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HEPATITIS C TESTING AND PRE-TREATMENT EVALUATION

Jennifer Price, MD, PhD
Associate Professor of Medicine
Director, Viral Hepatitis Center
Division of Gastroenterology/Liver Transplant
University of California San Francisco

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[video transcript]

00:08
It gives me great pleasure today to welcome Dr. Jennifer Price to present to us on this co-sponsored webinar. And I'd like to introduce Dr. Price before she begins. She is an Associate Professor in the Department of Medicine and Division of Gastroenterology and Hepatology at the University of California, San Francisco, and Director of the UCSF Viral Hepatitis Center. She leads the UCSF HCV Project Extension for Community Health Care Outcomes, Project ECHO, a model of medical education and care management focused on building capacity for HCV care among primary care providers throughout Northern California. She's a Founding Director of the Deliver Caravan, a mobile unit aimed at improving access to hepatitis C screening and low threshold HCV treatment among at risk communities. Welcome, Dr. Price, I turn it over to you.

01:08
Great, thank you for that introduction. everybody hear me? Okay.

01:12
We do.

01:13
Okay, fantastic. So, thank you for inviting me to give this webinar, I'll be focusing on hepatitis C testing, and the pre treatment evaluation. So I won't be speaking very much about the actual treatment, but basically everything you need to know before you get somebody started on treatment. And there should be plenty of time at the end to do some Q&A. If you have any questions, feel free to enter them into the chat.

01:43
So here are my disclosures. And our learning objectives are to understand in whom screening for hepatitis C is indicated, understand how to test and evaluate for hepatitis C, and understand the components of evaluation prior to treatment initiation.

01:59
So we're going to start with a polling question about screening. And the question is which of these patients should be screened for hepatitis C? A, 55 year old male with a remote history of injection drug use. B, a 78 year old Russian female with normal liver enzymes. C, a 27 year old male who is actively using drugs. D, a 34 year old pregnant female. Or both A and C. Or all of the above? Okay, so. And the correct answer is all of the above, but the screening recommendations have really changed over the past several years. And we'll go through that in the next set of slides.

02:43
So first, I wanted to review the prevalence and the incidence of chronic hepatitis C in the United States. On the left, we have the prevalence of hepatitis C, and it's estimated that 2.2 million persons in the United States are living with chronic hepatitis C. And this map of the US shows

where people are located living with hepatitis C, the darker red areas are the areas with a higher density of people with Hep C. And where I am in California, and where you guys are in New York, it's a darker red area. So still over 2 million people living with hepatitis C. And unfortunately, what you can see on the right side of the slide, is that not only is the prevalence high, but the incidence has been rising over the past several years. So from 2011 to 2017, new hepatitis C infections have more than tripled. And that's really been in parallel with the opioid crisis, and we'll talk a little bit more about that as well. But these prevalence and incidence data have really informed our screening guidelines.

03:49
So another important thing to know about hepatitis C screening is that unfortunately, about half of people with chronic hepatitis C are still unaware of their status. So on the left side of the slide, we have data that was published recently by some of my former colleagues, they looked at the NHANES database, which is a US based nationally representative survey that's done in different waves. They looked at the 2013 to 2016 wave, they looked to see if people are aware of their hepatitis status. And on the right side, you can see that among those who are Hep C RNA positive, only half were aware. So there's a big gap in awareness, and we see that not just with hepatitis C but also with hepatitis B.

04:38
So in 2015, the World Hepatitis Alliance launched a three year global campaign called Find the Missing Millions on World Hepatitis Day, and the campaign materials are included on the slide. Some of the materials in these are available in over 30 languages. So it's really important to try to increase awareness of hepatitis and hepatitis screening, to meet all these people that don't know that they are living with with viral hepatitis.

05:09
So why does it matter to screen people for hepatitis C? The main reason is that chronic hepatitis C may lead to cirrhosis and liver cancer, also known as hepatocellular carcinoma. And we'll talk more about that later in the presentation when we're talking about the workup of people with hepatitis C. But you can't treat and cure somebody, obviously, unless you identify them. So it really has to start with screenings. So we can identify, treat, and cure hepatitis C, and then also prevent new infections.

05:42
So in the first part of the talk, I'm going to be reviewing the hepatitis C screening recommendations and really the evolution of these recommendations for risk based screening, to baby boomer screening, to now the most recent recommendations which are universal screening.

05:58
So this slide shows many of the established risk factors for hepatitis C. Hepatitis C is most efficiently transmitted through blood exposure. So people who have a history of blood transfusions or organ transplantation, particularly before the blood and organs were were screened for hepatitis C, are at high risk of having been exposed to hepatitis C. Injection drug

use, current as well as history, even one time use, is a well established risk factor of hepatitis C. Other risk factors include chronic haemodialysis use, perinatal transmission from mother to child transmission, occupational exposures like needle sticks among healthcare workers, and we do see patients who have received foreign health care or dental health care who were exposed iatrogenically.

06:47
So these are some of the major risk factors for hepatitis C infection. And in 1998 until relatively recently, the hepatitis screening recommendations were really based on these risk factors. So in 1998, when screening was available, the CDC recommended risk based screening, meaning you would ask your patients if they had any of these risk factors, and if they did, then you would test them for for hepatitis C. However, we know that that's not good enough, because more than half of people living with hepatitis C are not aware that they are infected. And so that really made people revisit these screening recommendations, and really the failures of the recommendations. And the risk based screening is really challenging, because these risks are ever risks. So if you're seeing a new patient, let's say your primary care provider, and you're seeing a 60 year old woman for the first time, you may not be asking her about a blood transfusion she she received in childbirth several decades ago, or about experimenting with drugs several decades ago. So there's real gaps in the risk based screening, and they're not necessarily feasible to reach all the people who've been exposed to hepatitis C.

08:00
So that led researchers to look and see okay, who specifically is at higher risk of having been exposed to hepatitis C, if we were going to look at sort of large groups of populations. And this, again, are data from that NHANES survey, but this is from the earlier wave, so that 1988 to 1994 wave in blue and the 1999 to 2002 wave in purple. And what they did was they looked at positivity for Hep C antibody in the NHANES cohort, and found that the highest prevalence of positivity was in this birth cohort, people who were born between 1945 and 1965. So this showed that people born between 1945 and 1965, were at particularly higher risk of having been exposed to hepatitis C, particularly because of one of these risk factors in the remote past.

08:57
So that led to the 2002 CDC expansion of the screening recommendations to include not just risk based screening, but also one time screening for all people born between 1945 and 1965, without prior ascertainment of risk factors.

09:17
So that's what we had for a while, for the past eight years or so, and then we have now revisited the screening recommendations because the epidemiology of hepatitis C in the United States is also changing, as I alluded to in one of the opening slides. So what I show here is on the left, you can see the percent of newly reported Hep C cases, this is in California. So these are data courtesy of Rachel McLean from our California Department of Public Health. But I know that in New York, you guys have similar data. And what you can see is in 2007, most of the newly reported hepatitis C cases were among that birth cohort of people who are born between 1945 and 1965. So this helped inform, of course, the screening recommendations in this birth cohort.

But like you can see, shifting over to the right, is in 2015 now in this graph, you can see that the percent of newly reported Hep C cases is not just in that birth cohort, but also there's a second wave in much younger individuals. And that second wave is being driven by the opioid epidemic. And so what we're seeing is most of the younger people who are testing positive for hepatitis C have experienced injecting drugs, and that is the main route of transmission. So it's really been this second wave of incident hepatitis C that has informed the newer screening recommendations.

10:52
And this is another slide showing the same point, but this is looking at US data, so the whole country. And you can again see the new cases of acute hepatitis C in the US, this is incident cases. And this is by age group. And across the the past several years, there has been an increase in cases in each age group, but you can see that the largest number of cases and the biggest increase is among the 20 to 39 year old age groups. That's the purple and the orange on this slide.

11:26
So it's really because of these rising cases that in 2019 the AASLD, which is our main liver society, recommended one time universal screening for hepatitis C among all adults. And then in March of 2020, this year, the US Preventive Services Task Force recommended one time screening in all adults aged 18 to 79. So really consistent with what AASLD had recommended a year before. And a month later, the CDC had the same message recommending screening at least once for all adults 18 or over. And they also added for all pregnant women during each pregnancy.

12:09
So this slide just summarizes where we are now in terms of our hepatitis C testing recommendations. And this green table is from our AASLD IDSA hepatitis C guidelines. And their recommendation is one time routine opt out Hep C testing for all individuals aged 18 or over. One time testing should also be performed for all persons less than 18 if they have behaviors, exposures, or certain conditions associated with an increased risk of hepatitis C. And then they also recommend periodic repeat hepatitis C testing in people who have behaviors, exposures, or conditions associated with an increased risk of hepatitis C exposure. Now, the US Preventive Services Task Force and the CDC don't go this far in terms of recommending periodic testing in people in high risk, aside for the CDC with pregnant women, but that is what the AASLD recommends. And that includes annual hepatitis C testing in all people who inject drugs or for HIV infected men who have unprotected sex with men, because these are two risk groups that are particularly high risk of getting infected.

13:24
So now that we've established that the universal screening is the guideline, we'll move into how you should screen. We'll talk a little bit about the available tests and then talk more in detail about what the algorithm is and how to interpret your results when you're communicating these results to the patient.

13:44
So when we talk about hepatitis screening tests, we're really talking about two different tests. The first is the hepatitis C antibody, or anti Hep C. And this is usually a third generation ELISA test that's high sensitivity and high specificity. And a reactive test indicates that someone's been exposed to hepatitis C. So they either have a current infection, or they may have resolved infection. What's important to recognize is that once someone's infected, they will almost always be reactive forever. Some people lose their antibodies, so not everybody is going to remain antibody positive, but the vast majority of people who've been exposed to hepatitis C will remain antibody positive, even if they spontaneously clear or even after their cure. So it's a really good first time screening test, but it's not something that you'll be able to use in people who you know already have a positive but you're not sure if they still have the virus. But like I said, it is the primary screening test we use. And then the next test that we use to confirm that someone's actively infected is the hepatitis C RNA, which you could also call that the the viral load. And if this comes up positive or detectable, that indicates that someone is actively infected. And there's a couple different ways that you can order this. There is a qualitative test, which will just say yes or no, that's less common to order. The quantitative test will give you actual viral load, and that's more helpful, so that's usually what we order. And the other thing to note is that this will become positive before the hepatitis C antibody test in a newly infected individual, which we'll get to in this next slide.

15:25
So here's a graphic that shows you what happens with your patients ALT level and their Hep C RNA level, and when that antibody comes up positive in someone who has acute hepatitis C. And oftentimes, we don't actually catch somebody with acute hepatitis C, but if we did we may see the liver enzymes go up quite high, and then go back down. And similarly, we'd see their Hep C RNA go up and then go back down, and then it can fluctuate a bit. Usually the Hep C RNA after acute exposure will be positive by the second week, but the Hep C antibody will take much longer, so that won't be positive until week 10, on average. So in someone in whom you suspect that they may have acute hepatitis C, you're not going to want to rely on the antibody.

16:19
So let's move into the screening algorithm. This is from the CDC website. And this is really how we recommend the sequence for someone that you're screening for hepatitis C, you'll start with that antibody test. And then if it's negative, you'll stop there. So no antibodies detected, and for most people, you'll stop there. So no more testing needed. If they're antibodies positive, then the next thing you want to do is do the Hep C RNA to see if they are actively infected. If the RNA is not detected, then they're do not currently have Hep C infection. If the RNA is detected, then that indicates that they have current Hep C infection, and that's when you want to link somebody to care. Now, depending on where you're doing the screening, you could combine these two steps. If you're doing a blood based screening, like you're sending your patient to the lab for the Hep C antibody, you can actually order it so that it reflexes to the RNA. So it'll only get the RNA run if the antibodies positive, and that saves you one of the steps. If you're doing sort of community based screening like we do in San Francisco at community based sites where you are not doing a venapuncture for that antibody test, but you're doing a finger stick, for

example, then you'll do it in two phases. So you'll wait for the antibody to come back reactive, and then draw the blood if it is reactive so you can send for the Hep C RNA.

17:45
Now, there are some caveats to this algorithm, the main thing being if someone you do suspect that they've been exposed recently in the past six months, then you will not want to rely entirely on a negative Hep C antibody, so either test for the Hep C RNA at that time, or if you only want to do the antibody you could wait and repeat the antibody after it's been several more weeks to confirm that they haven't seroconverted. And then there are some scenarios that someone may have a negative Hep C antibody, but still have chronic infection. And that's in someone that you are concerned they're not mounting an antibody response. So we usually think about this as somebody who's immunocompromised. So if I have a patient that I have a relatively high degree of suspicion that they may have hepatitis C but their antibody is negative, and especially if they're immunocompromised, I will send the Hep C RNA just to confirm. And I have detected some occult cases that way.

18:51
So when you're interpreting the Hep C testing results with your patient, if they have the Hep C antibody, the interpretation is that no antibodies detected and you can report to them that no further action is needed except for in those few special scenarios. If their antibody is reactive, you're going to presume that that's a positive. And that's when you're going to test for the Hep C RNA to identify for current infection. If their Hep C antibody is reactive and the Hep C RNA is detected, then that tells you that the patient has current hepatitis C infection, you've confirmed it with the positive RNA, and that's when you're going to provide counseling and link the person to care and treatment. And then finally, if the antibody is positive but the RNA is not detected, that tells you that they don't currently have the infection, and so no further action is required in most cases. Most cases this is going to be a true positive, the test is very sensitive, it's also very specific. But there may be some people that have absolutely no risk factors and you don't really think it's positive, you could repeat the antibody if they desire, but the really important thing is just to confirm that the RNA is not detected. And that means that they do not have active hepatitis C. If they do have ongoing risks for exposure, then in the future you'll want to test them for the Hep C RNA and not the Hep C antibody, because you already know that they're reactive. So for example, somebody with a history of prior injection drug use who's still using injection drugs, if they're antibodies positive, but the RNA is negative and the future you can just go straight for the RNA to see if they've seroconverted.

20:43
Okay, so that is, that's all I have prepared for the Hep C screening. And now we're going to move into the phase where if you've screened somebody who is positive, and you've confirmed that they have active infection, and now you want to evaluate them for treatment, what are the steps for the treatment evaluation? And we'll go through all the different steps of what I talk about with patients and what I ask patients, but there's three main things that I want to make sure that you come away with. One is how to stage fibrosis. The second is what pretreatment labs are needed before you start someone on treatment. And then the third is, what some of the

thoughts are in terms of drug-drug interactions and the medication reconciliation that you might think about when you're preparing somebody for treatment.

21:31
So first, let's do another polling question. So which of the following statements are correct and you want to select all that apply. So A, fibrosis staging isn't necessary prior to Hep C treatment. B, liver biopsy is required for fibrosis staging. C, liver directed physical exam, routine blood tests, and imaging can allow for the accurate diagnosis of cirrhosis in most people. D, simple serum calculators like APRI and FIB4 perform well in predicting cirrhosis. Or E, fibroscan is necessary to have an accurate diagnosis of fibrosis staging. Okay, so nobody thought that fibrosis staging isn't necessary, you're correct. Fibrosis staging is necessary. Liver biopsy is not required for fibrosis staging. The liver directed physical exam and routine blood tests etc. can allow for accurate diagnosis in most cases, and yes, simple serum calculators do perform well. Fibroscan is excellent at giving you a good estimate of fibrosis stage, it's not necessary. So you don't have to do it. Although some of you may need to do it still because of insurance requirements before your prior authorizations. We used to have those requirements in California where we had to do a fibroscan on our patients before prescribing treatment, but we do not anymore.

22:56
Okay, so I wanted to spend a little bit of time, I'm a hepatologist so I have to talk about staging of fibrosis, but I want you to sort of understand what these stages are and what the surrogates are for fibrosis staging. When we talk about fibrosis stages, we often are referring to this METAVIR fibrosis stage distinctions, which are really histologic distinctions. So if we were to do a liver biopsy, then our pathologist would give us the stages from F0 to F4. F0 being no fibrosis, F1 being fibrosis at the portal tract without septa, F2 being fibrosis at the portal track with rare septa. That's what we call significant fibrosis is F2. F3 is when you get fibrosis at the portal track with numerous septa without cirrhosis, I'll show you a picture of all these in the next slide. And that's what we call advanced fibrosis is F3 or greater. And then F4 is cirrhosis. And if you look, these little cartoons show you there's different stages. So F1, you see a little bit, you see this little bit of scar tissue here, but not very much. F2 you're starting to see some bridges forming between the different portal tracts. This is one portal tract here, there's another portal tract here. F3 you're really seeing more of the scar tissue extend across the portal tracts. That's why we call it bridging fibrosis, with scar tissue that is kind of bridging between the portal tract. And then F4, you're seeing those bridges have already established and now you're getting these nodules, which is what we see typically in patients with cirrhosis. So that's what would happen if you were to do a liver biopsy in or patients with hepatitis C, you would get back one of these stages.

24:41
But in most of our patients living with Hep C, we don't have to actually do a liver biopsy anymore we can do a non invasive surrogate. And the reason that it is important that we try to stage people before they get started on treatment, first of all is that the fibrosis stage may affect the treatment regimen and the duration of treatment. Particularly if someone has cirrhosis. But also it really helps us assess the prognosis for the patient. So we may detect that someone has early cirrhosis and that really impacts how you're going to counsel them beyond their Hep C cure.

And including in that is whether or not after their Hep C is cured they will need ongoing surveillance for an end stage complication of liver disease like esophageal varices, or hepatocellular carcinoma.

25:27
So briefly, before we go into the Hep C focused evaluation, I just wanted to review the natural history of cirrhosis with all of you. So when you have chronic liver disease from hepatitis C or from really any other cause, Hepatitis B, or alcohol related liver disease, or non alcoholic fatty liver disease, a subset of patients with liver disease will go on to develop fibrosis, advanced fibrosis, and cirrhosis if their liver disease is not treated. Once someone has cirrhosis, we call them compensated cirrhosis if they don't have any clinical symptoms of cirrhosis. And people can have compensated cirrhosis for years and not even know that they have it until they see you to get their Hep C treated, for example, and then you work them up and diagnose them with cirrhosis. Once they develop a clinical symptom of cirrhosis, then they move from compensated cirrhosis into what we call decompensated cirrhosis. And those clinical symptoms include a ascites, variceal bleed, hepatic encephalopathy, or jaundice. And any of those would then push somebody into decompensated cirrhosis, which is a more advanced phase of cirrhosis. And that's really important because the long term survival actually decreases significantly when somebody moves from a compensated to decompensated cirrhosis state. And usually when someone's decompensated, that's when we start thinking about and talking about a transplant evaluation, for example.

27:01
In terms of surveillance, the two main complications of cirrhosis that we can try to prevent are the variceal bleed or hepatocellular carcinoma, which can occur in patients with or without decompensated cirrhosis. They can have compensated or decompensated cirrhosis to increase the risk of hepatocellular carcinoma. So it's really important that we identify their cirrhosis stage in order to make our recommendations about doing upper endoscopy for varice surveillance, or hepatic imaging every six months for HCC surveillance.

27:39
So now having established that, let's move into the Hep C focused evaluation. So these are the things that I talk about with a patient when I'm first evaluating them after a new Hep C diagnosis, or if they're new to me. So first, I want to estimate when the hepatitis C was likely acquired, that just gives you an estimate of the duration of infection, whether it's chronic, whether it's acute, if they've had it for a long time. If they have had it for decades, that somewhat increases your suspicion that they are at higher risk of having developed cirrhosis up until this point, although it's not certain. You want to assess for ongoing risk factors because you want to counsel them on risk factors for transmission. We'll talk a little bit more about that. And then you definitely want to ask them about any prior work workup or treatment experience that they've had. So have they had a liver biopsy before? Have they previously been treated? Have they been exposed to DAA therapies. The liver biopsy will just help you know what their fibrosis stage is, and a lot of people that have had a prior liver biopsy have been treated. Because we used to do biopsies in people before they got started on treatment. But the prior treatment history is actually really important because that will help you decide what the appropriate

regimen is for your patient. And then I do a full review of systems where I am really focusing on symptoms that may be attributed to hepatitis C. So fatigue is a very common symptom of hepatitis C, when we had more restrictions on DAAs in California, severe fatigue could be one of the indications for treatment. So I would always make sure to document that if my patient had severe fatigue. But also rashes, joint pains, neuropathy and chronic kidney disease could be extrahepatic manifestations of hepatitis C. And then you also want to make sure that you do a review of systems for any of those symptoms of cirrhosis that I talked about. So did they have ascites? Do they have peripheral edema? Have they ever had a GI bleed? Have they had overt confusion, which is more extreme form of hepatic encephalopathy? Or have they had sleep reversal or foggy thinking, which is really milder hepatic encephalopathy.

29:54
We also talk with them about risk factors for fibrosis progression. So common in alcohol use, whether they have metabolic risk factors like diabetes or metabolic syndrome, whether or not they have co-infections that increase the risk of fibrosis progression such as Hepatitis B or HIV. These all could make you more suspicious that someone has more advanced fibrosis or cirrhosis. But they're also really important for counseling after somebody has achieved Hep C cure.

30:24
And then, like I said, I do a social history to ask about any illicit drug use for risk of Hep C reinfection or transmission to others. Ask about their social or living situation and their motivation and potential for adherence. And this may influence the regimen that you treat somebody with, some of the medications like Mavyret, for example, should be administered with food. So if someone has food insecurity, that might not be the best option for them. On the other hand, if someone has unstable housing and really wants to take a short of a treatment as possible because they're concerned about being able to hold on to their meds, Mavyret is an eight week course. Whereas sofosbuvir velpatasvir is a 12 week course. So I always try to gauge what's going to be the best regimen for my patient and what their preference would be, depending on their own circumstances, if I have a choice between the regimens. And then finally, you want to review their current medications. And I always make sure to talk about herbal supplements, over the counter supplements, and antacids in particular, because there could be important interactions with the DAAs, which we'll talk about at the end.

31:42
So that's the history and then when we do a physical exam, I'm really focused on any clues to the presence of cirrhosis. So palmar erythema, there is a picture of that here. It's where the palms on the hands get red, and that's associated with the high estrogen levels in cirrhosis. So that may be a clue that someone has cirrhosis. We also look for these spider telangiectasias which are also potential clues on the skin that someone has cirrhosis. Gynecomastia in a man can also be a clue, as can a firm liver edge, and then a palpable spleen, if someone has splenomegaly then you're also concerned that they have portal hypertension. And then of course, any of the signs of decompensation as well, which include jaundice, scleral icterus, pleural effusion so if you have decreased breath sounds particularly on the right side and they have an effusion that could be a hepatic hydrothorax. If you see ascites, here's an obvious

example of ascites. Or if you see caput medusa where you get the dilated superficial blood vessels as a result of portal hypertension. And then I always also check for asterixis and my patients because that's a sign of hepatic encephalopathy. And here on the slide is a little picture of how we do it.

33:00
Moving on to the laboratory clues of cirrhosis, one of the earliest clues will be thrombocytopenia. So as someone develops advanced fibrosis and cirrhosis, the platelet count may decrease. And that's often one of the first signs, so whenever I see a platelet count of less than 150 and somebody who I'm working up with hepatitis C, that always raises a red flag to me that they might have cirrhosis. The transaminases may be elevated in someone with Hep C, an elevated AST or ALT does not necessarily mean that someone has cirrhosis, and in fact, we often see normal AST and ALT in our patients with cirrhosis. And sometimes we refer to that as sort of a burnt out liver, all the inflammation is gone and now it's mostly just scar tissue. But one of the signs with the AST and ALT is when the ratio of AST to ALT is greater than one, that also raises suspicion that someone might have advanced fibrosis or cirrhosis. We see no albumin in our patients with cirrhosis. And then we can also see elevated bilirubin and an elevated INR, although that typically accompanies more advanced cirrhosis.

34:12
So even if I see a low platelet count, that doesn't necessarily tell me that someone has cirrhosis, I always do a non invasive fibrosis estimate. I always do this prior to treatment. And there's lots of different options. I'll go into some of the details of these. What I recommend to you guys is just pick the one that works for you, the one that's accessible to you, and just make sure that you do it in all of your patients. So you can use some really simple calculators using readily available labs as clinical information, like the APRI or the FIB-4. You can use a FibroTest or FibroSure, which is a commercially available test that uses a combination of different laboratory markers. It can be a little bit more expensive, but most insurances will cover it at least in my area. And then we'll talk a little bit more later about the imaging like the FibroScan and the ultrasound elastography.

35:02
But in terms of the really simple tools, the APRI stands for the AST to Platelet Ratio Index. And all you need for this is an AST count and platelet count, and you can go to this website that I included on this slide which is at the University of Washington. If you just type APRI calculator into your search bar, you'll come up with the University of Washington website. And you can plug in the numbers very quickly in clinic, and if it's greater than two, that is fairly specific for cirrhosis. If it's greater than 1.5, then you're concerned that the patient may have significant fibrosis or cirrhosis. The other calculator that you can also access on that site is called the FIB-4. And that also uses AST and platelet count, but also incorporates the ALT and the age. If FIB-4 is greater than 3.25, then you're concerned that the patient has cirrhosis, and you will treat them as if they have cirrhosis. The FIB-4 performs a little bit better than the APRI. But together, they predict advanced fibrosis with a positive predictive value of 93%. And what's really great about these calculators is that you're going to be getting these before you get anybody started

on treatment, so you don't have to get any fancy special tests. This is all going to be part of your pre treatment labs, that I'll talk about later in the talk.

36:25
In terms of imaging, the most common one that I use is the vibration controlled transient elastography or FibroScan. And essentially what that is an ultrasound based test, but instead of taking pictures of the liver, we have a patient lie down on the exam table as if they were to get a liver biopsy and the operator pushes a button on the probe and that sends a shear wave through the liver. And the ultrasound based probe will calculate the velocity of that shear wave. And so essentially, the more scarring there is in the liber, the faster the shear wave velocity, which gets correlated into liver stiffness value, so the higher the liver stiffness. So it's a pretty fancy machine, but we can do it in our clinic because we have a machine in our clinic and it gives us pretty pretty quick results. The ultrasound elastography uses that same principle of the elastic shear wave and calculating the velocity of that, there's a couple different versions of ultrasound elastography There's ARFI and then their shear wave elastography, this might be available to you in your radiology suite. And the advantage of these ultrasound elastographies is that if you get it at the same time, they're getting a regular ultrasound of the abdomen. So the FibroScan, you're not getting a regular ultrasound of the abdomen. Ultrasound elastography you're getting the pictures of the liver, and then you're also getting the liver stiffness measurement. So that's the appeal of that. And then magnetic resonance elastography is again the same principle, but it's done in an MRI scanner. And instead of having the probe, you have this sort of table tennis like paddle that goes over the liver, and that's what induces the shear wave. So you can interrogate a larger area of the liver, and it performs very well in estimating fibrosis and can be better in some patients that have a larger body habitus. The negative is that it is more expensive, and it's not as readily available.

38:34
And this is just an example of how the FibroScan or VCT is done. This is someone laying on the table and this is what the machine looks like. And here's the probe. And here's the normal liver, which is nice and smooth. So the shear wave moves through the liver slowly and you get a low liver stiffness measurement. And if there's cirrhosis, then the shear wave moves through the liver very quickly, and you get high liver stiffness. One other advantage of the FibroScan is that at the same time that you're measuring the shear wave velocity, you can also get an estimate of the fat content in the liver also known as hepatic steatosis. Because of the ultrasound waves that are going through the liver from the probe, if the ultrasound attenuates at a low weight through the liver, that suggests that there is not much fatty liver and so you would get a low controlled attenuation parameter value or CAP value. If someone has a lot of steatosis, that ultrasound waves attenuate very quickly and you get a high CAP value. So this is very valuable for me as a hepatologist because we see a lot of patients with fatty liver disease, and so we can get the FibroScan to get the liver stiffness and the CAP value at the same time.

39:51
So when somebody does have cirrhosis, then the next step that we do is we really want to estimate the severity of the cirrhosis. And the most common way that we do this in terms of pre Hep C treatment planning, is by using the Child-Turcotte-Pew score calculator. So I included all

the components of the Child Pew score on the slide here, you can again go to that University of Washington website, and they have this calculator there. So you don't have to memorize all of this. But it's a really handy tool. And you can quickly add up the different points to determine if your patient has compensated or decompensated cirrhosis. And the five main components are those two symptom components. So encephalopathy or ascites. You're given a one if you have no encephalopathy, and a one if you have no ascites. You're given a two if you have mild or moderate encephalopathy or ascites. And on this I include my patients, for example, who are well controlled, their encephalopathy is controlled on lactulose, or their ascites is well controlled on lasix and aldactone. And then you get a three if you have really severe encephalopathy or ascites. And then the other three parameters are the bilirubin, albumin, and INR. So you can quickly look at that from the labs. And so you add up how many points your patient has, and if they have mostly ones, except for 1 two, they'll have five to six points, and they're a Child A. They're compensated cirrhotic. If they have seven to nine points, they're decompensated. And it's really useful to add these up in your patients with cirrhosis, because they might not have overt symptoms of decompensated cirrhosis but when you add up the points, if they do have a low albumin or an elevated bilirubin, they actually may be decompensated based on the labs. And it's really important because that determines which treatment regimens are appropriate for that patient. When somebody has decompensated cirrhosis, there are fewer treatment regimens and the guidelines are a bit different, but you want to make sure that you avoid any protease inhibitors. So it's really important to calculate this. The Child C is the most cirrhotic. And those patients you probably know that they're decompensated, but it's still helpful, in my opinion, to do the calculations.

42:09
And I find that this is actually also helpful for counseling patients because usually, especially when they have a new diagnosis with cirrhosis, they have obviously a lot of questions and they want to know how severe is the cirrhosis? How bad is my liver? And I find it really helpful to be able to objectively add these up and then say, if I were to grade you from A to a C, A being best and C being the worst, you would be an A minus or you would be a B plus. And I find that really helps patients understand that cirrhosis itself is also a spectrum because sometimes when they hear F4, they're thinking I have stage four liver disease. And I like to explain to them that there's a wide variety of clinical presentations, even among people that have cirrhosis.

42:55
So finally, you've done all your history and your physical exam, and you determine if someone has cirrhosis or not, what are the labs that you're going to order before you start somebody on treatment? So these labs are actually lifted from the hepatitis C guidelines that you can access online. There's a new simplified algorithm that tries to make things really simple in terms of what you need. And basically, if they don't have cirrhosis, and they are treatment naive, all you need is some time before starting treatment you want to confirm their viral load. You want to get a genotype, that's actually not in this simplified algorithm, but I still need to get that for insurance purposes. And I'm not sure what it is for you guys, but usually we'll get a genotype so we'll know what type they have. And then you want to do one time HIV and hepatitis B surface antigen testing, because you want to know if they're co infected with HIV or Hepatitis B. I also do a full Hep B serology so that I know if someone's immune to Hepatitis B. And I also check a hepatitis

A IgG, so I know if they're immune to hepatitis A, because if they're not immune then I'll recommend vaccination for hepatitis A and B.

44:04
So that's time before starting treatment, and then within six months of treatment initiation, you should get a CBC, a creatinine, and a liver panel. So that includes the ALT AST, albumin and bilirubin. And all of these things will give you the information that you need to calculate a FIB-4, so that you can quickly calculate a FIB-4. You will need their age of course, but you'll be able to calculate then whether or not they're greater than 3.25 or less than 3.25 and confirm that they don't have cirrhosis. And then finally, if you're about to start treatment in a woman who's of childbearing age, you want to get a serum pregnancy test and counsel about pregnancy risk of Hep C medication.

44:45
If they have cirrhosis, the algorithm is very, very similar. There's just a couple caveats. So anytime before starting treatment, you still want to get the viral load. You definitely want to get the genotype if they have cirrhosis and you're planning on using sofosbuvir velpatasvir for reasons that we don't have to get into. And again, you want to get the HIV test and the hep B surface antigen test. And then the distinction here compared to the prior slide is that instead of within six months of treatment initiation, within three months of treatment initiation you want to get a snapshot of the labs. So CBC, creatinine, and the liver panel, and then you also want to get an INR, which you don't need to get in a non cirrhotic patient. And all of this information will be enough for you to calculate the Child Pew score and make sure that they're still compensated. And then again, the serum pregnancy test and counseling if there's a woman of childbearing age. The additional pre treatment assessment in the patient with cirrhosis, like I said, you're going to want to calculate the Child Pew score to make sure that they're not decompensated. And then you also want to get an ultrasound of the liver within six months because once somebody has cirrhosis, they meet the guidelines for HCC screening, and that includes an ultrasound of the liver every six months. The advantage of the ultrasound is it can also assess for subclinical ascites.

46:12
Okay, and then the final piece before you get someone started on treatment is the medication reconciliation. So like I said before, you want to obtain a thorough medication history, including over the counter medications and herbal supplements. At our practice, we recommend that our patients discontinue herbal supplements while they're on treatment. And then we also caution our patients regarding acid suppressive medications because the acid suppressing medications particularly the PPIs can reduce the absorption of some of the DAAs, particularly about velpatasvir and ledipasvir, possibly also glecaprevir. You don't have to memorize all the drug drug interactions, there are some really great resources. One of my favorites is the University of Liverpool Hepatitis Drug Interactions, which is this website. And I'll show you a screenshot in a couple of slides. But this is really, really nice, because you can just put in the Hep C meds and you can put in all of your patient's meds and you can look for any DDIs. You can also of course, look into the package inserts to see if there's any drug drug interactions or drug databases. And

then if you do have patients on herbal supplements that don't want to stop, there are some resources to look up natural medicines.

47:26
This is from the AASLD IDSA hepatitis C guidance. And I won't go through all these details, but they do show some of the common drug classes that have been associated with some of the drug drug interactions with the DAAs. And the most common are the acid reducing agents, like I said amiodarone with the sofosbuvir. The anticonvulsants, often will have, not always, but often will have drug drug interactions, you want to make sure you run everything through the interaction calculator. And then another common class is the statins. Sometimes you have to reduce the dose of a statin or switch to a different agent. Or sometimes you might want to just stop a statin completely while someone's on their Hep C treatment.

48:13
And this is just a screenshot of that University of Liverpool website that I love. So you could put in the hepatitis drug, like I was putting in Mavyret here, and then the co-medications that your patient is on, and then it gives you really red, orange or green. So hard drug drug interaction, don't co-administer. And you could look for an alternative regimen. A potential interaction, and if you click on more information it gives you all the information about that. For the green light, no interaction expected. This is really a very useful resource. I use it pretty much in all my patients who I'm getting started on treatment who are on any other medication.

48:59
So finally, pretty much everything that I've talked about can be summarized in this slide before you're starting someone on hepatitis C treatment, here are the steps that you need. So you'll determine the genotype and viral load, you'll determine if they have cirrhosis, yes, no, you'll determine their treatment history. And then other sort of circumstances, if they're a special population, like they have decompensated cirrhosis, if they have drug interactions, etc. For us in California, we have to also consider the insurance preference because most of the payers have formulary preferences. And then after all of that information, you can determine what your Hep C treatment and what the duration will be.

49:42
And then finally, these simplified algorithms that have all of the assessment for patients with or without cirrhosis can be found at the Hep C guidelines website and they have these one page PDFs that are really handy that you could print out and keep them at your side so you can always reference them if you have any questions. So I will stop there and answer any questions that you have. I hope my internet lasted, I saw that it was a little unstable at a couple points. But I'm happy to answer any questions in the chat or if you want to ask them out loud.

50:16
Thank you so much, Dr. Price. There were no problems at all with the connection. It was excellent, comprehensive presentation. So I'd like to invite individuals to type questions into the q&a or into the chat. I don't think we have the option of unmuting you, but feel free to try to unmute yourself and speak up if you have any questions. We'd love to hear them directly from

you. But otherwise, please feel free to put them into the q&a or the chat. Dr. Price, I'll start off with one question. Is there ever an indication in the pre treatment assessment for ordering AFP as a part of the standard labs that are ordered? You certainly did not include that, but I've heard some people ask that at times.

51:09
Yeah, I didn't include that, but that is a great question, that's indicated if someone has cirrhosis, and that's part of the HCC surveillance. So it's not necessary before you start Hep C treatment. But with the ultrasound that I get in my patients with cirrhosis, I get an AFP as well.

51:26
Thank you. Okay, great question. Do patients need to be sober to take Hep C treatment?

51:36
Great question. The answer is no, they don't have to be sober. The caveat is it depends on where you live in terms of authorizations from insurance. But from a medical perspective, there's very good studies now that show that the cure rates are quite high even people who are still drinking alcohol are still using illicit drugs. As long as they're able to take their medications and complete their treatment course. We used to have a lot of restrictions in terms of sobriety for accessing medications, but in California at least, those restrictions were liberalized several years ago. And we've been able to successfully get people through treatment and cured, even if they weren't sober.

52:24
Thank you. And a follow up question from Katherine is if homelessness is one of the biggest determinants of whether someone gets treated?

52:38
Well, that's another really good question. If you look at people experiencing homelessness, the treatment uptake rates are much, much lower than in people that have housing stability. And there's a lot of reasons for that, but homelessness itself should not preclude treatment. And we actually in San Francisco have a lot of outreach efforts to treat Hep C among people experiencing homelessness. One of the biggest barriers that we have is reaching people. So it's hard for people to make it into, you know, the viral hepatitis clinic, for example. So we're doing a lot of community based testing and treatment. And that's actually been very convenient for folks. But another challenge that they have is holding on to their medications. So in San Francisco, we have a few different programs trying to reduce that barrier. So there's one group that offers lockers, for example, that people can store their medications. We have a mobile van, where we'll bring out the medications on a weekly basis. And then we fashion these little like necklaces for people so they can hold on to their meds. But that's been the biggest challenge in our patients experiencing homelessness.

53:54
Thank you. Silvia Fallon is asking what are the major contraindications, if any, to starting someone on Hep C treatment?

54:04
Yeah, that's a that's a another good question. Provided there aren't any drug drug interactions, right? And so all that testing and medication reconciliation that you did, there's no barriers there. There's a couple scenarios that give me pause before I start a treatment. One is if someone's life expectancy is less than a year and treatment is not going to affect life expectancy or quality of life. That's a main contraindication. The other larger category of patients that I see is actually if somebody has end stage renal disease and is on dialysis, and they're awaiting a kidney transplant, I will hold off on treating their hepatitis C because that will allow them to accept the hepatitis C positive kidney, which will shorten their waiting list time in our region at least by several years. So I will do the whole fibrosis assessment, and as long as they don't have cirrhosis and really as long as they don't have significant portal hypertension, I tell them to go ahead and get their kidney transplant first and then I'll treat their Hep C. Those are the two main ones that I see. So, not very many contraindications.

55:16
Thank you. Question from Ronan Arnon. What about Hepatitis B assessment if positive?

55:27
Yeah, so if Hepatitis B surface antigen is positive, then you would follow that up with a Hepatitis B DNA, or an E antigen and an E antibody, just as you would somebody who didn't have hepatitis C who was diagnosed with hepatitis B. So I hold off on treating the Hep C until I've figured out their Hepatitis B, where they are in natural history of hepatitis B and what sort of phase of hepatitis B they're in, and then I determine if they need treatment for hepatitis B. Most people will say if they're Hepatitis B positive, they should just get started on hep B treatment before you treat their hepatitis C. I occasionally get patients that really don't have a treatment indication for their Hepatitis B, they have very low viral load, their ART is normal, and they don't have any fibrosis and certainly no cirrhosis. And so in those patients, I sometimes will treat the hepatitis C and just monitor their Hepatitis B really carefully without treating them first.

56:26
Thank you so much, Dr. Price.

[End]