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Kris V. Kowdley, MD

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This independent CME/CE activity is supported by an educational grant from Intercept Pharmaceuticals, Inc.
Kris V. Kowdley, MD, is the director of the Liver Care Network and Organ Care Research at Swedish Medical Center in Seattle, Washington. Dr. Kowdley received his BS in biology and anthropology as a member of the Dean's List at Columbia University, and his medical degree from Mount Sinai School of Medicine. He completed his internship and residency at Oregon Health and Science University and a fellowship in gastroenterology and hepatology at Tufts University School of Medicine.

Dr. Kowdley has presented his research in liver diseases at more than 135 national and international medical centers and scientific symposia. He is the author of more than 375 articles, book chapters, reviews, and commentaries in this field and has been published in *Annals of Internal Medicine, Archives of Surgery, Gastroenterology, Hepatology, American Journal of Physiology,* and *New England Journal of Medicine,* among other professional publications.
Faculty

Gideon Hirschfield, MB, BChir FRCP PhD
Clinical Senior Lecturer
University of Birmingham
Honorary Consultant Hepatologist
Queen Elizabeth Hospital
Birmingham, United Kingdom

Gideon Hirschfield, MB, BChir FRCP PhD, is a clinician and academic with a special interest in hepatology, particularly autoimmune liver disease. He trained at University of Oxford followed by University of Cambridge. He completed his clinical training in London and Cambridge. His PhD was awarded after research at the Royal Free Hospital in London. After just more than 4 years at the University of Toronto, where he developed his clinical and research focus on the genetics of autoimmune liver disease, he joined the University of Birmingham in 2012 as a senior lecturer and consultant hepatologist. Dr. Hirschfield is well published scientifically and clinically in his field, having made important contributions to the understanding and clinical management of diseases, such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and nonalcoholic steatohepatitis (NASH). His papers have been published in *Lancet, Gastroenterology, Clinical Liver Disease, Seminars in Liver Disease, Nature Genetics, Hepatology, New England Journal of Medicine*, and other prestigious journals. As an invited lecturer, he has delivered presentations on liver diseases at numerous major national and international medical meetings. His goal is to continue to translate scientific advances into new therapies for patients with liver disease, particularly those with currently unmet needs, such as PBC, PSC, AIH, and NASH.

Faculty

Marlyn Mayo, MD
Program Director
Gastroenterology Fellowship Program
Associate Professor
Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Marlyn Mayo, MD, received her medical degree from Baylor College of Medicine in Houston, Texas, and completed her internship and residency in internal medicine at University of California, Irvine. She subsequently completed fellowships in gastroenterology and hepatology at the University of Texas Southwestern Medical Center in Dallas, where she is currently an associate professor in the department of Internal Medicine, Division of Digestive and Liver Diseases.

Dr. Mayo is recognized for her expertise in autoimmune liver diseases, particularly PBC. She has been the recipient of several grants from the National Institutes of Health, American Liver Foundation, and the pharmaceutical industry to study the pathophysiology of PBC and the treatment of its complications. She has published book chapters and multiple original scientific articles and review articles in journals such as *Gastroenterology, Hepatology, and Clinical Liver Disease*, on the subject of cholestatic liver disease and its complications.
Introduction

Kris V. Kowdley, MD
Director, Liver Care Network
Swedish Medical Center
Seattle, Washington

Primary Biliary Cirrhosis—Why It’s Important

- Primary biliary cirrhosis (PBC) is a chronic, autoimmune, cholestatic liver disease
- Patients with PBC are at increased risk for
  - Liver-related outcomes, including cirrhosis, liver transplantation, hepatocellular carcinoma, and death
  - Esophageal varices and variceal bleeding, osteoporosis, and a host of other extrahepatic complications
- Quality of life is impaired by symptoms of fatigue, pruritus, and dry mouth and eyes
- Standard-of-care therapy has limitations

Primary Biliary Cirrhosis—What’s New and Exciting

- Increased understanding of the pathophysiology of disease
- Identification of diagnostic markers
  - Earlier diagnosis has triggered a position paper suggesting the name be changed to “primary biliary cholangitis”\(^1\)
- Improved criteria for evaluating and assessing patient response to therapy
- Emerging therapeutic options based on recent identification of key targets for intervention

Clinician Knowledge of Untreated or Suboptimally Treated PBC

<table>
<thead>
<tr>
<th></th>
<th>Highly Confident Respondents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regarding the Effect of Untreated/Suboptimally Treated PBC on Disease Progression/Mortality</td>
<td></td>
</tr>
<tr>
<td>Heps</td>
<td>Gastrost</td>
</tr>
<tr>
<td>74</td>
<td>55</td>
</tr>
</tbody>
</table>

Reasons for Suboptimal Therapy

<table>
<thead>
<tr>
<th></th>
<th>Highly Confident Respondents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heps</td>
<td>Gastrost</td>
</tr>
<tr>
<td>64</td>
<td>38</td>
</tr>
</tbody>
</table>

Abbreviations: Gastros, gastroenterologists; Heps, hepatologists; PBC, primary biliary cirrhosis.

Primary biliary cirrhosis (PBC) is the most common of the autoimmune liver diseases. It is best thought of as a chronic, immune-mediated, lymphocytic cholangitis. The consequence of the destructive inflammation is cholestasis with secondary liver injury from bile acids. The cause of disease is not known, but PBC is believed to arise on the background of host genetic risk to autoimmunity, alongside exposure to environmental triggers.

The majority of patients with PBC are women. In fact, 1 in 1000 women over the age of 40 years live with PBC. Although the average age at diagnosis is between 50 and 60 years, a substantial number of younger women are diagnosed with PBC. Women who present when younger than 50 years of age frequently have more treatment-resistant disease.

Inflammation in the liver is characteristically identified by elevation in liver biochemistry values, particularly, chronic elevation of serum alkaline phosphatase values. Associated symptoms of disease, when present, include pruritus and fatigue. Late-stage disease is recognized as a biliary cirrhosis and is associated with development of portal hypertension, liver cancer, and liver failure. Jaundice is a common feature of late-stage disease.

Diagnosis focuses on excluding alternate disease and identifying antimitochondrial antibodies, which are found in over 90% of patients. Patients without mitochondrial antibodies frequently have specific antinuclear antibody immunofluorescent profiles. Elevated serum immunoglobulin M values are frequently recognized in PBC. In most cases, liver biopsy is not needed to confirm a diagnosis, as the combination of cholestatic liver chemistry and antimitochondrial antibodies is very specific for PBC.

At presentation, most patients are noncirrhotic, but after approximately 10 years of disease, as many as 40% will have progressed to advanced fibrosis or cirrhosis. PBC is, therefore, not a benign lymphocytic cholangitis but rather a potentially progressive autoimmune cholestatic liver disease associated with future risk of liver failure and impaired quality of life.

Once a diagnosis is established, treatment with lifelong ursodeoxycholic acid (UDCA), given at a dose of 13 to 15mg/kg/day, should be offered to all patients. Therapy is aimed at ameliorating bile duct inflammation. It is not a cure, however; neither does it treat symptoms. Most patients tolerate UDCA, although some develop side effects that include bloating, diarrhea, weight gain, and hair thinning.

Since PBC is an autoimmune liver disease, it is recognized that a small percentage (<5%) of patients can develop features of autoimmune hepatitis. Making such diagnoses is difficult, however, because patients with PBC frequently have hepatic features, particularly symptomatic younger patients with more aggressive UDCA-resistant disease. As it is very hard to codify such “overlap” or “crossover” syndromes, most experts recommend careful attention to liver histology when doubt arises, with treatment of the predominant disease process first, and addition of immunosuppressive therapy if sufficient features exist histologically, biochemically, and serologically to justify a treatment trial.

Treatment success is based on the patient’s biochemical response to UDCA, with a variety of algorithms available to determine UDCA efficacy and subsequent risk of disease progression. All response criteria focus on improvements in liver biochemistry, and most usually look for a change after 12 months of therapy. For patients who fail to get satisfactory biochemical responses to UDCA, there is currently no second-line therapy approved by the FDA or recommended by treatment guidelines. With the potential approval, for the first time in decades, of second-line therapies for patients with PBC—such as obeticholic acid, a novel farnesoid X receptor agonist—it is important that clinicians become confident in recording the individual risk of disease progression for patients. This is most evident by documenting the biochemical response to UDCA, thereby stratifying patients’ risk of disease progression and their individual need for second-line interventions. The most sophisticated tools for stratifying risk at present include the GLOBE score (http://globalpbc.com/globe) and the UK-PBC risk score (http://www.uk-pbc.com/resources/tools/riskcalculator/).
Diagnosis, Stratification of Risk, and Initial Treatment in PBC

Gideon Hirschfield, MB BChir FRCP PhD
Senior Lecturer/Honorary Consultant Hepatologist
Centre for Liver Research
University of Birmingham
Birmingham, United Kingdom

Outline

- PBC Diagnostic Markers
- Patient Evaluation for PBC
- Current Standard-of-Care Treatment
- Risk Stratification & Treatment Response Endpoints

Diagnostic Considerations

Spectrum of Autoimmune Liver Injuries
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- IgG4-related disease

Differential for Cholestatic Liver Biochemistry
- Drug-induced liver injury
- Inherited cholestasis
- Idiopathic ductopenia
- Malignant infiltration
- Nonalcoholic fatty liver disease
- Obstructive biliary lesion
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Sarcoidosis

What Are the Diagnostic Markers in PBC?

- PBC is the most common adult autoimmune liver disease
- The overwhelming majority of patients are women in middle age who have circulating antimitochondrial antibodies
- Cholestasis is usually reflected as a predominant rise in alkaline phosphatase values
- At presentation, most patients are largely asymptomatic
  - Over time, however, symptoms such as pruritus and fatigue are recognized to be associated with significant impact on patient quality of life

What Are the Diagnostic Markers in PBC?

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- IgG4-related disease

PBC Phenotype

<table>
<thead>
<tr>
<th>Age</th>
<th>Usually &gt;45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female &gt; Male (9:1)</td>
</tr>
<tr>
<td>Serology</td>
<td>AMA in ~95%: disease-specific ANA in ~30%–50%, ASMA may be present</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>IgM typically elevated</td>
</tr>
<tr>
<td>MRCP</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver Histology</td>
<td>Lymphocytic infiltrate: inflammatory duct lesion; granuloma may be present</td>
</tr>
<tr>
<td>Coexisting IBD</td>
<td>Not typical</td>
</tr>
</tbody>
</table>

Interpretation of AMA, ANA, and Immunoglobulin Testing in PBC

- AMA
  - Positive in >90% of patients with PBC, depending on assay
  - In the correct context, AMA reactivity, with an elevated ALP and no significant elevation in AST, is associated with a >95% PPV of histologic PBC
- ANA
  - 2 ANA immunofluorescent patterns are specific to PBC: multiple nuclear dots and perinuclear/circumferential membranous
  - Automated ANA assays will likely not detect these reactivities
  - Laboratories should perform immunofluorescence if ELISA-based assays for gp210 and sp100 are not available
- Immunoglobulins
  - Elevated IgM is a sensitive but not specific characteristic of PBC
  - Elevated IgG is primarily observed in AIH

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cirrhosis.
### “Overlap” or “Crossover” Scenarios

<table>
<thead>
<tr>
<th>Immunoserologic Overlap</th>
<th>Radiologic Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Positive ANA/ASMA titers and elevated IgG in AMA-positive PBC</td>
<td>• Clinical features of AIH with cholangiographic abnormalities consistent with inflammatory cholangiopathy</td>
</tr>
<tr>
<td>• AMA-positive AIH</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical Overlap</th>
<th>Histologic Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AST/ALT &gt; 5 x ULN in PBC or PSC</td>
<td>• Lymphohasmatoid infiltrate and interface hepatitis with bile-duct lesions consistent with either PBC or PSC</td>
</tr>
<tr>
<td>• ALP &gt; 3 x ULN in AIH (GGT &gt; 5 x ULN in children)</td>
<td></td>
</tr>
</tbody>
</table>

Also, varying combinations of the above, including temporal variations: consecutive vs sequential presentations

### Take a Good History

- **Symptom burden**:
  - Pruritus
  - Fatigue
  - Sicca syndrome: dry eyes/mouth/vagina
  - Abdominal pain
  - Arthralgias
  - Remember: some patients remain asymptomatic

- **Relevant medical history**:
  - Autoimmunity (personal or family)
  - Smoking
  - Recurrent urinary tract infection
  - Pruritus during pregnancy

### Autoimmune Liver Disease—Patient Evaluation

#### Cholestatic Profile

<table>
<thead>
<tr>
<th>Symptoms History</th>
<th>Hepatic Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP/GGT ↑; ALT/AST &lt; 5 x ULN</td>
<td>no significant ALP ↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AILD is usually entertained after common liver disease (alcohol, viral, metabolic, drug-induced) is excluded</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MRCP</th>
<th>Autoimmunoglobulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑/liver biopsy if MRCP non-diagnostic</td>
<td>Doppler ultrasound</td>
</tr>
</tbody>
</table>

### Evaluation of Patients with Cholestatic Profile

- **AMA**
  - **+**: PBC
  - **−**: ANA

- **MRCP**
  - **+**: Specific PBC
  - **−**: Non-specific

#### Ultrasound:
- immunoglobulins
- medications: thyroid; osicul screen; lido: bone density; Sokol's screen

#### References:

### Outline

- PBC Diagnostic Markers
- Patient Evaluation for PBC
- Current Standard-of-Care Treatment
- Risk Stratification & Treatment Response Endpoints
Treatment of PBC

- Present treatment is restricted to ursodeoxycholic acid at a dose of 13–15 mg/kg/day\(^1\).
- Second-line therapies are expected soon.
  - For example, obeticholic acid is a farnesoid X receptor agonist that has been studied in phase II and III studies\(^2-4\).

Outline

- PBC Diagnostic Markers
- Patient Evaluation for PBC
- Current Standard-of-Care Treatment
- Risk Stratification & Treatment Response Endpoints

Risk Stratification & Treatment Response Endpoints

- Established Response Criteria Models
  - **Barcelona**\(^1\) (2006)
    - ALP decreased by >40% from baseline or normalized after 1 year UDCA
  - **Paris-II**\(^2\) (2008)
    - All 3 of the following: ALP ≤3 x ULN; AST ≤2 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA
  - **Rotterdam**\(^3\) (2009)
    - Albumin and bilirubin normalization when 1 or both were abnormal at baseline; albumin OR bilirubin normalization when both were abnormal at baseline after 1 year UDCA
  - **Toronto**\(^4\) (2010)
    - ALP <1.67 x ULN after 2 years UDCA

- Modifications of Biochemical Response Criteria Models
  - **Paris-II**\(^1\) (2011)
    - All 3 of the following: ALP ≤1.5 x ULN; AST ≤1.5 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA
  - **Early Biochemical Response**\(^5\) (2013)
    - Barcelona, Paris-I, or Toronto criteria met at 6 months UDCA

What Are Appropriate Baseline Factors and Treatment Endpoints to Assess Risk of Progression in PBC?

- High confidence and applicability
  - Baseline and on-treatment ALP, bilirubin
  - Baseline and on-treatment AST/platelet ratio
  - On-treatment biochemical response criteria
- Moderate confidence and applicability
  - Presenting age
  - Baseline disease-specific ANA
  - Baseline and on-treatment transient elastography
  - Baseline and on-treatment ELF score
- Indeterminate confidence and applicability
  - Gender and baseline symptom profile
  - Baseline and on-treatment novel histologic scores
  - On-treatment direct portal pressure measurement

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; ANA, antinuclear antibody; ALD, alpha-1 antitrypsin deficiency; AST, aspartate aminotransferase; ALT, alanine aminotransferase; UCEDA, ursodeoxycholic acid; ULN, upper limit of normal.

Optimized Response Criteria Models

- Biochemical + APRI
  - Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤ 0.54 after 1 year UDCA

- UK-PBC Risk Score
  - Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA

- GLOBE Score
  - Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA

Biochemical Response + APRI—Transplant-Free Survival Risk Classification

- Low risk
  - Biochemical responder + APRI ≤ 0.54

- Intermediate risk
  - Biochemical responder + APRI > 0.54
  - Biochemical nonresponder + APRI ≤ 0.54

- High risk
  - Biochemical nonresponder + APRI > 0.54

UK-PBC Risk Score Calculation

- Score comprising "fractional polynomial terms, baseline survivor function at 5, 10, and 15 years, and regression coefficients for the best-fitting fractional polynomial model"
  - Baseline survivor function = 0.98 at 5 years; 0.941 at 10 years; and 0.893 at 15 years
  - Liver biochemistry values are after 12 months UDCA: ALP, ALT or AST, and BILI
  - ALB and PLT values are baseline

UK-PBC Risk Score—AUC in Validation Cohort Compared with Other Models

<table>
<thead>
<tr>
<th>Response Criteria Model</th>
<th>5-Year</th>
<th>10-Year</th>
<th>15-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-PBC Index</td>
<td>0.96</td>
<td>0.95</td>
<td>0.94</td>
</tr>
<tr>
<td>Barcelona</td>
<td>0.56</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>Paris-I</td>
<td>0.81</td>
<td>0.81</td>
<td>0.80</td>
</tr>
<tr>
<td>Toronto</td>
<td>0.65</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>Paris-II</td>
<td>0.75</td>
<td>0.75</td>
<td>0.74</td>
</tr>
</tbody>
</table>

GLOBE Score Calculation

- Score comprising age at start of UDCA; beta coefficients of identified variables; natural logarithm transformation of BILI, ALP, ALB, and PLT after 1 year UDCA; and a baseline survival estimate

This tool is provided as an information resource only and is not to be used or relied upon for any diagnostic or treatment purpose.

GLOBE Score Formula:

\[(0.044378 \times \text{age at start of UDCA therapy} + 0.93982 \times \text{NL(BILIxULN at 1 year)}) + (0.335648 \times \text{NL(ALPxULN at 1 year)}) - 2.266708 \times \text{ALBxLLN at 1 year} - 0.002581 \times \text{PLT at 1 year} + 1.216685\]

UK-PBC Risk Score—Downloadable Spreadsheet Calculator

This tool is provided as an information resource only and is not to be used or relied upon for any diagnostic or treatment purpose.
Predictive Significance of ALP and Bilirubin Values

![Graph showing survival rates for normal and abnormal bilirubin levels.](image)

**Abr**

<table>
<thead>
<tr>
<th>ALP ≤ 2 x ULN</th>
<th>ALP &gt; 2 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Bilirubin</td>
<td>79%</td>
</tr>
<tr>
<td>Abnormal Bilirubin</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Notes**: ALP, alkaline phosphatase; ULN, upper limit of normal.

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GLOBE Score—Transplant-Free Survival Threshold

![Graph showing transplant-free survival rates for GLOBE Score >0.30 and ≤ 0.30.](image)

**Abbreviations**: ALP, alkaline phosphatase; ULN, upper limit of normal.


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GLOBE Score—Online Calculation


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PBC Follow-up Algorithm—UDCA

**Nonresponders at 12 Months**

![Algorithm flowchart showing follow-up for nonresponders.](image)

- **ALP > 2 x ULN?**
  - **Yes**: Consider HCC surveillance.
  - **No**: Follow-up with goals of sustained response, nonprogressive LSM, and symptom relief.

**Responders at 12 Months**

![Algorithm flowchart showing follow-up for responders.](image)

- **APRI > 0.54**
  - **Yes**: If cirrhotic, consider HCC surveillance.
  - **No**: Consider need for 2nd-line agent/clinical trials.

**Notes**: ALP, alkaline phosphatase; APRI, AST/platelet ratio index; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.


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PBC Follow-up Algorithm—UDCA

**Conclusion**

- Primary biliary cirrhosis (PBC) is most common in middle-aged women.
- Taking a good history is essential.
- Diagnosis can typically be made based on persistent cholestatic liver profile and antimitochondrial antibody positivity after other common liver diseases have been excluded.
- Ursodeoxycholic acid is the only approved PBC treatment.
- On-treatment biochemical response is the most robust endpoint by which to stratify risk of progression.
- Lack of biochemical response is associated with a high risk of progression and a poor outcome.
Ursodeoxycholic acid (UDCA) is currently the only FDA-approved therapy for primary biliary cirrhosis (PBC). However, UDCA has never been demonstrated to have a significant impact on extrahepatic symptoms of PBC, such as fatigue and pruritus. In addition, many patients will not respond biochemically to UDCA, and they are at risk for disease progression and liver-related complication of PBC, such as variceal bleeding or hepatocellular carcinoma (HCC).

Patients with PBC and cirrhosis are particularly at increased risk for developing HCC. Current guidelines recommend screening cirrhotic patients for HCC using ultrasound with or without alpha fetoprotein every 6 to 12 months. Recent data, however, indicate that older male patients, even if not cirrhotic, who do not respond biochemically to UDCA are also at risk for HCC and suggest that they also should be screened. Other cancers, such as breast cancer, appear to be no more common among PBC patients than in the general population.

Development of varices and variceal bleeding may occur in patients with PBC prior to the onset of cirrhosis. In most instances, however, variceal bleeding occurs in the setting of portal hypertension due to cirrhosis. Thus, screening for varices is recommended only in patients suspected of having cirrhosis. Management is the same as for other etiologies of cirrhosis with varices.

Osteoporosis is more common in patients with cholestatic liver diseases, including PBC, and should be actively sought through screening with bone densitometry every 2 to 3 years. Supplemental calcium and vitamin D should be administered. Recent data suggest that the best dose for calcium is 1200 mg per day and vitamin D supplements should be targeted to achieve a serum level of 33 ng/mL. Bisphosphonates, such as alendronate, have been demonstrated to be safe and to improve bone density in PBC, but studies with newer drugs are lacking.

All fat-soluble vitamins (A, D, E, and K) may have difficulty being absorbed from the intestine when bile acids are not present in sufficient quantity. Vitamin A often becomes deficient early in patients with PBC, so levels should be followed as well and replaced as needed.

Long-Term Management of Liver and Non-Liver Complications in PBC

Marlyn Mayo, MD

Fatigue and pruritus are the two most common and most vexing symptoms of PBC. There is no proven pharmacologic therapy for fatigue in PBC. Modafinil has been used successfully in some patients, but placebo-controlled trials are needed because fatigue in other diseases often responds very well to placebo. Modafinil is also poorly tolerated in approximately half of patients.

Pruritus is characteristically intermittent but progressive. Typical features include diurnal variation in severity, exacerbation by heat, and involvement of the palms and soles. Although patients are often prescribed antihistamines by their clinicians, there are no data to support that these are effective or that histamine is involved in the pathophysiology of itch in PBC. No single therapy works for all patients. A “step-up” approach to therapy of itch is usually recommended, beginning with lifestyle modifications and bile acid binding resins, then progressing to rifampicin, naltrexone, or sertraline if itch persists. Farnesoid X receptor agonists, such as obeticholic acid, an emerging therapy for PBC, may be associated with itching, so learning to manage pruritus effectively is timely and important.

Sicca syndrome (dry eyes, dry mouth) is present in the vast majority (80%) of patients with PBC. Often overlooked by physicians, it may lead to discomfort and early caries. Therapy begins with moisture replacement, but cholinergic stimulants and immunosuppression with topical calcineurin inhibitors may be needed to control symptoms.

Lastly, a variety of extrahepatic diseases have been associated with PBC in the literature, and the practicing physician should be aware of these associations in order to recognize the symptom complexes when they arise. Common associations include thyroid disease, gallstones, renal disease, and arthritis. Some of the uncommon associations include lichen planus, ulcerative colitis, and autoimmune anemias.

Management of the patient with PBC involves attention to the myriad of associated symptoms, diseases, and complications, which are often not responsive to therapy with UDCA.
Long-Term Management of Liver and Non-Liver Complications in PBC

Marilyn Mayo, MD
Associate Professor
Department of Internal Medicine
Digestive and Liver Diseases
University of Texas Southwestern Medical Center, Dallas, Texas

Overall Management of PBC

- Start UDCA and assess response
- Determine stage of disease
  - Institute HCC and variceal screening for cirrhotics
- Assess and address
  - Osteoporosis
  - Fat-soluble vitamin deficiency
  - Fatigue
  - Pruritus
  - Sicca syndrome
- Be aware of these extrahepatic manifestations
  - Common: thyroid disease, gallstones, renal disease, arthritis
  - Uncommon: lichen planus, ulcerative colitis, anemias

Abbreviations: HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.


PBC and Cancer Risk—Meta-Analysis of 17 Studies

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Ratio (95% CI)</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>18.89 (10.81-26.79)</td>
<td>(n = 13,576)</td>
</tr>
<tr>
<td>Cervical</td>
<td>3.81 (-4.85-12.47)</td>
<td>(n = 420)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.06 (-1.36-5.48)</td>
<td>(n = 3221)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.10 (0.81-1.40)</td>
<td>(n = 8466)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.10 (0.43-1.76)</td>
<td>(n = 3880)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.90 (0.58-1.23)</td>
<td>(n = 5945)</td>
</tr>
<tr>
<td>Uterine</td>
<td>0.71 (-0.70-2.13)</td>
<td>(n = 2078)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.27 (-1.25-1.79)</td>
<td>(n = 2679)</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis.


Factors Associated with HCC Risk in UDCA-Treated PBC Patients—Multivariate Analysis (N = 4565)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paris-I not fulfilled</td>
<td>3.42 (P &lt; .0001)</td>
</tr>
<tr>
<td>Male</td>
<td>2.41 (P &lt; .0001)</td>
</tr>
<tr>
<td>Thrombocytopenia (per 50 x 10³/mm² decline)</td>
<td>1.42 (P &lt; .0001)</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.31 (P = .009)</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.


Surveillance for HCC in Patients with PBC

- AASLD PBC guidelines
  - Patients with cirrhosis should be screened every 6–12 months using ultrasound with (or without) alpha fetoprotein
  - Beware the older male nonresponder, even if not cirrhotic

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis.


Surveillance for Varices

- Patients with cirrhosis should be screened every 1–3 years using EGD
  - Interval based on decompensation
- Varices with bleeding may occur in noncirrhotic PBC patients

Abbreviations: EGD, endoscopy; PBC, primary biliary cirrhosis.

Effectiveness of Screening for Esophageal Varices in Patients with Early-Stage PBC

- Retrospective chart review of PBC patients, N = 325
- 8/127 (6%) had esophageal varices when stage I or II

<table>
<thead>
<tr>
<th>AASLD</th>
<th>Levy et al</th>
<th>Angelo et al</th>
<th>MABPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Cirrhotic (stage IV) PBC</td>
<td>Mayo risk score ≥4.5 and/or platelets ≤140,000</td>
<td>Mayo risk score ≥4</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>53%</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>Specificity</td>
<td>85%</td>
<td>56%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALB, albumin; BILI, bilirubin; MABPT, Mayo sex, low ALB (<3.5 g/dL), elevated BILI level (≥12 mg/dL); PT, prothrombin time.

Rate of Nonresponse to Bisphosphonate Stratified by 25-Hydroxy Vitamin D Level

- Real-world setting, postmenopausal women with low BMD (N = 210)
- Patients with a mean 25(OH)D ≥33 ng/mL (predetermined cutoff level) were approximately 4.5-fold more likely to achieve favorable response (P < .0001)

<table>
<thead>
<tr>
<th>25(OH)D Serum Concentration</th>
<th>Nonresponse</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 ng/mL</td>
<td>79% (52/66)</td>
</tr>
<tr>
<td>≥30 to &lt;40 ng/mL</td>
<td>50% (34/68)</td>
</tr>
<tr>
<td>≥40 ng/mL</td>
<td>33% (25/76)</td>
</tr>
</tbody>
</table>

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALB, albumin; BILI, bilirubin; MABPT, Mayo sex, low ALB (<3.5 g/dL), elevated BILI level (≥12 mg/dL); PT, prothrombin time.

Surveillance for and Managing Risk of Osteoporosis in Patients with PBC

- Decreased bile acid secretion may lead to impaired absorption of fat-soluble vitamins ADEK
- Monitoring guidelines
  - AASLD: no specific recommendation
  - Medicare: no more than once annually
  - Reasonable practice: annual vitamin A, D, PT (surrogate marker for K)
- May need to increase frequency of surveillance with new bile acid pool-lowering therapies

Surveillance for Fat-Soluble Vitamin Deficiencies in Patients with PBC

- Decreased bile acid secretion may lead to impaired absorption of fat-soluble vitamins ADEK
- Monitoring guidelines
  - AASLD: no specific recommendation
  - Medicare: no more than once annually
  - Reasonable practice: annual vitamin A, D, PT (surrogate marker for K)
- May need to increase frequency of surveillance with new bile acid pool-lowering therapies

Fatigue in Patients with PBC

- Loss of capacity to recover from activity
- Associated with autonomic dysfunction, loss of sleep, and cognitive impairment
- Role of modafinil for fatigue
  - Produces significant and sustained reduction of ESS
  - Some patients relapse
  - >50% of patients don't tolerate side effects
  - Dizziness and GI upset are common reasons to discontinue
  - Worsening of migraines

Abbreviations: ESS, Epworth Sleepiness Score; GI, gastrointestinal

Reduction in Fatigue Score After Modafinil for 12 Weeks in Patients with PBC

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>Modafinil (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisk Fatigue Impact Score</td>
<td>-1.5</td>
<td>-3.5</td>
<td>0.91</td>
</tr>
<tr>
<td>Fatigue Severity Score</td>
<td>0.0</td>
<td>-3</td>
<td>0.36</td>
</tr>
<tr>
<td>PBC-40 fatigue domain</td>
<td>-8</td>
<td>-4</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Abbreviation: PBC, primary biliary cirrhosis

Surveillance for Fat-Soluble Vitamin Deficiencies in Patients with PBC

- Decreased bile acid secretion may lead to impaired absorption of fat-soluble vitamins ADEK
- Monitoring guidelines
  - AASLD: no specific recommendation
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Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALB, albumin; BILI, bilirubin; MABPT, Mayo sex, low ALB (<3.5 g/dL), elevated BILI level (≥12 mg/dL); PT, prothrombin time.
Pruritus in Patients with PBC

- Occurs early in cholestatic diseases,¹ later in hepatocellular diseases
- Localized vs generalized
  - Palms and soles
- No primary rash¹
- Exacerbated by
  - Pressure
  - Heat¹
- Circadian rhythm (worse in evenings)¹,²
- Periodic exacerbations and improvements²


Behavioral Modifications for Pruritus in Patients with PBC

- Loose, absorbent clothes
- Cool (not dry) environment
- Frequent use of cool emollients
- Avoid pruritogenic medications (narcotics)
- Trim nails
- Controlled sun/ultraviolet exposure

Management of Pruritus—EASL Guidelines

- Cholestyramine up to 4g x 4/d
- Rifampicin 150 mg/d
  - Increase up to 600 mg/d EOW
- Naltrexone up to 50 mg/d
- Sertraline up to 100 mg/d
- Consider experimental approach
- Consider transplantation

Sicca Syndrome Management—Dry Mouth

- Professional dental cleaning every 6 months
- Sugar-free candies/gum
- Rinsing with water
- Saliva substitutes
- Pilocarpine or cevimeline if refractory to all of the above

Sicca Syndrome Management—Dry Eyes

- Artificial tears
- Pilocarpine or cevimeline if refractory to artificial tears
- Cyclosporine eye drops if refractory to all of the above
- Tear duct plugs

Be Aware of Extrahepatic Associations

- Low DLCO₂, 40%–50%
- Lichen planus, 0.5%–1%
- Ulcerative colitis, 30%–50%
- Artropathy, 4%–38%
- Psoriasis, 1%–13%
- Gallstones, 3%–26%
- Hypothyroidism, 11%–32%
- Graves' disease, 3%–6%
- Raynaud's, 7%–14%
- Autoimmune anemias, 1%–2%
- CREST, including esophageal dysmotility, 3%–4%
- Renal tubular acidosis, 20%–33%
- Bacteriuria, 11%–35%

Abbreviation: DLCO₂, diffusing capacity for carbon dioxide.


Be Aware of Extrahepatic Associations

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- Lichen planus, 0.5%–1%
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- Artropathy, 4%–38%
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- CREST, including esophageal dysmotility, 3%–4%
- Renal tubular acidosis, 20%–33%
- Bacteriuria, 11%–35%
Conclusion

- Management of PBC patients requires a comprehensive approach
- Screening for HCC and varices in cirrhotic patients
  - Highest risk in men who do not respond to UDCA
- Surveillance and management of osteoporosis
- Surveillance and management of fat-soluble vitamin deficiencies
- Management of pruritus and fatigue
- Symptomatic and preventative management of sicca syndrome
- Awareness of multiple extrahepatic associations
Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease that predominantly affects middle-aged women. The diagnosis of PBC is straightforward and can be made by the presence of a positive antimitochondrial antibody (AMA) and cholestatic liver test abnormalities in the absence of known drug-induced liver injury or biliary tract obstruction.

Several exciting, new developments have recently taken place in the diagnosis, staging, and treatment of PBC. A position paper has suggested the name of this condition should be changed to “primary biliary cholangitis,” given the fact that most patients are now diagnosed prior to the development of cirrhosis. The role of biopsy has been called into question, as prognostic models have been refined to provide useful information about the natural history of the disease and the role of biochemical response with ursodeoxycholic acid (UDCA) treatment on natural history. These models have increasingly replaced liver biopsy for the purpose of staging and predicting outcome, emphasizing instead the value of alkaline phosphatase level along with serum bilirubin in predicting complications over time.

UDCA has been the mainstay of PBC therapy for more than 20 years and has been shown to reduce the likelihood of liver disease complications and need for liver transplantation or death. While the role of UDCA as an effective therapy has continued to be debated, it is increasingly clear that a biochemical response to UDCA portends a good prognosis. Two new prognostic models—the “GLOBE Score” and the “UK-PBC Risk Score”—have further refined the model using common laboratory tests and are available for clinical practice.

Several novel agents have been studied for PBC. The furthest along in development is obeticholic acid, which has been studied in phase II and III studies, both as monotherapy and in combination with UDCA. Compared with placebo, significant reductions in serum alkaline phosphatase were shown in patients receiving obeticholic acid alone as well as in patients receiving the combination therapy. The current dose of obeticholic acid being used in phase III clinical trials has been 5 and 10 mg, although doses up to 50 mg were studied in the monotherapy studies. The main adverse effect of obeticholic acid is pruritus, which is dose-related and generally responsive to bile acid sequestrants or dose reduction. Obeticholic acid is also associated with changes in serum lipid profiles, although the clinical significance of these changes in patients with PBC is currently unclear. Long-term studies examining the safety and efficacy of obeticholic acid in PBC are underway.

Other agents under investigation for PBC include bezafibrate and fenofibrate, peroxisome proliferator-activated receptor alpha agonists, and NGM282, a fibroblast growth factor 19 agonist. A recent long-term study showed bezafibrate in addition to UDCA was more effective in lowering serum alkaline phosphatase than UDCA alone. However, renal dysfunction was a concerning adverse effect associated with the combination therapy. Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including PBC. Preliminary phase II findings of NGM282 monotherapy showed significant reductions in serum alkaline phosphatase and transaminases relative to placebo, with mild adverse effects.
What Are the Limitations of PBC Standard of Care and How Will Emerging Therapies Improve Patient Outcomes?

Kris V. Kowdley, MD
Director, Liver Care Network
Swedish Medical Center
Seattle, Washington

UDCA—Current Standard-of-Care PBC Therapy
• UDCA is the only FDA-approved PBC therapy
• Recommended adult dosage is 13–15 mg/kg/day
• Typically administered in 2 divided doses

Abbreviations: FDA, Food and Drug Administration; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Effect of UDCA on Mortality and Liver Transplantation Risk

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or OLT&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>0.32 (0.14–0.74)</td>
<td>.005</td>
</tr>
<tr>
<td>OLT-free survival&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.92 (1.30–2.82)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; RR, relative risk; UDCA, ursodeoxycholic acid.

Optimized PBC Response Criteria Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical + APRI&lt;sup&gt;1&lt;/sup&gt; (2014)</td>
<td>Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤0.54 after 1 year UDCA</td>
</tr>
<tr>
<td>UK-PBC Risk Score&lt;sup&gt;2&lt;/sup&gt; (2015)</td>
<td>Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT, AST, and ALP after 1 year UDCA</td>
</tr>
<tr>
<td>GLOBE Score&lt;sup&gt;2&lt;/sup&gt; (2015)</td>
<td>Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST/platelet ratio index; AST, aspartate aminotransferase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

The Other Point of View—Findings from Cochrane Review

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.97 (0.67–1.42)</td>
</tr>
<tr>
<td>All-cause mortality or liver transplantation</td>
<td>0.96 (0.74–1.25)</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; UDCA, ursodeoxycholic acid.
Efficacy and Safety of Emerging Therapies

Targets for New Therapeutic Interventions

Consideration of Patients for Emerging Therapies

Outline

Management of Suboptimal Response

Limitations of Current Standard of Care

What Can Clinicians Do Next for Patients with Suboptimal Response to UDCA?

- No clear, proven choices
- Query patient for adherence
  - Barriers to adherence: weight gain, loose stools, hair loss
- Confirm UDCA dosage 13–15 mg/kg
  - Doubling UDCA dose has not shown benefit
- Check for comorbid liver disease
- Avoid coadministration of bile acid sequestrant
- Refer patient to clinical trial
  - Many promising drugs being investigated

Abbreviation: UDCA, ursodeoxycholic acid.

Reported Incidence of UDCA Treatment Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pells et al, 2013¹ (UK-PBC group)</td>
<td>60% of patients presenting at age &lt;40 years</td>
</tr>
<tr>
<td></td>
<td>10% of patients presenting at age &gt;70 years</td>
</tr>
<tr>
<td>Corpechot et al, 2011²</td>
<td>13%–37%*</td>
</tr>
<tr>
<td>Kuiper et al, 2009³</td>
<td>34%–38%*</td>
</tr>
<tr>
<td>Corpechot et al, 2008⁴</td>
<td>35%–39%*</td>
</tr>
</tbody>
</table>

*Depending on criteria used. Abbreviation: UDCA, ursodeoxycholic acid.

PBC Investigational Targets

- FXR
- PPAR-α
- FGF19

Abbreviations: FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cirrhosis; PPAR, peroxisome proliferator-activated receptor.

Farnesoid X Receptor Signaling

- Bile Acids (Primary ligands for FXR)
  - Binding
- FXR (Hepatocytes, biliary epithelium, small bowel enterocytes, renal tubular cells, adrenal cells, adipocytes, beta cells)
  - Gene Expression
    - CYP7A1, NTCP, OATP
    - MP23A, GST α/β
  - Bile Acid Efflux
  - Gene Expression
    - CYP7A1, NTCP, OATP
  - Bile Acid Synthesis and Uptake
  - Indirect Effects
  - Direct Effects

**Peroxisome Proliferator-Activated Receptor Alpha Activity**

- Regulates bile acid synthesis and detoxification
- Modulates phospholipid secretion, which helps protect bile duct epithelium by formation of micelles


**Fibroblast Growth Factor 19 Signaling**

- Fibroblast growth factor 19 (FGF19) is an endocrine hormone that helps regulate bile acids, carbohydrate, lipid, and energy metabolism
- It also has a role in regulating hepatic cell proliferation
  - FGF19-FGFR4 signaling is associated with hepatocellular tumorigenesis
- An engineered FGF19 variant has been shown to be capable of targeting the bile acid homestasis function, but not the proliferative function, by suppressing hepatic Cyp7a1 expression


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**Outline**

- Limitations of Current Standard of Care
- Management of Suboptimal Response
- Targets for New Therapeutic Interventions
- Efficacy and Safety of Emerging Therapies
- Considering Patients for Emerging Therapies

---

**Drugs in Phase II/III Testing for PBC**

<table>
<thead>
<tr>
<th>Target/Class</th>
<th>Drug</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesoid X receptor (FXR) agonist</td>
<td>Obeticholic acid</td>
<td>III,</td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptor alpha</td>
<td>Bezafibrate</td>
<td>III,</td>
</tr>
<tr>
<td>agonist</td>
<td>Fenofibrate</td>
<td>ongoing</td>
</tr>
<tr>
<td>Fibroblast growth factor 19 analog</td>
<td>NGM282</td>
<td>II</td>
</tr>
</tbody>
</table>

**OCA—Phase II Monotherapy and Combination Therapy Trial Designs**

<table>
<thead>
<tr>
<th>OCA Monotherapy Trial</th>
<th>OCA + UDCA Combination Therapy Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>OCA 10 mg</td>
<td>OCA 10 mg</td>
</tr>
<tr>
<td>OCA 50 mg</td>
<td>OCA 25 mg</td>
</tr>
<tr>
<td>12-week double-blind treatment</td>
<td>OCA 5 mg</td>
</tr>
</tbody>
</table>

Primary endpoint:
Percent change in serum ALP from baseline to end of study

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

**OCA—Phase III POISE Trial Design**

<table>
<thead>
<tr>
<th>Continue prestudy UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 73)</td>
</tr>
<tr>
<td>OCA 10 mg (n = 73)</td>
</tr>
<tr>
<td>OCA 5 mg (n = 33)</td>
</tr>
<tr>
<td>OCA 9 mg (n = 36)</td>
</tr>
</tbody>
</table>

Entry: ALP \(\geq 1.67 \times \text{ULN}\) and/or bilirubin \(\text{ULN}\) but \(<2 \times \text{ULN}\)

12-month double-blind treatment

Positive response: ALP \(<1.67 \times \text{ULN}\) and bilirubin \(\text{ULN}\) and \(\geq 15\%\) ALP reduction

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; WNL, within normal limits.

### OCA—Phase III POISE Trial

**Primary Endpoint**

- **Responders (%)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo (n=73)</th>
<th>Titrated OCA (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>*P &lt; .0001 vs placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>*P &lt; .05 vs placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change from Baseline in ALP**

- Primary endpoint: Proportion of subjects achieving ALP < 1.67 x ULN with bilirubin ≤ ULN and 15% reduction in ALP.

**Abbreviations:** ALP, alkaline phosphatase; OCA, obeticholic acid; ULN, upper limit of normal.

### OCA—Analysis of Phase II and III International Trials

- **Hepatobiliary injury**: Increased plasma ALP and bilirubin correlate with disease progression.
  - ALP > 1.67 x ULN and normal bilirubin after 1 year of UDCA.
  - This analysis evaluated the phase II monotherapy and phase III POISE studies:
    - The POISE primary composite endpoint: ALP < 1.67 x ULN + ≥ 15% reduction and normal bilirubin, shown to correlate with survival.
    - Change from baseline in ALP, bilirubin, GGT, ALT, AST.
  
### OCA International Trials—Subjects Achieving Composite Endpoint

**Primary Endpoint:** Composite endpoint of ALP < 1.67 x ULN, ≥ 15% ALP reduction, normal bilirubin.

**Change in Direct Bilirubin**

- Subjects (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo (n=134)</th>
<th>OCA Titrated (n=70)</th>
<th>OCA 10 mg (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALP, alkaline phosphatase; OCA, obeticholic acid; ULN, upper limit of normal.

### OCA International Trials—Change in Alkaline Phosphatase

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo (n=134)</th>
<th>OCA Titrated (n=70)</th>
<th>OCA 10 mg (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

### OCA International Trials—Changes in Serum Liver Biochemical Tests

**Change from Baseline**

- **ALT (ULL)**
  - **AST (ULL)**

**Abbreviations:** ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

**Graphic courtesy of Kris V. Kowdley, MD.**
### OCA International Trials—Absolute Change in Lipid Levels from Baseline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II OCA</th>
<th>Phase II OCA + UDCA</th>
<th>Phase III OCA ± UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 23)</td>
<td>OCA 10 mg (n = 24)</td>
<td>Placebo (n = 34)</td>
<td>Placebo (n = 73)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>3.5</td>
<td>9.7</td>
<td>1.4</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>-1.5</td>
<td>-12.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-1.8</td>
<td>-2.7</td>
<td>-8.9</td>
</tr>
</tbody>
</table>

- Treatment with OCA has been associated with increase in LDL-C and decrease in HDL-C and triglycerides.
- Clinical significance is unclear.
- Absolute differences are small.
- Patients had high HDL-C at baseline, typical for PBC patients.

### OCA—5-Year Phase II Monotherapy Extension Trial

- Double-Blind Phase (N = 59)
  - Baseline
  - OCA 16 mg
  - OCA 50 mg
  - 1.5 ULN

- Open-Label Long-Term Safety Extension Phase (N = 28)
  - OCA initiated at double-blind dose: 10-mg dose titrated up to 50 mg based on tolerability and efficacy.

- Primary endpoint: Percent change in serum ALP from baseline to end of study.

### OCA Monotherapy—Biochemical Reductions from Baseline Through Year 5

<table>
<thead>
<tr>
<th>All Patients, Mean Reduction (SD)</th>
<th>Patients with No Added UDCA, Mean Reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (U/L)</td>
<td>-269 (322)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>-350 (382)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>-41 (39)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-23 (29)</td>
</tr>
<tr>
<td>Total Bilirubin (µmol/L)</td>
<td>-2 (7)</td>
</tr>
</tbody>
</table>

### OCA Monotherapy—Alkaline Phosphatase Reductions Through Year 5

- ALP reduction was significant by Month 3 and remained significant throughout treatment (P <.05).

### Bezafibrate + UDCA—Long-term Outcome in UDCA Nonresponders with Dyslipidemia

- Prospective, randomized, controlled, multicenter study (N = 27).
- Continuation of UDCA vs bezafibrate add-on to UDCA after ≥24 weeks; therapy continued through 8 years.
- Primary endpoints:
  - ALP levels
  - Mayo risk score
  - Total bilirubin, AST, albumin
- Other endpoints:
  - Overall survival
  - HCC incidence
  - Creatinine – safety endpoint

### Summary of Adverse Effects

- 5 placebo patients (4%) and 6 OCA 10 mg patients (6%) reported at least 1 treatment-emergent serious adverse effect.
- None in OCA 10 mg were considered drug-related.
- Pruritus was the most common adverse effect reported across all treatment groups.
- Most pruritus treatment-emergent adverse effects were mild or moderate in severity.
- Uptitrating OCA dose from 5 mg–10 mg at 6 months mitigated the incidence of pruritus and improved tolerability as assessed by patient discontinuation rate due to pruritus: 1% in titration group vs 9% in 10-mg group.

### Adherence
- OCA, obeticholic acid.

### Abbreviations
- ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
- OCA + UDCA—Long-term Outcome in UDCA Nonresponders with Dyslipidemia
- OCA initiated at 10 mg at 6 months.
- Pruritus was the most common adverse effect reported across all treatment groups.
- Most pruritus treatment-emergent adverse effects were mild or moderate in severity.
- Uptitrating OCA dose from 5 mg–10 mg at 6 months mitigated the incidence of pruritus and improved tolerability as assessed by patient discontinuation rate due to pruritus: 1% in titration group vs 9% in 10-mg group.

### References
Bezafibrate + UDCA—Key Long-term Outcomes at 8 Years

- Mayo risk score significantly lower in patients who received bezafibrate + UDCA compared with patients who received only UDCA
  - 0.91 vs 1.42 (P<.05)
- Mortality rate and incidence of HCC were not significantly different between the 2 groups
- Creatinine levels were significantly higher with combination therapy vs UDCA only
  - 0.94 vs 0.56 (P<.05)
- "We should pay close attention to adverse events during this long-term combination therapy"

Abbreviations: HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid.

Fenofibrate—Phase II Findings in Patients with PBC and Incomplete Response to UDCA

- Open-label study (n = 20)
- ALP levels decreased significantly
- Rebound in ALP levels occurred following fenofibrate discontinuation
- Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including PBC

Abbreviations: ALP, alkaline phosphatase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

NGM282—Phase II Findings of Engineered Variant FGF19 in PBC

- Double-blind, placebo-controlled trial in patients with PBC and incomplete response to UDCA (n = 45)
- Preliminary findings
  - ALP, ALT, and AST levels decreased significantly
  - Pruritus not exacerbated
  - AEs mild; most common being headache and lower GI symptoms

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FGF, fibroblast growth factor; GI, gastrointestinal; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Drugs in Early Investigation for Efficacy in PBC Disease Activity

- Prednisolone and azathioprine in combination with UDCA
- LJN452

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Outline

- Limitations of Current Standard of Care
- Management of Suboptimal Response
- Targets for New Therapeutic Interventions
- Role of Emerging Therapies
- Considering Patients for Emerging Therapies

Which Patients Should Be Considered for a Clinical Trial?

- Patients with a partial response or no response to ursodeoxycholic acid (UDCA)
- Patients who are intolerant of UDCA
  - Diarrhea, abdominal pain
  - Worsening pruritus
- Patients with evidence of progressive disease
**Actions Needed to Reach the Goal of Improved Care of PBC Patients**

- Improve community, patient, and PCP awareness of the disease and its presentations
- Improve physician awareness of the need for therapy with UDCA and assessment of response
- Use a systematic approach to management with built-in triage for high-risk/nonresponding patients
- Apply a systematic approach to the evaluation of second-line therapy and implementation into stratified management pathways
- Improve awareness, assessment, and treatment of symptoms in PBC using systematic approaches

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

**Conclusions**

- PBC is a slowly progressive disease that is associated with morbidity and mortality
- UDCA has been a mainstay of therapy
- Additional treatment options needed
- Fatigue and pruritus limit health-related quality of life
- OCA is in late-stage development
- Other therapies are being studied

Abbreviations: OCA, obeticholic acid; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
**Personalizing PBC Therapy: Case-Based Panel Discussion**

**Faculty Panel**

**Patient Presentation**

- Mrs. F is a 44-year-old woman who presented to her PCP for fatigue
- Past medical history was notable for hypothyroidism
- Physical examination showed no spider angiomas, xanthomas, or xanthelasmas
- Liver and spleen were normal in size and there was no muscle wasting

**Laboratory Evaluation**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>230 U/L</td>
<td>9–46 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>180 U/L</td>
<td>10–40 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>440 U/L</td>
<td>40–125 U/L</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>0.8 mg/dL</td>
<td>0.3–1.0 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.5 g/dL</td>
<td>3.6–5.1 g/dL</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>13.2 seconds</td>
<td>12.0–15.5 seconds</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

**Hepatology Referral**

- The patient was referred to a hepatologist
- Additional testing showed:
  - ANA positive at 1:320
  - AMA positive at 1:80
  - SPEP showed a elevated gamma globulin fraction (>1.5 x ULN)
- Liver biopsy showed:
  - Florid bile duct lesions and multiple non-caseating granulomas
  - Interface hepatitis with an intense plasma cell infiltrate
  - Portal and periportal fibrosis (Stage 2)

Abbreviations: ANA, anti-nuclear antibody; AMA, anti-mitochondrial antibody; SPEP, serum protein electrophoresis.

**Diagnosis**

**Overlap syndrome with primary biliary cirrhosis and autoimmune hepatitis**

The diagnosis was based on a mixed pattern of both hepatocellular and cholestatic liver enzyme elevation and liver biopsy findings

**What Should We Do Next?**
**Initial Treatment**

- Patients who have overlap syndrome with PBC and AIH may need to be treated for both PBC and AIH
- Budesonide 9 mg per day
  - Preferred therapy for AIH in the absence of cirrhosis
- Ursodeoxycholic acid at a dose of 13–15 mg/kg/day in 2 doses with meals
  - Approved therapy for PBC
- Re-evaluate in 3 months

**Abbreviations:** AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis.

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**On-Treatment Laboratory Monitoring**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value (3 months)</th>
<th>Value (6 months)</th>
<th>Value (12 months)</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>65 U/L</td>
<td>30 U/L</td>
<td>20 U/L</td>
<td>9–46 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>50 U/L</td>
<td>27 U/L</td>
<td>22 U/L</td>
<td>10–40 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>175 U/L</td>
<td>155 U/L</td>
<td>124 U/L</td>
<td>40–125 U/L</td>
</tr>
</tbody>
</table>

- "At 6 months the patient subsequently expressed an interest in a steroid-sparing regimen with lower cost than budesonide
- TMPT genotyping was done and the patient was negative for "slow metabolizer" alleles
- She was started on azathioprine at a dose of 75 mg per day (1.0 mg/kg) and 3 months later budesonide was discontinued

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; TMPT, thiopurine methyltransferase.

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**Case Conclusions**

- The patient had a complete biochemical remission
- Given the patient’s absence of cirrhosis at baseline and a complete response to treatment, she has an excellent prognosis
- Repeat liver biopsy is not needed as long as the patient remains in a biochemical remission
- This case demonstrates that there is a spectrum of autoimmune liver diseases that range from PBC to AIH; some patients may have an overlap syndrome
- When overlap syndrome with PBC and AIH is present, both PBC and AIH must be treated

**Abbreviations:** AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis.

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**Case 2—Patient Presentation**

- Ms. E is a 58-year-Caucasian woman who presented with fatigue and mild pruritus
- Past medical history
  - Hypothyroidism
  - Mild osteopenia
- Physical exam
  - No xanthelasmas
  - Mild hyperpigmentation
  - No ascites, jaundice
  - Hepatomegaly

**Case 2—Laboratory Evaluation**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>92 U/L</td>
<td>9–46 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>89 U/L</td>
<td>10–40 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>640 U/L</td>
<td>40–125 U/L</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>2.2 mg/dL</td>
<td>0.3–1.0 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1 g/dL</td>
<td>3.6–5.1 g/dL</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>12.8 seconds</td>
<td>12.0–15.5 seconds</td>
</tr>
<tr>
<td>Platelet count</td>
<td>135,000/mm$^3$</td>
<td>150,000–350,000/mm$^3$</td>
</tr>
<tr>
<td>CBC</td>
<td>Normal but for platelets --</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>AMA</td>
<td>Positive; 1:640</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Ultrasound Findings**

- Nodular liver
- Borderline splenomegaly

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, antinuclear antibody; AMA, antimitochondrial antibody; CBC, complete blood count.
Diagnosis

Primary biliary cirrhosis

Initial Treatment

• Ursodeoxycholic acid at a dose of 15 mg/kg/day in 2 doses with meals
  – Approved therapy for PBC
• Re-evaluate in 6 months
• EGD for variceal screening

Abbreviations: PBC, primary biliary cirrhosis.

Case 2—On-Treatment Laboratory Evaluation at 6 Months

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>52 U/L</td>
<td>9–46 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>50 U/L</td>
<td>10–40 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>460 U/L</td>
<td>40–125 U/L</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>2.1 mg/dL</td>
<td>0.3–1.0 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.2 g/dL</td>
<td>3.6–5.1 g/dL</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>12.9 seconds</td>
<td>12.0–15.5 seconds</td>
</tr>
<tr>
<td>Platelet count</td>
<td>125,000/mm$^3$</td>
<td>150,000–350,000/mm$^3$</td>
</tr>
<tr>
<td>CBC</td>
<td>Normal but for platelets</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count.

On-Treatment Ultrasound and FibroScan Findings at 6 Months

• Ultrasound:
  – Unchanged from baseline
• FibroScan:
  • 14 kPa; median interquartile range 12%

Questions

• Should you perform liver biopsy?
• What do you advise the patient about natural history of PBC?
• Should you add colchicine or methotrexate?
• Should you consider overlap syndrome?
• Would the patient be a candidate for an OCA clinical trial?

In UDCA nonresponders, consideration should be given to include patients in clinical trials, including OCA trials.

Abbreviations: OCA, obeticholic acid; PBC, primary biliary cirrhosis.

Conclusion

In UDCA nonresponders, consideration should be given to include patients in clinical trials, including OCA trials.
Hepatocellular Carcinoma
Sicca/Sjögren’s Syndrome
Esophageal Varices/Variceal Bleeding
Osteoporosis and Other Extrahepatic Complications

Primary Biliary Cirrhosis
Symptoms: Fatigue, Pruritus

Cirrhosis, Transplantation, Liver-Related Death

Evaluation of Patients with Cholestatic Profile

Ultrasound; immunoglobulins; medications; thyroid; celiac screen; lipids; bone density; Sjögren’s screen

Ultrasound: non-specific

Specific

PBC

+ ANA

- - -

AMA

++

Non-specific

MRCP +/- Liver biopsy if MRCP non-diagnostic

Evaluation of Patients with Cholestatic Profile

Hepatocellular Carcinoma
Sicca/Sjögren’s Syndrome
Esophageal Varices/Variceal Bleeding
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Optimized Response Criteria Models

Biochemical + APRI (2014)
Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤ 0.54 after 1 year UDCA

UK-PBC Risk Score² (2015)
Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA

GLOBE Score³ (2015)
Prognostic index comprising baseline age, and bilirubin, AUP, albumin, and platelet count after 1 year UDCA

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST/platelet ratio index; AST, aspartate aminotransferase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid

Audience Q&A