[MUSIC PLAYING]

SHAHID M. MALIK: So to summarize the last 40 minutes, stop drinking and stop eating.

[LAUGHTER]

So switching gears, I'm going to be talking today about advances in cholestatic liver disease. I've no disclosures. So a lot of people get a little bit confused about the definition of cholestasis.

A lot of people associate it with the gallbladder. So it's funny. I give a talk to the medical students about gallbladder and I joke that, compared to the liver, the gallbladder only has two functions. This is not scientific.

So top 10 says, a website, it has an impact factor of about less than 10. But gallbladder is sandwiched between appendix and male nipples when it comes to the most useless body parts. So the true definition of cholestasis is bile stoppage. It's a Greek word. And it's most overt form of course, it presents as jaundice.

But in early stages, it leads to a preferential increase in the cholestatic liver enzymes. Alk phos and GGTP, to put it in cartoon form, this is cholestasis.

So this is a differential of liver diseases that you should think, at least, when a patient comes in with a predominantly cholestatic injury. But of course, in the liver world and for the sake of my talk, we're going to be focusing today mainly on PBC and PSC. So I'm going to be reviewing 18 papers and four abstracts. I promise I'll stay on time.

These were all published within the last year and have relatively high impact factors. So just a quick summary. PSC is a chronic progressive disorder of unknown etiology characterized by inflammation fibrosis, in at least in large duct disease. Medium and large ducts, the diagnosis is made on a cholangiogram.

Of course, today, more often we're doing MRCPs as opposed to diagnostic ERCPs. About 40,000 cases annually in the United States. 70% of patients are male. The average age-- these are typically younger patients-- is 40. And of course 80% of patients have concomitant inflammatory bowel disease, most often ulcerative colitis. There is an increased risk of colon cancer when you have concomitant colitis.

PSC leads to an increased risk of cholangiocarcinoma and increased risk of gallbladder cancer. There is no medical, or at least FDA approved, medical treatment for the disease. And about 50% of patients will eventually require a liver transplant and a mean of 15 years.

This is a cartoon of PSC showing the structuring of the large and medium ducts. This is a cholangiogram showing the classic beaded appearance we see in the biliary system. It still remains, probably a top five cause or indication for liver transplant in the United States.

So the ASLD has not published their guidelines on PSC in over 10 years. But the British Society recently published their guidelines and got, in August. And just a couple of highlights from their guidelines.

So as we know, Urso or Actigall is not to be routinely used for patients newly diagnosed with PSC. ERCP should be performed with expert assessment, and it's mandatory that dominant strictures be sampled, and we're going to be talking a little bit about that. This I found interesting.

At least in the British Society they don't come hard on these surveillance of cholangiocarcinoma. And there's no recommendations on routine cholangiocarcinoma surveillance. They do, however, recommend ultrasounds yearly in patients that have a gallbladder. And then if you have developing cirrhosis routine, HCC surveillance with an ultrasound plus or minus NFAP per year.

So the AGA wrote an expert review. Lindor is the senior author. This was published in*Clinical Gastro.*

So they say that the surveillance of cholangio and gallbladder cancer should be performed, especially within the first year of the diagnosis of PSC. It seems that about half of cholangiocarcinomas are diagnosed within the first year of the diagnosis of the disease. And they do recommend either an ultrasound, CT, or MRI with or without a CA 19-9 every six to 12 months.

No surveillance in patients less than 20 or those with small duct disease because they generally have a benign course. And then strongly considering a cholecystectomy in patients that have gallbladder polyps 8 millimeters or greater. So this was an interesting paper published just a week or so ago. And got out of Germany over 250 patients with PSC.

And basically what they were looking at is they divided them in about a half, scheduled ERCP with dilation of dominant strictures, regardless of whether or not a patient has symptoms until you get resolution. So you do your ERCP, you dilate the dominant stricture, then you go at four weeks, three months, and then every six months as needed. And the schedule dilation of a dominant stricture improved transplant-free survival and overall mortality pretty dramatically. So that could be something to consider in patients with PSC and a dominant stricture.

But ERCP should not be taken lightly, of course. Not only in patients with PSC, but patients with cirrhosis. This is a study out of India, looking at 260 patients with cirrhosis undergoing ERCP. The etiology, very common of what we see in the United States, nearly 3/4 with alcohol, nash, and viral. Only 4% with PSC.

These were sick patients. 3/4 were decompensated. But you can see the one-month mortality in these patients approached 10%. And if you had a MELD score greater than 18, the odds ratio for an adverse event was 5.6.

To put that into perspective, we spend a lot of time in risk assessing patients with cirrhosis, for example, for surgery. So if you take a 54-year-old alcoholic with a MELD of 18 and risk assess him for a cabbage, his 30-day mortality is 8% compared to an ERCP in a child's b or c, which is approaching 10%. So the take home message is this is by no means a benign procedure and patients and providers need to be aware of the risks associated with that test.

I'm going to be talking now about two validation scoring systems in patients with PSC. The first one is from Amsterdam. 500 patients with PSC, mean age of 39. Most of these were large-duct disease. Most of them were male.

So they use seven clinical parameters at the onset. Whether or not you're large or small duct age, albumin, alk phos, AST, bilirubin and platelets. So everything readily available when you're first seeing a patient.

So I just put one of my patients through this. A 24-year-old female, her alk phos, when I saw her initially, was 400. AST was a little bit high. This can be found online.

And then it predicts the patients five, 10, and 15-year transplant-free survival. So some pretty sobering numbers in a 24-year-old with an alk phos of 400. Her five-year transplant survival is about 50%, which seems very consistent with the literature of this disease.

This is another scoring system that you may like a little bit better. This is out of the UK. 1,000 patients.

So in this, again, seven parameters, but what they do in this scoring system is they stagger it. So you do the initial age, and then bilirubin at diagnosis, and then two years platelet, a diagnosis, and then two years, alk phos at diagnosis in two years, a variceal bleed by two years. So if you put my same patient through that calculation, for example, it gives a very similar.

But this may be a little bit more-- providing a little bit more prognostic information, depending on the patient's course over the last couple of years. So FSR receptor agonist-- it's interesting. So a beta cholic acid, which was FDA approved for PBC about five years ago, there was one study that made it to abstract form two years ago at ASLD, but never came to publication.

This is a paper, published in hepatology, looking at another FSR agonist, a phase two, relatively small study-- 52 patients. But in this particular patient there was a 21% reduction in alk phos at 12 weeks, which was statistically significant when compared to placebo. And the nice thing at least about this medication is there was very few side effects, at least when compared to historical controls of a beta cholic acid. So something maybe to look forward to in a disease right now where we have no FDA approved medications.

This is a study looking at overall improved outcomes, and medications potentially associated with those outcomes in patients with PSC. So 2,900 patients. This was a Swedish cohort. Again, demographics very consistent with PSC.

14% of patients were on statins and statins were associated with a reduction in all cause mortality and the need for liver transplantation. And that was not necessarily affected whether or not the patient was on Urso. So statins, more and more I think, are being shown to be beneficial in potentially all forms of chronic liver disease.

So just two quick abstracts from the liver meeting. This was a validation, prognostic value, of liver stiffness. As Ramon and Jay had previously mentioned. So it seems to be validated in patients with PSC as well. So you can see, over in the graph, once you start approaching a liver stiffness of 9.5, which correlates to about F2 fibrosis, mortality starts to increase and then shoots up when you start to approach numbers closer to 14.

And then just quickly, there does seem to be some role for checking bile acids in patients with PSC. They seem to have prognostic value and should be considered in the management when caring for these patients. In this particular study, they looked at total bile acids, but then also subdivided us specifically into DCA, which is not something we routinely break down here, at least based on our lab.

So moving on to primary biliary cholangitis, formerly of course, known as PBC. This is a chronic liver disease resulting from progressive, immunologic destruction of the small bowel ducts. 95% of patients are female. The diagnosis is usually made in the fourth and fifth decades of life.

Fatigue and pruritus are the classic symptoms. But many patients, of course, are asymptomatic. In order to make the diagnosis of PBC, you need two of the following three. So predominant elevation in your cholestatic enzymes, a positive AMA which is usually seen in about 95 percent of patients with classic PBC, and a liver biopsy showing a florid duct lesion.

PBC used to be one of the more common indications for liver transplant, but since the approval of Actigall, the prognosis of patients with PBC, at least diagnosed before the onset of cirrhosis, is quite good. This is an artist's rendition of PBC. You can see generally middle-aged females, pruritus is a common symptom.

And this is a liver biopsy on the left. Onion-skinning in a patient with PSC. This is on every GI board exam. And then a florid duct lesion over in the right, which is a pathognomonic lesion in PBC.

So this is a paper published out of *Clinical Gastro.* Looking at age and sex response to Urso and transplant-free survival in patients with PBC. Nearly 4,000 patients-- a retrospective study. So the interesting thing about this study, and what is becoming a common theme, is younger patients seem to have a much more aggressive course, at least when it goes on to developing advanced disease, liver-related outcomes, and the need for liver transplant. You can see the hazard ratio in patients diagnosed under the age of 35 is incredibly high.

There's not many patients with PBC diagnosed at that age, but when it occurs you need to follow those patients very carefully. This is looking at the incidence and prevalence of PBC in Sweden. 5,000 patients matched with 10,000 controls. Again, that underlying theme of patients, diagnosed at a very young age, having an increased risk of death.

Factors associated with progression of early stage PBC, published again in *Clinical Gastro.* So 1,600 patients, mean age was 55. So the interesting thing in this study is despite patients having early disease and presumably being placed on weight-based Actigall, still up to a third to a half of patients will go on to develop moderate to advanced disease.

And again, this is also a common theme in PBC, which is the response to Actigall and normalization of alkaline phosphatase seems to be a very good predictor. And on the flip side, if you're seeing patients with PBC, that are not responding, those are patients that you should think for either beta cholic acid or clinical trials. So fibrates have been looked at in PBC.

This is my only paper outside of 2019, but this is the initial *New England Journal* study looking at 100 patients who had an inadequate response to Urso. They were randomized to receive a fibrate. And about 70% had normalization of their alkaline phosphatase at six months.

So fibrate drugs are used to lower cholesterol. These are relatively old medications approved for medical use in 1978, but they're not available. At least besa fibrate, which is what these studies looked at, are not available in the US.

It is, however, a second line agent in Japan. The study was published in *Hepatology* earlier this year. They looked at 118 patients treated with combination Urso and fibrate, and the combination seemed to significantly decrease all the prognostic scores and improve long-term survival.

So pruritus is common and undertreated, based in this study. So remember Actigall, although it does seem to improve patients' biochemically and improve overall survival, does not seem to improve pruritus. And basically this study is saying that perhaps we're under treating patients itching symptoms with the PBC.

Smoking and risk of PBC, this was a meta-analysis suggesting just another reason to get your patients to quit smoking. Hopefully, there may be some association. Trends in liver transplant for PBC, in Europe.

So this is 6,000 patients with PBC. It was 5% of their all comers, when it comes to transplant. PBC was the only indication over the last three decades showing a consistent decrease in liver transplant, and most of that, of course, is because of Actigall.

This is part of the single biggest study in PBC. This is SRTR data looking at 8,000 patients with PBC, basically showing that their long term outcomes are quite good, perhaps a lower weightless mortality when compared to hepatitis C. But PBC does recur after liver transplantation.

This was published in *Gastro.* In January, 785 patients with PBC, who underwent liver transplant and recurrence based on biopsy, was 22% at five years, and 36% at 10 years. Some factors associated with a recurrence included a younger age at diagnosis, the use of pro-graph, and recurrence was associated with an increase risk of graft loss.

Just a quick word to the fellows. If you look at this study out of Europe, this was 785 patients over a almost 35 year span out of 16 centers. And if you look at all of the transplants done in Pittsburgh, just one single center, we've transplanted over 600 patients. So just to wrap up real quick two abstracts from this year's ASLD.

Fibroids may also have a role when it comes to itching in both patients with PBC and PSC. And then lastly, this study was a extension study for a beta cholic acid, in patients with PBC, showing potentially that it has five-year solid outcomes with no real safety observations. At least in this particular cohort, patients dropping out for pruritus was only about 5%.

So my 11 take home points. Number one, scheduled dilation of dominant stricture may have mortality benefit in patients with PSC. ERCP should be performed with expert multidisciplinary assessment. ERCP in patients with cirrhosis, especially those with amount of 18, carries a one month mortality, approaching 10%.

The Amsterdam and UK online validation scoring seems to be helpful and readily available with clinical data. FibroScan has very good prognostic value, and PSC. Statins may have mortality benefit. There is ongoing studies, looking at a new FSR agonist for PSC.

Younger patients, those less than 35 diagnosed with PBC, have a more aggressive course. Although, many patients with PBC will respond. Up to a third will not. And alk phos is probably the best short-term clinical predictor.

The role of fibroids in mortality benefit and symptomatic relief, especially with the itching, Urso-- or I'm sorry-- beta cholic acid has durable biochemical response at five years. And PBC, as an indication for liver transplant, has dropped nearly five-fold. Recurrence of PBC post-liver transplant is not uncommon. And number 11, you should probably think twice before agreeing to give a talk on a Saturday, the day following your 10-year anniversary.

[LAUGHTER AND APPLAUSE]