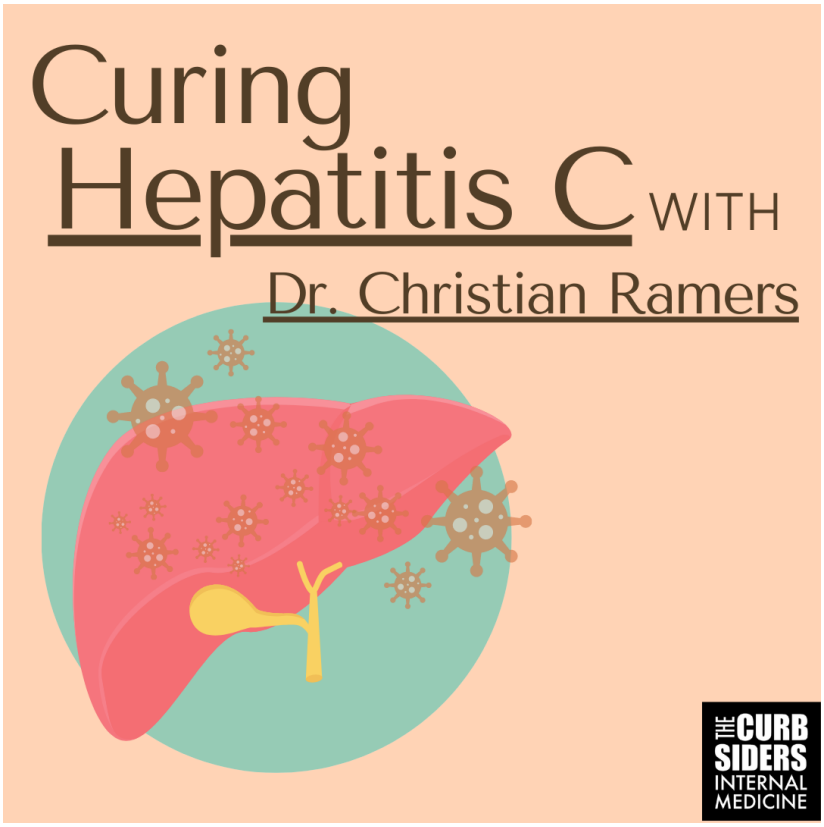
#329 Curing Hepatitis C



[Disclaimer]

Matthew: Well, Paul, we're back.

Paul: [laughs] Good energy, yeah.

Matthew: Yet again, it's a weeknight, we probably should both be in bed, but who needs to sleep? This is The Curbsiders. I'm Dr. Matthew Watto, here with my great friend, Dr. Paul Nelson Williams. Tonight on the show, we're going to be talking about a simplified approach, hopefully inspiring some of our listeners to treat hep C in primary care. We have a great guest, Dr. Christian Boyd Ramers. But Paul, before we get to that, and before we introduce our wonderful guest cohost, can you tell people what is it that we do on the Curbsiders?

Paul: Sure. Happy to as always, Matt. As a reminder, we are *the* internal medicine Podcast. We use expert interviews to bring you clinical pears and practice-changing knowledge. As you alluded to, we are joined by the great Dr. Emi Okamoto, who produced and wrote this episode. Emi, how are you?

Emi: Great. Tired, but great, [laughs] [crosstalk].

[laughter]

Paul: Why don't you tell us who we talked to and what we talked about?

Emi: Yeah, thanks. We had a great conversation with Dr. Christian Boyd Ramers. He's a Med-Peds trained physician from Duke, who completed infectious disease fellowship at University of Washington with an MPH in Global Health. He brings a passion for infections and addictions to his work at the Family Health Centers of San Diego, which is a large federally qualified health center system. He's a husband, father, front yard farmer, amateur road cyclists, half marathoner and former rock star. And he teaches us how to cure hep C. It's easier than you think, and we can get towards that dream of elimination. So, without further ado, I hope that we can deliver a great episode.

Matthew: A reminder that this and most episodes are available for free CME credit at *curbsiders.vcuhealth.org*. We wanted to mention that Dr. Ramers has acted as a speaker, consultant, and investigator with both Gilead Sciences and with AbbVie. However, no tradenames were used on this episode, and we discussed a balanced range of therapeutic options in the discussion.

Christian, we've been talking for a while now and I'm sure you're happy to get started. Can you give the audience a one-liner about yourself? Maybe tell them something about what you like to do outside of medicine?

Christian: Yeah, sure. It's great to be with you guys. My name is Christian Ramers, 46-year-old male, Caucasian, Cuban American. I live in San Diego where it's sunny almost all year, so I grow as much food as I can in my front yard raised beds. I got broccoli, peppers, arugula, lettuce, artichokes going right now and a couple citrus trees that are not performing all that well but a fig tree that puts out about 50 pounds of figs every year.

Matthew: Sounds like a dream.

Christian: Yeah, that takes a lot of my time. And then the rest of time I'm either running or riding a bike around San Diego.

Matthew: Paul, I think now for six years, we've been on record saying we both wanted to start-- yes, many of our guests are gardeners. Paul and I always say how we admire that. I think one time Paul grew a tomato that a squirrel promptly ate. So, just great to hear that you're doing some real farming there, Christian. That's fantastic.

Christian: Front yard farming, it's the wave of the future.

Emi: What do you do with the 50 pounds of figs?

[chuckles]

Christian: Yeah, fig jalapeno jam is one of my favorite things to make, and my next band name actually I should say.

Matthew: Yeah.

Christian: We eat figs raw. We put goat cheese on them. We put them on pizza. Lots of fun with figs.

Matthew: Paul, everyone's seems to be doing so much better than us. What is happening?

Paul: [laughs] That's a low bar to clear. I do want to follow up, because I noticed in your bio, you former rock star is thrown in there, and you mentioned bands. Now that you've introduced the topic, I do want to follow up on that. So, tell me about your music career.

Christian: Yeah. I identify as a drummer who plays a little bit of guitar and sings around the campfire sometimes, but I've been playing drums all the way through high school and college. And college, I went to UCLA, and there's quite a scene on the Sunset Strip, and my band called Hiatus got to the point where we were gigging pretty regularly at Whiskey and the Roxy and Troubadour and those places. And then, med school happened [chuckles]. And just recently--

Paul: [chuckles] Yes, it does. Yeah.

Christian: Recently reconnected with a couple of friends, spouses of my co-attendings here, and then that got killed by COVID. That was another band called Half Car Garage. Our practice space was literally a half of a garage, not very conducive to social distancing. And so, we're on pause right now. I've been playing a lot more acoustic guitar just in the house since then, but I am, as I said, a drummer by trade.

Matthew: Yeah, screaming in each other's faces in a small, enclosed space is the perfect way to spread it.

Christian: Exactly.

Matthew: That's a shame. Well, it seems like maybe you'll be getting back to some rocking in the near future here.

Christian: I certainly hope so. Yeah.

Paul: [laughs]

Matthew: Okay.

Paul: Some rocking. That sounded very [unintelligible [00:05:42].

[chuckles]

Matthew: I'm hip.

Paul: [laughs] Hello, fellow kids.

Matthew: Yeah. Paul, I've given up on trying to be cool. Now I'm more just into embarrassing my children. So, I feel this is on brand.

Paul: You've achieved your final form.

Matthew: Yes. [chuckles] My final. I don't think final form, Paul. Got some weird stuff as an old man is going to start happening. We'll see what that's going to be like. I'll become more and more eccentric. Emi, before we get on to the first case, did you want to ask anything else? Or, should we get on?

Emi: Christian, do you have any books, movies, shows you've recently got into or you could recommend to our audience?

Christian: Yeah. I got asked that recently. I haven't read much other than COVID for the last two years, but I do have a recommendation and it's timely. It's *Mountains Beyond Mountains*. The story of Paul Farmer. I trained at Duke, he was a Dukey as an undergrad, real inspiration for me to go into infectious diseases and global health, and just a huge loss to the community. There's a chapter in there called "A Light Month for Travel," where I think he was on four continents in one month doing work in Peru and Rwanda and in Haiti, as well as attending in Boston, and so just a true inspiration in a major loss. I know a lot of other medical people that were inspired by that book. If you haven't read it yet, I would suggest that.

Matthew: Well, I think, probably, Paul, we can't do Picks of the Week tonight, so we should probably get to the case because we want to make sure we get Christian-- I'm sure he's got some really great dinner from his garden that's going to be happening tonight, so we probably should move on.

[silence]

Emi, do you want to read the first case from Kashlak?

Emi: Yeah. So, we have Theo. He's a 58-year-old man with obesity and well controlled hypertension and hyperlipidemia. He's on lisinopril and atorvastatin. And he recently moved to the area. He opts for some routine screening and you get an HCV, hepatitis C virus antibody, based on an EMR pop-up recommendation. So, that HCV antibody results positive. He denies any past history of drug use, tattooing, or other exposures. So, Christian to start us off, who should we be screening for HCV in the first place?

Christian: Easy answer here, it's basically everybody, all adults. This is something that I think flew under the radar as COVID was really taking everybody's attention. The US Preventive Services Task

Force, the CDC, the AASLD, IDSA guidelines essentially all aligned, slight differences in the details of each of them, but essentially all three of them aligned and said, "We should be screening all adults universally for hepatitis C. And there's a lot of rationale behind that, mainly because it's a curable disease now, and you can prevent morbidity and mortality. And we're not very good at deciding who really should be screened. Previous to this recommendation, it was really risk factor based screening, and then age cohort based screening, where we had the baby boomers born between 1945 and 1965, that were recommended to be screened, as well as anyone who either admitted to you or-- I was comfortable telling you that they had a major risk factor for hepatitis C.

Hepatitis C is one of those diseases that it's not always fun to talk about. If you're seeing a patient in primary care, and you have 20, maybe 40 minutes with them, it's not the first thing that comes up in conversation is, "Yeah, I actually got a tattoo in my cousin's Winnebago," or, "I spent some time in prison and shot some drugs." So, the idea that a clinician could be, or a patient can be comfortable enough to tell a clinician, those risk factors that really didn't work all that well. So, risk factor-based screening, we think missed a whole lot of people. With these recommendations, it really accounts for the idea that we should just be making this routine part of primary care. Essentially, all adults should be screened at least once. So, this is pretty well aligned with HIV screening recommendations now. And then those who have additional risk factors, this is where you get into a little bit of nuance differences between the guidelines of USPSTF and CDC. But additional risk factors, such as people that have ongoing risk, injection drug use, sexual partner with hepatitis C, that type of thing, or an actual event, like a needle stick in a hospital that would warrant additional screening.

For high-risk groups, we would recommend annual screening, that would be people who inject drugs. Actually, men who have sex with men as well should have annual screening, people living with HIV, dialysis patients, annual screening. And the idea is that we've been missing a lot of people and just need to be finding them.

Matthew: Do you recommend using the hep C, so the hep C antibody with the reflex to PCRs, that seems like the most efficient way to go, so you don't have to worry about reordering the second test after the first one's positive?

Christian: Yeah. We now have substantial published evidence that doing an antibody first, waiting for that to come back, bringing the patient back to get a viral load is resulting in substantial loss of along the cascade. We want to get from point A to point B, which is sort of diagnosing the hep C and then treating it, and we've made it too complicated. We've put all these barriers and all these steps in the middle. And there's something quick and easy that we can do, which is check the box under EHR that says "reflex antibody to viral load" that literally just takes one of those drop off points and eliminates it completely.

Matthew: Yeah. Paul, have you had this happen where you get the patient that doesn't really seem to have a reason they come back with a positive antibody?

Paul: Yeah. Well, sure, constantly. The other thing is, as we're getting better at screening, I'm not sure my particular branch of Kashlak, a lot of folks who come to the ER just get automatic screening as well.

And so that I'm seeing these people on follow up who have positive tests that need to address and the risk factors are not really there. They're just caught because they happen to make their way through the health system. So, that seems to happen a fair amount.

Christian: There's two additional thoughts on here I wanted to get to. This case, Theo is a guy with no stated risk factors. As I mentioned that maybe because he's not comfortable telling you, it may be that he doesn't remember. But that's really the point, is that we're not really good at identifying risk factor-based screening. So, this is why we should do it universally. And the second is, there are several unique situations where it still is warranted to do only an antibody test first and then a viral load. And that is if we're going out to the community, because we have now rapid antibody tests. So, we can do an antibody test and get it back in 20 minutes. We're doing this at our syringe exchange. We're doing this at methadone clinics. Really getting out of the traditional model of sitting back in our offices and waiting for patients to come to us. If we're going to push towards finding people who have not been found yet or who the system hasn't served very well, or who don't go and get their regular annual checkups with their providers, which is increasingly the population affected by hepatitis C. We need to get out of our comfort zone and get out onto the streets. Rapid antibody tests are a very important tool for that.

Now, what you do need to do there is immediately have a way to draw that person's blood, because if you have results in 20 minutes, it's positive. You still don't want to have that person lost between antibody and viral load testing. So, we tested our local syringe exchange, and the ones that are reactive are positive immediately they're getting their blood drawn.

Matthew: How are you collecting the rapid test? Is it a blood test or a swab? I'm actually not familiar.

Christian: It's a little confusing, because oral is in the brand name of the actual test, but it is a blood-based test. So, it's a little finger stick on the device, and then 20 minutes later, you have a result.

Matthew: Okay, great. That sounds something, probably most primary care clinics don't have that, or at least I haven't come across it. But it sounds, like you said, if you're doing community outreach, it makes a lot of sense to do that sort of thing. So, for this person, if we were seeing him, how might you talk to him about this positive result? Let's say that we didn't have the reflex test ordered. So, we just have a positive antibody and a freaked-out patient? How might you counsel?

Christian: The language that you use is really important here, and really what an antibody test tells you is exposure. We can tell him, "Look, we don't know for sure that you have active hepatitis C, but it certainly looks like you have been exposed. And we'll have to wait for the viral load to see if it's really active." I think it's worth stating that, he doesn't have any known risk factors, he's been screened because of universal screening here, this is great. The EMR pop-up, I know that was mentioned in a disparaging way, but it actually serves a good purpose here. But I also wanted to talk just briefly about, does he fall into any specific risk factor group, and he actually does, being of relative baby boomer age. And the reason baby boomers were initially targeted by the first round of CDC guidelines was because of risk factors from a long, long, long time ago. And that is that tattoo parlors.

Tattoo parlors didn't become sterile facilities really until the 90s. And that happened in a very disorganized way across the country, really run by local county public health programs and local jurisdictions. Anybody that has had a tattoo in the last 30, 40 years, or really forever, is at risk of hep C transmission through the ink because hep C is such a robust virus that it hangs around for hours, and hours and can infect people that way. Those of you going to get tattoos, you should ask and make sure that they use sterile needles and don't reuse the ink.

Then, the other reason that baby boomers are so highly affected is the blood supply was really contaminated, essentially, with hepatitis C, and there were years where 300,000 people per year were infected. Until hepatitis C was identified. I always quiz my residents and medical students on this, "When was hep C identified?" And they say, "Oh, 1952," or something like that. They identified it in the late 90s, and mid-90s, actually. I was born well before the 90s. If I got into a car accident and needed a blood transfusion when I was a kid, that's a risk factor for hep C transmission. And, of course, baby boomers were young adults in the 60s, 70s, 80s, really, before hep C was even named or identified. They used to call it non-A, non-B hepatitis.

Matthew: Do you think this is going to become a rare infection, since we have such good treatment now, we're doing universal testing?

Christian: Yeah, I hope so. This is something that Paul Farmer's colleague, Jim Kim, would call a "knowledge implementation gap," we know what to do. It's easily treatable. It's easily curable. Our therapeutics are fantastic, 95% cure rate. We just need political will. We need all of those organizing efforts to rally behind the idea of eliminating hepatitis C. And the World Health Organization has done a lot of that. The CDC is division of viral hepatitis has been trying to rally that as well. It's definitely possible. The fact that COVID has set us back a lot, we've had a lot of more injection, drug use issues, and fentanyl deaths, to be honest, and a lot of people using drugs, heroin and other opioids, it's a little disappointing. But the answer to that is to get more people comfortable treating in their primary care office, and get more people comfortable treating different types of patients. And that's what I hope to talk about a little bit later is that, traditionally, you would say, "I'm going to make this patient prove to me that they're going to be a real goody two shoes patient and they're going to come to five visits on time, not late, and show me that they're a good patient." And we just really can't operate in that model anymore. If we're going to reach this this dream of elimination, we need to get out of our comfort zones and entry people that aren't sort of the model patients. We need to meet people where they are on the street.

I'm sworn to never end a sentence in a preposition because I'm married to an English teacher. So, don't say "meet people where they're at." It is "meet people where they are," and get out and entry people in mobile clinics, in prison, on the street. Get out of our comfort zone to, to treat those people. If we make that cognitive leap, and we drop our judginess at the door, we can get there. I'm an optimist. I'm hopeful being in this field, you have to be an optimist. And then I hope we'll talk later too about. It's not just about the virus, it's not just about the liver, this whole idea of treating and curing somebody from hepatitis C, has amazing collateral benefits. And I've seen it over and over again, anecdotally. I'm trying to think of a way to design a study to show this, but there are amazing things that happen in people's lives once you cure their hepatitis C.

Matthew: I'm making a note to try to swing back to that as we get on in the case. Emi, Do you want to read the next part here?

Emi: Yeah. For Theo, he had hep C antibody positive and you get a reflex viral load, you were able to call the lab fast enough. And it comes back at zero with no virus detected. What does this mean for Theo? What are you counseling him about?

Christian: It's one of those things that you learn in medical school, things are supposed to be a certain way, and then you get out to the real world and they're not that way at all. It's like, "What? That doesn't make any sense." He's antibody positive, but remember, the language here is really important. That means he was exposed. And it doesn't necessarily mean he has an active chronic infection. And it's a little surprising when you see this, first of all viral load zero, what does that mean? Well, it means that he either was treated and cured, which I think he probably would remember. Although some people don't. Some people say, "Oh, yeah, I was treated for hep C, it was a three-shot series that I got. One at zero, one at one to two, and one at six." No, that was actually your hepatitis B vaccine series. [Matt chuckles]

What it means is he doesn't have active hepatitis C. The second possibility, which is much more likely as he had spontaneous clearance. This is something that occurs, it depends on the cohort. And it actually depends on the region. In some African cohorts, it's close to 40% to 50%, spontaneous clearance rate, we don't fully understand why that is. But most cohorts will show you 30%, 25%, 30%, spontaneous clearance rate. There have been some factors identified that correlate with clearance. Younger age, female gender, a couple of genetic markers, something called the IL28B marker, which way back when we actually used to assay for that and try to use it to inpatient decisions, they don't really do that anymore. But that codes for a native interferon, that helps us fight viruses and people that have the CC allele, it's A, C or T, you get one copy for mom, one copy from dad. If you're homozygous there, you're actually really good at clearing hepatitis C and probably other viruses.

And then having an esoteric illness, you're actually getting sick from your initial acute hepatitis C is associated with probably a stronger immune response and a more likelihood that you're going to clear it spontaneously. So, the advice that you give to Theo is, first of all, when you tell him about the antibody test, use the language of exposure, make sure you have that follow up, so you can go over the viral load with him. And then you can tell him, "Look, it looks like you were exposed, and you had some spontaneous clearance. You do not have hepatitis C currently anywhere in your body." And that's a cognitive leap that some people can't understand. They're like, "Well, yeah, my test is positive, I have it." And you're like, "No, you don't have it." They're like, "Yeah, but my test was positive, I have it." And you go around in circles. But without the virus there and viral loads are incredibly sensitive tests, there is no hepatitis C in his body. It's not latent. This is not a virus that has a latent phase. It's gone. It's not there.

You probably need to just counsel that person, that you probably were exposed by some risk factor, maybe we should just keep an eye on you and maybe test you later in your life. But that person does not need treatment. I do still like to work their liver up a little bit, because you never know what

happened. There are some rare cases of late spontaneous clearance. So, this person may have had hepatitis C for a number of years, that's kind of rare. But while they're there in your office, might as well use our tools and workup their liver a little bit just to fully reassure them.

Paul: What does that sort of liver evaluation look like? Is it just a matter of checking serologies? Do you recommend imaging for these patients? How aggressive are you in terms of seeing if there was an impact or not?

Christian: Not too much different from what I would do if I was going ahead to treat this patient. And thankfully, it's gotten much more simplified, in terms of going forward. Number one, serologies, yes, because at some point in this guy's life, he was exposed to blood borne pathogen. And blood borne pathogens, just like many other infectious diseases like to travel in packs. We definitely want to check for HIV and hepatitis B serologies, and the full range of hep B serologies. I like to see all three of them, the surface antibody, the core antibody, and the surface antigen. And then in terms of a liberal workup, I think we'll get to it, but if we're moving forward with treating this guy, we just want to get a CBC metabolic panel to get our transaminases. And then probably we get an INR that's part of the workup for a more cirrhotic patient, and then some basic imaging with abdominal ultrasound.

Paul: Can I ask before we move on and make him more complicated? In terms of subsequent rescreening or retesting for hepatitis C? I mean, I would imagine the antibody itself is a limited utility. So, I guess I think some patients are sort of asking, "Can you keep checking me just to be sure? Are you doing that with viral loads? And how often are you doing that? And what does that I mean?" I'm sure they're going to be patient specific variables. But in general, how do you approach subsequent testing for these patients?

Christian: This really depends on what his risk is of additional exposure, really. So, I would really try to build rapport, make him comfortable telling you about additional risk factors. Maybe he's a gay man and didn't want to tell you that. Maybe he does have injection drug use that he didn't want to tell you. So, I would really trust myself to be a good physician with bedside manner and make him feel open and honest with me. And then if those risk factors are identified, such as anal sex or injection drug use, or tattoos, non-sterile tattoos, then I would look at more of an annual testing. The guidelines fail us a little bit on the language, they say, sort of periodic retesting, but we interpret that to mean roughly annual testing if risk factors are present.

Matthew: This is with PCR testing, because once they have the positive antibody, does that generally remain positive lifelong after that?

Christian: Yeah, it generally does. I just read a paper recently that they're looking into, some people lose it, but it's a very small proportion of the population. Most people will stay antibody positive really for life. So, yes, you're talking about a viral load for rescreening that person.

Matthew: Emi, what's next with the case? Or what else are we going to do to Theo here?

Emi: Yeah. We're going to move into the multiverse.

Matthew: [laughs]

Emi: So, here we have Theo, but in this reality, he is hep C antibody positive. Now he has a reflex HCV, with an RNA at four million international units per ml. So, now we have a different version of Theo. And it seems like a different case, seems like infection here. So, Christian, how are you approaching this patient now that we have these lab results?

Christian: Great. This is going to be the more common situation, actually more than half of the time you'll have a patient that actually has a viral load. So now we can really move towards working him up and treating him. When I walk in the room, first thing in my mind is, "Let's get him to treatment as fast as possible," because we don't really have to hold back anymore, and we should be getting into different patient populations and really have the goal to be treating everybody. Really regardless of what we find in the workup.

The correct answer to any internal medicine board question is, you start with a good history and physical exam. I'd like to get a really good detail exposure history, and we didn't pick anything up on the first pass, but maybe something will come up once he's back to go over that result. So, you're looking for risk factors of exposure to blood borne pathogens, sexual exposure, injection, drug use tattoos, that type of thing. We want to do a focus history on liver related problems. And I think our audience probably knows what those are. So, we want to ask about alcohol, we want to ask about decompensating type events, upper GI bleeding, acidities, jaundice, those types of things. And then, of course, the physical exam findings of decompensated liver disease.

Most of the time, you don't find those, but I do want to make a drop of pearl here, which is that it really depends on the clinical scenario. If Theo was 28 years old, there's almost no chance he's going to have cirrhosis, unless he was infected at birth. But he's 58, and like I said, the epidemiology tells us that most baby boomers were infected a long time ago. And so 58, 60, 70 year old walks into my office for an initial hep C visit, I have a much higher pretest probability of cirrhosis there. So, I'm going to be looking carefully at his physical exam feeling his liver myself, to see how stiff it feels, looking for palmar erythema and spider angioma on the physical exam, and jaundice and that type of thing.

And then moving to testing, we want to make things more simple. We don't want to make more testing than is actually needed. And there's several publications on these simplified algorithms that are expert opinion. There's also a new simplified algorithm that the AASLD and IDSA guidelines allude to, and it's really, really trimming things down to the minimum that's necessary in order to do what you need to do. And so those things, I think, I mentioned earlier would be a CBC, a metabolic panel where you get transaminase and renal function. You already have your HCV RNA, you want to do HIV testing and hep B serologies, coinfections, looking for those. And that's it. If he's a woman of childbearing age, consider a pregnancy test or just a good sexual history about pregnancy risk, but that's pretty much it. That's your baseline workup right there.

Paul: I'm noticing a glaring absence of genotype. Can you talk about where that went or what we're supposed to do with that?

Christian: As an infectious disease person that really wants culture and sensitivity and a pathogen and to know as much as we can about that specific pathogen, this has been really hard to let go. But the fact is that we use only pan genotypic therapies now, and this is a change from the last five years where therapies were genotype specific, and we really needed to tailor them. And it actually got quite complicated there for a while. But we're down to, at least in the US, and actually globally, I should say as well, not really caring which genotype it is. For most patients, you can just move ahead and not do that. And that's because the therapies will treat all genotypes. Now, as a specialist, I have to tell you that I do have some little asterisk there that in a sicker patient and a cirrhotic patient in a reinfected patient, if there's other extenuating circumstances, I will still send a genotype in some patients. But for your general straightforward patient, you really don't need to do it.

Matthew: So, you mentioned older patients, what you're more heightened, like looking for cirrhosis, they have a higher risk of that. And the FIB-4 score is one that we've talked about it, there's calculators for it, is that good enough to do? What else are you doing specifically to work up the liver, if it's that patient where you have a little bit more of a heightened risk, or you're little more worried about the liver?

Christian: I mentioned the just the basic labs that you have to send, but there's a basic action, that is almost the most important thing that you can possibly do at this stage, which is to stage his liver. To do a very thoughtful fibrosis assessment. And I use the word fibrosis assessment as a general term, because under that umbrella, there are several ways to do that. In this day and age, none of them involve a big needle going into your abdomen. [chuckles] So, thankfully, we really don't use liver biopsy anymore. As you mentioned, there's something called a FIB-4, and another thing called the APRI, which are very similar to each other Those are just very quick and easy calculations that you can do, just using those labs, I mentioned a CBC for the platelet count, and then you get the transaminases, and the FIB-4 uses the age as well. And those are pretty good, but I never rely solely on those.

The reason is that, when you look at the components of those two things, platelets go on the term, the denominator, and then AST/ALT in the numerator. And we all know, as good internist, that many, many things can make your platelets go up and down and many things can make your transaminase go up and down. So, you have to be kind of thoughtful about it, and use it as a guide, but not the whole end-all be-all to stage somebody. I like to triangulate with at least two methods. Another method that you can use is something called a FibroTest. And many places that don't have access to the third method, which we'll talk about in a second, can send to any commercial lab something called a FibroTest, or sometimes FibroMeter, there's different sort of versions of that. And those are proprietary tests that will spit out back to you a fibrosis score. They measure some things in the plasma that we don't need to get into. But those are useful, but those also are not the end-all be-all. So, you have to triangulate and do at least two different ones, and use your clinical brain and say like 58-year-old what's the light pretest probability here? If you have access to it, by far the best way to stage somebody is using elastography.

Elastography is a general term for a couple of different technologies. You can do magnetic resonance elastography, you can do something called shear wave elastography, you can do something called transient elastography, which is more broadly known as fiber scan. And that's the most widely available

version of that. So, if you do have that in your local area, I would really try to go for that because that tends to correlate pretty tightly with what your fibrosis stage is going to be. We still use the METAVIR staging system, which puts in F0, F1, F2, F3, F4 label on the patient. F4 being the same thing as cirrhosis. And that's a system that was really developed to score liver biopsies, but we're really just not using those anymore.

Just a final statement about that is that the transient elastography or FibroScan would be my preferred way to stage somebody. And that's because the APRI and the FIB-4 are good at the margins, if they're very, very low, you can have a pretty strong negative predictive value for cirrhosis. Very, very high, very strong positive predictive value. If they're in the middle, it's kind of like, okay, that doesn't really tell me one way or the other, and that's why you need at least a second method to stage somebody's liver.

Matthew: I think now probably we should recap a little bit, because that was a lot of information there. And what we're talking about here is the simplified, what do you need to do in these simplified patients. So, these are patients that like aren't pregnant, they don't have known cirrhosis, they haven't been treated for hep C before. So, it should be a pretty straightforward person that we're treating. What we talked about the labs was we were checking for other viruses, like HIV, hepatitis B, and you like to send all the tests for hepatitis B, not just one antibody. And then a CBC, CMP and send an INR. And basically, we're looking for liver disease with-- you use at least two different tests, either one of the scores like the FIB-4, or the APRI or some sort of elastography.

As you mentioned, the test, I think that's a great pearl, because a lot of the times you get the person if you calculate a FIB-4, they come in in that F2 to F3, which is the middle range. It's not the lower end, or the higher end, which is where those tests are most helpful, I guess from avoiding further testing. And, Paul, am I missing anything there that you think is important for the for the recap or the summary here?

Paul: No. I think you hit the high points.

Christian: One of the things that's absent from there, which is an ultrasound. You don't necessarily need an ultrasound. It's probably good practice. If somebody is close to cirrhosis, if they're F3, if your work has done and they have towards the middle to the higher end of fibrosis, then, yeah, we wanted an ultrasound. With the main purpose being, it does help you, it's additional information to help you stage more accurately. It's a good way to pick up cirrhosis and another data point on the whole workup that we're doing so far. And then ultimately, if somebody is close to an F3 or F4, it's used as a cancer screening tool. And we would be doing that going forward, looking for tumors or nodules in the liver.

When I'm teaching residents about ultrasounds, there's really a couple of key things that I'm looking for that a real red flags for cirrhosis, and that tends to be spleen size, portal vein diameter. Thankfully, those two are easy to remember because you're looking for spleen size about 12 centimeters, portal vein diameter about 12 millimeters. And then often a radiologist will give you some qualitative information about the liver. They'll talk about a scalloped margin or a nodular margin or a difference in the size of the lobes relative to each other or just a liver span and they'll comment on shrunken liver. Those are all characteristics of a cirrhotic liver which one-- they would draw my attention to the rest of my workup as well.

I should mention if you have confidence that from your workup thus far, that the patient doesn't have cirrhosis based on their labs, their FIB-4, their APRI, their age, their clinical history, maybe they told you, "I got a needle stick three years ago and that's the only possible time I could have gotten hep C." Or, "I used drugs five years ago and stopped three years ago," then you have a very nice window. Remember, the history is really useful here. Then you have a such a low pretest probability of cirrhosis, then you don't really need to go that extra step for ultrasound. You can save the system some money, it's not probably necessary and get them treated earlier.

[silence]

Emi: We were able to get those labs. And we have CBC and CMP, which were remarkable for ALT of 62 and AST of 54. All else was normal, including a platelet count of 220, albumin 4.2, and a total bili of 0.5. Both his HIV and his hepatitis B serologies are negative.

Christian: Great. Using those numbers, we can calculate a FIB-4 and APRI score. I presume both of them are going to be relatively low, maybe a little bit in that middle range that we talked about is not being totally definitive. Looks like his FIB-4 is going to be around 1.8. And the APRI is going to be around 0.74. Each of those have different scales, so don't compare them to each other. A FIB-4 that bothers me in terms of being predictive of cirrhosis is going to be about 3.25. And an APRI that bothers me being predictive of cirrhosis going to be about 1.5 or higher, so he's kind of relatively low on both of those.

I feel I can read the tea leaves a little bit in his transaminases. There are some patterns that we sometimes see, with AST being higher than ALT. We're taught in medical school that that's an alcohol phenomenon, alcoholic hepatitis. It also is seen in more advanced cirrhosis. I've had hepatologist explain this to me. There's a biochemical reason why to do it, hepatitis dying and that type of thing, but I can't explain that because I'm not a hepatologist. [chuckles] But suffice to say when the AST is above the ALT, a two to one ratio, it's not always alcohol, it could also be cirrhosis.

The albumin and bilirubin, I think are important because those also can be red flags in terms of cirrhosis, you do get hypoalbuminemia when the productive capacity of the liver is impaired. Number that bothers me is 3.5 and lower. There have been associations from clinical trials that albumin lower than 3.5 in a cirrhotic patient is indicative of a poor outcome. And then bilirubin obviously goes up when the liver stops working too well. And then out of all those labs, the most valuable and the most cost effective probably is the platelet count. 220 is a nice, healthy, robust platelet count. There are some algorithms including a published simplified algorithm that goes even more simple than the AASLD guidelines that says, "Just use the platelet count." And it's so highly predictive of cirrhosis that you can just simplify down to that.

150 is really the line where I start to get a little nervous. If you're below 100 in a hepatitis clinic at cirrhosis until proven otherwise. But don't turn your brain off. Remember, we're still good internists. There's things that platelets are acute phase reactants. My patients with acute HIV and osteomyelitis and TB, their platelets are 500, 600. So, remember that it goes up and down with inflammation. And

then don't forget of why platelets are valuable it's because of the spleen. So, I have a couple of patients that are great lessons in terms of teaching residents and med students about this. People that came to my clinic with cirrhosis, clearly low platelets, thrombocytopenia, 75-85 range, became incarcerated, and then came back and their platelets are magically in the 200s. And it's like, "What happened?" I look at the records, he didn't get treated for hep C, and cirrhosis would not be reversible that quickly anyway. What happened is he got into a prison yard fight and had his spleen taken out. And so that shows you that it's really the spleen, that the hypersplenism that happens because of portal hypertension, that makes those platelets go low. So don't turn your brain off, you got to still think about what it is. But suffice to say a platelet count of 220 is nice and healthy. And I think there's no indication so far that this guy has cirrhosis.

Emi: Great. To back that up, we also got the transient elastography. It shows 9 kPa, which is stage F2 for hepatitis C, or moderate liver scarring is what the report reads out.

Christian: Right. So, we've triangulated our fibrosis assessment a little bit. We have the APRI in the FIB-4 not definitive. So, good thing we have that elastography. By the way, if you didn't have that, you could go with another method that FibroTest, a different blood test. But kPa is kilopascals, that's a measurement of elasticity, or sort of squishiness. And really what this is, is an extension of your physical exam. When you palpate somebody's liver, you're literally feeling how many kilopascals their liver is and if you've ever felt that, obviously cirrhotic liver, it is really firm and that's going to be high kilopascals or a high elasticity measurement there. And Emi mentioned in hepatitis C patient 9 kPa means F2 There's actually slightly different scales, and this is all in the literature of the elastography machine. It's all based on empiric measurements in the literature. So, you will have a different scale from alcoholic cirrhosis that you will for hepatitis C, then for autoimmune hepatitis. And also, HIV hep C coinfected patients do have slightly different scales. But thankfully the machine sort of does that step for you. It spits out a number of F2, which you know from listening to this podcast is not cirrhosis, and it's not close to cirrhosis. F3 would be a little concerning, did we sample wrong? Did we miss it a little bit? I do still get concerned about F3 patients, because maybe we slightly missed it. Those people actually still deserve a little bit of ongoing monitoring, but F2, non-cirrhotic, you can actually go ahead and just move forward with that.

Matthew: Paul, what do you think? Is this time to talk about treatment now?

Paul: [chuckles] Yeah. Christian, you said, "We should move forward, let's be explicit." Can we please treat this patient? Are we allowed to treat this patient? I guess what would be the arguments for or against?

Christian: Not many arguments against treating. They're just little bumps in the road, maybe the patient doesn't quite understand why he should be treated. And that's our job to explain the benefits. No more ongoing transmission. Should he have any blood exposure to his family or friends or loved ones? And then no more liver progression. F2, I kind of celebrated F2, that he's not cirrhotic. But if we just let this go and sit on it for five more years, then he's probably going to show up as an F3. And then eventually an F4. And this is a disease where we really want to treat it, the earlier the better, because it's really obvious what's going to happen if we don't treat. Not everybody, there are people that that go

their whole lives and don't ever develop cirrhosis, just like there's people that smoke cigarettes, and don't ever develop lung cancer. But we want to try to interrupt that process. And on average, you can say that about 10% to 20% of people over 10 to 20 years will develop cirrhosis due to hepatitis C. So, absolutely, yes, we should have been the moment we walked into the room on the first day thinking about treating him. So, let's do it.

Paul: I think before we move into the specifics of choosing a treatment, sort of where to go from here, probably, so I think are to be explicit about our goals to have people in primary care treating hepatitis C, with confidence encouraged. But I guess who are the patients that we should be concerned about or require? This might be the point to sort of talk about who needs to be referred out and/or when do we need to help a specialist? When should we not be quite so bold as we're going to be with Theo here?

Christian: There's only a couple of categories, I think we're a primary care provider wanting to treat hepatitis C probably should get some help. Cirrhotic patients, it's a gray area, I have to say. I wouldn't pick a cirrhotic patient as your first person to treat. Cirrhotic patients certainly do need additional specialty care that a primary care provider is really not the best equipped to do. Cirrhotic patients, many of them are going to need endoscopy for esophageal variceal surveillance. If they are very sick, they may need treatment and management of decompensation. And then if their MELD score gets really, really high, you should think about a transplant evaluation. Having said that, I work in a federally qualified health center where 11 of our hep C treaters in primary care are very comfortable treating cirrhotic patients. So, it just depends on your comfort level. But wouldn't choose it as my first patient to go ahead and treat. HIV hep C coinfected patients, probably need the management of an HIV specialist as well just because of drug-drug interactions and that type of thing.

Patients with renal failure, a little bit more complicated. Although both of our recommended therapies now can be used in those patients. It's really less complicated than it was. Patients with ongoing injection drug use or substance use disorder, that's a really important consideration. And there's many models of care that really integrate hepatitis C therapy with addiction medicine. So, that's probably something where you might want to phone a friend and get some help there. And then alcohol use, really shouldn't be a contraindication to going to treating him, we think of that as almost a separate liver disease. One that's really easy to treat and manage, and one that's a little harder. The alcohol use being a little bit harder.

And then the last thing I'll mention is hepatitis B. The reason we sent that hepatitis B serology is because they're both blood borne pathogens, they can travel together. And then it is a little bit more complicated in a co infected patient with hep B and hepatitis C. And that's because you generally have a phenomenon called Competitive Inhibition of those two viruses. They both live in hepatocytes. They somewhat inhibit each other's growth. When you wipe out that hepatitis C viral load with our DAA medications, there's a possibility that hep B can flare. I consider it, like two college roommates hanging out together. And one goes back home for the weekend, what does the other one do? They throw a party. Hep B can really get going actually when you take that competitive inhibition away by treating hepatitis C. Those are the ones where you need to phone a friend, maybe get an infectious disease specialist or GI, or even an experienced primary care person to help you to manage those.

Matthew: How do you talk to them about medication? The guidelines have two choices in there, which is nice. It makes it easy. What's your spiel when you're talking to the person about the two different medicines and how you might choose between them?

Christian: Upfront, I say they're both excellent. They both will deliver a 95% or higher cure rate. And we now use the word cure. That's also called SVR12, or sustained biological response, 12 weeks after finishing therapy. Other than that, they're just superficial differences between the two. And this is where it gets a little bit hyper local, where you need to know what is being covered by your local insurance company. And I can't tell that tell you, you just have to look what's local. And then they have slightly different pill burdens, slightly different durations, some patients feel very strongly about that. When you just lay the two options in front of the patient, and if you're agnostic about it, they say, oh, no, I don't want to go longer. I want a shorter option, or some are just really bad at swallowing pills, and the pill burden is really important to them. They are slightly different from each other in terms of drug-drug interactions. And really, that's about it. I'm much more interested in getting them treated with the regimen that their insurance will cover and that they will take. The two of them are both fantastic, in terms of SVR rates.

Matthew: Can you mention some of the drug-drug interactions, big ones that might just push you one way or the other? I guess we should probably at this point, say the names of the two regimens, and you're going to teach us some hip lingo for the two different ones.

Christian: Right. I know from the prior Curbsiders episode that you went through how to tell what class the drugs are in. So, I'm going to maybe quiz you on these but-

Matthew: Oh, boy.

Christian: -the combination [chuckles] regimens, the first is called glecaprevir-pibrentasvir, and the second is called sofosbuvir-velpatasvir. Now that's a mouthful for even me to say, and I say those words all the time. So, we generally abbreviate them in slang. The first one we call GP for glecaprevir-pibrentasvir. And the second one, we call Sof/Vel for sofosbuvir-velpatasvir. The suffix of each of those words tells you what class the drug is in. So, glecaprevir ends in a P-R-E-V-I-R. PR for protease inhibitor. Pibrentasvir, the A-S-V-I-R is NS5A inhibitor suffix. Sofosbuvir, the B-U-V-I-R is an NS5B inhibitor. And then, velpatasvir, similar to pibrentasvir, that A-S-V--I-R tells you it's an NS5A inhibitor. So, two separate regimens.

Paul: I mean, if you'd give me a chance, I would have said that, by the way.

[laughter]

Matthew: I was going to say, "That would have taken me 100 takes."

[laughter]

Christian: I mean, come on, you went over it five years ago on this very podcast.

Paul: [crosstalk] [chuckles] Obviously, let's get the basics here, Christian.

Matthew: [laughs]

Christian: We call them GP in Sof/Vel. Slight differences in duration, one of them is eight weeks long, one of them's 12 weeks long for most patients. And then slightly different pill burden, one of them is three pills. Once a day with food, the other one is one pill once a day with or without food. So, just really subtle differences between the two.

Matthew: What are some big drug-drug interactions that we need to be aware of when we're-- what classes or what specific agents?

Christian: I would encourage people to just think about classes, and then look it up. And there are fantastic resources to look up what the drug interactions are. In general, statins are going to be something to think about. And it actually depends on the statin. And I do this all day, every day, and I still don't commit this to memory because it's tricky. It really depends on which statin the patients on. It doesn't follow any type of pattern. Patients on a statin, you should really just look it up. And maybe now's a good time to go over the resource that everybody uses that treats hepatitis C, and that's the Liverpool *hep-druginteractions.org* website. It's a website, that's great. And they also have an app that you can put on your phone as well.

I love it because it gives you not only the drug interaction in a red, yellow, and green, kind of stoplight format, but it tells you what's actually happening. And it gives you area under the curve and that type of thing. Whether a dose adjustment is necessary or not. Statins, one major class, anti-epileptics are another one. Those are just kind of bad actors in terms of cytochrome P450 interactions. There are some patients with seizure disorder that are untreatable with current regimens because the interactions are really so severe. So, actually myself have, I do urban primary care, some people don't get into see their neurologist and I end up being the one managing their epileptics. There are some other ones, some of the newer anti epileptics that do not have interactions. So, that's something to think about.

I treat a lot of TB here in San Diego. There's a lot of people are on rifampin, which we're actually using more and more for latent TB infection. Rifampin is probably a preferred agent for latent TB. Now we're using it on a four-month course. So, watch out for that. And then antacids is the last one. And it's different grades, both PPIs, H2 blockers as well over the counter. Calcium and magnesium-based antacids do need to be thought about because some of the hepatitis C medications require stomach acidity to be properly absorbed. None of these are really insurmountable, but those are the major classes to think about.

Matthew: You go to the Liverpool calculator, you put in what the patients are taking, what regimen you're thinking of putting them on. And if it pops up the interactions, in some cases, you might have to tell the patient to what lower the dose or just stop it all together for the 8 to 12 week, what is a typical way you resolve these?

Christian: It's usually going to be a dose reduction, switch to a different statin. If it's a statin, those are the ones where a pravastatin in particular has the least interactions with these medications. In severe cases, you might have to stop, but if that's the case, you should be able to use the other hep C regimen because they're not identical and non-overlapping drug interaction profiles. One other thing which comes up a lot, is a lot of the medicines we use to treat addiction, injectable naltrexone or oral naltrexone or buprenorphine or methadone, really don't have any significant interactions with DAAs, which is really nice, because the population that we're treating more and more are people with recent or ongoing injection drug use, don't really even have to worry about those drug interactions.

Matthew: For the audience, we're recording with two cats right now, which just makes me so happy.

[laughter]

Matthew: Back to this. This is great. Christian, you basically told us, it sounds there's a lot of set up as far as that we've done so far. But then we get to this point where it's like, "Oh, yeah, either take three pills once a day or one pill once a day." We've the interactions, maybe we make some counseling there. But this seems almost too good to be true that we're going to cure 95% of the people with this. Do you think this is something that more primary care doctors, how far down the line do you think it'll be before this is just routine, like us treating, I feel comfortable starting people on insulin and all the diabetes and blood pressure meds, and most of the heart failure meds, you think it's going to go that way with this as well?

Christian: I think so. I would give a shout out to the younger physicians that are in training. If you learn about this as a resident, and it just becomes something kind of normal to you, you're going to do this throughout your career. It's just not hard, it's something easy to incorporate. Those that are kind of closer to retirement are like, "Do I really want to learn a whole new set of things? Let's just let my local GI or ID person do that." But going forward, this really should be something that a primary care physician should do. I should mention, Emi and I work globally. There are general practitioners, and even medical officers that are nonphysicians treating using these medications globally. They're so safe. There's no reason we shouldn't have more treaters going forward.

Matthew: Paul, maybe this will have to be the next thing that I fully learned after training, how to do because I do find that-- once you start to get one person in the area, we're in a practice that does it, they can teach other people. I have some friends that I can call now [chuckles] to walk me through the first patient or two. You're making it sound very doable here. So, hopefully the audience will feel the same way.

Christian: Yeah. I want to add just a couple extra things. There are different care models that have really helped facilitate this, one is called Project ECHO. And that was developed in New Mexico, University, New Mexico, in Albuquerque. 200 miles away from a lot of the rural sites there and basically a multidisciplinary central team at the hub with a hepatologist and pharmacists and psychiatrists were able to sort of coach and mentor, hundreds of primary care folks around the state to treat hep C within their own clinics. That model is now around the world and really used for many infectious diseases and

many other diseases. So, if there's a local ECHO around your neighborhood, that's a great way to ensure that you have backup with a specialist for the more difficult cases.

Also, if you don't have ECHO, just getting to know a local GI or ID just for those difficult cases. And the less straightforward things, I think, is important to do. But I want to also make a point about how good it feels to cure a disease in your own practice. One of the motivators that I've seen amongst primary care folks, is seeing hypertension and cardiovascular disease and obesity and diabetes all day, those are not really easily curable things. And sometimes you get a major victory where somebody is able to get off their diabetes meds because they lost 20-30 pounds. But that's a rare win. With hepatitis C, you're literally curing a disease, and not only does that make the provider feel good about themselves, that they're stopping out disease and curing something. But the benefit to a patient I think goes beyond what we as providers can ever even imagine.

I've had patients tell me that hepatitis C represents this monkey on their back. Their incarceration when they were 20 years old and stupid, and they regret those. Or, a tattoo that they never really wanted to get or a relationship or sharing needles with somebody, a period of during the life when they were injecting drugs. To be able to literally cross that off their problem list has profound effects on people's self-efficacy, and just the way they see themselves. And time and time again, I mentioned this before, people just come back at the six month follow up and say, "Hey Doc, I quit smoking." Nothing I did. I didn't ask them to do that. But they just have this totally different feeling from being able to do something like this and accomplish something in a world that for many of these people has been a hard life, a hard experience for some of them.

Matthew: These are the collateral benefits that you were mentioning before. We promise we get back to them. Paul, what were you going to ask?

Paul: Probably not important, and this may change, I think, in the short term, but I think one of the barriers that I see for a lot of primary care doctors is not fear of the medications, but just fear of the documentation and the requisites that goes into it to get it approved by insurance companies right now. And I think that will probably evolve over time. But I guess the question I was going to ask is, is there any tips particularly be mindful in terms of initial documentation to sort of maximize your chances for approval? I feel like there's things like, I was taught to document no active mental health issues to preclude treatment. And I counseled them on the importance of abstinence from substances and they're going to live longer than five years. There's all these sorts of little nuances that are seem reasons and barriers. Are there any sort of broad documentation tips, until this becomes very easily available that you might recommend to our listeners?

Matthew: I would recommend that you reference the guidelines because the guidelines are generally in favor of treatment, and they're easily accessible *hcvguidelines.org*, the AASLD, IDSA guidelines. And many payers will fall back on the guidelines in terms of whether they're going to approve something or not. For example, don't send a genotype on your patient, and the insurance comes back, "You have no genotype, you can reference the simplify guidelines." And say, "Well, I don't really have to." Unfortunately, this is all very hyper local. Some insurance companies will require a counseling statement, a statement that the patient's going to live more than six months, because that's actually in

the guidelines that you someone has to have more than six months life expectancy and not be on hospice for you to treat their hep C. Some of them make you actually talk about substance use and whether somebody has been counseled about not being reinfected.

This gets to the hyper local level. There are some resources to give you a general sense of where your state is. And there's a website called *stateofhepc.org*, that is put together by a group at Harvard Law School that really grades different states on their requirements and has information there about the general restrictions, whether you have to be a specialist to treat, whether you need to treat a certain level of fibrosis or higher, and whether you need to demonstrate sobriety. I don't want to get into too many specifics, because it's different in every place. But I will say the general trend is all in the right direction to make things more easily accessible. In many, many states have dropped all those three restrictions. California, I'm happy to say actually does not even have prior authorizations anymore for DAA medication. Lot of those barriers that formerly were there in 2015 and forward when these medicines first came out, are really getting a lot better.

Matthew: Well, for interest of time, I think we should talk about the follow up testing or the on-treatment monitoring. And then we have one shorter case at the end that I think we just wanted to hit a couple of additional points. Anything major we're looking out for while they're on the medications, adverse events or side effects or labs we're supposed to be checking?

Christian: The good news on side effects is they are not very common. I usually say 10% to 15% of people in the clinical trials will have something general, like nausea, headache, or fatigue. That means 85% to 90% of people don't really have those. Most of them will go away within the first couple of days. Out of the 1600, 1700 people that we've treated and cured, one or two that actually had to stop the treatment during it. It's just really easy for people to get through. The simplified guidelines now tell us, and wait for this, this is big, no on-treatment monitoring necessary at all. If you haven't identified renal failure, or HIV coinfection, or hepatitis B coinfection, and we haven't in our case here, you don't need to check labs at all. We used to check obsessively that viral load [chuckles] and watch it fall at week two and week four and week eight. Insurance companies used to require it, that really should be all gone now, because those values really don't have any influence on whether somebody gets cured or not.

There's one thing I want to just drop as a pearl here, which is this particular patient, I think you mentioned was obese. I always am thinking about other additional liver diseases such as alcoholic liver disease, and then such as non-alcoholic fatty liver disease. So maybe at the end of treatment, I'm going to send another set of labs, just maybe that metabolic panel. And what I'm doing there is just to see what those transaminases look like. If we've gotten rid of his hep C and his transaminases are still abnormal, and abnormal for a man according to AASLD is above 35. Don't trust your lab range. That's just a function of how much alcohol people in your local area drink. It's a standard deviation function. 35 for a man and 25 for a woman, those are the normal values. And if your patient doesn't reach that by the time they're finished with hep C treatment, then you got to think, "Maybe he does have some fatty liver." And then that's a secondary problem to work up later.

Matthew: At which time point are we getting that next viral load to see where they're at? Is it at the 12 weeks after they finish their last pill? Or, is it at the same time as they're taking their last pill?

Christian: Yeah, it's the first one, 12 weeks after. If you can't remember, it's SVR12. And that means sustained virologic response 12 weeks after finishing. Some people take a little longer to finish. And there's really interesting data now on people that don't have the greatest adherence. Clinical trials are now showing, if it takes somebody four months to take a three-month regimen, guess what? They still actually get cured. Or, if they miss a pill a couple of days or even up to several days, we're not going to encourage this obviously, for our patients. But your adherence does not have to be perfect. These medicines will still cure people, even if they're not perfect with their adherence, but you do need to start that clock for the SVR12 on the day, they take their last pill. 12 weeks after that you check them. If the viral load is undetectable, they're cured, and we can use that C word. If it's detectable, you got some work to do, they might be one of those 2% to 5% that they can get cured on the first round. And then I would say that's a good chance to get a specialist involved as well.

Matthew: Yeah. Sounds like it. Okay, Emi, I think we should resolve this first case and move on to our last case, because I think there's some extra points you wanted to hit there. So, what happens with Theo?

Emi: Yes. We started Theo on Sof/Vel once a day for 12 weeks. He did very well. He came back 12 weeks after finishing and had no RNA. We could use the C word, that is a cure.

Matthew: You did it, Paul.

[laughter]

Paul: It feels great. [laughs]

Christian: Maybe one additional thing is what happens next for Theo. You might be wondering, what do you do? Does he need any more follow up? Since you've done a very good job documenting his fibrosis status, you know he does not need additional workup for cirrhosis. He does not need hepatic carcinoma screening with ultrasound and an AFP going forward. Really can just return to primary care. The only other concern would be, does he have fatty liver? And you'd know that by his transaminases by checking them maybe without SVR12. And then does he have a risk of reinfection? And that's about it.

Matthew: Fatty liver and primary care, that's well within the normal primary care wheelhouse. Okay, Emi, and now on to the final case with our last few minutes here.

Emi: We have Karen, she's 28. She first saw your colleague in the ER for forearm cellulitis from on and off injection heroin use. Your colleague treated the cellulitis, gave a naloxone prescription. And she also drew labs which returned HIV negative, hepatitis B surface antigen and surface antibody negative, which correlates to likely uninfected and non-immune, and hepatitis C antibody positive with a reflex viral load of one million. Your colleague knows of your HIV treatment skills and refers her to you.

Christian: Great. This is a case that we're seeing more and more actually, very typical of new hepatitis C infections in the United States, depending on the study 60% to 70%, or even 80% of new infections are occurring in young people who inject drugs. So, really typical case. The pretest probability of cirrhosis in this case is almost zero. If you take a good history, you probably will find out that she started smoking heroin, maybe started taking pills, led to injecting heroin, probably within the last five to 10 years. And that's very low likelihood that she is going to have cirrhosis. Still want to do the additional workup that you would normally do, and kudos to your colleague for referring her to you and sending that HIV and hep B and hep C labs because like I mentioned, Karen is not likely to just present to your clinic and ask for hep C treatment. We really need to go out and find these patients.

The elephant in the room here is ongoing heroin use. What are we going to do about that? Well, there are an increasing number of people who prescribe suboxone in primary care. As we strive to provide patients with a medical home, that would be very appropriate to provide hepatitis C treatment and cure as well as buprenorphine, or another medication for opioid use disorder. We've had great success in my own environment in FQHC, where the hep C treatment program, the primary care clinic, and the medication assisted treatment program are fully integrated. There's no wrong door. Somebody walks in and wants MAT for their heroin use, they get pushed over to get their hep C treated. Someone's in primary care and get screened, they get pushed to both places. And someone in my hep C program who has opioid use disorder, we have all those resources. There's a breed of infectious disease and addiction medicine provider that's becoming more common. I'm one of them. I'm boarded in both. We should be comfortable treating the substance use disorder, at the same time that we're actually treating the hepatitis C.

Now, people may be reluctant to treat somebody like this, because they might think, "Well, they're going to be flaky. They're not going to complete treatment. They can't stick to a schedule. They've got different priorities. The heroin is probably more important to them. We now have literature supporting the idea that that's probably false. Most people can complete treatment. The landmark trial here is something called simplify, where over 100 active injection drug users or people using drugs were recruited and had their hepatitis C treated, and the SVR12 rate in that trial was 94%. They did a great job of measuring adherence, using electronic blister packs. And there's a publication by an author named Cunningham, that literally shows the number of missed doses, and there were quite a few of them. But despite that, 94% SVR12 rate, so that should really reassure us that these patients can be treated and cured.

You might say, "Well, this is a 28-year-old infected for only a couple of years, low risk of cirrhosis. Why are we treating this person?" Well, maybe she's sharing needles. Maybe she's a risk of ongoing transmission. And if we ever want to get to that dream of eliminating hepatitis C, this is exactly the person that we have to be treating. We need to be getting out of our comfort zone, and we now have literature showing us that we can do that. So, a couple of major points is, is integrating opioid use disorder treatment into primary care and integrating it with hepatitis C treatment. And then pushing ahead and treating patients that you may not have been comfortable treating before, to really give them the chance to be treated and cured, because most of them will.

Final consideration is reinfection. And we now have pretty good literature and a meta-analysis actually showing that the rates of reinfection of people actively injecting drugs are lower than you might think. And I'm going to pause and let you think of a number in your mind of what percent of people actively injecting drugs may be reinfected. And the actual number from the meta-analysis is 5 per 100 person years. So, it's really quite low. And I think we're doing a disservice to those other 95 people that could have been treated and cured because of our own judgment.

Final point I'll make is that what if somebody does get reinfected? Well, we can just retreat them again. Often we don't have complicated issues with drug resistance or going to second line regimens or anything. If someone gets reinfected, that's probably a naive virus, and we can just use the same regimen and get them cured again.

Matthew: Christian, this has been really fantastic. Definitely inspiring. We need to try to delve into this, maybe at some point, I will treat, our audience, I'll report back. Give me some time, but I would like to try to see about doing this in our primary care clinic where I'm currently working. But, Christian, can you give us some take home points for the audience, maybe two or three that you really want to make sure they remember?

Christian: Yeah, Matt, I hope you report back that you have cured people, it's a great feeling as a provider. I just like to say that it's easier than you might think. It's doable. And we, as medical students, and residents, are always used to studying for a test until we know absolutely everything. And we don't want to start until we're fully ready. I would just encourage people to just jump before you know where you're going to land. As long as you feel supported and have resources, and we'll get to those in a second. And have a friend that you can phone or a specialist that you can refer to or an ECHO project that you can present cases to, you're not going to fail. This is pretty straightforward. It's pretty easy to do, and it's incredibly satisfying. So, I would just encourage you to go ahead and do it. Some of those resources, the guidelines are fantastic. They're a little more detailed than you probably need because they get into some complexities there, but at least you know that it's there. That's *hcvguidelines.org*. That's the AASLD, IDSA guidelines. The Liverpool drug interaction site we refer to as *hep-druginteractions.org*. If you want to look for a Project ECHO program around you, the ECHO website is going to be in the show notes as well. And then my favorite just full comprehensive curriculum, I'm a little biased because I wrote one of the chapters on it, but it's the *hepatitisc.uw.edu*. That's the University of Washington. They have curricula which are fantastic, very visual. David Spach, who was my mentor up there at University of Washington, just has beautiful pictures. They've got a whole program for HIV, hepatitis B, hepatitis C, STDs. And that is essentially a modular curriculum for everything you might need to know. And so that's there to support you as well.

Matthew: Yeah. I can say I went through some of that to prepare for the episode. And I found it really easy to use and very helpful and just lots of great information. All right. Well, thank you so much, and we will let you get to whatever wonderful dinner you're having this evening.

[music]

Paul: This has been another episode of the Curbsiders, bringing you a little knowledge food for your brain hole.

Emi: Yay.

Matthew: [laughs]

Paul: [laughs] I did not like that one. Get your show notes at the *curbsiders.com*. And while you're there, sign up for our mailing list to get our weekly show notes in your inbox. Plus, twice each month you'll get our new Curbsiders Digest, recapping the latest practice changing articles, guidelines and news in internal medicine.

Matthew: And we're committed to high value, practice changing knowledge, and we want your feedback, so please subscribe, rate, and review the show on Apple Podcast or on Spotify now, and you can also contact us at the *curbsiders@gmail.com.* Reminder that this episode and most episodes are available at *curbsiders.vcuhealth.org* for free CME credit. A special thanks to our writer and producer for this episode, Emi Okamoto, and to our executive producer, Beth "Garbs" Garbitelli. Our social media is run by Elizabeth [unintelligible 01:16:38], Tima Karginov does the website, Stuart Brigham composed our theme music. And until next time, I've been Dr. Matthew Frank Watto.

Emi: And I've been Emi Elizabeth Okamoto.

Paul: And as always, I've been Dr. Paul Nelson Williams. Thank you, and goodbye.

[music]