduces the rate of development of esophageal varices, but does not reduce the rate of bleeding from these varices
  - There has been no evidence that UDCA decreases fatigue or pruritus, or that it has any benefit on osteoporosis or autoimmune features associated w/ PBC
- Patient compliance may be better when a single daily dose is used, compared to divided doses
  - Single daily dose is just as effective as divided doses
- Assess biochemical response after 1 year of UDCA therapy

Obeticholic Acid (OCA)

- May be used as monotherapy in patients intolerant to UDCA or in combination w/ UDCA in patients w/ inadequate response to a year of UDCA therapy
- **Action:** Modulates the synthesis, absorption, transport, secretion & metabolism of bile acids resulting to a choleretic effect
- Liver chemistries & inflammatory markers improved w/ therapy
- Most common adverse effect is pruritus
- Use is not recommended in decompensated PBC

Other Agents

- Fibrates may be considered as an off-label therapy in patients w/ inadequate response to UDCA therapy but not in those w/ decompensated liver disease
- Immunosuppressive drugs have been studied for PBC because of the autoimmune nature of the disease
  - Immunosuppressive therapy, in addition to UDCA, may benefit PBC patients w/ AIH
  - Corticosteroids combined w/ UDCA had shown improvement of liver function serum parameters & histologic grades in controlled trials
    - Budesonide in combination w/ UDCA had been shown in clinical trials to improve liver function serum parameters as well as liver histology in patients w/ grade I-III fibrosis
  - A few studies have shown some benefits from treatment w/ Azathioprine & Ciclosporin but adverse effects may limit usefulness
  - Studies have found insufficient evidence regarding the benefit of additional treatment w/ Colchicine, Methotrexate, or Silymarin
- Mycophenolate mofetil, Chlorambucil, Penicillamine, Thalidomide, Seladelpar, leukotriene antagonists, antiretrovirals, molecular therapies, & monoclonal antibodies are promising therapies that are currently being studied

B PREVENTION & TREATMENT OF COMPLICATIONS

- Patients w/ cirrhosis & inadequate biochemical response to treatment [ie diagnosed at early age (eg <45 years), presented w/ advanced disease stage] have a high risk of developing PBC complications
- Assess PBC activity & progression w/ tests for albumin, total bilirubin, AST, ALT, ALP, GGT, PT every 3-6 months
- Assess esophageal/gastric varices complication w/ an upper GI endoscopy annually, & liver cirrhosis w/ an abdominal US w/ or without serum alpha-fetoprotein every 6 months

Fatigue

- As there is currently no recommended therapy for fatigue, patient education & counseling regarding this symptom is important
- Determine & treat other causes of fatigue, eg anemia, hypothyroidism, sleep disorders

Pruritus

- Pruritus has a significant effect on a patient's life & is often refractory to medical treatment
- Lifestyle changes such as avoidance of itchy or tight clothes & use of moisturizers or emollients, tepid baths, or ice packs may be helpful

Cholestyramine

- Cholestyramine is the main drug used to treat cholestasis-associated pruritus
- **Action:** Binds bile acids in the gut lumen promoting its fecal excretion
- Most effective in patients w/ intact gallbladders if taken before & after breakfast, because this is when the largest amount of bile is available for binding by the drug
- Drug takes effect within 1-4 days of starting therapy
- Effect is optimal w/ daily treatment
- Given 2-4 hours before or after other medications because Cholestyramine can also bind other oral drugs
- Patients unresponsive to Cholestyramine can be given Rifampicin, opioid antagonists eg Naltrexone & Naloxone, or Sertraline

Antihistamines

- May be used to control mild pruritus early in the course of the disease
  - Should be used w/ caution in patients w/ cirrhosis or signs of encephalopathy because antihistamines can depress brain function further
- Not typically very effective & most of the relief results from sedation

Others

- Other medications for the treatment of pruritus are Rifaximin, Dronabinol, Phenobarbital & Metronidazole
- Newer agents include a peroxisome proliferator activator receptor (PPAR) agonists, autotaxin inhibitors & ileal bile acid reabsorption transporter inhibitors

Portal Hypertension

- Portal hypertension may develop earlier than cirrhosis from nodular regenerative hyperplasia
- Nonselective beta-blockers may help relieve portal hypertension
- Patients may also benefit from shunt surgery
- Patients should be screened endoscopically for varices upon diagnosis of PBC & every 3 years thereafter
- Prophylactic measures to prevent bleeding should be carried out in patients w/ varices

Metabolic Bone Disease

- Osteoporosis is often subtle & can only be detected by measuring bone mineral density using dual energy X-ray absorptiometry (DEXA)
- Patient's bone mineral density should be assessed at the time of diagnosis of PBC & every 1-2 years thereafter
- All PBC patients should be advised to engage in regular weight-bearing exercise & if required, to stop smoking & drinking alcohol
- Vitamin D & calcium supplementation should be given
- In patients w/ evidence of osteoporosis, bisphosphonates are of benefit
- Estrogen hormone replacement therapy may be needed in certain patients
  - Transdermal administration may be the preferred route

B PREVENTION & TREATMENT OF COMPLICATIONS (CONT'D)

Sicca Syndrome
- Symptoms of the sicca syndrome should be elicited by direct questioning
- Patients w/ dry eyes should be given artificial tears initially to prevent complications eg corneal ulceration
  - Ciclosporin or Lifitegrast can be used in patients unresponsive to other therapies
- Patients w/ dry mouth should be given saliva substitutes & undergo monitoring of oral health
- Pilocarpine or Cevimeline can be given to patients w/ dry mouth or dry eyes who are unresponsive to other therapies
- Liquids should be given w/ food & medications to ease swallowing
- Lubricating jelly & moisturizers may be used in female patients w/ dyspareunia

Malabsorption of Fat-Soluble Vitamins
- Replacement of fat-soluble vitamins (eg vitamin K) may be given using their parenteral or water-soluble forms
- If bilirubin level is >2 mg/dL, monitor vitamins A, D, E & prothrombin time yearly

Hyperlipidemia
- A complication of chronic cholestasis, hyperlipidemia seen in PBC is apparently not associated w/ increased risk of cardiovascular disease
- Statins & fibrates may be given to patients w/ PBC
  - Fibrates may occasionally cause a paradoxical increase in serum cholesterol levels

Thyroid Dysfunction
- Thyroid-stimulating hormone should be determined at the time of diagnosis of PBC & regularly thereafter ie yearly

Raynaud's Syndrome
- More of an issue for patients in cold climates
- Patient should be advised to avoid exposure of extremities to cold & to stop smoking
- Calcium antagonists may relieve extremity symptoms but may worsen esophageal dysmotility

C LIVER TRANSPLANTATION

- Liver transplantation is the only life-saving procedure for patients w/ progressive PBC & consequent liver failure
  - Increasing bilirubin & decreasing albumin levels & a prolonged prothrombin time are signs of disease progression
- A referral for a liver transplant evaluation should be done in patients w/ decompensated cirrhosis, total bilirubin >6 mg/dL, a MELD score of at least 15 & >7.8 from the updated Mayo Clinic Natural History Model for PBC
- Consider liver transplantation in refractory ascites, recurrent spontaneous bacterial peritonitis, recurrent variceal bleeding, hepatic coma, HCC or hepatorenal syndrome type I
  - Uncontrollable pruritus resistant to medical therapy may also be an indication for liver transplantation
- Patients w/ PBC recurrence post liver transplant can be given UDCA therapy

Dosage Guidelines

BILE ACIDS & DERIVATIVES

Drug	Dosage	Remarks
Obeticholic acid	**Non-cirrhotic or compensated Child-Pugh Class A patients:** 5 mg PO 24 hrly May increase to 10 mg PO 24 hrly after 3 mth if liver chemistries remain abnormal & patient is tolerating the medication well **Child-Pugh Class B or C or patients w/ prior decompensation:** 5 mg PO once wkly May increase to 5 mg PO twice wkly (at least 3 days apart) after 3 mth if liver chemistries remain abnormal & patient is tolerating the starting dose May titrate to 10 mg twice wkly (at least 3 days apart) based on patient's response & tolerability	**Adverse Reactions** • GI effects (abdominal pain, constipation); Other effects (pruritus, fatigue, dizziness, arthralgia, edema, skin rash, palpitations, fever, decreased HDL-C level, abnormal thyroid function) **Special Instructions** • Avoid in patients w/ complete biliary obstruction, hepatic disease or decompensation, gastroenteritis, peritonitis, dehydration • Monitor liver function & for changes in serum lipid concentrations during therapy
Ursodeoxycholic acid	8-16 mg/kg/day PO divided 6-12 hrly If liver values improve after 1st 3 mth of therapy, dose may be taken 24 hrly in the evening	**Adverse Reactions** • GI effects (diarrhea, pulpy stools, N/V, constipation); Other effects (pruritus, headache, insomnia, depression, bronchitis, myalgia, arthralgia) **Special Instructions** • Avoid in patients w/ acute cholecystitis, obstructive hepatobiliary disease, inflammatory bile duct disease, parenchymal liver disease, colitis, acute gastroduodenal ulcer • Use w/ caution in patients w/ peptic ulcer disease or IBD • May be given only in patients w/ an intact & functioning gallbladder

BILE ACID SEQUESTRANT

Drug	Dosage	Remarks
Colestyramine (Cholestyramine)	4 g PO 6-8 hrly	**Adverse Reactions** • GI effects (eg constipation, rarely cause fecal impaction, abdominal pain, bloating, flatulence, etc) **Special Instructions** • Administer other medications at least 1 hr before or 4 hr after bile acid sequestrants • To minimize GI effects, start w/ low dose & increase slowly

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.