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CIRRHOSIS IN PATIENTS WITH HCV: WHAT CLINICIANS NEED TO KNOW

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[video transcript]

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00:58
Thank you so much, Jeff. And glad to be here today. This afternoon, Happy New Year. And what better way to start and to speak about cirrhosis. So the topic for today is cirrhosis in patients with Hepatitis C, what clinicians need to know as a hepatologist. I see many patients with cirrhosis and kind of the full spectrum of fibrosis and today I hope to cover how we diagnosed patients with cirrhosis and how we Stage patients particularly with Hepatitis C for fibrosis stage and cirrhosis and what we do to monitor those patients. So the learning objectives, just briefly, the first one is to really define fibrosis and define cirrhosis and patients with Hepatitis C, what does it mean to have fibrosis and cirrhosis? And how do you counsel patients when they may have these conditions. The second will be to focus on the diagnostic tools and methods that we have available to us to be able to stage fibrosis and diagnose cirrhosis, which in some situations is not very straightforward, actually. And lastly, to review the major aspects of treatment and monitoring best practices for patients who have cirrhosis from Hepatitis C. So just to begin, I wanted to start with a case that we actually had in one of our CEI clinical preceptorships. This was a case submitted by Margarita de Freder, Rhesus from Hudson headward headwaters Health Network, and I think it's very relevant to the discussion we'll be having today. So this was a patient that she saw it was a 54 year old male history of Hepatitis C with a diagnosis of Hepatitis C back in 2006. The patient stated that he contracted Hepatitis C following a blood transfusion following mechanical valve replacement in 1982. So he underwent evaluation by a gastroenterologist for treatment for the Hepatitis C with interferon before we had available direct acting antiviral agents, and he was considered to be too high risk, given his comorbidities and the fact that he was on Coumadin. And he was kind of sounds like was lost to follow up and had not been reevaluated for treatment until he was seen back in the office in 2018. So if we think here about how long he's had Hepatitis C, he reportedly was diagnosed back in 1982. And now is really treatment naive, has not been treated, and seen at the office in 2018. Many years later. That being said, he denies any symptoms, and overall was feeling well. So he had an ultrasound of his liver and the ultrasound showed that he had a slightly coarse and echo texture of the liver. But no other major significant findings of the liver, no ascites. He was that I suppose cool suspect to me. And these are just some of the initial intake labs that were obtained that show that he did have active Hepatitis C with a viral load of

6.5 million genotype one, and he was asked for Hepatitis A and B immunity, who is found to be non immune. And so this was kind of the initial labs. So when you see this patient, one question that should come up pretty quickly as well. What is his disease stage does this pay Shouldn't have fibrosis, does this patient maybe already have cirrhosis? And how can we figure that out what additional data is needed? So just to get everyone thinking about the case, I have a polling question here. So if you had to put your money on it, would you say this patient has a no fibrosis? B advanced fibrosis, C cirrhosis, or D indeterminate. And we could take a minute or so to choose one of these answers.

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Not seeing the polling come up on the screen. Is it? Oh, there we go. Now I do. Okay, so the answers that people chose so 40% said advanced fibrosis. 20% said cirrhosis. 10%. Said no fibrosis and 30% said indeterminant. So kind of all across the board. And this question doesn't really have a perfect answer, because the truth is, we really don't have enough information based on what I shared about the case to know for sure what he has, but definitely, the ultrasound showed that there was coarsened liver echo texture to nonspecific finding, but may suggest that there's cirrhosis, but we really don't have enough information from what I shared so far to know for sure. The other thing to think about in this case is the duration of his disease. He's had Hepatitis C for decades now. So it is theoretically possible and feasible that he would have cirrhosis by now given the duration of disease. If I had told you that he was diagnosed with Hepatitis C A year ago, for example, it would be unlikely that he has already developed cirrhosis. So the next question that I have is what would you do to determine whether this patient has cirrhosis? And this is another polling question, I promise this is the last. So would you do a additional bloodwork B? Would you get additional imaging, for example, on MRI or a CAT scan? Would you do a liver biopsy? D is none of the above and E is all of the above?

07:58
Okay, I think we can close the poll and see. Okay, so the results show that half of the audience said that they would vote to do additional bloodwork, which I do agree with for sure. 21%, said more imaging. So I also agree that more imaging would be helpful and will kind of go into detail about which imaging, we can use 0% said liver biopsy, and that's, I would say the correct answer. It is very, very rare that we need to do a liver biopsy nowadays to determine if someone has cirrhosis or to really stage the degree of scarring in their liver. Because we have so many other tools available to us to do this non invasively. And then 14% said none of the above and 14% said all of the above so that there are some people that would do a liver biopsy, I would say although liver biopsy is considered gold standard in the sense that it is the most direct look at the liver to determine fibrosis stage because of the risks associated with it and because of other tools that we have. Really it's very rare that we nowadays need to do a liver biopsy to determine strictly for the purpose of determining fibrosis stage and if someone has cirrhosis, great, okay. So, to start, you know what, what is liver fibrosis? So basically, the way I discuss it with patients is I say that it really is scarring in the liver just like when you fall down and you hurt your knees, you develop some a scar there or scab, kind of similar in the liver and it can progress over time. So it's the accumulation of extracellular matrix as a result of an imbalance in production and degradation of this extracellular matrix. response and it occurs in response to chronic liver injury. So whether it's from Hepatitis C or from really any other liver disease, the All

roads lead to fibrosis. So whether they have alcohol related liver disease, Fatty, non alcoholic fatty liver disease, Hepatitis B, Hepatitis C, all over time can lead to fibrosis. And it's a very dynamic process. And this also I like to emphasize in my discussion with patients, because just because you have a certain degree of fibrosis at one point in time does not at all mean that it's irreversible, and you're stuck with that forever. In fact, quite the contrary. So for example, we know and patients who have cure of their Hepatitis C, over time, there could be regression of their fibrosis, or improvement in their fibrosis. But also if the Hepatitis C is left untreated, and or if they have other chronic liver diseases, it can progress and lead to cirrhosis. So in this diagram, on the right, we see pictures of liver biopsy specimen again, we don't routinely do liver biopsies for fibrosis staging, but these are examples of what we would see. And basically on the left, and a, you see that there is no blue. So the blue is that trichrome stain, it's a stain that we use for fibrosis, staining. So on the left, there's no really no blue that you're seeing. And so there's no fibrosis, so F zero, and then we classically stage from F zero to F four. So in B, you start seeing more blue, more fibrosis around the portal tracks, and so that's F one or maybe even leading to F two as you start developing these kinds of septic these long areas of blue. Then when you go to see you have what's called Bridging fibrosis, you really start seeing extension of this blue fibrosis scar. And then on in panel D, this is cirrhosis. So this is equivalent to F four, which is cirrhosis. And here you see kind of nodule formation where you have a lot of a lot of trichrome stain showing the development of nodules and that's when you have cirrhosis. So what are the stages of fibrosis? I just mentioned, there are different staging systems. The one that is most commonly used is the meta Vir staging system and we stage it from F zero to F four and I actually do discuss this with patients I say, you know, you can have scarring in your liver and we grade it from zero to four. Zero means no scarring four means that you have cirrhosis and then there's F two and F three in between. And then the end spectrum or a four is cirrhosis. So cirrhosis reflects the injury repair process in the liver. As I already mentioned, there are multiple different causes and if you have more than one cause it can be synergistic. So for example, if you have someone with Hepatitis C, who also drinks a lot of alcohol or someone with Hepatitis C, who also has, you know, non alcoholic fatty liver disease. If you have two causes, you can have more rapid progression to cirrhosis. And it's characterized histologically by these regenerative nodules surrounded by fibrous tissue and a distortion of the hepatic architecture. So you can envision in this x planted liver if you saw this on an imaging study like an ultrasound or a CAT scan, you can see some nodularity which can suggest that maybe there is cirrhosis. And it's also important to keep in mind the timeline for the development of cirrhosis. It does not happen overnight. And so as I mentioned in the first case that I mentioned, you really need to have enough time to get to the point of cirrhosis and that's why that's an important aspect of the history that you obtain from the patient. So generally speaking with Hepatitis C, when you start with a normal liver, and you have Hepatitis C infection, it turns to chronic Hepatitis, although some people may of course have acute Hepatitis and clear it. But if they do have development of chronic Hepatitis, it takes about 20 to 25 years to develop cirrhosis. So over two decades classically, although again, can be more rapid if there's another coexistent disease. And then, you know, maybe up to three decades to develop the kind of end stage complications of cirrhosis, which includes a hepatocellular, carcinoma, and decompensated liver disease and of course, that death. But I think it is important to keep that in mind when you're trying to think about disease stage and the duration of their, from the time they're infection to

when they're seeing you. Although of course, many patients don't know when their actual exposure was, so it may not be the easiest history to obtain.

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And when we think about cirrhosis, we think about it broadly in two categories. So once you get to that end stage of fibrosis F four and you have those regenerative nodules and you have cirrhosis, we think about it as either compensated or and simpler terms that you may use with patients asymptomatic versus decompensated symptomatic, and about five to 7% of patients with asymptomatic cirrhosis may progress to D compensated and what is the compensated mean? D compensated is when they actually start developing signs and symptoms of liver failure, as well as portal hypertension or increased pressure related to cirrhosis. And I'll go into a little bit more detail about the symptoms that would be manifested in in this D compensated state. So when we think about compensated versus the compensated with compensated, you only you would actually diagnose cirrhosis based on blood tests, radiology or biopsy, which we don't really do. And the patient may actually look perfectly well, they may look completely healthy, and it's almost just based on labs and imaging that you may discover that they have cirrhosis, for example, we do get consults every now and then where there's an incidental finding of cirrhosis on imaging and someone who really hadn't had symptoms up until that point. So just having cirrhosis does not necessarily mean that they will have symptoms. Generally speaking, the labs may also not be really that abnormal, the synthetic function of the liver will be preserved the albumin the bilirubin, and the INR may be completely normal when they have this early cirrhosis, and they won't have any clinical signs of liver failure. When they present for example, there will be jaundice or ascites. But they may have small varices, for example, that have not bled and these viruses may also be seen on imaging. Another hand when you move to decompensated cirrhosis, then it becomes a little bit more obvious and here. Cirrhosis can be diagnosed again with blood tests, radiology or biopsy, but their labs will be abnormal. There be abnormal indices of livers and synthetic functions. So they will have elevated INR, although albumin perhaps and elevated bilirubin, and then the actual signs of decompensation that we look for are listed here. And basically, they are the following, they will either have a ascites variceal bleeding, so just having very small variances does not mean you're decompensated. Yet it's once you have the Varus he'll bleed, that's what's considered decompensation or hepatic encephalopathy, so confusion related to the liver disease. And then as a further spectrum, i They may also develop hepatic renal syndrome. But that's not that's not one of the three main d compensations we see kind of off the bat but may develop in some patients. So what are the major complications, again, kind of just reviewing that so the putting them in different categories. So some of the major complications are related to portal hypertension. So you have increased pressures from the liver, which leads to the development of ascites. So fluid buildup, as well as variceal bleed. There's also liver insufficiency. So your liver is not functioning well. And so that can lead to defects and their ability to clear toxins. So development of encephalopathy, the development of jaundice due to liver dysfunction, and then cirrhosis also can lead to malignant transformation. So liver cancer hepatocellular carcinoma, and when you think about these complications, that is really what informs our monitoring of patients with cirrhosis, and is basically the prevention or the screening for some of these complications such as federal cellular carcinoma and Pharisees. And then the treatment of these complications if they develop. And then once you develop ascites, kind of the further end speech complications in

patients who have ascites is you can develop infection in the ascites fluid or spontaneous bacterial peritonitis, SBP and or hepatic renal syndrome. So, how do we diagnose or assess for fibrosis or cirrhosis in patients with Hepatitis C? So you have someone who comes to you for the first time they have a history of Hepatitis C, do you need to stage them for fibrosis? And the simple answer is we really should assess the fibrosis stage and evaluate for cirrhosis all patients with a history of chronic Hepatitis C. Of course, as I mentioned earlier, if they know they contracted Hepatitis C six months ago, for example, it would be unlikely that they have developed advanced fibrosis. That being said, it's often not easy to pinpoint when actually the infection occurred, especially if they're a chronic injection drug user or have long standing risk factors. So the easy answer is really every patient who is seen with Hepatitis C should be assessed for fibrosis stage. And when we meet these patients, what are the symptoms of cirrhosis? The first thing I would say is many patients especially with that early cirrhosis can be completely asymptomatic. But those that do have symptoms may have nonspecific symptoms such as anorexia, weight loss, fatigue, weakness, some may develop pruritis, or itching of the skin. And then you can also see these decompensation so in a patient who is known to have cirrhosis, I always ask them, Well, have you ever had volume overload? Have you ever had abdominal distension and fluid in your belly? Have you ever had gastrointestinal bleeding? Have you ever had confusion and even if when you initially see them, they don't seem to have any signs of these, it's important to know if they have had these signs in the past, for example. But again, patients with cirrhosis can also be completely asymptomatic, especially if they're compensated. So why do we ask in the history so many of these I already alluded to so very important to know the duration of Hepatitis C and their risk factor history. So what were their risk factors even if they don't know what exactly they contracted When were they exposed to these risk factors. Alcohol history is important because that would give you an idea of how rapid their fibrosis progression may be also metabolic disease history. So I mentioned non alcoholic fatty liver so some of these metabolic risk factors can also contribute to more rapid progression of fibrosis. Also relevant is family history of liver disease and cirrhosis. There also genetic predisposition to more rapid disease progression. So if they have multiple family members with cirrhosis, that's important to know. And again, whether they've had a history of one of these D compensations that I mentioned, like ascites, variceal, bleed or hepatic encephalopathy. And on physical exam, there are also some findings that you may see. So generally speaking, patients with cirrhosis, especially decompensated cirrhosis tend to have lower blood lower blood pressure due to systemic vasodilation. So it's not a typical to see a patient with cirrhosis with systolic blood pressure in the 80s, low 90s. And it's not it's just where they are and so not necessarily cause for alarm if they come in with a blood pressure systolic 85. And then on the skin exam, you may note some findings such as Palmer erythema, which is shown here and the finger on the right spider NGO Mehta. Jaundice of course also, gynecomastia can be seen due to the hormonal or high estrogen state related to cirrhosis and then an abdominal exam obviously, you can see ascites fluid you can see these prominent veins that cap Madhu say and palpate, a large spleen splenomegaly and testicular atrophy as well. And again, a lot of patients with cirrhosis may also not have these physical exam findings. And then in terms of imaging, so what we saw in our case, and what you may see is a nodular liver although it's really not the most specific binding, there are other conditions where you can also see a nodular liver so I wouldn't use that as a way of definitively diagnosing someone with cirrhosis, although it can be suggestive. I think what's more helpful on imaging if you have cross sectional imaging like a cat

scanner MRI is seeing splenomegaly. And seeing collateral vessels are a sign of intraabdominal viruses, because those signs really point to portal hypertension. And those are more informative than seeing a liver that is a bit nodular.

25:20
In terms of laboratory findings, liver tests may be normal in patients with cirrhosis, they also may be elevated. So ASC classically is higher than 80. In patients with cirrhosis, and their alkaline phosphatase and GGT may also be elevated. The bilirubin and INR would be elevated if they're the compensated and they may develop hyponatremia. If they're D compensated and then developing a pad of renal syndrome. Of course, they're platelets would be lower and platelets less than 150 are correlated with significant portal hypertension. So that's an important cutoff to keep in mind, someone with platelets under 150 shouldn't raise your suspicion for having significant portal hypertension. And they may be anemic and have low hemoglobin as well. So what are the methods that we have available to us for fibrosis and cirrhosis assessment, I mentioned some of the laboratory changes that that we can see. Also, on imaging, I mentioned that, you know, we can see a nodular liver or splenomegaly and varices, which is very helpful. But there are other tools that we have available to us that are possibly more helpful. And I'll go over some of those. And liver biopsy I put it here because it is a method that can be used but again, nowadays is very rarely used solely for the purpose of diagnosis of cirrhosis or fibrosis staging. So the first tools that are, you know, widely available and are good places to start are blood based markers or or scoring systems for fibrosis and cirrhosis assessment. And the two common ones that that are used and are readily available are the pre score and the fifth four score. These are calculators that you can find online, you can Google fib four or pre and easily find them and can be done really anywhere that you have lab results available. There are also other tests like the natural novel fibrosis score is specific for fatty liver so not as relevant to Hepatitis C patients. But then there are other proprietary tests called the fiber test fiber meter and HEPA score. And there's some variability and availability depending on where you are at one institution. For example, we have the fiber meter available here. And these are basically proprietary markers that are also from that you can use with a blood test, and also estimate whether someone has advanced fibrosis or no fibrosis. These tests are good at estimating to see if someone has at the extremes to see if someone definitely you know is likely to have cirrhosis versus no fibrosis at all. They're not so good at staging in the middle like f2 and f3 fibrosis, for example. And then we have elastography available to us. And this is probably the tool that we in our practice use most commonly. And that's because it is available to us and if it's not available to you, that's perfectly fine as well. And you're you can really get good information from using these blood tests scoring systems, but we have transient elastography or fiber scan and it is very well validated and is a tool that we have in our office that basically similar to an ultrasound that can immediately give you the answer and after scanning the person's liver, it can give you a score which tells you where they fall in terms of fibrosis stage. There's also Mr elastography so MRI technology that incorporates elastography, which also is still variable in availability, depending on what health system but also is gaining a lot of favor in terms of fibrosis assessment. So to look at the a prehensive for and a little bit more detail, you know they're simple, they're fast, they're inexpensive, the prespore just uses that as t and the platelets and that's it. And when this formula if the score is over two that is highly predictive of cirrhosis, the fifth four and corporates In addition to the platelets and as t also the Al T and the person's age,

and if the cutoff if the FIB four is less than 1.45, you are pretty confident in saying they do not have cirrhosis. And if it's over 3.25, then it is highly predictive of cirrhosis. So for example, if we had a an example patient, this is a 53 year old male with chronic Hepatitis C, he has ASC of 75 al to 50 CC, the ASC is higher than the ELT and a platelet count of 150. Right there at that cut off that I mentioned, for portal hypertension. So if you calculate his pre score, it is 1.724. So it's high, but it's not over two, so to just that, he probably may not have cirrhosis. But then the FIB four is 3.75. And that is over 3.25 and suggests cirrhosis. So here, the FIB four is probably a bit more accurate because this patient did indeed have cirrhosis and just even looking at that platelet count alone clued me into the fact that he is definitely consistent would be consistent with having him having cirrhosis and portal hypertension. And this is how the transient elastography or fiberskyn looks this is what we use in our practice. So basically, the it's it takes about five, five minutes to do this test. And our nurses are trained in fiber scan and are able to do this in the office and and so the basically what it does is it measures the shear wave that passes through the liver and it's correlated with liver stiffness, which in turn is correlated with fibrosis or scarring. And it spits out a number after you complete the measurements. So this number of 4.4 puts you in the range of no fibrosis anything less than around six or so with Hepatitis C means no significant fibrosis and you can correlate it with fibrosis from F zero to F four. The caveats about this particular test is the patient does need to be fasting for at least four hours before the procedure. And it's a little bit more challenging in patients who are obese, but there is an XL probe that can be used in patients who are obese, which is a bit more accurate. And in patients who have elevated liver tests and ongoing inflammation for example, patients with acute Hepatitis C may have elevated liver tests that may actually falsely elevate the score because inflammation itself also increases liver stiffness, and may not be entirely accurate. But this is how we interpret it to depending on the disease. We have different cut offs in the liver stiffness score that the fiberskyn generates. So for example, with Hepatitis C, a liver stiffness score of over 14 suggests that you have f4 fibrosis or cirrhosis. The other aspect and this is also relevant to clinical practice is that sometimes combining multiple tests may improve accuracy. And this is something that is not uncommon to do that I that I do in clinical practice. Sometimes you have findings that are opposing using the different tools, for example, the FIP for may suggest that they have cirrhosis. But then when you do the fiber scan, the fiber sand score, the liver stiffness is only 11 que pas. And so you kind of have to take several data points to make an informed assessment. And it's not always straightforward. So this is one study that looked at that where they actually did have biopsies and almost 400 patients with Hepatitis C, and they correlated the findings on these different scores with the liver biopsy to see which score or which combination was most accurate. And if we look, for example, on the column to the left, that a pre score, the accuracy increases as you add other measurements to it. So although it's 86% Concordance, with biopsy with a pre alone, it's 89% if you add on Fibro meter, goes up to 93% in terms of concordance for liver biopsy, if you combine a PRI with fiberskyn And I think that that is a very important point. It's not always the easiest To make the diagnosis of cirrhosis or have an accurate fibrosis stage by using several data points as well as of course, their history and other aspects will help you make more accurate assessment.

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There are also newer imaging technologies that estimate fibrosis. So I mentioned this before we now have Mr elastography so and it is available to us we use it in clinical practice and some

data suggests that it is more accurate than transient elastography than fiber scan. So that is one tool that is available. There's actually also ultrasound tools which are becoming more widely available that also incorporate elastography so ultrasound that can measure fibrosis stage, and these are less commonly used in clinical practice, but they are becoming increasingly available. So if your center has ultrasound, they may have the Southstar graphy tool available that you can that you can use as well. So when do we use these non invasive tests? Well, a lot of it comes down to availability, availability and cost your particular center so you know, the pre the FIB for our simple biomarkers that can be used and they're relatively low cost. Then we have these composite biomarkers, the proprietary tests, the fiber test fiber meter, which are more expensive and not as widely available. And then we have all of these imaging tools, imaging tools available as well. And which one you use or which combination you use, you know really is a combination of factors that may lead to your decision including local resources and costs validation in specific disease states, so some may be more validated and Hepatitis C than others for example, transient elastography or fiber scan has been studied a lot in Hepatitis C patients, whereas Mr elastography not so much. And then quality and risk factors are. So all of these, you know, are important factors in your decision of which tools to use. But I think the most important aspect is that if you have several tools available, I think sometimes it's helpful to get a more accurate assessment. So this is to summarize the diagnosis of cirrhosis in patients with Hepatitis C and the steps that that are needed. So you start of course with history and physical exam, and even based on that you can really get at the answer depending on what you see. For example, if you see someone who already has a Sadie's who tells you they've had a Versaille bleed who hasn't had a good Sepilok with it, and then has this Palmer thema spider angiomas even just based on the history of physical exam, you know they have cirrhosis. And you may not need additional advanced imaging techniques to diagnose that. Then laboratory testing so just platelets under 150,000 would be helpful, you also raise your index of suspicion and as t is greater than Al t. And then using these laboratory based scoring systems is very helpful as well, the FIB four and pre score. And then the next step would be liver imaging, ultrasound and liver stiffness measurements. And, you know, based on imaging, you can see if they have splenomegaly, or viruses that would highly suggest cirrhosis, and of course elevated liver stiffness. If the non invasive tests are discrepant, and it's still unclear if they have cirrhosis. It's relatively rare after you've taken all these steps, but you can consult with hepatology at that point. So once we diagnose a person with Hepatitis C with cirrhosis, what additional monitoring treatment is needed or is done. So generally speaking, even if they do have compensated cirrhosis, or they're asymptomatic, I still recommend seeing them every three to six months really, in my practice, I see everyone with cirrhosis every three to four months. And because things can always change, so they may be compensated when you meet them and then something happens and then they become the competent and you really don't want to miss that. So in these visits, I checked their bloodwork, I look for signs and symptoms of decompensation. Have they developed new ascites are they developing early signs of confusion of encephalopathy? And then I calculate I use the labs to assess their Are cirrhosis severity. And these include meld scoring Child Pugh, which I'll go over next. And then also very important in someone with cirrhosis, especially if now they're decompensated, you need to start thinking about whether liver transplant is something that needs to be discussed. And the main screening and test that they need outside of their visits and our practice is endoscopy for versi. Screening and imaging every six months for screening for hepatocellular carcinoma. The reason that we

worry about the compensation and we see these patients relatively frequently to determine if they're developing any sign of decompensation is we know that the onset of decompensation significantly reduces survival. So this is quite an older study. But it just clearly demonstrates that survival significantly decreases once they have D compensated cirrhosis. And so with the onset of the first D compensated event,that should be a trigger to consider referral for liver transplant evaluation. So even if their blood tests don't look that alarming their bilirubin is normal. By now they come in and they have new encephalopathy or new ascites. This is a sign to begin to think about liver transplant. And this isn't just the median survival in patients with compensated cirrhosis around nine years. But once they have decompensated Cirrhosis is much much lower at 1.6 years. And we have scoring systems that we use and patients with cirrhosis to determine how sick they are and also to use to prioritize for liver transplant if it comes to that. The most common score that we use and that's still used for liver transplant prioritization is the MELD score. And this is a score that estimates three months or 90 Day risk of death and it incorporates creatine so the kidney function Billy Rubin and INR with this formula again meld scores very easy to find online Mel calculator and you plug in these numbers and you get the MELD score and the higher the MELD score, the higher of course is the risk of death and the higher is the urgency for liver transplant evaluation. So for example, if they have a create Nina one and bilirubin have to INR 1.5, which those numbers don't even seem that high or that alarming. This is a MELD score of 20, which signifies a 20%. Three month mortality just shows you how sick these patients are. And it's useful actually to have the scoring system is that you can kind of counsel patients on, you know their need for liver transplant potentially. And then a modification on the MELD score, which was more recently implemented, although not that recent at this point is the melt sodium. So this was the study that found that incorporating sodium into the score and calling it melt sodium was improved improved our prediction of probability of death at 90 days significantly. And so since

43:36
Well, currently, now we use the melt sodium as the score for liver transplant listing priority so people with the highest melt sodium score or higher on the list for liver transplant, people with the lowest melt sodium are lowest on the priority list. And believe it or not, there's actually yet another potential update. This has still not been implemented in clinical practice. But Ray Kim who have published the meld sodium recently published the meld 3.0, which right now is under discussion of being implemented in terms of transplant prioritization. And the male 3.0 actually incorporate albumin which is a sign of reflects synthetic function or synthetic dysfunction, and also whether the person is female because studies show that the melt sodium disproportional This made it more difficult for females to be higher on the list due to their creatine and related to their muscle mass. So potentially in the coming years, the Mel 3.0 will be the scoring system used but not yet. The other score that many of you are probably aware of is the Child Pugh score. So this is also useful because it incorporates somewhat subjective measures but important measures of liver disease unction in addition to the INR the albumin and bilirubin, it also incorporates whether the patient has a ascites and encephalopathy. So two of the major D compensations and after you calculate the score, you can categorize the patient into a child's class A, B, or C depending on the number of points they have. And, of course, Child Pugh C is the most severe liver disease and as we mentioned has implications in terms of Hepatitis C treatment in patients. So, the Child Pugh score is important because if the patient is D

compensated or has Child Pugh D or C, you need to adjust the Hepatitis C treatment regimen. So for example, if they have child a, you can use the simplified criteria for Hepatitis C treatment, you can really treat them in the same way that you would treat a patient who does not have cirrhosis at all. But if they have Child Pugh B, and if they're D compensated, you need to adjust the regimen or the duration of treatment. So for example, you may need to add Dr. American or extend duration of treatment for 24 weeks. And very importantly, in someone with the compensated liver disease, we don't want to use protease inhibitors. So we do not use glecaprevir pibrentasvir or Mavra for patients with decompensated liver disease. The other aspect of monitoring is for liver cancer. So patients with Hepatitis C who have developed cirrhosis are at increased risk of developing liver cancer, or hepatocellular carcinoma. And that's the reason that we do ultrasound or other imaging studies every six months so that if we discover an early lesion, small cancer, we can actually treat it with relatively not as invasive ways and they can still qualify, they can still be eligible for liver transplant. So that's why we recommend screening every six months. And there are certain factors among patients with Hepatitis C, which can increase their risk of developing liver cancer, of course concurrent disease, so other concurrent liver disease, synthetic dysfunction and the more advanced their Cirrhosis is if they have decompensated cirrhosis, they're more likely to develop liver cancer. Although I would say we definitely have had patients who even have f3 fibrosis, not even cirrhosis, who have developed the rare cancers. How do we screen for HCC? So the recommendation is to do imaging with AFP Alpha Theta protein every six months, and ultrasound is fine. But if you find something then you really need cross sectional imaging. This is from the liver society guidelines in terms of the sequence so you do surveillance ultrasound, and then if it's negative, continue with the surveillance ultrasound. But if it's positive, if there's a lesion seen, then you really need diagnostic imaging with CT or MRI. The only caveat to this, I would say is that certain patients, for example, depending on body habitus, ultrasound may not be as accurate. So you may choose to do a cross sectional imaging, you know, maybe alternating with ultrasound and those types of patients. And then based on the lesion that you see, there's a score UK scoring system that determines whether it is likely that it is actually a liver cancer and HCC This is the light red scoring system. And once the once it's confirmed, then there's a whole algorithm for treatment. But definitely, you have many more treatment options if it's discovered early and if the lesion is small. This I already mentioned that although technically you should be able to screen with ultrasound every six months. There is some variability in the quality of the ultrasound. So sometimes you may need cross sectional imaging, maybe alternating with ultrasound, particularly if someone is morbidly obese, for example. And there are many barriers to HCC screening, it's very challenging to get patients to adhere to this, especially if they're, you know, doing imaging every six months for many, many years and they feel like it's not really doing anything for them and they get tired to go to all these tests. So It's important to educate patients. And to emphasize the importance that, you know, we really need to do this so that we can, if we identify something we find that early on, we can still treat it. And then the other aspect is screening for viruses. So, we know that as you progress in this, from compensators to decompensated, you have the development of increased portal hypertension and the potential for their seal hemorrhage. And once you have a very seal bleed, that also significantly decreases your your, it increases your mortality. So we really hope to prevent these variceal bleed if possible. Generally speaking, most patients with cirrhosis should be screened for viruses. But we do know that patients who have platelet count over 150, and who have a

liver stiffness less than 20, on fiber scan, for example, are very unlikely to have very significant or clinically significant portal hypertension. So those are patients in which you can actually avoid endoscopy. So this is from our guidelines from 2017. I would say in practice, many hepatologist still end up doing at least one endoscopy. But it is important to keep this in mind that if they're very compensated, and they really don't have signs have significant portal hypertension, it's very unlikely that they would have their season you can actually avoid doing this endoscopy. And the right you see a picture of how varices would look. And these are pretty large. And once we identify them, then we have a protocol for ongoing follow up. If they're small, we actually don't need to treat them. So not everyone would Pharisees needs a treatment if they're small. But if they're medium or large, then we're able to ban them during endoscopy or put them on a beta blocker and this is the list of beta blockers available.

52:07
And then finally, when do we consider liver transplantation So definitely if their MELD score is high, so anyone with the MELD score based on labs greater than 12 to 15 should be referred and anyone with any signs of decompensation. That's a sign for consideration or referral for liver transplant. There is some consideration for timing of Hepatitis C treatment around liver transplant. I don't have too much time to go into that in detail, but I just know that it may inform your decision about timing of treatment whether it's before or after transplant. So to finish off, go back to our case I provided very little information initially, but additional bloodwork was obtained and per the bloodwork and that patient, the pre score was point 273. And the FIB four score was 2.15. So kind of conflicting scores, the fiber shore score was consistent with F four indicative of cirrhosis. In that practice, there was no transient elastography there's no fiber scan available. But based on these laboratory testing, what I can definitely say is this patient likely has advanced fibrosis and possibly early cirrhosis and needs to be monitored as such. So the patient was treated with mavyret for 12 weeks, and he had SVR 12 And he was recommended to have ongoing follow up for HCC screening and liver disease management. Because even though he was cured, he does have advanced for both fibrosis pathway cirrhosis and needs this ongoing follow up. So to summarize, you know, I think we need to assess all patients with Hepatitis C for fibrosis stage and for cirrhosis and we have a variety of tools available to us. Some patients are very straightforward. Others like the case that I mentioned is not as straightforward but you can really get closer to the answer by using several different tests as well as of course the physical exam. The it is important to monitor the MELD score and the Child Pugh score on patients and we see them relatively frequently every three to four months because these things can change and that should prompt potential referral for liver transplant. And all patients with advanced fibrosis cirrhosis, you do need to do HCC screening and Pharisees if indicated. And again, to not forget that liver transplant is an option once they have advanced or decompensated liver disease. All right, so I think that brings us to the end and we have a few minutes for questions. wins. So I'd be happy to take them. Should I go to the next slide?

55:04
Sure. Thank you. Dr. Krishna, thank you so much for that masterful, comprehensive overview of cirrhosis. First question is Does anyone know of transplant resources in New York City for

uninsured patients? A lien? Steiner has a 45 year old patient with decompensated cirrhosis who does not have an uninsurable?

55:28
That's a great question. You know, the transplant team has social worker and I find finance, finances person, I know that sometimes they are creative, at least at our institution in terms of coming up with solutions. But if they don't, for example, can they get them temporary Medicaid? Or can they think of other solutions? I don't know if specific resources, but every institution is probably different. Either way, that patient should be referred to a transplant center and have the evaluation and then, you know, have the meet with the social worker, see what options are available? And see if it is a possibility, but it does it is a significant challenge. I mean, if there's really no way to get insurance coverage, then it's very challenging.

56:20
Thank you. I was gonna ask you, Dr. Kushner, do you have a good sense of what the current landscape is in terms of like insurance requirements around fibrosis staging for approval of the medications? Will insurance companies accept staging just based on a pre or before? Does it vary a lot? Curious if you have some sense of that?

56:48
You know, and in my experience, we don't You don't necessarily need fiber skin, you know, we as a clinician indicate their fibrosis score, but we do not submit to them necessarily our fiber scan results. So to my knowledge, although you know, we always do have fiber scan available, but but to my knowledge, I am not. I think that a PRI and fifth floors or fiber meter is good enough assessment for insurance companies. I may, I don't you may have some additional information. But to my knowledge, we don't submit an actual fiber scan result.

57:30
Thank you. Yeah, I mean, in our practice, most patients don't have Fibro scans, and traditionally, the medical providers were doing five parameters. But I think now we're trying to move more towards more simplified, are pretty unfit for and at least some of the insurance companies are accepting that. So I was actually curious what others were finding as people are trying to make things simpler and more rapid in terms of getting patients on treatment.

57:58
That's another question. We can I can follow up with, you know, with the our specialty pharmacy to see for sure, and then we can follow up with that audience.

58:07
Thank you again, Dr. Kushner. Thank you, everyone.

[End Transcript]