[MUSIC PLAYING]

KAPIL CHOPRA: We have a lot to cover. And so I think, in the interest of time, I should get started. This is the first part of the topic, complications of liver cirrhosis. And you have a second part that follows after this. So why are complications of liver cirrhosis so important? I mean, clearly it's a leading cause of mortality among US adults. And that's the rank it gets, the 12th leading cause. But if you go back into a different age group, and people between this age group, it becomes even more important.

So the fifth leading cause of death in this age group. And, like any other chronic disease that you and I are familiar with which leads to a lot of health care expenditures, diabetes, and it's not well kind of [INAUDIBLE] known, but cirrhosis is responsible for as many fatalities as diabetes. Clearly, it's an increasing burden on the health care system and we'll see where we are with this. And what's humbling is this last line. I mean, even today. Once a patient with liver cirrhosis is admitted to the hospital, whatever the reason for hospitalization, one out of 10 will probably not to leave the hospital alive.

And, you know, this is true for general, what I call General Hospital data. If we look at our own data and whether we are tertiary, quaternary, whatever higher level of health care. Our statistics are about 30%. So when I'm around in the hospital and I look at my census and I bring this to the attention of almost every fellow, out of every 10 people we see, three are probably not going to leave the hospital alive. And this is irrespective of the reason they were admitted.

So why are people with liver cirrhosis admitted to the hospital? The things listed to the left are reasons why you and I see people when we're around in the hospitals, so complications of portal hypertension, and, if I extend it, this would be variceal bleeding. If I put this in the right order, it's bleeding, ascites, and then complications of ascites, like SBP, the ballerina's syndrome, and then hepatic encephalopathy. So I'll just change the order here in terms of frequency. This is very under-recognized infections. Infections and cirrhosis has become a very hot topic, and it could be many, you know, nosocomial, community acquired, et cetera. And then these are some of the common sources of infection.

Acute kidney injury, I mean, the kidneys of a precious organ, for us, is part of the malady question. And whenever we're around in the hospital we pay very good attention to this because a lot of bad outcomes occur because of this kidney injury. And there's different manifestations of acute kidney injury, HRS, ATN, et cetera. There's this new entity out there, ACLF. It's kind of a buzz word. I think it's a little loosely used right now. The specific definitions for ACLF, I'm not going to go into that today.

But it's becoming more and more recognized as the reason why people decompensate are coming to the hospital. And again, it's just an extension of cirrhosis. So cirrhosis with outside the liver involvement. So extrahepatic organ failure. Again, the different systems listed here. And HCC, HCC is a complication of cirrhosis. OK, it's probably going to be one of the most important complications in the next decade to come. Some of these patients don't come to our own service. Meaning the liver service other medical service. They're admitted under the oncology service.

But sometimes a manifestation of HCC is just encephalopathy. And when you work up the encephalopathy, it turns out to be, this patient had underlying cancer. Now when a patient is discharged from the hospital, which are the different routes that the patient can go? This is a very nice review article from the Mayo Clinic that I borrowed for this talk. So our people can go back home. People come back into the hospital. And we talked about this. Readmissions is a very hot topic again. Hot topic not just because hospital gets paid differently now.

But it's something that you and I need to recognize, and I'll show you some data. Because lots of good data is emerging, why people come back into the hospital. In other fields of medicine, cardiology, et cetera, this was well worked out almost a decade ago. And I feel this data is just emerging. So we'll see a little bit about why people come back into the hospital. Clearly some people are sick, will go to rehab. I think one of my focuses when around in the hospital, is the patient a candidate for transplantation.

Because I spend a lot of time if the patient's going to be a candidate or a potential candidate, because I try and work in that direction. So you want to recognize potential candidates for liver transplantation. It's also important to recognize when you cannot do much. So end-of-life care, palliative care, et cetera, is a very important mode of discharge from the hospital. Again, when you round [INAUDIBLE], we should recognize why this is so important. And I think it's underutilized as of now. And then some people, obviously, will not make it.

So why do people come back into the hospital? So admissions and readmissions now. So, again, you can look at one or two studies. What are the predictors of readmission? So clearly the sicker the patients, the higher the [INAUDIBLE] go. The lower the sodium, these are subtle gates for liver sickness, right? High [INAUDIBLE]. And the high number of medications. Again, you can see the data is so simplistic, but how do you utilize this in real life? I think we still have to kind of work this out.

And again, if you look at predictors of 30 day readmission, again, sicker the patient, male, and, for some reason, diabetes. Again, diabetes is linked to the metabolic syndrome, which is now linked to nonalcoholic fatty liver disease, which is probably accounting for 50% of people with decompensated cirrhosis. So nonalcoholic fatty liver disease has overtaken hepatitis C as the leading cause for decompensated cirrhosis today in almost every center in the US.

What was humbling in this, this is actually a consortium a North American consortium published in one of our journals. Look at the 90 day readmission rates. I've never seen such data probably in the last 20 years of practicing medicine. 50% of our patients are back in the hospital at 90 days. I mean, this is very closely tracked right now. Every week, each of us gets an email. If I was the attending on some patient and the patient was readmitted within a certain time frame, I have to now provide the hospital some justification. And then, what the hospital is going to do with that, they're looking at ways of reducing this all. Can we change this?

And then we talked about the reason for high [INAUDIBLE] diabetes. Nosocomial infections, again, this goes back to the infection. And then, again, this is a very nice data set on admission. What could predict readmission? Again, [INAUDIBLE] use of lactulose means history of encephalopathy. Were they on prophylaxis or not for SBP? [INAUDIBLE] albumin. And then on discharge, I think one thing I do want to highlight here is BPI use. It's now coming out. Study after study is showing BPI use is now, again, what the link is, I'm not willing to commit today. There's lots of speculation. C diff, infections, SBP, et cetera.

But I think we overuse BPIs in general in gastroenterology. Last thing is, again, I think a nice thing to know. Don't be in a hurry to push a patient out of the hospital. Sometimes you and I are kind of in charge of the hospital stay. Meaning you direct the hospital stay even if you're the consultant. But the shorter the index hospitalization, it makes sense, that patient is going to bounce back. So sometimes keeping the patient a day or two longer may be to the advantage of trying to work out a better discharge plan.

OK, so we've talked about these complications. I just came across this paper a month ago as I was preparing for this talk. This is from UCSD. It's an internal medicine paper, and I think it's very true. I mean, I think the title of the paper is probably enough. Increased risk of in-hospital mortality. And non ICU, that. I mean, look at the words. In patients with cirrhosis after a cardiac arrest. I mean, the simple thing is, you can go to this paper that she already published in one of our journals.

People with cirrhosis are usually admitted to non ICU settings. And that means you and I need to keep a very high index of our threshold. Why to admit somebody to an intensive care. And a lot of times, you and I have seen this, you get a call from the ER, it's a [INAUDIBLE] or a questionable [INAUDIBLE]. Lead patient reaches the floor, they crash on the floor, and they're coming down to the ICU. Those patients are less likely to do well. And the causes of cardiac arrest, in this patient population, were all kind of simple things that account for bad hemodynamics. So GI bleeding, sepsis, and respiratory failure.

So I think, this is a data set. This is just an observation study. This is the first one I've seen, and I think this will lead to, hopefully, new algorithms for full management of the hospitalized cirrhosis patient. So this my, I don't know if I've asked this question. Maybe, I've done it for several years. So I think the second and third year fellows are probably not allowed to take a dip at this. OK, so this is, anyone can offer to answer. Which of the following statements about survival in patients with cirrhosis is false? So patients with decompensated cirrhosis have a five year survival rate that exceeds 50%. The development ascites and encephalopathy is associated with a reduced short term survival. The risk of variceal bleeding has declined over the last four decades. HCC is now the most common cause of liver related death. And the annual in-hospital mortality for patients has remained stable in the US. Which one is false? Anyone?

SPEAKER 2: C.

KAPIL CHOPRA: OK. So C, I think I would accept that answer. Clearly we're doing much better. But I think what I was looking for here is A, correct. Yeah. Now, simplistically, and cirrhosis this is not simplistic, so the answer is correct, I think. And I'll put this into context. Clearly the hospital mortality for bleeding was over 50% a decade ago. And it's now probably come down to about the 30% range. So that answer also acceptable. OK, when we see a patient with cirrhosis, so when you see a patient with cirrhosis either in the hospital or in the office setting, liver cirrhosis is a very frightening diagnosis for the patient, for the family, for the caregivers. A primary care physician doesn't know what to do.

So quickly, and this is based on very good data you and I have to think, is this patient compensated versus decompensated. We'll see how we define decompensated cirrhosis. Because you have to use these terms appropriately because there's a big difference. And there's a big difference in survival. Patients with compensated cirrhosis will live for more than 10 years. The average lifespan of that patient is about 10 to 12 years. Whereas once a patient decompensates, this is a Kaplan-Meier survival curve, right? So the survival will drop steeply.

So if you look at 24 months or two years, the survival of a patient with decompensated cirrhosis is less than 50%. How do we define decompensation? There are four events. The first one is bleeding. The graph says your esophagus varices, it's not just development of varices, it's bleeding from varices. And this is pretty nice to know, because in a given patient with cirrhosis, most patients will follow this type of natural history. So the first complication would be bleeding you to your esophageal varices. The next complication is ascites. And then if you look at the graphs for encephalopathy and HCC, they are pretty much parallel to each other. Which means, like I said before, any new onset of encephalopathy, you go back and you look for HCC, is this patient up to date with their screening, et cetera. Because these two complications may come together.

And this goes back to what I said earlier, and Ben pointed this out. So clearly liver cancer is on the rise. And these are three different eras, so to say. I still think we haven't seen the peak of HCC. Whether it's due to hepatitis C or nonalcoholic fatty liver disease. These are causes of death. So death due to liver failure is down. Death due to variceal bleeding is down. And, for some reason, people with cirrhosis can bleed from non variceal causes. We had a patient this last week. Again, the mortality is much higher when the bleeding is due to something else. So, and roughly, a patient will proceed from one state to the next state at this rate. So 5% per year is the number to remember for transition from the compensated to decompensated state.

Now what I'm going to share with you over the next half an hour, so a lot of new guidelines. And these are actually beautiful publications. They are all available on the society website. So the combination, the management of portal hypertension, which is what I'm going to talk about pretty much in the next half an hour, is based on some guidelines by the liver society, which is the AASLD. Clearly, endoscopy is a huge part of this management. So the ASGE also has some very nice guidelines. And when you kind of combine, that these are very extensive publications.

But they are very nice topics to go to, because these are peer reviewed. They're updated from time to time. And whenever I have a question, even today, I would just go back and refer to these guidelines. The tips one is a little old right now, but these, the first one and the third one are very nice. The latest guidelines kind of, I had to redo my lecture. With full disclosure, I mean I've done this talk for, probably now, is my 16th year or 17th year, right? I literally had to redo my lecture when the new guidelines came out in this early part of this year.

Because they've kind of changed the whole, not the whole concept, but they're redefining cirrhosis and portal hypertension. So I'm still trying to get together. You know, it's only six months since the article was published. And every time I go back I try to learn something new. They're now trying to define cirrhosis in different stages. And it's kind of a little bit of the same thing that I told you earlier. We talked about compensated, decompensated, there's another stage coming out now, late decompensation. I don't know what this means. And then in this bucket, I think this is good for me to give this talk. But I think what this, I'll tell you what the basis of all of this is. I think portal hypertension is now becoming the backbone of any complication of cirrhosis. So you can have cirrhosis without portal hypertension, cirrhosis with portal hypertension, and cirrhosis with complications of portal hypertension.

And portal hypertension is probably superior to any other tool in assessing the severity of liver disease. Just listen to this statement, because I had to go back and read it again. It's superior to a liver biopsy. It's superior to lab testing. It's superior to [INAUDIBLE]. So portal hypertension by itself, and, you know, it's nice of me to read this or to tell you all this, because you know the gold standard for portal hypertension, which we don't do routinely in clinical practice, is measurement of portal pressure. Which is kind of the standard of care in some parts of the world.

And if I extend that, it's basically, a lot of these guidelines are coming out from Europe. And even the latest guideline is a combination of American and European literature. But we don't measure portal pressure very routinely, so how to take it to the bedside, I don't know yet. But clearly, and this is what I meant by that, what I said earlier. I'll be very brief, because this is very, very complicated right now. So we'll talk about this hepatic venous pressure gradient because this is the gold standard, now, for defining portal hypertension. So, as I said, you can have compensated, where you don't have portal hypertension. You have compensated, where you have portal hypertension.

Now when you have a gradient that's more than 10, the label that's going is clinically significant portal hypertension. And I think it's a very important terminology, which we use in practice, you know, CSPH. You don't always have to have portal pressure to measure CSPH. You can, sometimes, by the platelet count, by imaging, or by endoscopy. It's obvious that the patient has portal hypertension. So there are subtle gates to call a patient who has clinically significant portal hypertension. But again, the definition is more than 10 millimeters. And then, obviously, once you decompensate, this pressure goes up.

Now you can have, as I said, you can have varices will only develop when this gradient exceeds 10. And you can again have more than 10 and no varices or more than 10 with varices. Clearly, once than 12, you have varices. Complications of portal hypertension will only happen when this gradient exceeds 12, which we said decompensated is the same as complications. And then the treatments are different. I think this whole thing is directed towards management. So if you have patients with cirrhosis, but you don't have portal hypertension, can you prevent portal hypertension? It's a fantastic concept, right? Because, and I think that we're all, we're not there yet, but if you look at a disease like hepatitis B, for example.

If you take away the cause, you actually prevent development of cirrhosis. Or if you already have cirrhosis, cirrhosis will now reverse. That's the only disease we've shown so far that we can reverse cirrhosis. I mean, this is an area of lot of new therapies, antifibrotic therapies. And we take alcohol as a simple example. When people quit drinking, liver disease progression is prevented. So these are some examples of therapies over here. Clearly, once you already have portal hypertension, what can you do to prevent decompensation?

What can you do to prevent the first bleeding episode? Our mainstay of literature is here. So prevent decompensation. If you're obese, lose weight. Alcohol, you know, quit alcohol. Hepatitis C can be cured now with therapy. So these are examples of these type of therapies. We'll talk about how do you prevent the first building episode.

Clearly, management of bleeding bleeding is what is a very important thing. And then once you've already bled, how can you prevent rebleeding? So this is called, the other things in literature are prophylaxis. It's called primary prophylaxis.

The wording is self-explanatory. If you want to prevent the first bleeding episode, it's called primary prophylaxis. Once the patient already bleeds, it's called second to the prophylaxis. And there was a word called pre-primary prophylaxis, which I think was unsuccessful. So I think most of our clinical management is geared towards preventing the first bleed. And then controlling the actual bleed, and then preventing rebleeding. And then clearly, once the patient's already decompensated, if the patients are transplant candidates, they really should be considered for transplantation.

So I already talked about this. I'm not going to spend too much time. So restratification is based on the definition of no clinically significant portal hypertension. And on a very simplistic way, the bad side is, if you have gastroesophageal varices, whether you have them on imaging or endoscopy, that patient already has clinically significant portal hypertension. And then this puts my whole one hour talking to one side, OK? If you're able to work out what stage this patient is, the therapies are different at different stages, OK? So let's see. We give examples of, how can you approach-- Remember, as I said, portal hypertension is the backbone.

This is a beautiful slide that kind of helps put this whole thing into context. How can you manage portal hypertension, or how can you prevent portal hypertension from progressing? So let's address the etiology. We should basically address the mechanical component. Antifibrotic therapies, weight loss, alcohol, etc. Use of this agent, carvedilol, directs more the function component of the hepatic resistance.

You can use portosystemic shunt. A lot of our treatments are geared towards these type of agents. And non-selective beta blockers somatostatin, vasopressin, octreoride, etc. Which addresses this part of the physiology. And then, clearly, once a patient bleeds, whether they have endoscopy or radiologic techniques. And then again, I could spend an hour on this slide itself just working out the pathophysiology of portal hypertension. But you can see why this is so important, as it directs our therapies.

Moving on. How do you define portal hypertension? I mean, normal portal pressure's between 5 and 10. Portal hypertension is when there's more than 10. The most common cause of portal hypertension is cirrhosis. There are other causes of portal hypertension, noncirrhotic, which I'm not going to go into today. One quick slide on measurement of portal pressure. In the next three years, at least during your training here, we do a lot of this at this hospital.

It's a great time to learn. We don't do these techniques. These are usually done with interventional radiology. Whenever a procedure is done, I always take the fellows down. We go to IR, we ask them questions, and we try and see what they do.

And generally, when a patient is going for TIPS or a transjugular liver biopsy, we always get that opportunity to measure the portal pressure. The usual technique is transjugular. And basically what is done is, you wedge the hepatic vein. So you measure the hepatic vein wedge pressure.

You're all familiar with the Swan Ganz technique for pulmonary artery wedge pressure monitoring. So it's the same technique, the same principle over here. Hepatic vein wedge pressure is equal to portal pressure in the absence of portal vein thrombosis. Like pulmonary artery wedge pressure is equal to left ventricular end diastolic pressure if you don't have pulmonary arterial thrombosis.

So that's our gold standard. And again, learn about the techniques, see the reports. As you see them more and more, I think you'll become more comfortable as you interpret what is called portal hemodynamics. And then depending on the different pressures, you always get three types of readings when you look at a report. You'll get the wedge pressure, the wedge hepatic vein pressure. You get the free hepatic vein wedge pressure, and minus this is equal to the HVPT, which is the gradient.

This question was in my liver boards when I took it. And they gave me different combinations and they said, they're trying to figure out what is the cause of portal hypertension. So you can figure out, prehepatic, hepatic, or Post-hepatic.

OK. Now, we don't do this in clinical practice, what I showed you earlier, right? So what do we really do in clinical practice? We use noninvasive techs. So one technique that's coming out, again this is a new concept, the stiffness of the liver by elastrography. So liver stiffness is defined-- this is a physics principle. So when liver stiffness exceeds 20 kilopascals, that's equal to significant cirrhosis. A portal hypertension. And that correlates with clinically significant portal hypertension. So when we can't do portal pressure, which I think is not practical, we do these noninvasive techniques.

So you can measure liver stiffness. You can look at platelet counts. Any platelet count less than 130 is where the portal hypertension is significant. If your platelet count is over 150, that patient's unlikely to have esophageal varicies. Clearly, as I said, if you already have imagining-- and a lot of times, you go down, look at a CT scan, the radiologist will call that this patient has gastroesophageal collaterals. Those are not indications for prophylaxis, but that is enough for you and I to say that this patient has clinically significant portal hypertension. And again, if you do an endoscopy, and we had a patient that once serviced, the question asked for us was, does the patient have significant portal hypertension or not? And I think before I came on service, we were planning to do an HVPG. Patient was reluctant. We took the patient to endoscopy. We showed varices. We don't even need, now, to go back to the HVPG.

Now, if your stiffness is less than 20, or your platelet counts are more than 150, you don't even have to do an endoscopy. Because the probability of having significant or high risk varices is so low. So this is used, actually, when not to do an endoscopy. So people who do not meet these criteria, screening for endoscopy is recommended. So we always do an index endoscopy in a patient with cirrhosis. So we suspect you know clinically significant portal hypertension because that's where we did act prophylactic approaches.

If you don't have portal hypertension at the onset, as we said, you can progress. The rate of progression is about 5% per year, so you have to monitor these patients for their lifetime. You can't do HVPG every year. No one's going to accept that. So you have to come up with noninvasive methods.

And again, HVPG is OK, but ultimately we adopt a simple noninvasive method. We do a endoscopy again and again. OK? And you can kind of work out when to do a repeat endoscopy. The guidelines allow you anywhere from one to three years.

This is kind of an in-between statement. I think you have to do them at least every two years if you have ongoing liver injury. So alcohol, hepatitis C, obesity, etc. Or potentially, you could say a patient with hepatitis C that was cured. You can even do them once every three years.

On the other hand, if the patient's decompensating, then you probably have to do them every year. So this is a patient with compensated cirrhosis. Small varices on screening endoscopy. You can repeat this every year or every two years. On the other hand, patients with compensated cirrhosis without varices who develop decompensation, you do this every year.

You initially decided two years, but the patient came in and got decompensated. You're now allowed to go back and do your repeat endoscopy. Some of this is also related to quality metrics. I mean, you don't want to overdo endoscopy just because you and I love doing endoscopy. I'll be honest. I love doing endoscopy.

So, as I said earlier, you can't monitor HVPG. Routinely, outside clinical trials, and the problem is these tests have limitations. So noninvasive tests do not correlate accurately but we're not ready to say that HVPG should be done in every patient every year. How do you manage people with portal hypertension? I think, as I said, the initial objective is to prevent development of clinically significant portal hypertension or decompensation. So you always focus on the cause. I mean, you have to counsel the cause. Alcohol, obesity, hepatitis c.

We do use nonselective beta blockers. And my head spins right now when I read this topic. But it used to be such a simple topic. But now I think there's lots of new literature that's emerged, which, I think, is pretty common sense approaches. But these drugs are not as benign as they were made out to be, OK? And I'll show you some of the data. At the same time, I think the pendulum has now swung.

Literally, in the last five years, I've seen papers that came out that said you should not be using them in some situations. And now the recommendation has become a little softer because I think people went back and said, that was the wrong message to give. So I think as trainees, you are obviously dependent on guidance from your attendings. I think, stay tuned. I don't think the jury's out there as to which type of patients benefit, and some patients are likely to not benefit from the use of these drugs. And I'll show you some of the literature on that.

So pre-primary prophylaxis, which means, if a patient with cirrhosis, you do an endoscopy, no varices. Can you start a beta blocker to prevent development of varices? Very attractive concept. But remember, almost every study-- not almost, every study in portal hypertension is an RCT. The literature is so rock solid in portal hypertension. These are literally randomized controlled trials. I've not seen many fields in GI where the literature is so rock solid. OK. So clearly, it was beta blocker versus placebo. You know, the beta blocker actually had a higher mortality rate. So the answer is today, you do not use beta blockers to prevent [INAUDIBLE] varices. It's a very attractive concept, but I think this answer has been addressed.

This is big thing. Can you prevent the first bleed in patients who have medium to large varices, not small varices? Again, small varices do not warrant the use of a beta blocker, OK? And the answer is, yes. And these are the three agents that have been tried, or need these three, nothing else-- Propranolol, nadolol, and this drug now which is not a nonselective beta blocker. I put carvedilol in a different kind of bucket because it's also an alpha blocker.

But these are the only three drugs that have been tested. And there is, again, good data to show you can prevent the first bleed, or what is called primary prophylaxis, only when you have these situations. And I don't mind them. You can use any of these drugs. More and more I'm using carvedilol. I just think the drug is a very easy drug to use. Propranolol is a very old drug, but it's a horrible drug. Patients don't like it.

I used to use a lot of needles because it's once a day, but I think carvedilol is a very attractive drug to use. And I hope you know the literature becomes more solid. And once you start a beta blocker there's no need to go back in to do another endoscopy.

What the reccomendations-- I mean, is a nice statement. You don't need to combine both approaches. Some patients don't tolerate beta blocking and you can just go back and do band ligation. You can do band ligation as primary prophylaxis, but you don't have to combine the two, OK? So nonselective beta blocking plus EVL is endoscopic varital ligation. It's not recommended for primary prophylaxis. Another very important statement. We do not use TIPS in primary prophylaxis. OK. Again, nice to know.

So this was medium to large varices. Small varices, this is where it becomes a little twisted. Early on I said, no. But again, each of you who have done endoscopy in this room know that our patients who have small varices but they have high risk, stigmata.

So again, you're kind of dependent on the endoscopist to say, hey, these are small varices but they have high-risk stigmata so I'm going to use a beta blocker. OK. I think this is a little controversial area, and I don't mind saying, but the guidelines do allow us. This is, again, giving examples of different drugs and what doses you use.

Once a patient bleeds, what do you do? I think some principles of management of a bleed, which I think you are probably familiar with. Don't over transfuse your patient. There's enough literature now, whether our literature, ICU literature, et cetera, et cetera. You don't have to go for a hemoglobin more than seven or eight because there's increased mortality when you over transfuse these patients. OK.

You have to use antibiotics. And this is for variceal or non-variceal bleeding. Seven days. And it's been shown that use of antibiotics influences mortality. So just a simple intervention as antibiotics can help with mortality outcomes. And this is AASLD guidelines that provide the drug of choice is ceftriaxone. One gram once a day. Different hospitals have different antibiotic preferences. Doesn't matter. You just have to use something.

You can discontinue the antibiotic. This is what they allow you, and I said earlier on seven days. That's max. But if the bleeding has resolved, or when you're stopping the octreotide infusion, which is usually anywhere between three and five days, you can stop the drug. Basal active drugs. The drug of choice here is octreotide. I hope we get terlipressin in the future.

There's lots of trials going on, but you and I use octreotide. And again, when you get a call from the ER, a call from the ICU. Whether you know this is variceal or not, I think this drug has to be started. As soon as you suspect. We had a case this week. We didn't that was variceal or not, but it turned out to be non-variceal when we went in, but you have to start this drug right away. We don't have somatostatin and terlipressin right now.

Gold standard is endoscopy should be performed within 12 hours. I don't think that's a problem in this hospital. But again, in hospitals where you don't have access to immediate endoscopy. I think in this hospital it happens within six hours if I had to say. And again, the reason for delay may be patient getting to the ICU, intubation, etc. And the minute you confirm this is variceal, you have to go in and do what we call band ligation, which I'll talk about shortly.

Now, this is also a very important statement in the guidelines. I mean, you and I are pretty good at preventing or stopping the acute bleed. I think endoscoping techniques, whether it's band ligation or endoscopic sclerotherapy, will control the bleeding. If I had to go by the book, the book says 80% to 90%. In our hands, in this institute , I think it's over 90%.

So your patient has stopped bleeding. But now you have to go and think, how can you prevent the next bleed? It doesn't end there. Please. And I think those around with me know this. OK? Because you know, it's nice if they come back in three weeks and we'll do a [INAUDIBLE]. OK. But can you do something different? Because if the patient rebleeds in between, now you're going to be scrambling for rescue.

So I think you have to be a little proactive. So instead of going for a rescue approach, which is usually in crisis, and those patients don't do well, let's think about what can we do to prevent the next bleed. And this is now well shown in a paper which was published in the New England Journal, which I think I have on this slide. What is called preemptive TIPS. And which type of patient population?

We had a patient-- again I point to Jeff because I've done a lot of service with you in the last few weeks. I think Jeff did a pretty good job in controlling the bleed. But we had our question, should we should we go for a TIPS? And you don't have to do it for everybody. But if you are active bleeding during the endoscopy, which is rare. But if you ever see a patient that is actively bleeding, that's one type of patient. Because that patient is going to be a higher risk for subsequent rebleeding or failure.

And clearly, the sicker the patient. So a child class C or a child class B with active bleeding. Plus, the patient should have no contraindications to the TIPS. And I think we got stuck in that patient because we felt the patient was had contraindications for TIPS. But if the patient meets those other criteria, the right thing to do is, within 72 hours, within three days of that bleed, you now go down and get that TIPS done. Don't let the patients leave the hospital before the TIPS is completed. I think this is a very important kind of concept. Paper after paper has shown that this is the right thing to do, OK?

If you don't do an early tips, which is fine, you know you don't have to, patients remain in the hospital anywhere from two to five days. The five day thing is not that rigid anymore. Look at how it's become soft. Which we didn't practice for a while, but it's nice to see this come in the guidelines. You can literally stop the octreotide drip after 48 hours because the risk of rebleeding drops so dramatically.

But anyway, not to confuse the newcomers. Today we use it for five days. And then you only start the beta blocker when you switch off the octreotide drip. There's no need to do it early on. I mean, that's a disaster. Patients on octreotide. Patients still in the ICU. They're belly-eating and somebody goes and starts a big dose of a beta blocker. That patient will crash in the hospital, OK? And generally once you start the beta blocker, I like to see the patient for at least a day in the hospital. I get very nervous in sending the patient out until I know how the patient's going to tolerate. We talked about rescue TIPS. And then, clearly, once the TIPS is done, for whatever indication. Preemptive arrest, you can stop the octreotide infusion pretty much right away.

Moving on. Successful resuscitation, successful control, patient leaves the hospital. Now, you want to prevent rebleeding, OK? So rebuilding is a combination approach. beta blocking plus endoscopy. And you can do the endoscopy at whatever interval you wish. Literally, the guidelines allow you between two and eight weeks should be your next endoscopy. If I pick a middle of the line, most of us will do it between week three and week four. I think it's safe. You don't want to go back in too early. The reason being, it's such a mess down there. If there's ulcers, then you can't really do much. You're wasting the endoscopy.

On the other hand, if you put one band or two bands in the index endoscopy, there's no harm in going back at week two. As I said, most of us will put anywhere from two to four bands, so the right time would be around three to four weeks. But literally, the guidelines will allow you to two eight weeks. If the TIPS is done, then there's no need for anything. You don't have to go back for endoscopy. You don't have to put the patient in a beta blocker. OK.

It's interesting. Carvedilol is not there in the recommendations for prevention of recurrent bleeding. I just found this out when I was reading this topic. It's very nice, because these are such solid studies that we don't really look at these other literatures. As of now, and I don't know the answer here, for rebleeding, this is a prevention of rebleeding, it's either propranolol, nadolol ligation.

So this is my summary slide for what I said in the last 15 or 20 minutes. This is my rule of three. I just made it up because I was taught this way and I think it kind of works. A patient with cirrhosis has a 30% chance that they have varices on the index endoscopy, OK? That's why we justify an index endoscopy. So you have cirrhosis, again, it's 35 to 80, but this is just my way of remembering one in three will have varices. Those who have varices, 30% will bleed in the next one year. So this is my rule of three.

Those who bleed, 30% will die during their next bleed. This mortality is higher today than the mortality due to acute myocardial infarction today in 2017. And this is not well recognized. That's why we make a push for these patients to be in the intensive care setting, because literally 30% of patients, or one out of three will actually die during their next bleed. And those that survive, 2/3, this is my rule of three again, will survive. And then 2/3 will rebleed in the next 12 months. So it's very nice to know the natural history of portal hypertension as we move forward.

Everything I've said so far was on esophageal varices. Now, people can bleed from other sources. And I'll go through some of these because these are also seen in practice. These are slightly more difficult for you and I. The think about gastric varices, this is more for the fellows doing endoscopy, identify the varices accurately, OK? The classification given to the right is just what is the standard classification for gastric varices. I think I would urge fellows, there's lots of atlases out there. You can go back and see. Endoscopy is a very subjective field of GI medicine. I think I may have a slide. You're pretty much at the mercy of your attending now. If he or she calls it x, it's going to be x. And you will be your own control. You'll see the first year fellow, the second year fellow, the third year fellow. Then you'll find yourself changing as you move forward.

So today you're going to use your attending as your reference but there are lots of these atlases. The GI endoscopy website, the ASGE, has very nice videos etc., which are standardized ways of looking at this. And I'll show you something in the esophagus. But in the stomach or gastric varices, this classification is very, very important, OK? GOV 1 to isolated 1 and 2. Most common is this one. This is just a continuation of the esophageal varices along the lesser curve of the stomach. So GOV 1, which is most common. More than 80%. These behave like esophageal varices. So a lot of times, if we see this, we can even band this up just beyond the GE junction. It's OK. I mean, you have to have an attending who is willing to do this, but you can literally treat this like esophageal varices. The rest of them, GOV 2, IGV 1 and 2 require a separate kind of approach.

So again, prevention of GI bleeding. The beta blocker literature is not as solid for this as opposed to esophageal varices. We still use beta blocking, but the literature is not that solid. Again, radiology techniques like TIPS, there's another radiology technique, are not recommended unless the patient bled. OK. So again, prophylactic approaches. Only beta blocking.

Clearly, once the patient bleeds, you can do one of these two. Endoscopy for gastric varices has a very small role, if not no role. I mean, you can diagnose the varix, but you can't control the bleed. Because we don't have those agents that are currently-- they're not approved in the US. There's glue, which is not approved in most of North America. Some centers do have it under special permission from the FDA. So for all practical purposes, gastric variceal management is interventional radiology techniques. So, the TIPS, and then that there's another procedure called BRTO.

So clearly, you can manage the acute bleeding like you would the usual, transfusions, vasoactive drugs, antibiotics. As I said, you can try band ligation for GOV 1. We don't have glue, but ultimately the procedure over here is TIPS. And then prevention of rebleeding. Same. endoscopic therapy, nonselective beta blocking, TUPS. And there's this new procedure which is pretty neat that done through IR, which is, maybe, superior for gastric varices as opposed to the TIPS procedure. Again, this is prevention of bleeding. Those who have already recovered, a combination of nonselective beta blockade, EVL, glue. And for these, again, TIPS will be our TO. OK. Again, [INAUDIBLE]. I don't know any of you will ever get trained, because we don't do it here. So I think this is more academic, for informational purposes.

Another area is ectopic varices, and the most common site of these varices are around stomas. So you get stomal varices. You You can have varices from the small bowel, etc. So they go under the bucket of ectopic varices. And again, the management is purely radiologic approaches. It's very important to identify the vascular anatomy. A lot of times, we choose the correct radiologic procedure, whether it's an arteriogram with venous phase imaging, etc. So you have to know this. We work very closely with radiology. Those who are around with me know, the two places I stop every day on rounds is radiology and then if somebody has a biopsy, in pathology. So we work very closely with these two departments. and I think I've always urged the fellows, if you get a chance to do an elective in abdominal imaging. You and I have to know that area so well and the department here is excellent in terms of teaching and the way they are.

This is the controversial areas and the guidelines have put them under special populations. So literature emerged in the last five years that certain patient populations did not do well with nonselective beta blocking, refractory ascites, and people with SBP. And they actually showed an increased mortality in this patient population. So my God, I said, this is going to change the whole practice of medicine, or at least portal hypertension. And then I think as you tease out the literature, these papers are very difficult. They're very good papers though.

All the papers are observation studies only. They are all retrospective, OK? So those of you who want to analyze these papers, be very stringent as you look at these papers. Nobody's yet done a prospective randomized study going forward. And I think that's what will be needed, ultimately. But some of these patients we're getting crazy doses of these medicines. 116 milligrams of propanolol, 80 milligrams of nadolol. I've never used these drugs in the last 20 years. My patients are not as solid as this. I don't know. Most of my patients will not tolerate. I can barely get 40 milligrams of nadolol if I'm lucky. Some patients, I may get to 80 if I'm lucky. But most of my patients are between 20 and 40. So I think, as you read through the papers you realize this is not how we practice anyway.

And I think the mechanism is all through alteration of renal blood flow. If we go back and look at the mechanisms, why these people did badly. We were dropping their blood pressures. We were creating such havoc in hemodynamics. So I think bad things were going to happen. So again, look at the next 10 patients with cirrhosis when you're around in the hospital. They'll have systolic pressures that are barely 90 or 100. I mean, they're so vasodilated.

They have such, you know, low SVRs that the pressures run low. So if you run pressures that are below a certain level, systolic pressure is less than 90, serum sodium is less than 130 or HRS. I think this is a recommendation. You can stop the beta blocker temporarily. But when the situation resolves, you can go back and see whether you can restart the beta blocker. I think it's a very common sense guideline. I love this because the way it's written will kind of help resolve the controversy. I don't think personally the controversy is over I think it's started five years ago I think is ongoing for a while before we start seeing literature

OK. What can you do for people who have bled? Why not primary prophylaxis? I love this because I think this is one of the most common clinical situations. It was not highlighted as much before. I'll translate this into everyday life. You see a patient with cirrhosis in the office, you do index endoscopy. Medium, large varices.

You put them on a beta blocker. And you're a good doctor so you go up on the beta blocker. You should try. Just don't start them on a drug and leave it. You can optimize the dose. But despite all that, nine months later the patient had a massive bleed. This patient is complying with everything that you said, but the patient bled. In my opinion, that is a classic everyday example.

OK. So why not primary prophylaxis with the nonselective blocker? What to do? You know, it's sad. Initially, I was trying to emphasize that portal hypertension is so rock solid. But the randomized trials. This patient population, there is no trial. I can't tell you, in clinical practice, how important this is. They come in bleeding. You stop the bleed. Fine. Again, endoscopic techniques work very well. But now, what to do? Are you going to put the patient back on the same drug? But you can say, that patient really failed. And in my opinion, and this is just an opinion right now, I would actually push for a TIPS. Those who work with me know this on rounds. This is not a standard, but I was very pleased to see this coming out in the guidelines. That you could either do beta blocking plus band ligation, or you can now consider TIPS. So again, I go back to, if there are no contraindications with TIPS, my approach would be-- and please, my disclaimer here is, this is in the absence of any randomized controlled trials, OK?

Patients with cancer who bleed, you follow the same approaches. There's nothing different. So on the last few slides. I think I'm just within time right now. We need to see better noninvasive tests, OK? I don't think we are there. Elastography, which is liver stiffness. People are also measuring stiffness of the spleen. I don't know if you've seen literature emerging. Elastography for spleen as emerging.

Because whatever you and I can do-- you can say we'll do an HVPG, but that's not going to be practical. So we have to come up with better noninvasive tests for the diagnosis of clinically significant portal hypertension. I think MR technology is headed in this direction. You know we're using a more elastography now left, right, and center. The Mayo Clinic has standardized this and our group has adopted. So literally in the last 12 months, when you get an MR over here, if you want MR elastography, you have to ask for it. OK. So when you order it, get it done because it's no different. The patient's already going into the MR machine. It's easy for us to get MR elastography.

What to do with that, I don't know yet. But you know literature has to emerge. So we have to come up with better noninvasive tests. Because we're going to follow these patients for their lifetime. So we need tests that we can repeat, and repeat, every year. Again, when we use medication-- so if you use a beta blocker, what happens to those tests? Again, the European literature says, use a beta blocker, go back and measure the HVPG. That's that practical. We use heart rate and blood pressure, right? So maybe these noninvasive methods will help you see the effect of our therapies. Because right now we very primitive. Measuring blood pressure and heart rate is the only surrogate that we have.

Addressing fibrosis. I think it's going to happen in your lifetime. in clinical practice. Antifibrotic approaches. Because there's clinical trial after clinical trial. They're all phase one. That means they're barely out of the lab. Because remember, the end stage of any organ injury, or the end stage of inflammation, whether it's the liver, pancreas, lung, is scarring, is fibrosis. So if we start having therapies that are antifibrotic. And 10 years ago when I heard this, I thought this was science fiction. This is never going to happen. I probably said this somewhere.

Clearly, I was not correct. Because now you go to the ASLD every year. They'll be a little section on this. Antifibrotic. And the problem is, these drugs are not specific to organ. So you use a caspase in the liver, and that will help the liver but cause a problem in some other organ. This will happen, I think, in clinical practice in your careers.

And that's a very hot topic because, how can we not talk about the gut microbiota? This is literally in NASH and portal hypertension. And we don't know how antibiotics influence mortality in portal hypertension. We use them, but we really don't know how this is worked out. So maybe the gut microbiome is going to play some importance. So I think there's another area for research.

We talked about this preemptive procedure. I think we can do better in defining which patient population should get an early TIPS. Because like I said, the patient population, I define, in my opinion, that as a preemptive TIPS. Because we stop the bleed, then we're trying to prevent the next bleed. But are we doing more harm or no good? We don't know yet.

And this is my last two slides. Because again those of you who are following this the literature. Statin use and cirrhosis. Oh my God. I shudder when I read these papers because there's at least two or three papers out now. These are large databases, remember. These are not prospective studies. But you go back into a database and look at 30,000 patients. Statin use or no statin use. And there's data emerging, that people who receive statins maybe did better. Better in terms of portal hypertension outcomes. I'm not ready to prescribe a statin right now because I think these drugs have their own problems. There's clearly increased adverse effects of statin use in cirrhosis.

But there's something out there. Farsenoid x receptor and these new bile acide therapies. This is the one that was approved right now for primary biliary cholangitis and maybe NASH Obeticholic acid is an example. There's lots of other drugs going come out.

Anti-coagulation. There's already a paper from Italy. Use of anti-coagulation in cirrhosis can prevent some of the complications. So a lot of the pathophysiology of portal hypertension is vascular. Entrahepatic vascular disease. And literally, there's a six month study. Lovenox versus placebo. In decompensated cirrhosis the Lovenox arm did better. Again, not ready to everyday practice.

Lastly, I think we need to do better for gastric varices. So I think I'm going to end on this note because I just found this in a paper published. This has actually now come out in two or three papers. The window hypothesis. It's still a hypothesis because it's not really proven. So too early, the beta blocking is not indicated. The stuff to the left, OK? That means you have no varices and the portal pressures are still low. The window is closed earlier on. Then the window opens when the portal pressure starts going up, so maybe beta blocker therapy is useful. Now, there comes a time, as the patient becomes too sick, refractory ascites and SBP, where the beta blockers become useful.

So I think you may see this more. I mean literally, I saw the first paper. This is from this year. But I saw the first paper coming out about two or three years ago. So this is from the Mayo Clinic again, the concept of beta blocker therapies. I'm going to stop on this note and I'm happy to take any questions. I think what I would have liked to go through is, a little more endoscopic techniques. But I just have an hour for the topics so I have to stop. So thank you very much. And again, best of luck for your training.