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Management of the Patient with Chronic Hepatitis C

Announcer:
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Dr. Lim: It's my pleasure to introduce you to our program today, which will be addressing the topic "Management of the Patient With Hepatitis C." My name is Joseph Lim. I am Professor of Medicine and Director of the Viral Hepatitis Program at Yale University and I'm joined by my colleague, Dr. Steven Flamm, who is the Professor of Medicine and Surgery at Northwestern, where he serves as Medical Director of the Liver Transplant Program. So, welcome Steve.

Dr. Flamm: Thank you, Joe.

Dr. Lim: It's going to be a lot of fun to have a conversation today about some basic topics including epidemiology, diagnosis, management of a patient with hep C, including assessment of liver fibrosis. The global prevalence of hepatitis C is substantial, an estimated 71 million persons. An estimated 2.4 million persons here in The United States, based on the most recent NHANES survey, approximately three-quarters of these individuals are baby boomers. The current recommendations have largely been focused on screening individuals for hepatitis C if they're born between the years 1945 and 1965. However, there has been a lot of movement to expand screening recommendations. And so Steve, What do you feel are the key precipitants for the change in screening recommendations and what are some of the populations that we really ought to be focusing more on in the screening process?

Dr. Flamm: That's a great question, Joe. You know, as the therapies for hepatitis C have improved, one of the goals – not only in The United States but all around the world – is to eradicate hepatitis C. And what's become clear in these last 5 to 10 to 15 years is despite the availability of diagnostic testing for hepatitis C, we in The United States still have not diagnosed around 50% of the people that actually have it.

As you know, about six years ago, they augmented the recommendations, the CDC did, by telling us that we should screen, in addition to people that had risk factors for acquisition, people born between 1945 and 1965 because, as you just mentioned, three-quarters of the people in this country that have hepatitis C were born in that cohort. But still, because of the opioid epidemic where so many young people are now acquiring hepatitis C, we were missing many, many patients with hepatitis C. And that's why The United States Preventive Services Task Force and the CDC have all begun within the past six months to recommend screening everybody 18 years and older.

Dr. Lim: Absolutely. I think there's a recognition that if we're truly going to have an impact on trying to eradicate hepatitis C here in The United States at least, we need to find patients who remain undiagnosed. The main surveys exclude some of the highest populations – persons who inject drugs, incarcerated, institutionalized, pregnant women potentially as well. One of the things that we can really hopefully highlight here is that it's not just screen baby boomers anymore. And so the next question is once someone has done their job, they have screened appropriate individuals for hepatitis C with antibody and that test is positive, what are the next pieces of information

that you would want to obtain so you can reach a treatment decision?

Dr. Flamm: Once you have a positive screening test, what you need to follow with is the confirmatory test. So, prior to starting therapy on a patient, you need to check the hepatitis C RNA test to confirm infection.

Dr. Lim: So, once the RNA is positive, what are key variables or pieces of information that you need before you start treatment?

Dr. Flamm: One of them is the genotype. There are six all around the world and when a patient has hepatitis C, they usually have one specific genotype. In the past, the genotype dictated which antiviral regimen you use. Nowadays, though, there are what we call pangenotypic regimens, meaning regimens for treatment of hepatitis C that cover all six genotypes. We still check genotype most of the time, although it really doesn't impact therapy too much.
Several years ago, FDA became aware of people with hepatitis B infection that was quiescent but still present, that activated when patients were treated for hepatitis C. So, we now are guided to check hepatitis B serologies before we treat patients for hepatitis C and if the hepatitis B surface antigen is positive, those are patients that probably would best be cared for under the direction of a hepatologist.

We also need to determine the amount of fibrosis a patient has in their liver. This has some prognostic value with treatment, but if patients have cirrhosis, and many asymptomatic patients can have advanced liver disease, these are patients that are at risk for liver cancer and should be screened with ultrasounds or cross-sectional imaging. We want to find out about substance abuse, and that includes alcohol and what medications they're on because there are some medication interactions that are important to know prior to starting therapy.

Dr. Lim: Absolutely, and I think that's something that is really important because once they're diagnosed, many patients want to get started on treatment but part of our job is to make sure that we treat responsibly. In regards to the drug-drug interactions, there is a website that many of us use at www.hep-druginteractions.org. Now, I want to go back to liver fibrosis and assessment for cirrhosis.

Dr. Flamm: We used to use liver biopsy in all patients with hepatitis C. But we've learned that there are non-invasive ways to assess fibrosis. There are serum blood tests that are readily available around The United States and they're not too expensive.

There's a newer technology that is essentially detecting how stiff the liver is. A stiffer liver has more fibrosis and a less stiff liver has less fibrosis. Many centers around the country do have the technology to assess fibrosis with transient elastography. There are radiologic techniques such as MRE, which is MRI but basically for elastography. It's extremely important, Joe, to determine if a patient has cirrhosis or near cirrhosis when you treat them for hepatitis C because they are at increased risk for hepatocellular carcinoma and those patients should be screened for liver cancer, even if later you cure them.

Dr. Lim: Absolutely, that's such an important clinical point. Now, regarding the assessment of fibrosis, I could not agree more that there's a lot of heterogeneity. There are a subset of patients who have obvious clinical evidence of cirrhosis at baseline and those probably don't need a lot of additional testing. But, for the majority who don't have obvious cirrhosis, our approach has been to combine two non-invasive tests, usually one of which is serum based using a serum assay, and one that's elastography based such as transient elastography or MRI elastography. And if there's alignment between the two, that alignment suggests an accurate estimate of fibrosis. But, if there's a lot of disparity, if something suggests mild fibrosis but the platelet count is on a low side, that's where we tend to consider a liver biopsy. At the end of the day, what we're trying to do is identify patients with cirrhosis.

Let's go to the next topic, which is addressing the choice of antiviral agent. I do want to highlight for our listeners that there is a website that is an incredibly useful resource, www.hcvguidelines.org, which is updated on a regular basis to highlight emerging evidence and formal recommendations by the liver and infectious disease societies. That being said, what are key variables that influence your choice of antiviral agent?

Dr. Flamm: That's a great question, Joe. In many cases in The United States, the choice of an antiviral regimen is made by third-party payers for us. But in an ideal world, we should choose a pangenotypic regimen that covers all six genotypes. The World Health Organization has made such a recommendation. There are two approved for initial therapy of hepatitis C. One is glecaprevir and pibrentasvir, and one is sofosbuvir and velpatasvir. Both of the regimens are approved in HIV. Both are approved with compensated cirrhosis. Both are now approved for renal failure. So, there aren't a lot of issues that necessarily instruct one or provide impetus that you would use one regimen versus another.

One, though, is important and that's the presence of decompensated liver disease. If a patient has any of the complications of cirrhosis such as ascites or hepatic encephalopathy or esophageal variceal bleeding in their past, these patients are considered decompensated. Regimens that have a protease inhibitor in them are not recommended or contraindicated in such patients because there were reports in years past of patients worsening in regards to liver disease. You use a regimen that doesn't have a protease inhibitor, like sofosbuvir and velpatasvir.

And then you mentioned earlier drug-drug interactions. Any other comments, Joe?

Dr. Lim: No, I agree entirely. We're now in 2020 in a scenario where basically we have two regimens that are applicable to nearly every population and subgroup and, with the exception of decompensated cirrhosis, even for patients with HIV co-infection. Historically, they've had lower rates of response and were viewed as a special population. The only thing special or unique about this population now is probably the drug-drug interactions. And finally, I think the payer issue is one that unfortunately persists to this day and both the private payers and public payers as well, and there's significant heterogeneity across states in terms of access to HCV DAAs. Based on issues such as fibrosis, sobriety, some payers will require the prescription to be given by a specialist.
So, I do want to segue to how you manage patients on treatment and post-treatment. What is your approach at Northwestern in terms of which labs you check, how often, when do you see the patient?

Dr. Flamm: Another great question, Joe. You know, these regimens are so well tolerated that you really don't have to check, in uncomplicated cases, blood tests at all between the beginning of therapy and the end.

At Northwestern, after we have those initial blood tests that we discussed earlier and we commence therapy, nurses at week four of therapy do a liver panel and they do the hepatitis C RNA test. The vast majority of the time that hepatitis RNA test comes back negative. This is highly motivating. Patients become even more motivated to take their medications every day and finish therapy off, which optimizes chances of success.
We then don't check blood tests again until the end of therapy, at which time again a liver panel and hepatitis C RNA test is obtained, and then we check them again 12 weeks after medications are discontinued to determine if a patient has a sustained virologic response. Now again, there are more complicated cases such as patients with hepatitis B exposure. What do you do at Yale?

Dr. Lim: We have a very similar approach. I must admit that we were relatively late adopters of trying to scale back the visits and laboratory monitoring, but now in 2020, we are largely seeing patients on an as-needed basis at month one and at end of treatment. But, those are really driven by individual patient issues such as concerns for adherence, side effects or specific labs that were potentially abnormal. We do still do the lab tests at week four and if the RNA is undetectable, we don't see them again or check labs until 12 weeks after treatment.

Now, the definition of a sustained virologic response or SVR is 12 weeks after completion of therapy and obviously most patients are going to be undetectable on treatment and will go on to achieve SVR 90-95% of the time. If you have someone who does have SVR 12, at what point do you feel comfortable discharging them? And what are sort of the recommendations that you give to your patient at that time point?

Dr. Flamm: If a patient is a non-cirrhotic patient, a patient that I'm not concerned that has risk factors to get hepatitis C again, because you can get hepatitis C again even if it's cleared, in a patient that we think doesn't have a second liver disease like alcohol use or fatty liver, non-alcoholic steatohepatitis or something else, once they achieve SVR, one year after that I just do one more hepatitis C RNA check to ensure that they don't have a late relapse, which is very rare, and then I discontinue them from the practice.

If they do have risk factors for transmission, they are reassessed either by me or their primary care doctor for hepatitis C again on an ongoing basis. If they have a second liver disease, they are reassessed and lastly, if the patient has cirrhosis and they are cleared – I touched on this briefly earlier – they still remain at increased risk for hepatocellular carcinoma and they still need to be screened. This is one of the biggest mistakes that I think I see in patients that are managed elsewhere, a cirrhotic that's cleared that no longer is screened for hepatocellular carcinoma. The sad thing is those patients can develop HCC years later and if it's not picked up early by screening, often is a terminal diagnosis when it presents. So, it's very important to remember this and to keep those patients in the practice.

Dr. Lim: Oh, I couldn't agree more. The number one take home point here for this topic, is that after treatment is completed, our work is not done in those patients who have advanced disease defined as stage 3 fibrosis or cirrhosis. And the guidelines still do recommend that we continue liver cancer screening twice annually with ultrasound, with or without AFP, indefinitely.

Similar to your practice, we are checking a year later with HC RNA and LFTs, and we actually add on some type of fibrosis assessments with the idea that if patients have undetectable virus, normal liver enzymes and no evidence of advanced fibrosis, we will generally discharge that patient from the clinical practice, but of course with advisement to continue avoidance of significant alcohol consumption and to avoid significant weight gain, recognizing that there is a subset of patients who actually still have positive LFTs, usually from fatty liver or something else, who may require longitudinal care. But with that exception, we generally are trying to identify patients who we can discharge from the specialty clinic. I'd like to go ahead and close but I just wanted to see whether any final words of wisdom, Steve.

Dr. Flamm: Just, we all around The United States have to work on improving our diagnosis of hepatitis C and really try to have these new recommendations for screening have traction, and then we need to treat as many people as we can. Even people that are using drugs or who are consuming alcohol, if they are adherent – by the way, we certainly need to try to counsel them to not use drugs and to

not use alcohol. These are patients that we should actively try to treat and clear hepatitis C in. Hepatitis C in conjunction with those other problems is very deleterious to the liver and we can cure these patients and improve their clinical outcomes over time.

Dr. Lim: Absolutely and in fact from a public health perspective, this can be viewed as treatment is prevention, trying to eradicate hepatitis C within substance use communities and that's a critical point because I think that we're going to see a change in perspectives within our community that allows for treatment of patients, even with active substance use rather than precluding them. So with that, I thank you very much, Steve, for this fantastic conversation.

Dr. Flamm: Thank you. Thank you, Joe.

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