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EXPERT perspectives

Shifting Paradigms in Primary Biliary Cholangitis

A CE/CME Activity

Overview

In this video series, Kris Kowdley, MD, and Seth Sclair, MD, share insight into changes in the management of patients with primary biliary cholangitis. This progressive, autoimmune disease was previously referred to as primary biliary cirrhosis. One notable change discussed is approval of obeticholic acid for use in adults with an inadequate response to ursodeoxycholic acid, or as monotherapy in adults unable to tolerate ursodeoxycholic acid.

Content Areas:

- Diagnostic considerations
- Initial treatment with ursodeoxycholic acid
- Assessing response to ursodeoxycholic acid
- Obeticholic acid
- Investigational treatments
- Managing symptoms and complications

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https://www.annenberg.net/Primary-Biliary-Cholangitis-CME

CE/CME Information

Target Audience
This activity was developed for gastroenterologists, hepatologists, immunologists, primary care physicians, and other health care professionals who have an interest in primary biliary cholangitis.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Identify patients with primary biliary cholangitis (PBC) at the earliest stage of disease
- Initiate first-line treatment with ursodiol in appropriate patients
- Assess response/nonresponse to ursodiol
- Select second-line therapy based on available evidence
- Initiate obeticholic acid in appropriate patients
- Initiate evidence-based treatment to manage symptoms and complications

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Kris V. Kowdley, MD

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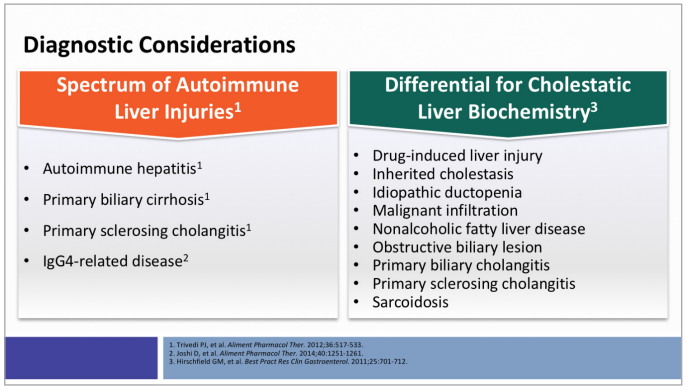
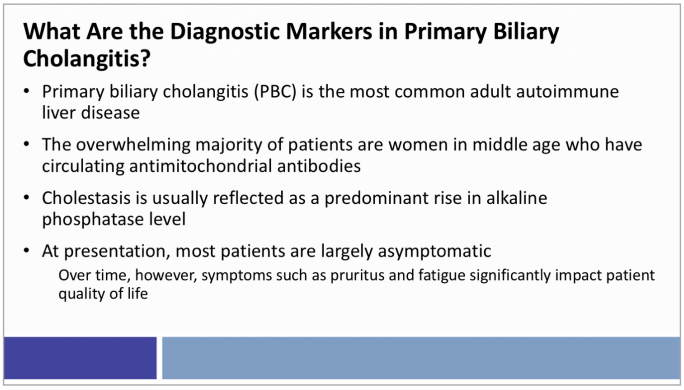
Diagnostic Considerations

Dr. Kowdley: Diagnostic considerations in the diagnosis and management of primary biliary cholangitis, as it's called now, are important to keep in mind. There is a spectrum of autoimmune liver diseases that may range from autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and IgG4 positive disease or IgG4-related autoimmune cholangitis and pancreatitis. It's important for the clinician to keep in mind the differential diagnosis for patients with cholestatic liver biochemical test abnormalities because there is a substantial number of conditions that can masquerade as PBC. These include, drug-induced liver injury, inherited cholestasis, idiopathic ductopenic disorders, malignant infiltration, nonalcoholic fatty liver disease, primary biliary cholangitis, primary sclerosing cholangitis, or sarcoid liver disease.

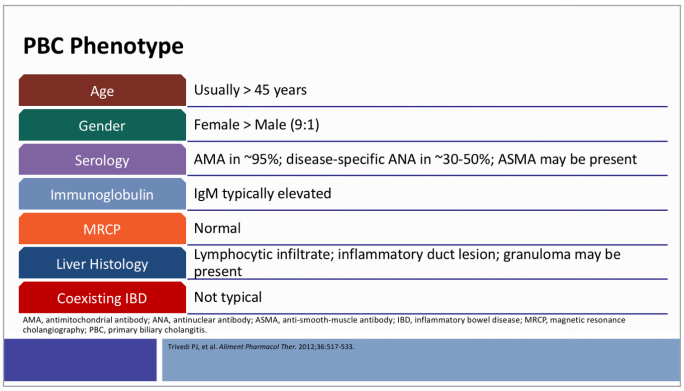


It's important to keep in mind the diagnostic markers in PBC. PBC is a common adult autoimmune liver disease but still overall quite uncommon, and some would consider this a rare disorder in comparison to nonalcoholic fatty liver disease or viral hepatitis. The overwhelming majority of patients are women in middle age who have circulating anti-mitochondrial antibodies. Cholestasis is usually presented and reflected as a predominant rise in serum alkaline phosphatase values and at presentation most patients are largely asymptomatic. Over time, however, symptoms such as pruritus and fatigue are recognized to be associated with a significant impact on quality of life.



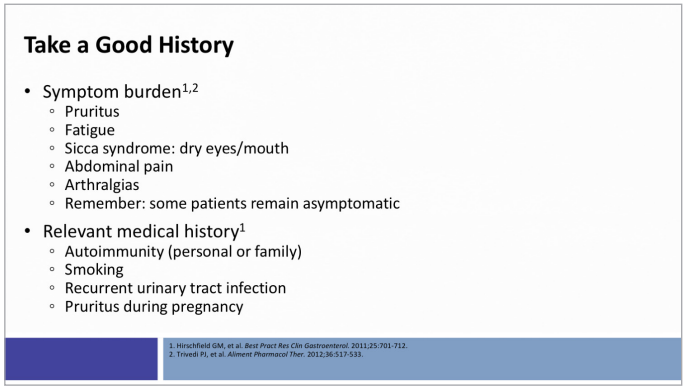
PBC phenotype generally is associated with age greater than 45 years. There is a strong female to male predominance of 9 to 1. The serologic tests that are abnormal are a positive anti-mitochondrial antibody in about 95% of patients and a disease-specific antinuclear antibody in about 30%–50% of patients. The anti-smooth muscle antibody or anti-actin antibody may also be frequently present. Serum immunoglobulin M values are typically elevated. However, MRCP, by definition, is normal, as this is a disorder of the small interlobular bile ducts, generally, smaller than 80 microns in size. Therefore, the large bile ducts seen on cholangiography should be normal.

Liver histology may be characteristic in this condition, with a lymphocytic infiltrate, potentially florid bile duct lesions, which are intense aggregates of lymphocytes around bile ducts, and there may be variable numbers of non-caseating granuloma. It is

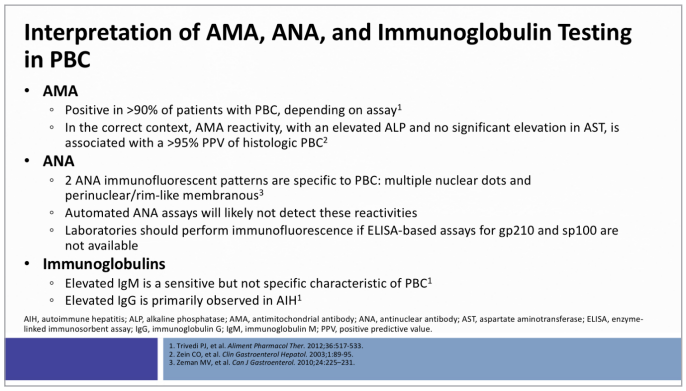


generally important to keep in mind that a patient with coexisting IBD, or inflammatory bowel disease, is more likely to have PSC, primary sclerosing cholangitis, as opposed to primary biliary cirrhosis. In PSC, the anti-mitochondrial antibody is generally negative.

It's important to take a good history. Symptom burden is important to characterize with regard to pruritus, fatigue, Sicca syndrome, dry eyes, mouth, abdominal pain, arthralgias may be present but some patients may remain asymptomatic. Therefore, it is important to take a relevant medical history. Important to seek other causes of autoimmune diseases and seek the presence of recurrent urinary tract infections, pruritus during pregnancy, etc.



The interpretation of the AMA, the ANA, and the immunoglobulin testing in PBC is important to keep in mind in that 90% of patients have a positive anti-mitochondrial antibody. The antinuclear antibody may be present in 2 immunofluorescent patterns that are specific to PBC. There may be multiple nuclear dots and perinuclear REM-like or membranous spots. Automated ANA assays will likely not detect these reactivities. Laboratories should perform immunofluorescence if ELISA-based assays for the gp210 and sp100 antibody are not available. IgM is the most sensitive immunoglobulin that is elevated in PBC, but it is not specific to PBC. It is important to remember that elevated IgG globulin or gamma globulin fraction is primarily observed in autoimmune hepatitis.

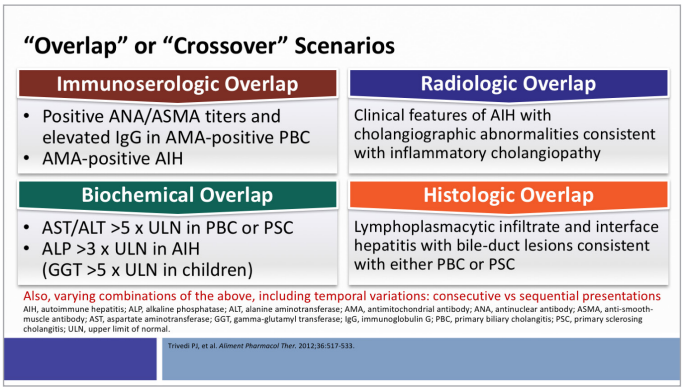


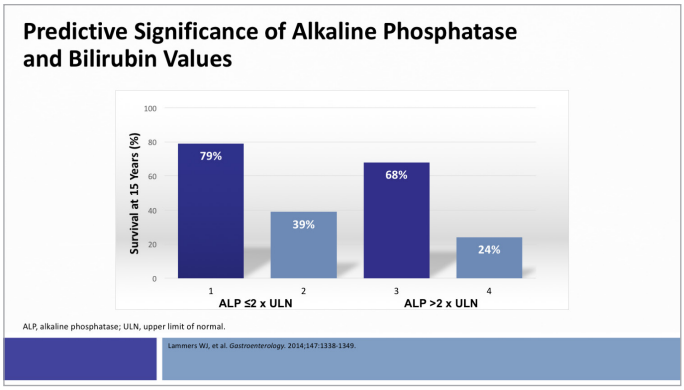
It's important to keep in mind that there could a variety of overlap or crossover scenarios and these have been defined as immunoserological overlap. That is a patient that has an autoantibody profile that could be more suggestive of autoimmune hepatitis vs PBC, or both. For example, in autoimmune hepatitis, the anti-smooth muscle antibody and the antinuclear antibody are positive and there are elevated IgG globulins, but sometimes you see that in a patient with PBC. Similarly, you can see a patient with autoimmune hepatitis who has a positive anti-mitochondrial antibody.

You may see biochemical overlap. Generally, in PBC, you have a predominant elevation of the alkaline phosphatase out of proportion to the ALT and the AST, but occasionally you see patients with autoimmune hepatitis who have a cholestatic profile characterized by an elevated alkaline phosphatase. Occasionally, in patients with PBC, there may be an elevation of liver enzymes, ALT/AST but not alkaline phosphatase.

There is radiologic overlap. This doesn't apply so much to PBC, but many patients with autoimmune hepatitis and primary sclerosing cholangitis may have overlapping features. Then, there is histologic overlap which is frequently a problem for clinicians because, in patients with PBC, there often is some interface hepatitis, low levels of piecemeal necrosis that raise the question of an overlap syndrome.

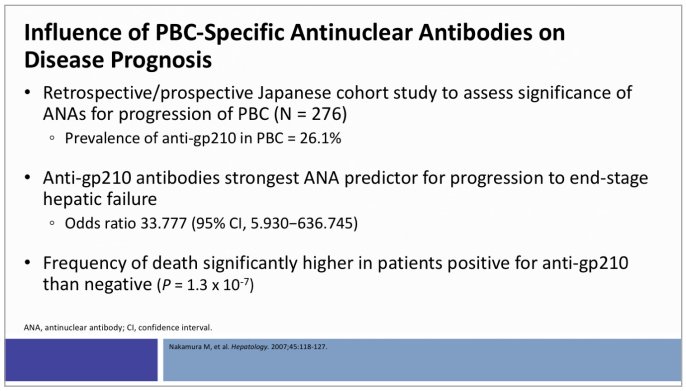
The key point to take away is the use of alkaline phosphatase and bilirubin values in determining prognosis.



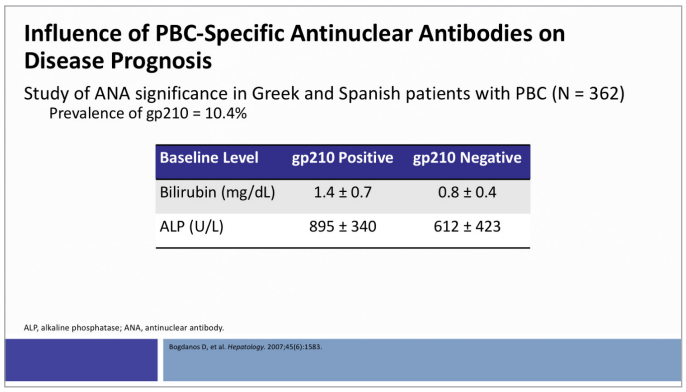


This slide shows that among patients with PBC who maintain an elevated alkaline phosphatase and an elevated bilirubin, the 15-year survival is significantly reduced compared to patients who have an alkaline phosphatase less than twice the upper limit of normal with a normal bilirubin. That difference in survival can range from 24%-79%. So it's important for clinicians to be able to recognize changes in alkaline phosphatase and, of course, bilirubin, for patients who have been on ursodeoxycholic acid for a period of time, and determine those who might be in need of additional therapies.

Now, I mentioned the gp210 antibody. This is a very interesting discovery that showed that patients who have this particular PBC-specific antinuclear antibody have much higher rates of aggressive disease and have a significantly higher rate of mortality compared to patients who have the anti-gp210 antibody. Some have advocated that patients with PBC should, in fact, have these checked routinely.

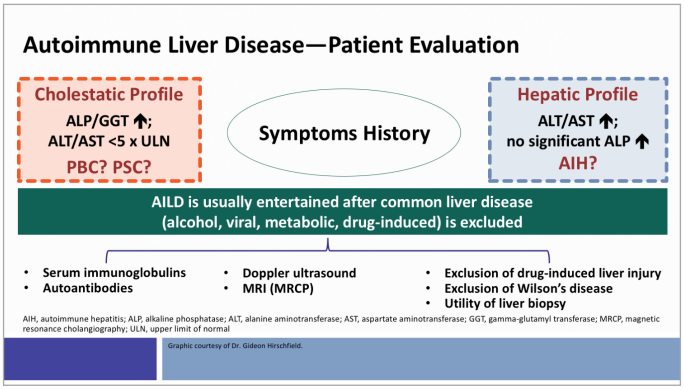


There's a study from Greek and Spanish patients with PBC showing, once again, much higher alkaline phosphatase levels and bilirubin levels in patients with a positive antibody.

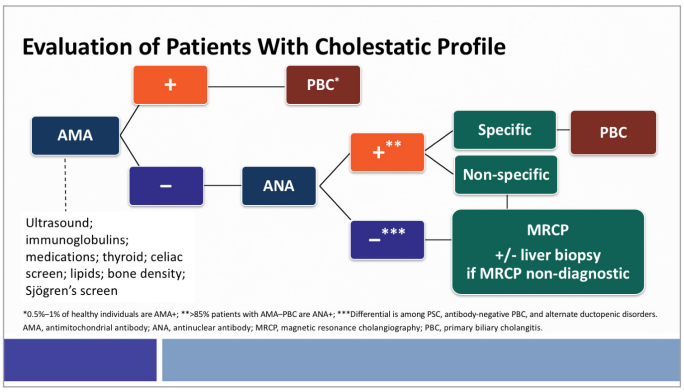


When assessing the patient, it's very important to clarify the patient's symptoms that may or may not be overlapping with PBC. Does the patient have dry eyes or dry mouth? Does the patient have bone disease? Does the patient have pruritus, and if the patient has fatigue, could it be related to chronic liver disease? If you've identified a patient with a cholestatic liver profile and have an elevated alkaline phosphatase and GGT, and an ALT/AST less than 5 times the upper limit of normal, you want to be thinking about a patient who may have one of these autoimmune liver diseases. By contrast, in a patient who has a hepatocellular profile without a significant elevation of alkaline phosphatase, autoimmune hepatitis should come to mind.

It's also important to keep in mind that drug-induced liver disease may frequently mimic any of these autoimmune conditions and so it is important to evaluate the drug and supplement history carefully. Exclusion of drug-induced liver disease, exclusion of chronic liver diseases, use of cholangiography, and appropriate interpretation of the autoantibody profile are very helpful.



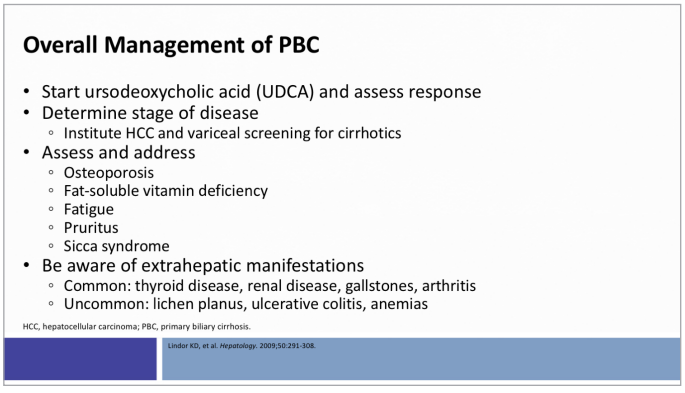
This slide shows in an algorithmic manner how to approach a patient with a positive anti-mitochondrial antibody. A patient that's AMA positive is very likely to have PBC. However, a patient with cholestatic pattern of liver test abnormalities who is AMA negative has a much larger differential diagnosis. First step would be to measure the antinuclear antibody and to make sure the patient does not have a chronic large duct obstruction disease, such as PSC.



Initial Treatment with Ursodeoxycholic Acid

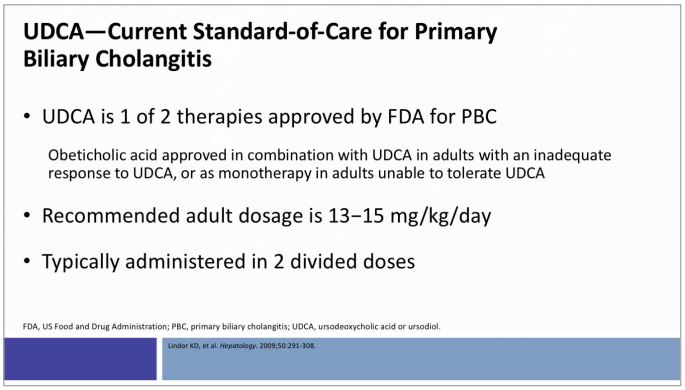
Dr. Kowdley: The overall management of PBC begins with starting ursodeoxycholic acid and assessing the biochemical response. As I've mentioned, the alkaline phosphatase and bilirubin after 1 year of treatment of ursodeoxycholic acid are very helpful in determining patients at high vs low risk. Part of the evaluation should include assessment of the stage of the disease, because for patients who have advanced fibrosis, such as stage 3 or stage 4, it is important to initiate hepatocellular carcinoma surveillance and screening for varices in patients with cirrhosis.

Part of our routine assessment is to assess for osteoporosis, especially in women who are post-menopausal, to evaluate for fat-soluble vitamin deficiencies and to manage or help manage fatigue, pruritus, and make the patient aware if they have symptoms of Sicca syndrome to seek appropriate specialty care. It's always important to keep in mind extrahepatic manifestations, such as thyroid disease, renal disease, and occasionally, skin disorders, etc.



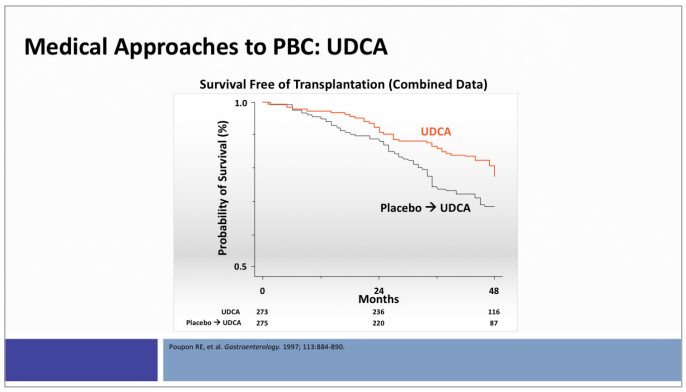
The current first-line standard of care for primary biliary cholangitis is ursodeoxycholic acid. This slide has now been updated to reflect that there is a new treatment, obeticholic acid, which has just been approved by the FDA for treatment for PBC.

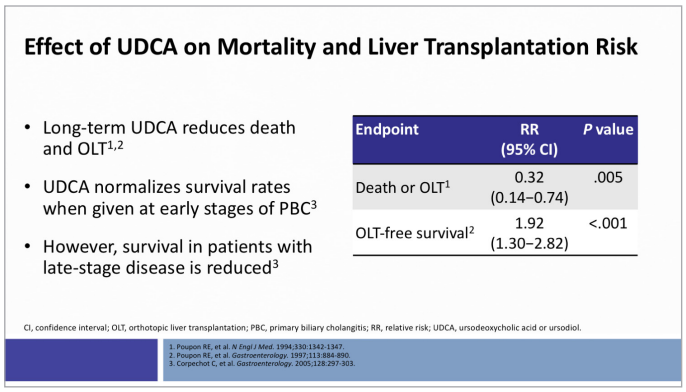
Historically, ursodeoxycholic acid, since the late '90s, has been the only therapy approved by the FDA for treatment of PBC. The recommended adult dose is 13 to 15 mg/kg per day and typically administered in 2 divided doses.



This landmark study by Raoul Poupon in 1997 showed in a 4-year randomized controlled trial that patients who are treated with ursodeoxycholic acid for 4 years compared to those who received placebo for 2 years and then open-label ursodeoxycholic acid for 2 years, had significantly improved survival—free of transplantation. Furthermore, this author showed that in patients with particularly early stage PBC who had progression, who had treatment with ursodeoxycholic acid, there was a life expectancy that was comparable to healthy, control populations in France. Whereas, in patients who were treated with ursodeoxycholic acid and compared to untreated patients, they still had improved survival, but in patients with advanced disease, the survival was significantly lower than would be expected.

The take-home message in terms of long-term ursodeoxycholic acid treatment is, in early stage patients, life expectancy can be expected to be normal. In advanced disease, although there may be reduced survival, this is still improved compared to no treatment.





There are some data about the effect of ursodeoxycholic acid on mortality and liver transplantation risk and here's a slide that shows long-term ursodeoxycholic acid reduces death or liver transplantation by a substantial margin. In fact, ursodeoxycholic acid potentially normalizes survival rates when given at early stages of PBC. In patients with late stage disease, there's still reduced overall survival. It is important to emphasize, despite the very long natural history of PBC, that early diagnosis and initiation of therapy is important and can improve life expectancy, survival, and need for transplantation.

Assessing Response to Ursodeoxycholic Acid

Dr. Kowdley: PBC is a heterogeneous disease and the risk of progression differs among different patients. It's important to recognize the baseline factors in a patient with PBC that are associated with increased risk of progression. What treatment endpoints should we be looking for in patients in whom we start ursodeoxycholic acid therapy, as potential indicators for those individuals that may be candidates for treatment with obeticholic acid or possibly other considerations of treatment or may be referred for a clinical trial?

Baseline and on-treatment alkaline phosphatase and bilirubin baseline and on-treatment AST/platelet ratio and on-treatment biochemical response criteria have high confidence and wide applicability. There are some other baseline factors and on-treatment data that may have intermediate confidence and applicability, such as age at diagnosis, the disease-specific ANA that I mentioned earlier, and baseline and on-treatment transient elastography. There are others that may not be as useful in predicting prognosis or in delivering risk assessment, and these include histologic scores and possibly measurement of portal pressure.

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
- Intermediate confidence and applicability
  - Presenting age
  - Baseline disease-specific ANA
  - Baseline and on-treatment transient elastography
- Indeterminate confidence and applicability
  - Gender and baseline symptom profile
  - Baseline and on-treatment novel histologic scores
  - On-treatment direct portal pressure measurement

ALP, alkaline phosphatase; ANA, antinuclear antibody; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; PBC, primary biliary cirrhosis.

Trivedi PJ, et al. *Hepatology*. 2016;63(2):644-659.

There are several established response criteria models that all essentially are permutations of trying to determine how a patient's laboratory tests and clinical findings may have improved after a period of ursodeoxycholic acid therapy. The Barcelona, Paris-I, Rotterdam, and Toronto criteria all have used variable measures such as reduction in alkaline phosphatase from baseline, maintenance of a normal bilirubin, and maintaining an alkaline phosphatase below a certain level, in this case, 1.67 after a period of ursodeoxycholic acid.

The Rotterdam criteria are interesting, in that they are a blended assessment of both risk and stage. This criterion uses albumin and bilirubin after 1 year of ursodeoxycholic acid therapy, and the best outcome was in patients who had a normal bilirubin and a normal albumin. The worst outcome was in those who had elevated bilirubin and a reduced albumin, with intermediate outcomes in patients with 1 of 2 criteria abnormal.

Established Response Criteria Models for UDCA

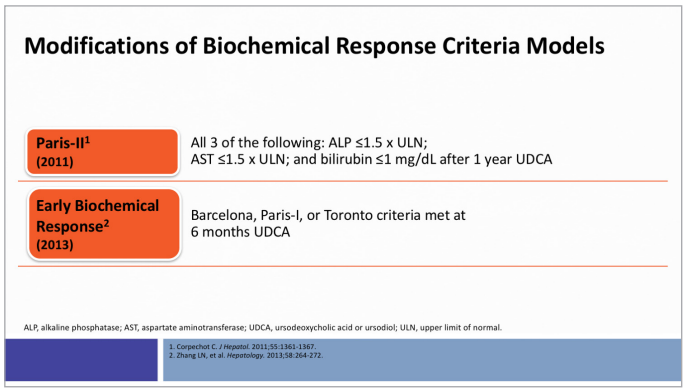
Barcelona[1] (2006)	ALP decreased by >40% from baseline or normalized after 1 year UDCA
Paris-I[2] (2008)	All 3 of the following: ALP ≤3 x ULN; AST ≤2 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA
Rotterdam[3] (2009)	Albumin and bilirubin normalization when 1 or both were abnormal at baseline; albumin 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

ALP, alkaline phosphatase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid or ursodiol; ULN, upper limit of normal.

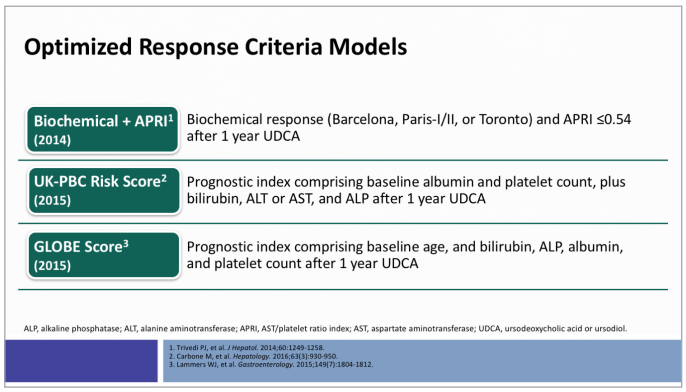
1. Parés A, et al. *Gastroenterology*. 2006;130:715-720.
2. Corpechot C, et al. *Hepatology*. 2008;48:871-877.
3. Kuiper EM, et al. *Gastroenterology*. 2009;136:1281-1287.
4. Kumagi T, et al. *Am J Gastroenterol*. 2010;105:2186-2194.

Some recent modifications of the biochemical response criteria model, such as the Paris-II, an early biochemical response criteria model, and these all demonstrate that patients who are on ursodeoxycholic acid for 6 months to 1 year can be considered to be in

a favorable prognostic criteria if they achieve alkaline phosphatase less than 1.5 times the upper limit of normal.

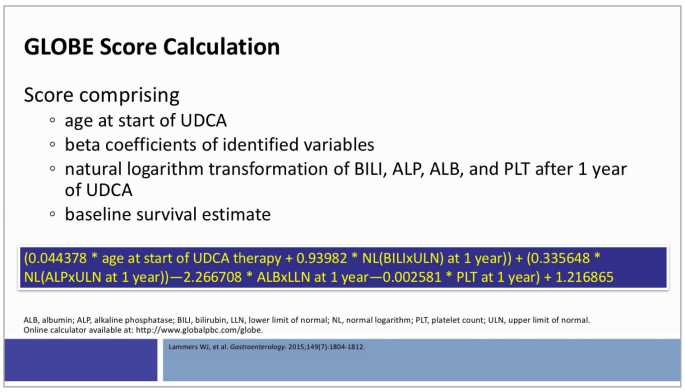


More recently, we have developed some optimized response criteria models that are very useful clinically and are conveniently associated with online calculators where risk assessment can be calculated right in the clinic at the bedside. The biochemical response model, when added to the APRI, was useful. The UK-PBC score, and particularly the GLOBE PBC score, are prognostic indices that have developed on prospective/retrospective or retrospective data collection using a variety of criteria and give you a risk assessment. If the risk assessment is above a certain number, the patient is in a higher-risk category, and below a certain number, in a lower-risk category.

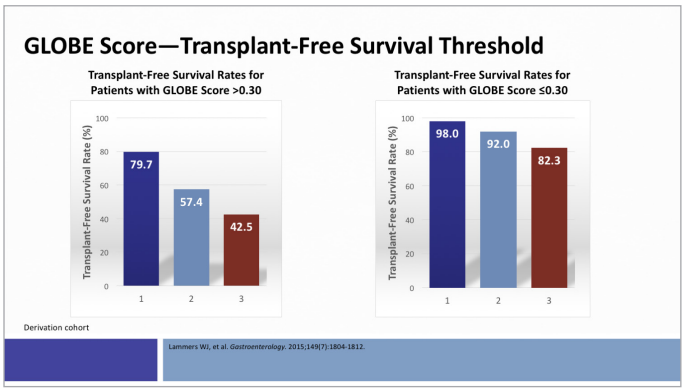


This shows you the GLOBE score calculation. Obviously, it's a bit detailed, but it is a freely available calculator that you can bookmark and enter the patient's data and provide the results or survival estimate.

Now, GLOBE score is a potent and useful score. As shown on this slide, transplant-free survival rates in patients with a high score or 42.5% vs 82% in patients with low score, and 5 and 10-year survivals are also shown here. I find the GLOBE score very



useful in my clinical practice. Since I have a practice that is almost entirely a referral practice, most of my patients have already been on ursodeoxycholic acid and are seeking second-line therapy, such as obeticholic acid or possibly enrollment in a clinical trial and so using the GLOBE score helps us stratify risk very effectively.

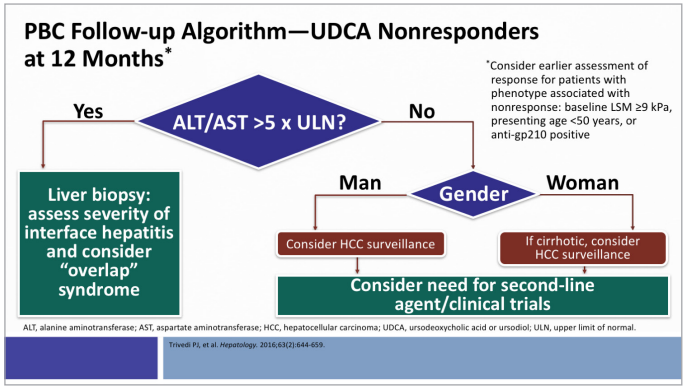


Here's an algorithm for how to follow patients who are ursodeoxycholic acid nonresponders at 12 months. How do you define nonresponse? For us, it's an alkaline phosphatase greater than 1.67 times the upper limit of normal. Some people use an alkaline phosphatase greater than 1.5 times the upper limit of normal and others an alkaline phosphatase greater than twice the upper limit of normal. For a patient who has not responded or had a partial response, it is important to assess whether they may possibly be in that relatively small group of patients with true overlap syndrome where the PBC component has been treated but the autoimmune hepatitis component may need immunosuppressive therapy.

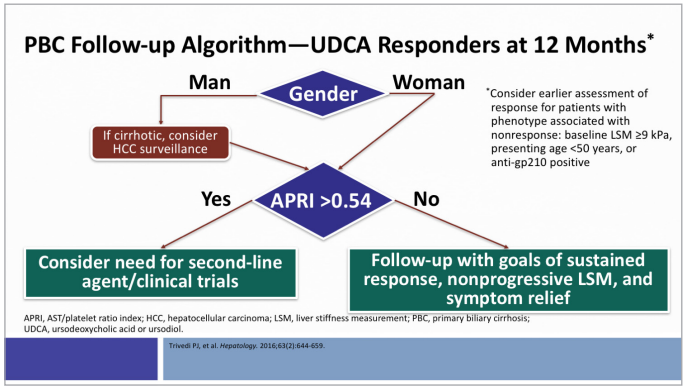
Certainly, if the ALT/AST ratio is greater than 5 times the upper limit of normal, it would be prudent to consider a liver biopsy to determine whether there are features of autoimmune hepatitis. I would emphasize that, at least in my opinion, it is wise to perform a liver biopsy before initiating immunosuppressive

therapy which could be chronic and long term without knowing for sure that we're treating this condition. A liver biopsy in this situation would be advisable.

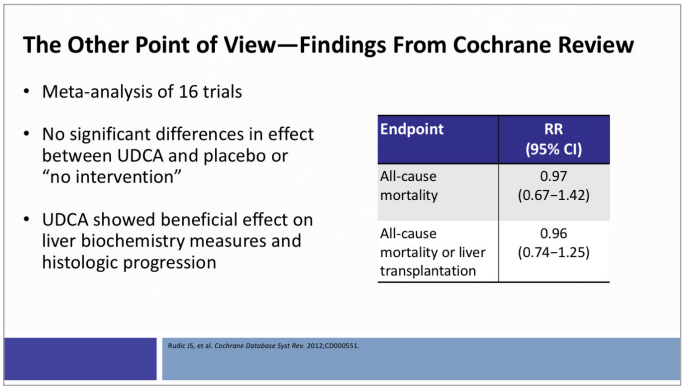
Now, if the patient is a man and has dot-proven PBC and continues to have elevated liver enzymes, it's also important to consider that this patient would be a candidate for HCC surveillance, as liver cancer in men, particularly with cirrhosis, significantly increases in terms of risk. For patients who have PBC who have persistently elevated liver enzymes or persistently elevated alkaline phosphatase, there is an appropriate consideration for either second-line therapy with obeticholic acid, which is now FDA approved and has been since mid-last year, or consideration of clinical trials.



Another way to stratify the patients who have been treated with ursodeoxycholic acid and have responded at 12 months is to evaluate the patient's APRI score and follow guidelines for HCC surveillance depending on whether they're men or women, and depending on whether they have more advanced fibrosis or not.

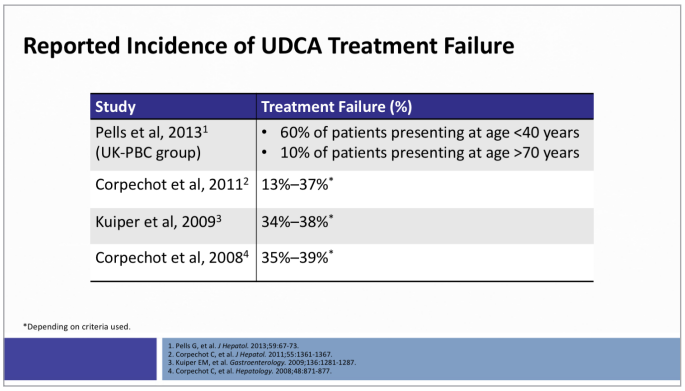


It's always important to review the fact that there is a contrarian point of view about the possible lack of efficacy of ursodeoxycholic acid. A Cochrane review meta-analysis of 16 trials found no significant differences in effect between ursodeoxycholic acid and placebo or no interventions and concluded that although ursodeoxycholic acid showed beneficial effects on liver biochemistry and even on histologic progression, all-cause mortality or mortality or liver transplantation was not significantly altered.



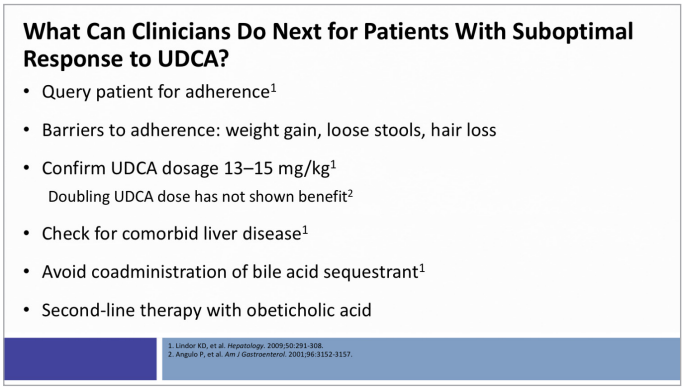
The problem with these studies and meta-analyses is they tend to have a variety of different populations of patients. Given that ursodeoxycholic acid is for a long-term, slowly progressive disease, outcomes in clinical trials will be largely determined by the duration of follow-up and by the proportion of early vs late-stage patients that were enrolled in the study. For example, if you look at ursodeoxycholic acid treatment failure, which is another criterion in which we evaluate patient status in trials, they may range from 10% for patients who present at older age and 60% who present at younger age. The likelihood of ursodeoxycholic acid treatment failure has been ranged to be as high as 39% or 60%, as I mentioned, and as low as 13%.

It is true that in addition to the severity of the disease at the time diagnosis, age of diagnosis is an important predictor of long-term outcome. For example, patients who are diagnosed at age greater than 70 years are much less likely to progress, whereas, patients who are diagnosed at age less than 40 years are much more likely to have progressive disease.



What can we do as clinicians for patients who have a suboptimal response to ursodeoxycholic acid? That is, those patients who have an alkaline phosphatase greater than 1.67 times the upper limit of normal after at least 6 months of ursodeoxycholic acid therapy or possibly as little as 3 months, and definitely after 1 year. It is important to question the patient for adherence, specifically to review the risks that the patient may not be adherent because of side effects which they may or may not be attributing to ursodeoxycholic acid, such as weight gain, loose stools, hair loss. Confirm the dosage is 13 mg-15 mg/kg/day and recognize that increasing the dose of ursodeoxycholic acid above that has not shown benefit.

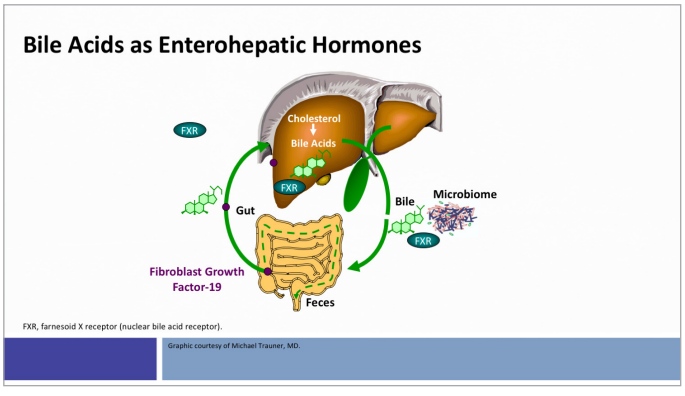
It is important to avoid coadministration with the bile acid sequestrant because these patients would probably not be absorbing the ursodeoxycholic acid or any other medications that are given at the same time. These are patients who are excellent candidates for consideration with obeticholic acid, which is now an approved second-line therapy for PBC.



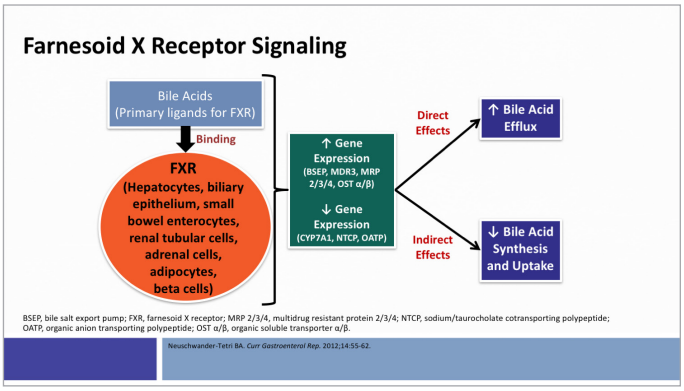
Obeticholic Acid

Dr. Kowdley: Obeticholic acid was approved for use in the United States in May of 2016 in combination with ursodeoxycholic acid in adults who have inadequate response to ursodeoxycholic acid or who are unable to tolerate ursodeoxycholic acid. Obeticholic acid is a farnesoid X receptor agonist. Let's start our discussion about this new treatment option by first reviewing the role of the FXR receptor in regulating bile acids.

It's important to remember that bile acids are not just detergents that help absorb fat. Cholesterol is the precursor for bile acids from which they are converted by biochemical changes in the liver, and bile acids are key in helping us absorb fat. Bile acids interact with the FXR receptors. Chenodeoxycholic acid has a small amount of agonism for the FXR receptor. Bile acids are then secreted into bile and also potentially interact through FXR through the microbiome. Finally, bile acids are reabsorbed as enterohepatic hormones through the enterohepatic circulation in the terminal ileum where FGF19 via FXR agonism can also play a role as an endocrine hormone in regulating liver metabolism and have many pleiotropic effects on inflammation, fibrogenesis, and choleretic pathways.

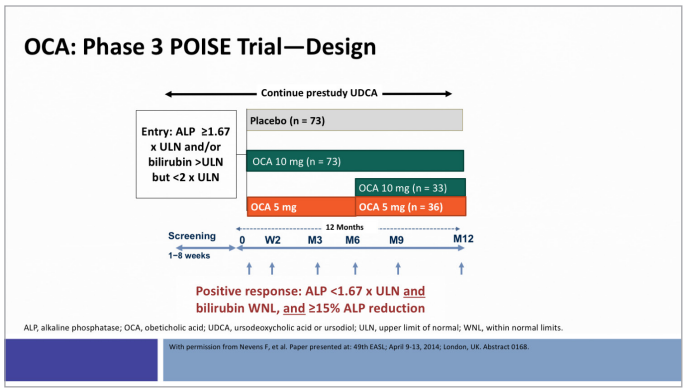


This slide shows how the FXR receptor signals and has a variety of downstream actions. Bile acids are the primary ligand for this receptor, which is a nuclear hormone receptor. They're expressed, if not ubiquitously, very widely. Their key effects are increased gene expression of bile salt export pump (BSEP) and multidrug-resistant genes, and a central effect of FXR agonism is suppression of gene expression of CYP7A or Cytochrome P45 7A1. This has direct effects in increasing bile acid efflux and reducing bile acid synthesis and uptake, so it's a 2-hit concept to reduce choleretic liver damage and promote excretion of bile acids, which can be toxic in the liver if they accumulate.

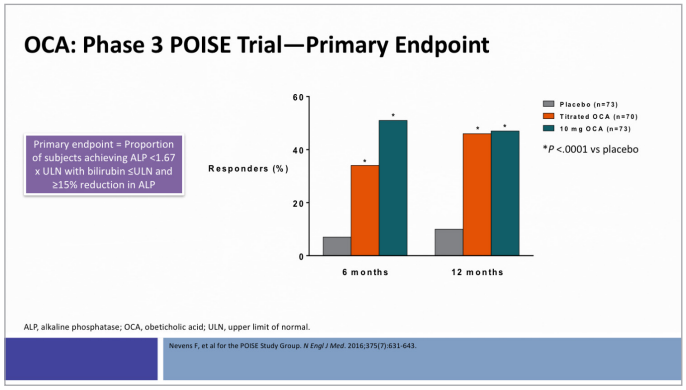


With this rationale, the POISE Trial, which was a phase 3 trial, that led to the approval of obeticholic acid for treatment with PBC, was designed to evaluate 3 arms. A placebo arm, a 10 mg arm, and an arm that started with 5 mg obeticholic acid and then up-titrated at 6 months to either 5 mg or 10 mg, depending on response. Entry criteria included an alkaline phosphatase greater than 1.67 times the upper limit of normal and/or a bilirubin greater than the upper limit of normal but less than twice the upper limit of normal. These were the patients that, hopefully, as we are all familiar with, would be classified, using all of the response models, as being high-risk patients for increased liver-related outcomes over time.

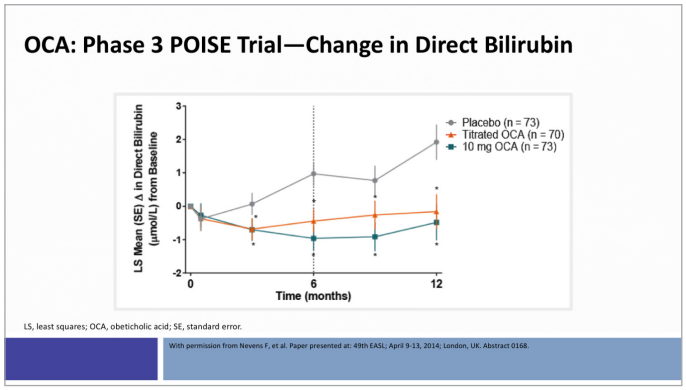
Response was defined on a composite endpoint of at least a 15% reduction of alkaline phosphatase, maintaining an alkaline phosphatase less than 1.67 times the upper limit of normal, and a bilirubin less than the upper limit of normal.



This slide shows the primary result of the POISE Trial. As can be seen, patients who were treated with obeticholic acid, both in the titrated arm and in the 10 mg arm, at 12 months had a higher likelihood of achieving this response composite endpoint at a rate of about 47%-48%, which was significantly higher than in the group treated with placebo.

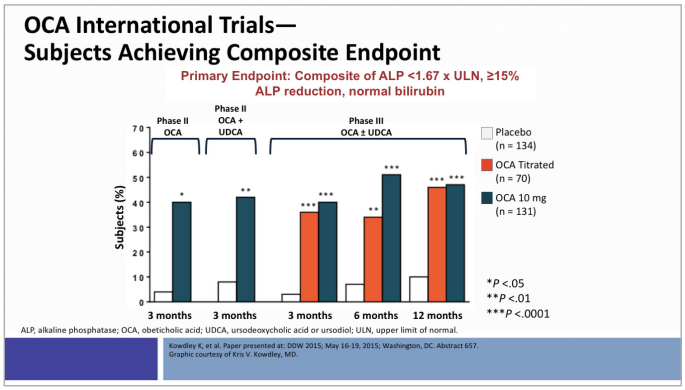


Interestingly, although the clinical significance of this may not be quite as clear, there was a significant reduction even in serum bilirubin. However, the scale here is in micromoles per liters. Interestingly, the placebo patient showed an increase, whereas, the treated patient showed a decrease.

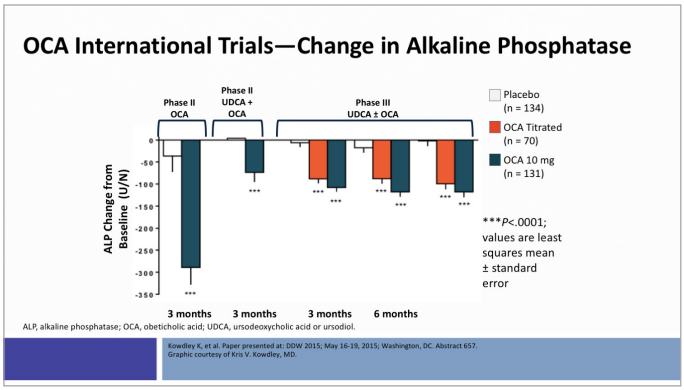


In addition to the key phase 3 study that I just reviewed, several Phase II and III international trials have been conducted to evaluate a variety of different doses of obeticholic acid and to determine the efficacy and safety of both monotherapy, as well as combination therapy with ursodeoxycholic acid. In these studies, obeticholic acid showed efficacy, not only in patients treated with combination therapy, but also in patients treated with monotherapy. The analyses that I'm describing here will have similar changes. Except for not using the POISE primary endpoints, but just looking at change from baseline of alkaline phosphatase, bilirubin, etc.

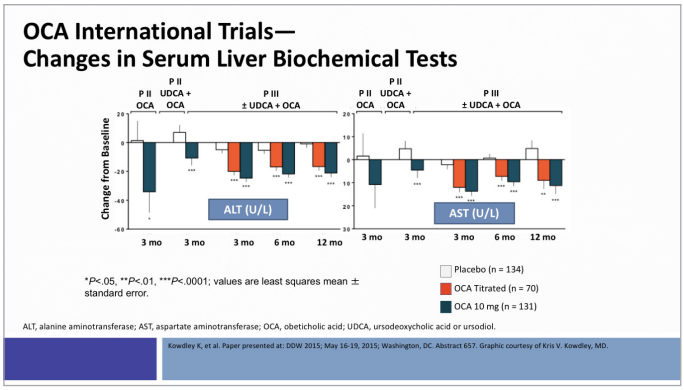
This composite slide shows the number of patients who, in a post-hoc analysis, achieved the composite endpoint in the Phase II studies and in the Phase III studies. As shown, both the patients in the Phase II studies of monotherapy and with combination therapy, in comparison to patients who are treated in the Phase III studies, were likely to achieve the primary composite endpoint.



This slide shows the change in alkaline phosphatase in the obeticholic acid international trials. As you can see, the percentage changed. An absolute change in alkaline phosphatase would be greatest in patients who are on monotherapy, as expected, and that is what is shown in this slide. The patients in the Phase II monotherapy study had a reduction in alkaline phosphatase of almost 300 units per liter. Patients who are already on ursodeoxycholic acid and had already achieved a reduction in alkaline phosphatase with ursodeoxycholic acid showed relatively smaller absolute reductions in alkaline phosphatase.



Consistent with our thinking that obeticholic acid may have direct anti-inflammatory effects and have favorable effects on necroinflammation in the liver and possibly secondary favorable effects due to reduction of cholestatic liver injury from bile acids, you can see that liver enzymes ALT and AST showed reductions in the Phase II studies, as well, in the Phase III studies.



Expected on-target effect of obeticholic acid is an alteration in lipid profile, particularly a reduction in HDL cholesterol and a possible increase in LDL cholesterol. Consistent with this expected side effect, there was a reduction in HDL cholesterol and an increase in LDL cholesterol, but in absolute terms these are not dramatically different. It is important to keep in mind that the long-term effects on lipids with obeticholic acid should be watched and patients should be monitored with regard to whether they need intervention with a statin. The profile of the typical PBC patient is characterized by high levels of HDL and generally they have lower rates of atherosclerotic cardiovascular disease. Nevertheless, the change in lipid values is a consistent finding and LDL and HDL cholesterol should be monitored in patients who are treated with obeticholic acid.

OCA International Trials—Absolute Change in Lipid Levels From Baseline

	Phase II OCA		Phase II OCA + UDCA		Phase III OCA ± UDCA		
	Placebo (n = 23)	OCA 10 mg (n = 20)	Placebo (n = 38)	OCA 10 mg (n = 38)	Placebo (n = 73)	Titration OCA (n = 70)	OCA 10 mg (n = 73)
LDL-C (mg/dL)	-3.1	3.9	3.5	9.7	1.4	3.5	-1.9
HDL-C (mg/dL)	-1.5	-12.7	3.5	-9.7	-3.5	-11.2	-16.6
Triglyceride (mg/dL)	-1.8	-2.7	-8.9	-2.7	4.4	-5.3	-14.2

- 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

C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OCA, obeticholic acid; UDCA, ursodeoxycholic acid or ursodiol.

Kowdley K, et al. Paper presented at: DDW 2015; May 16-19, 2015; Washington, DC. Abstract 657. Graphic courtesy of Kris V. Kowdley, MD.

What do the adverse events look like for the obeticholic acid international trials? Well, 5 patients who are on placebo and 8 patients who are on 10 mg of obeticholic acid, which is 4% and 6%, reported at least 1 treatment-emergent serious adverse event. None in the 10 mg group were considered drug-related.

The main side effect of obeticholic acid, which is a dose-limited side effect, is pruritus. Most pruritus treatment-emergent adverse events generally are mild or moderate in severity. A way to mitigate the symptomatic or severe pruritus in these patients is to start at the 5 mg dose and titrate up to 10 mg, as shown in the POISE Trial. Interestingly, with this approach, fewer than 1% of patients had to discontinue obeticholic acid due to severe pruritus, compared to almost 10% in the group that started at 10 mg. Much higher rates of pruritus have been reported in patients receiving 25 mg and 50 mg per day, but those doses are not part of the recommended advisable dose to start with in patients with PBC.

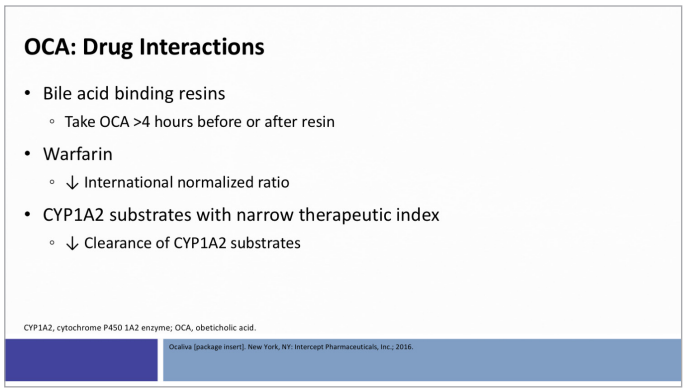
OCA International Trials—Summary of Adverse Events

- ≥1 Treatment-emergent serious adverse event
  - OCA 10 mg (6%)
    - None drug-related
  - Placebo (4%)
- Pruritus was the most common adverse event reported across all treatment groups
  - Most pruritus treatment-emergent adverse events were mild or moderate in severity
  - Uptitrating OCA dose from 5 mg to 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
    - 9% in 10-mg group

OCA, obeticholic acid.

Kowdley K, et al. Paper presented at: DDW 2015; May 16-19, 2015; Washington, DC. Abstract 657.

What about drug interactions with obeticholic acid? Obeticholic acid should be taken at least 4 hours before or after binding bile acid sequestrants because these will bind obeticholic acid and other drugs. There has been evidence to suggest that there may be decreased international normalized ratio, and so patients on warfarin should have their pro time monitored. Patients who are treated with CYP1A2 substrates with a narrow therapeutic window or a narrow therapeutic index should be monitored because of a reduced clearance of CYP1A2 substrates.



Investigational Treatments

Dr. Sclair: Let's turn our attention to other medications under investigation for primary biliary cholangitis. These medications act by mechanisms different from ursodiol and obeticholic acid. The PPAR-alpha peroxisome proliferator activator receptor alpha activity is responsible for regulating bile acid synthesis and it modulates phospholipid secretion, which helps protect the bile ductular epithelium.

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

Zollner G, et al. *Br J Pharmacol.* 2009;156:7-27.

Fibroblast growth factor-19 is an endocrine hormone that helps regulate bile acids in addition to carbohydrate, lipid, and energy metabolism. It has a role in regulating hepatic cell proliferation, but the FGF-19 FGF-R4 signaling is also associated with hepatocellular tumorigenesis. As an engineered FGF-19 variant, it has been shown to be capable of targeting the bile acid homeostasis functioning, but not the proliferative functioning.

Fibroblast Growth Factor 19 Signaling

- Fibroblast growth factor 19 (FGF19) is an endocrine hormone that helps regulate bile acids, and carbohydrate, lipid, and energy metabolism
- FGF19 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 homeostasis function, but not the proliferative function

Luo J, et al. *Sci Transl Med.* 2014;6(247):247ra100.

Here is a list of drugs in phase 2 and 3 testing for PBC. In the PPAR alpha class, we have the fibrates, both bezafibrate and fenofibrate. In the novel FGF-19 analog, the NGM-282 drug is under investigation in phase 2 trials.

Drugs in Phase 2/3 Testing for PBC

Target/Class	Drug	Phase
Peroxisome proliferator-activated receptor alpha agonist	Bezafibrate	3, ongoing
	Fenofibrate	2
Fibroblast growth factor 19 analog	NGM282	2

Dr. Kowdley, please discuss some of these investigational agents beginning with the fibrates.

Dr. Kowdley: There is a study that's examined bezafibrate with ursodeoxycholic acid and examined the long-term outcome in ursodeoxycholic acid nonresponders with dyslipidemia. Twenty-seven patients were enrolled in a prospective randomized controlled multi-center study. Patients received continued administration of ursodeoxycholic acid vs bezafibrate add, on to ursodeoxycholic acid after more than 24 weeks with long-term therapy. Primary endpoints were alkaline phosphatase levels, Mayo Risk Score, total bilirubin, AST, albumin, overall survival, hepatocellular cancer incidence, and safety with creatinine as an endpoint.

Bezafibrate + UDCA—Long-term Outcome in UDCA Nonresponders With Dyslipidemia

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

ALP, alkaline phosphatase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid or ursodiol.

Hosonuma K, et al. *Am J Gastroenterol.* 2015;110:423-431.

The Mayo Risk Score was significantly lower in patients who received bezafibrate with ursodeoxycholic acid. However, mortality rate and incidence of HCC were not significantly different between the 2 groups. Interestingly, creatinine levels at 8 years were significantly higher in the combination therapy group. Although they were still close to normal, there was a significant difference, 0.94 vs 0.56, and it was called out that we should pay close attention to adverse events during the long-term combination therapy. Bezafibrate is not available in the US, but these data bear watching.

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

- Mayo risk score (bezafibrate + UDCA vs UDCA)
  - 0.91 vs 1.42 (*P* <.05)
- Mortality rate and incidence of HCC were not significantly different between the 2 groups
- Creatinine levels at 8 years (bezafibrate + UDCA vs UDCA)
  - 0.94 vs 0.56 mg/dL (*P* <.05)
- "We should pay close attention to adverse events during this long-term combination therapy"

HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid or ursodiol.

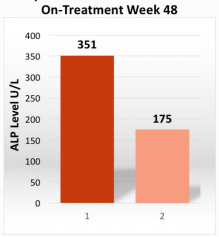
Hosonuma K, et al. *Am J Gastroenterol.* 2015;110:423-431.

Fenofibrate has been studied in a phase 2 study in patients with PBC and an incomplete response to ursodeoxycholic acid. Shown here is an open-label study of 20 patients. Alkaline phosphatase levels did decrease significantly with a rebound after discontinuation. Once again, the use of fenofibrate is limited by a labeled contraindication for patients with hepatic or severe renal dysfunction including PBC. Clearly, additional data with the safety and efficacy of fibrates in treatment with PBC is warranted and needed.

Fenofibrate—Phase 2 Findings in Patients With PBC and Incomplete Response to UDCA

- Open-label study (n = 20)[1]
- ALP levels decreased significantly[1]
- Rebound in ALP levels occurred following fenofibrate discontinuation[1]
- Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including PBC[2]

Comparison of ALP at Baseline and On-Treatment Week 48



ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid or ursodiol.

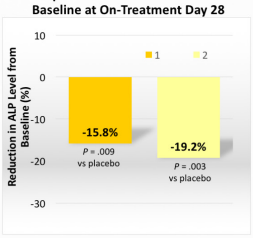
1. Levy C, et al. *Aliment Pharmacol Ther.* 2011;33:235-242.
2. Tricor [PI]. North Chicago, IL: AbbVie Inc.; 2016.

Dr. Sclair: Again, NGM-282 is an engineered variant of FGF-19 and has been studied in PBC in a double-blind placebo-controlled trial. These data suggest that NGM-282 is a potent regulator of bile acid synthesis and effectively reduces alkaline phosphatase levels when given to patients with PBC.

NGM282—Phase 2 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

Comparison of ALP Reduction from Baseline at On-Treatment Day 28



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid or ursodiol.

Globe Newswire. March 24, 2015. http://globenewswire.com/news-release/2015/03/24/718185/10126091/en/NGM-Biopharmaceuticals-Announces-Positive-Phase-2-Clinical-Data-in-Primary-Biliary-Cirrhosis-Patients-for-NGM282-a-First-in-Class-Investigational-Medicine.html.

Budesonide has also been studied together with ursodiol treatment of PBC. Budesonide is a non-halogenated glucocorticoid absorbed in the small bowel with 90% hepatic first-pass metabolism. There have been 3 studies that have looked at budesonide therapy in combination with ursodiol. Two were randomized studies using 3 milligrams and 6 milligrams of budesonide, respectively. The third was a non-randomized study using budesonide at a dose of 9 milligrams for 1 year. Cirrhotic patients were excluded as there's altered metabolism of budesonide in cirrhotic patients and there is actually an increased risk for the development of a portal vein thrombosis.

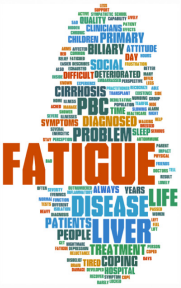
Both the randomized studies showed a greater reduction in serum alkaline phosphatase and improved the histology in both grade and stage and those treated with both budesonide and ursodiol. Actually, the ursodiol alone group had an histologic deterioration. In the non-randomized pilot study, there was only a very modest effect with budesonide, thus the use of budesonide is best reserved for patients with overlap syndrome with autoimmune hepatitis.

Managing Symptoms and Complications

Dr. Sclair: Let's talk about some of the symptoms and complications experienced by patients with primary biliary cholangitis. I'll begin the discussion by talking about fatigue and pruritus. Patients with PBC who are fatigued, both with and without cirrhosis, have lower heart rate variability and tend to be more hypotensive, all indicating autonomic dysfunction. Furthermore, these patients have accelerated reduction in muscle function on repeated sustained activity that correlates with the severity of fatigue. Such peripheral muscle fatigability appears to be related to excess muscle acidosis. The common pathophysiology here is probably related to mitochondrial dysfunction.

Fatigue in Patients With PBC

- Common at all stages of PBC
- Autonomic dysfunction
- Accelerated reduction in muscle function
  Mitochondrial dysfunction?



PBC, primary biliary cholangitis.

Griffiths L, et al. *Dig Dis.* 2014;32:615-625.

Modafinil is a medication that has been studied in the treatment of fatigue in patients with primary biliary cholangitis. Modafinil at 200 milligrams daily compared to placebo, did not really impact various fatigue scores.

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

Change from Baseline	Modafinil 200 mg (n = 20)	Placebo (n = 20)	*P* Value
Fisk Fatigue Impact Score	-1.5	-3.5	0.91
Fatigue Severity Score	-13	-3	0.36
PBC-40 fatigue domain	-8	-4	0.87

PBC, primary biliary cholangitis

Silveira M, et al. *Hepatology.* 2011;54(4 suppl):1211A-1212A.

Pruritus is also quite a common symptom in patients with PBC. It often occurs early in the disease course, as opposed to hepatocellular diseases where pruritus is a later phenomenon. It is often localized to the palms and soles. There is not necessarily a primary rash and it can be exacerbated by heat, for example, and is worse in the evenings. It's also characterized by periodic exacerbations and improvements.

Pruritus in Patients With PBC

- Occurs early in cholestatic diseases,[1] later in hepatocellular diseases
- Localized vs generalized
  - Palms and soles
- No primary rash[1]
- Exacerbated by
  - Pressure
  - Heat[1]
- Circadian rhythm (worse in evenings)[1,2]
- Periodic exacerbations and improvements[2]

PBC, primary biliary cholangitis

1. Rishe E, et al. *Acta Derm Venereol.* 2008;88:34-37.
2. Mayo MJ, et al. Primary biliary cirrhosis. In: Yamada T, ed. Textbook of Gastroenterology, 4th ed. Oxford, UK: Lippincott Williams & Wilkins; 2003.

Here is a list of important behavioral modifications regarding the treatment and management of pruritus. I find these very helpful. Usually wearing loose clothing, a cool environment, the frequent use of cool emollients, avoiding pruritogenic medications such as opioids, trimming the nails, and limiting sun exposure, all help with the symptoms of pruritus.

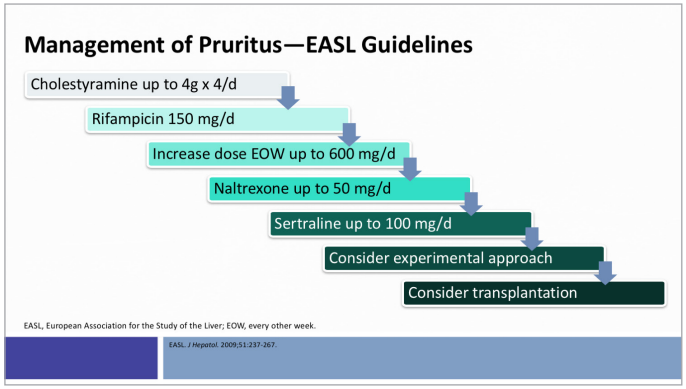
Behavioral Modifications for Pruritus in Patients With PBC

- Wear loose, absorbent clothes
- Seek cool (not dry) environment
- Use cool emollients frequently
- Avoid pruritogenic medications (opioids)
- Trim nails
- Limit sun/ultraviolet exposure

PBC, primary biliary cholangitis.

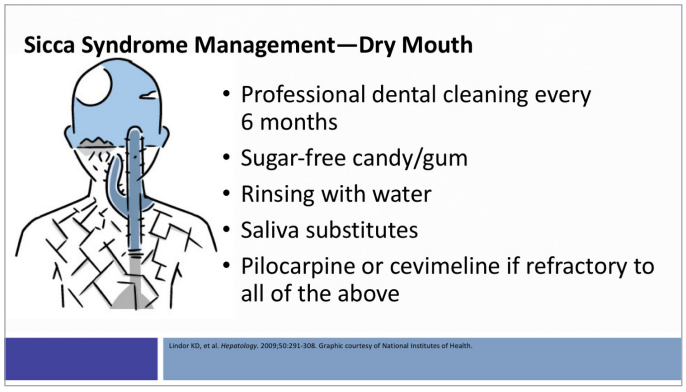
Finally, this is a very helpful treatment algorithm provided by the European Association for the Study of the Liver. The starting point is usually with cholestyramine up to 4 grams, 4 times per day. If that's ineffective, moving onto rifampicin

(investigational) 150 milligrams per day, which can be increased. Next, if rifampicin fails, then naltrexone up to 50 milligrams a day, and finally, sertraline up to 100 milligrams a day. In intractable pruritus, one always has to consider liver transplantation.

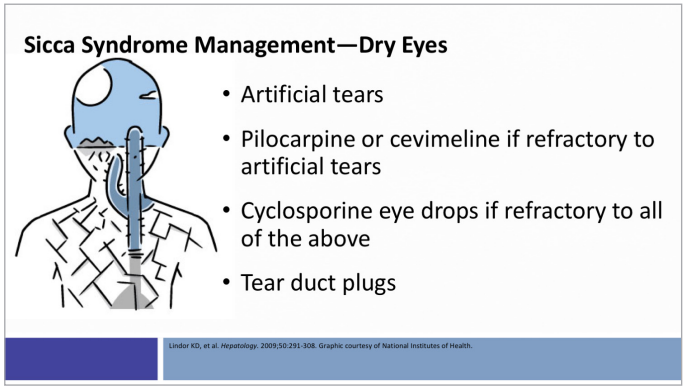


Dr. Kowdley, Sicca syndrome is something patients with primary biliary cholangitis often complain about. What advice can you provide our colleagues in helping patients manage these symptoms associated with Sicca syndrome?

Dr. Kowdley: Now, it's important for Sicca syndrome management to be emphasized to the patient and I encourage hepatologists and allied health providers who manage patients with liver disease to reinforce these with the patient. It's important to encourage a professional dental cleaning every 6 months. We are liberal in our encouraging patients to use sugar-free candy or gum. Keeping oral hygiene with rinsing with water or saliva substitutes and pilocarpine or other substitutes, if refractory, are reasonable.

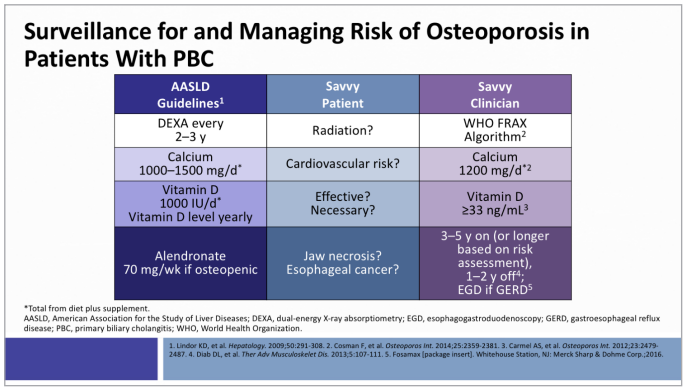


Dry eyes, it is important to remember to use artificial tears. Pilocarpine or cevimeline, if refractory to artificial tears, again may be considered, and we use cyclosporine eye drops if refractory to the above.
I have occasional patients who use tear duct plugs and have found them to be effective.



Dr. Sclair, osteoporosis is quite challenging in some patients with PBC, how should this be managed, in your opinion?

Dr. Sclair: Here, I'd like to review managing risk of osteoporosis in patients with primary biliary cholangitis. The American Association for the Study of Liver Diseases guidelines recommend obtaining a DEXA scan every 2 to 3 years, instituting therapy with calcium if there's osteopenia present, as well as checking vitamin D levels and supplementation, and for osteoporosis, using alendronate at 70 milligrams per week.



I'd like to share some interesting data with the role of using vitamin D levels and replenishing vitamin D in patients who are deficient, and promoting and improving outcomes and response rates of bisphosphonates. Here, you can see that with a vitamin D level ≥33 nanograms per milliliter, patients were almost 5-fold more likely to achieve a favorable response with bisphosphonate therapy.

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)

25(OH)D Serum Concentration	Nonresponse
<30 ng/mL	79% (52/66)
≥30 to <40 ng/mL	50% (34/68)
≥40 ng/mL	33% (25/76)

25(OH)D, 25-hydroxy vitamin D; BMD, bone mineral density.

Carmel AS, et al. *Osteoporos Int.* 2012;23:2479-2487.

It's important to also keep in mind deficiencies of fat-soluble vitamins in patients with PBC. Shown on this slide is an important study and a summary of various studies and the AASLD Guidelines showing that vitamins A, D, E, and K may be deficient in many patients with PBC. I published a paper years ago showing vitamin K deficiency was the most common. Shown here is vitamin A as the most common and vitamin D, followed by vitamin K. Vitamin E, since it's bound to lipids, generally, may be artificially high in patients with PBC and may explain why the deficiency rates in this study are low.

Surveillance for Fat-Soluble Vitamin Deficiencies in Patients With PBC

- Decreased bile acid secretion may lead to impaired absorption of fat-soluble vitamins ADEK[1]
- Monitoring guidelines
  - AASLD: no specific recommendation[2]
  - Medicare: no more than once annually[3]
- 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

Vitamin	Proportion of PBC Patients with Deficiency[1] (N = 180)
A	33.5%
D	13.2%
E	1.9%
K	7.8%

AASLD, American Association for the Study of Liver Diseases; ADEK, vitamins A, D, E, and K; PBC, primary biliary cholangitis; PT, prothrombin time.

1. Phillips JR, et al. *Am J Gastroenterol.* 2001;96:2745-2750.
2. Lindor KD, et al. *Hepatology.* 2009;50:291-308.
3. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=29510&ContrId=269&ver=38&ContrVer=1&Date=08%2f04%2f2014&DocID=L29510&bc=AAAAAAgAAAAAAA%3d%3d&

Monitoring guidelines are not particularly clear. Medicare would recommend no more than once annually. A reasonable practice in our clinic is an annual measurement of vitamins A, D, and K, now that it can be measured routinely. In patients on some of the new therapies that may lower the bile acid pool or block enterohepatic circulation, more frequent monitoring may be required.

Dr. Sclair, what complications of liver disease do you think are worthy of mention and deserve attention?

Dr. Sclair: Next, I'd like to turn our attention to PBC and cancer risk, as well as PBC and development of esophageal varices. Regarding PBC and cancer risk, the important association is clearly with hepatocellular carcinoma. Regarding surveillance for hepatocellular carcinoma in patients with PBC, the guidelines advocate for patients with cirrhosis to be screened every 6 to 12 months using ultrasound with or without alpha fetoprotein testing. However, data has suggested that the older male nonresponder to therapy, even if he is not cirrhotic, may carry an increased risk for the development of hepatocellular carcinoma.

Surveillance for Hepatocellular Carcinoma in Patients With PBC

- American Association for the Study of Liver Disease
  Patients with cirrhosis should be screened every 6–12 months using ultrasound with (or without) alpha fetoprotein[1,2]
- Beware the older male nonresponder, even if not cirrhotic![3]

1. Lindor KD, et al. *Hepatology.* 2009;50:291-308.
2. Bruix J, et al. *Hepatology.* 2011;53(3):1020-1022.
3. Trivedi PJ, et al. *Gut.* 2016;65(2):321-329.

Other factors that are associated with an increased risk of HCC in patients with PBC and treated with ursodiol are as follows: patients who do not meet, for example, the Paris-I Treatment Criteria or other treatment criteria, male patients, patients with thrombocytopenia and, as we know with other chronic liver diseases, increasing age.

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

Paris-I not fulfilled	3.42 (*P* <.0001)
Male	2.41 (*P* <.0001)
Thrombocytopenia (per 50 x 10^3/mm^3 decline)	1.42 (*P* <.0001)
Age (per 10 years)	1.31 (*P* =.009)

HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid or ursodiol.

Trivedi PJ, et al. *Gut.* 2016;65(2):321-329.

Regarding management of esophageal varices, patients with cirrhosis should be screened for esophageal varices every 1 to 3 years based on the presence of varices and also based on their degree of decompensation. An important thing to know is that varices may develop even in non-cirrhotic primary biliary cholangitis.

Surveillance for Varices

- Patients with cirrhosis should be screened every 1–3 years using esophagogastroduodenoscopy[1]
  Interval based on decompensation[2]
- Varices with bleeding may occur in noncirrhotic PBC patients[3]

1. Lindor KD, et al. *Hepatology.* 2009;50:291-308.
2. Garcia-Tsao G, et al. *Hepatology.* 2007;46:922-938.
3. Vlachogiannakos J, et al. *Eur J Gastroenterol Hepatol.* 2009;21:701-707.

This is illustrated in the following table. There have been a number of studies that actually stratify which patients are at most risk for the development of esophageal varices.

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

	AASLD	Levy et al	Angulo et al	MABPT
Criteria	Cirrhotic (stage IV) PBC	Mayo risk score ≥4.5 and/or platelets ≤140,000	Mayo risk score ≥4	Male sex, ALB <3.5 g/dL, BILI ≥1.2 mg/dL, and/or PT ≥12.9 sec
Sensitivity	53%	90%	93%	95%
Specificity	85%	56%	32%	47%

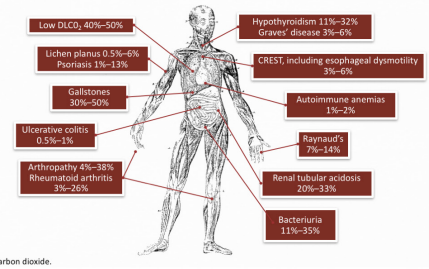
ALB, albumin; BILI, bilirubin; MABPT, Male sex, low ALB (<3.5 g/dL), elevated BILII level (≥1.2 mg/dL), and/or prolonged PT (≥12.9 s); PBC, primary biliary cholangitis; PT, prothrombin time.

Ali AH, et al. *J Clin Gastroenterol.* 2011;45(7):e66-e71.

As sometimes esophageal varices can develop even before cirrhosis is established in patients with PBC, there have been studies that utilized the Mayo Risk Score and platelet count to predict the presence of esophageal varices. A Mayo Risk Score staring at 4.5 and a platelet count lower than 140,000 may be predictive of esophageal varices.

Now, there are a number or extrahepatic associations with PBC including thyroid disease, Crest syndrome, autoimmune anemias, and gallstone disease to provide a few.

Be Aware of Extrahepatic Associations



$DLCO_2$, diffusing capacity for carbon dioxide.

Mayo MJ, et al. Primary biliary cirrhosis. In: Yamada T, ed. *Textbook of Gastroenterology,* 4th ed. Oxford, UK: Lippincott Williams & Wilkins; 2003. Human body graphic from: Lambert TS. Human Anatomy, Physiology and Hygiene. Hartford, CT: Brockett, Hutchinson & Co.;1854.

Dr. Kowdley: On behalf of my co-faculty, Seth Sclair, and myself, Kris Kowdley, I'm delighted that you were able to join us for this activity, Shifting Paradigms in Management of Primary Biliary Cirrhosis or, now as it's called, Primary Biliary Cholangitis. Thank you for your attention.

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