The questions below were submitted by attendees at our 2018 PBC Conference. Due to speaker’s time limit, all questions weren’t answered, so the speakers answered them after the conference. Many thanks to the speakers for taking the additional time to answer our questions.

The following is for information purposes and general recommendations in response to individual questions. Please be aware this is NOT medical advice or recommendations to an individual patient. Always consult your personal physician for specific questions about your medical care.

Christopher Bowlus, MD
University of California at Sacramento, Assistant Professor, Fellowship Program Director, Sacramento, CA

1. Beets, N-acetyl Cysteine, and Milk Thistle.

Diet and supplements to treat PBC and other medical conditions is an attractive approach. It offers the potential for safer and possibly less costly treatment. Unfortunately, there are limited data in PBC for the use of milk thistle and no data to my knowledge on beets or N-acetyl cysteine. Currently, the data does not support any claims that these approaches will slow the progression or improve symptoms of PBC.

2. PBC and the Brain.
There is growing evidence that PBC effects the brain and may play a role in the development of fatigue in PBC. To my knowledge there have not been any structural or other changes to the brain as seen in Alzheimer’s dementia. In fact, there has been no association between PBC and dementia. There was a recently completed study of a drug called rituximab to treat fatigue in PBC and unfortunately it was not successful. Any other study in PBC can be found at www.clinicaltrial.gov.

3. **Cirrhosis on Ultrasound with normal liver tests.**

Cirrhosis means that there has been extensive scarring in the liver and leads to a nodular appearance to the liver surface which can be seen on ultrasound. If the cirrhosis is extensive enough there can be restriction of blood flow through the liver leading to a condition known as portal hypertension. On ultrasound, this can be detected by an enlarged spleen and on a blood count the platelets are typically low.

Cirrhosis typically results after many years of liver injury which can be detected by elevated liver tests, alkaline phosphatase in the case of PBC. However, once the condition is treated, for example PBC with Ursodiol, the liver tests can be normal, but cirrhosis is already present will still remain. The treatment of PBC in the setting of cirrhosis is similar to that in the absence of cirrhosis with the exception that surveillance of liver cancer screening for esophageal varices should be considered.

4. **Ursodiol dosing.**

The recommended dosing for ursodiol is either twice daily or three times daily depending upon the formulation. However, even the formulation which is recommended to be given three times daily may be effective if taken twice daily.

5. **Frequency of blood tests and imaging.**

The frequency of blood tests and imaging vary depending upon the stage of disease, treatment, and patient and physician preference. At diagnosis, all patients should have at least an ultrasound. A FibroScan may also be helpful. I typically order labs to be done every 3 months for the first year after starting ursodiol and then every 6 months if the liver tests normalize and the disease is early. For later stage disease or when the liver tests do not normalize or if I start a new medication, I typically order liver tests every 3 months. PBC patients with very late stage disease, awaiting liver transplantation, or post-liver transplantation should have labs and imaging done more frequently.

6. **AMA but no PBC.**

There are 2 potential causes of having a positive anti-mitochondrial antibody (AMA) but not having PBC. First, the AMA may be a false-positive. This is most frequently seen with the M2 assay and usually is a low level M2 antibody. This can be confirmed by other tests for the AMA using different methods. Second, some people have true AMA, but have not developed the liver injury and do not have PBC. This is frequently seen in family members of PBC patients. If followed over time, many of these individuals will develop PBC. They should be monitored for elevation in the alkaline
phosphatase and treatment started if the alkaline phosphatase becomes persistently elevated.

7. Statins in PBC.

There is limited data on the use of statins in PBC, but the available data suggests that they can be used safely in PBC. There is no data to suggest that any one statin is safer or more effective in PBC.

8. PBC after liver transplant

The outcomes of patient undergoing liver transplantation for PBC are among the best of any group that has a liver transplant. PBC can recur after liver transplantation but it is usually mild and rarely lead to a need for a second liver transplant. There is emerging data to suggest that the use of ursodiol after liver transplantation may reduce the risk of recurrent PBC.

M. Eric Gershwin, MD
University of California at Davis, Chief, Division Rheumatology/Allergy & Clinical Immunology, Professor of Medicine, Director, Allergy-Clinical Immunology Program, Davis, CA

1. I developed inflammatory lung masses. Is this a known related diagnosis with PBC?

No, it should be unrelated. I hope someone is looking into it for you. It can be serious, or it may simply be old scarring from an old infection.

2. Hyperlipidemia is elevated cholesterol and triglycerides?

Yes, but it can mean more than that—ratios of lipids and types of cholesterol., your doctor should have a free brochure. If not, you can open this link: https://www.healthline.com/health/hyperlipidemia

Robert G. Gish, MD
Clinical Professor Consultant at Stanford University, Adjunct Professor of Medicine University of Nevada School of Medicine, Las Vegas, NV

1. How effective is endoscopy for bariatric bypass patients in screening for varices?

An upper endoscopy to assess for esophageal varices in bariatric bypass patients is quite useful since the esophagus has had minimal manipulation for most types of bariatric procedures and surgery.
2. For someone in Stage 4, how often should they be screen for HCC? Every 3-6 months?

For some patients with stage 4 (cirrhosis) primary biliary cholangitis, surveillance for liver cancer should take place every six months or every 12 months including blood tests for liver cancer (biomarkers that include alpha-fetoprotein, AFP-L3% and DCP) a full upper abdominal ultrasound for cancer surveillance is sufficient, remember screening is the first test, surveillance is ongoing testing at specific interval.

3. How often should a stage 4 patient have an endoscopy even if the first one is normal? Every 6 months or yearly?

EGD could be every two to three years depending on liver function and what is happening on ultrasound of the liver when measuring the portal vein diameter and spleen size. A normal portal vein should be less than 12 mm and a normal spleen should be less than 12 cm. If the portal vein is increasing in diameter and the spleen is increasing in vertical size this would indicate progressive portal hypertension and the need to move an upper endoscopy to a shorter frequency such as every six months to 12 months.

4. As a compensated stage 4 patient, whose labs are stable, what do I look for as signs of decompensation (other than my symptoms)? Is this sudden or a slow change (from compensated to decompensated)?

As a decompensated stage 4 patient, laboratory test should be done every one to three months. If a patient has compensated liver disease, meaning no encephalopathy, no ascites, normal international normalized ratio, normal direct bilirubin, then testing should be every 6 months. Signs of liver decompensation would be the signs or symptoms listed above. We must watch for jaundice, fluid on the abdomen called ascites, mental status changes that we consider hepatic encephalopathy, an increase in direct bilirubin more than 0.3 mg/dL, a worsening INR, and this is usually a slow change and is rare to have a sudden change unless there is gastrointestinal bleeding or an infection.

5. What is your website and email address?

My best website is robertgish.com, best email address is rgish@robertgish.com.

6. I have never been “staged”. Bottom line: What is the best way to diagnose stage?

Patients must be staged by multiple tests including imaging, elastography, APRI or FIB-4 score, we evaluate by looking at the AST to ALT ratio, the ALT should be higher than the AST in patients without cirrhosis, the platelet count should be over a 170,000 to be “normal”, a platelet count of under 100,000 would indicate to high probability the presence of cirrhosis, a liver biopsy can be done in special patients but is not currently standard for most patients to make the diagnosis of PBC or stage the liver disease. Liver disease staging is thus a matrix of assessment and must be no dependence on any one test to stage disease.
7. **What are the blood tests that should be done and how often? Imaging tests needed and how often?**

Blood tests in patients with primary biliary cholangitis should be done every six months and this should include a CBC with platelet count, a chemistry panel, a liver panel, and a direct and indirect bilirubin. Once the direct bilirubin is greater than 0.3 mg/dL then a coagulation test such as INR should be done twice annually. For imaging tests, see my comments above. A baseline ultrasound with portal vein diameter and spleen size should be done on every patient at baseline with a doppler technique.

8. **As an herbalist, can you give any suggestions for fatigue and inflammation? Essential Oils?**

A herbalist can be involved in managing patients with primary biliary cholangitis. The best herbal remedy for liver disease patients is coffee, this helps with fatigue and is profoundly anti-inflammatory and probably prevents liver cancer. I also consider "statin" drugs, they are typically used for cholesterol can be used to decrease portal hypertension also can serve as antifibrotic agents and prevent liver cancer. Other herbal remedies do not have peer reviewed publications and proof at the level that we consider in western medicine is lacking; there are some anecdotes and testimonial that herbs and supplements may help individual patients. Essential oils can help with a patient’s psychology and also help managing patient’s fatigue and cognitive thinking.

9. **Can you give more information about reversal of fibrosis? I did not know this was possible.**

Fibrosis can be reversed by decreasing inflammation in patients and I believe some patients on ursodeoxycholic acid or obeticholic acid can actually reverse fibrosis and of course these two drugs in some patients are used in combination in many patients. There is extensive information about reversal of fibrosis that would be posted on my website in about two weeks. You can download this PowerPoint presentations.

10. **I have PBC, AIH, Sarcoidosis and extreme Fatty Liver infiltration after losing 100 lbs. Can you give any ideas why fatty liver is going up?**

In patients with an overlap of primary biliary cholangitis, autoimmune hepatitis, “classic”, sarcoidosis and or fatty liver, each patient must be fully evaluated for nutritional deficiency such are carnitine deficiency. Vitamin E supplementation may help that fatty liver change and decrease inflammation. Aggressive management of high cholesterol and triglycerides is essential in patients with fatty liver or PBC with high lipids/fats in the blood. Aggressive management of hyperglycemia and diabetes is a key foundation of managing such conditions such as NASH. I would need to look at the patients’ medication profile to asses for other causes of fatty liver. This is a complex case and this type of patient presentation that requires a high level of input from an experienced hepatologist.

11. **Osteoporosis/Osteopenia and Prolia, Is Prolia injection recommended or have there been warning with PBC?**
Osteoporosis and osteopenia are diseases that commonly occur in PBC patients. Prolia injections have become a cornerstone of treating some patients with osteoporosis but there is little information about Prolia in primary biliary cholangitis patients. There are some reviews in the medical literature where this medication has been considered an option.

12. I was told by a doctor that Ocaliva failed their efficacy test. What does this mean for Ocaliva patients currently taking it?

Ocaliva or obeticholic acid is approved by the FDA and reached the primary in point of reducing alkaline phosphatase and actually had to meet a triple efficacy end point (see the package insert). This efficacy end point and FDA approval remains in effect and has been supported by follow-up publications and information. The only recent new information on Ocaliva is the warning about using it in patients with liver insufficiency and using the correct dose in patients with cirrhosis and liver dysfunction. This requires and experienced hepatologist to assess for liver dysfunction and to choose the correct dose for their patient. There have been no other changes about information concerning the documentation of Ocaliva’s efficacy in primary biliary cholangitis.

Silvia Hafliger, MD
Assistant Clinical Professor of Psychiatry Texas Medical Center/ McGovern Medical School UTHealth, Houston, TX

1. I've been told a transplanted liver lasts about 12-15 years and that I would need to be re-transplanted. What are the chances of needing a new transplant after 10 or 20 years?

Liver transplant can last 20-30 years depending on the cause of the illness. If your health permits and there is a reasonable chance that re transplant is the best treatment your will be offered a second liver. Autoimmune hepatitis / PSC are likely recurrent illnesses and are often re transplanted. It the liver failed due to lack of taking medication / substance abuse there is most likely not going to be a second transplant.

2. Will law likely change that currently restricts live-liver donation, especially in Texas?

There is no law restricting living liver donation. You need a surgeon and a center with experience in live liver donation. The surgeon has to be trained.

3. Is there an age limit or degree of health criteria that precludes a transplant?

Transplant is a major surgery and places great demand on heart/ brain/kidney. The older the person i.e. over 70 years the harder and longer the recovery. The recipient has to be able to handle 8-hour surgery / heart/ lung/ kidneys need to be stable. There is a point when a person is too ill for transplant. 20 % of patients listed may never get a
liver as their health has deteriorated. Often infection is the main reason / or cancer that has grown too big. There is no official upper age limit, but few centers will transplant over 75 yrs.

Marlyn Mayo, MD
University of Texas Southwestern, Associate Professor Department of Internal Medicine, Division of Digestive and Liver Diseases, Dallas, TX

1. One of the previous speakers said Hydroxyzine causes cardiac issues. I’ve been on Hydroxyzine and Sertraline for itching for a while. Is there an alternative for the Hydroxyzine? This combination works for me but I’d like to be proactive if Hydroxyzine is bad for me. What else can I take in its place?

It is very rare for hydroxyzine to cause heart problems in somebody who doesn't have underlying heart disease. However, there can be issues if you combine hydroxyzine with antibiotics that end in mycin or with some antidepressants. If none of these three conditions apply to you, I wouldn't worry about it. Other antihistamines often used for itch be PBC patients are Benadryl and Zyrtec (those are brand names, but the generics are fine). Benadryl is more sedating but also causes more dry mouth.

2. My dermatologist suggested I use daily sunscreen with zinc. Will this make a difference with itching?

If you mean will it make itching worse, I don't think so. If you are trying to use UV light to improve itching, the zinc, which blocks both UV-A and UV-B rays, might prevent the sunlight from helping.

John Vierling, MD
Professor of Medicine and Surgery, Chief of Hepatology and Director of Advanced Liver Therapies, Baylor College of Medicine, Houston, TX

1. Why does it seem like UTI’s are prevalent in so many of us? How can we treat it?

A prospective trial using urine cultures from women with PBC and women without PBC found no differences in the frequency of bacteria detected in the urine or the types of bacteria. This and other studies note that cirrhosis itself increases the risk of bacterial infections, including UTI. New guidelines of treatment of UTI have been published and you should consult with your physician about treatment.

2. We have 4 people in my family with PBC. Do you know of any genetic study we could participate in? How can I find one?

I am not aware of any enrolling studies for the genetics of familial occurrence of PBC, other than the monozygotic twin study of Dr. Gershwin.
3. Does being on Prednisone/AZA increase the likelihood of developing cancer (due to immunosuppression)?

In general, maintenance doses of prednisone do not significantly increase the risk of cancer. In contrast, azathioprine does confer a risk of cancer. This risk is partially dose related, and doses of azathioprine ≤ 2 mg per kg per day have a very low risk. It is noteworthy, that PBC does not respond to azathioprine, which is not used to treat PBC. In contrast, prednisone has been used successfully to treat PBC, especially in the early inflammatory stages 1-2.

4. Does having PBC/AIH increase the likelihood of transplant and/or HCC?

As noted in my lecture, the frequency of having PBC/AIH is very rare and most often represents a misdiagnosis. When PBC/AIH occurs, it can be controlled by adding immunosuppressive drugs to a baseline regimen of ursodeoxycholic acid at a dose of 13-15 mg per kg body weight per day. If PBC/AIH is untreated or progressive, it can advance the pace of progression to cirrhosis. Once cirrhosis occurs, transplantation is not inevitable. HCC is very rare in cirrhosis due to either PBC or AIH; current data indicate the incidence is approximately 1-1.5% per year.

5. If you are a non-responder to Urso and put on Ocaliva, why would you continue to take Urso?

Non-response to urso does NOT mean that you have failed to have any response, but only means that urso alone did not reduce your alkaline phosphatase to ≤ 1.67 X the upper limit of normal for the laboratory doing the alkaline phosphatase assay. Thus, urso likely resulted in some reduction of alkaline phosphatase and the addition of obetiholic acid gives you the best chance to lower alkaline phosphatase to the desired level.

6. Following transplant, and PBC returns in the liver, does it take the same “years” to cause massive liver damage?

PBC recurs after transplantation in approximately 30% of patients. When ursodeoxycholic acid is added to the treatment regimen, the pace of progression is slowed dramatically. PBC rarely causes loss of the transplanted liver.

7. I had PBC, then AIH. If you are in chemical remission of AIH, can it reoccur or be gone for good? Is AIH chronic (lifelong)? I am still taking medication for AIH (Imuran/Azathioprine), labs are all stable.

I am unsure about whether you did have or do have PBC. Rarely, AIH alone is associated with AMA, making the distinction difficult. Neither PBC nor AIH go away. However, drug-induced injury sometimes mimics AIH, leading to a misdiagnosis. Adequate treatment for AIH is defined by remission, which is a completely normal ALT (<20 IU/L for women and <30 IU/L for men). Stable labs above these levels of ALT indicate residual inflammation, requiring immunosuppression.
8. What do you think are the most promising therapies or treatments in phase 2 or 3 trials?

All of the phase II studies are using medications that make sense as potentially valuable therapies for PBC. As these studies progress, we may identify drugs that might be effectively combined to provide even more beneficial therapy for PBC. An important aspect of clinical trials is whether each therapy works in all stages of fibrosis in PBC. It is conceivable that certain drugs will work more effectively in stages 1-2 than in stages 3-4.

9. Do you see a correlation/overlap between PBC and common variable immunodeficiency?

No. CVI not associated with PBC, meaning that its frequency among PBC patients is not greater than the frequency of CVI in the general population.

10. I am a male PBC patient on 1500 mg of Urso, 5 mg OCA. Is there a direct correlation between PBC and the following? Low WBC (3.8), Elevated A1C (6.1) and Glucose (110).

Without information about your stage of fibrosis, this question cannot be answered. This is evidence of prediabetes, and most often is associated with overweight or obesity in adults. This is part of the “metabolic syndrome” of overweight/obesity, prediabetes or diabetes mellitus, elevated cholesterol and/or triglyceride, hypertension and elevated uric acid (with or without a history of gout). If this were the case, you would also be a risk for non-alcoholic fatty liver disease as a comorbid condition along with PBC. Progression of cirrhosis, due to any liver disease, increases the frequency of diabetes mellitus due to the loss of hepatocytes.

11. Stage 2 kidney disease

PBC does not cause chronic renal disease.

12. Elevated ferritin levels.

The key to answering this question is whether your percent transferrin saturation is <45%. If it is <45%, then your ferritin is NOT due to iron overload. The cause of elevated ferritin without iron overload is inflammation, which in turn is associated with inflammatory liver diseases like PBC and non-alcoholic steatohepatitis (NASH), inflammatory kidney disease, etc. If the percent transferrin saturation is >45%, you should be tested for hemochromatosis using the genetic HFE test.

Thanks to our Conference Speakers