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HEPATITIS C AMONG INFANTS, CHILDREN AND ADOLESCENTS

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4/28/2023

Hepatitis C among Infants, Children and Adolescents

[video transcript]

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speaker Dr. Ravi Jhaveri is division head for Pediatric Infectious Diseases at the Ann and Robert H. Lurie Children's Hospital in Chicago, and Professor of Pediatrics at the Northwestern University Feinberg School of Medicine. His research spans many aspects of Hepatitis C virus, with a particular focus on the burden clinical outcomes and treatment of HCV in infants, children and pregnant women, Dr. generi served on the AASL de IDFA Hepatitis C guidelines panel, as well as the AASL anti viral Hepatitis elimination Taskforce. He is a fellow of the Infectious Disease Society of America and currently served as chair of the IDSA standards and Practice Guidelines Committee. He is also a fellow at the Pediatric Infectious Disease Society, and serves on the PID s board of directors from 2015 to 2019. Dr. Jhaveri also currently served as editor in chief for the Journal of the PDF, excuse me, Journal of the pediatric infectious diseases, society, excuse me, and formerly served as the one of the CO editor in chief for the journal clinical therapeutics. Dr. Jhaveri, I will hand it over to you from here.

01:21
Thanks so much, Lauren, for that generous introduction. Good afternoon, everyone. It's really my pleasure to be here to speak about this topic, which is near and dear to my heart. All right, I would like to thank everyone, Jeff Weiss, Lauren Walker, Rukhsana, Bobby and Charlotte Miller for helping me with logistics and for inviting me to, to give this talk. And I thank all of you in advance for your attention today. I do like to start with acknowledgments rather than leaving them to the end just to acknowledge how important all these people have been over the course of my career. And in my work related to hep C, acknowledge my current funding support and some of the past funding support that we've had for the work we've done. And then I have these stated, relationships, none of which is really, or very few of which are directly impact. This work. As Lauren mentioned, I do have societal and guidance panel membership, which which does come from this work. Alright, so we're gonna go through, we're going to, in terms of objectives, we're going to talk a little bit about the epidemiology of hep C amongst infants, children, adolescents, we're going to discuss testing and diagnosis of hep C amongst infants, children and adolescents. And then we're also going to describe how to monitor and care for infants, children's and adolescents who are exposed to or with HCV. And for as far as format, I'm going to use an example cases, I'm going to weave in some of the research that we've done over the last several years to help make some of the points. So first, I just want to outline why is talking about hep C important and I recognize and appreciate that those of you are here, because you're interested in the topic, because you know why it's important, but allow me to just take a step back. So eliminating viral Hepatitis is a national and global health goal. Most of the discussion when we talk about elimination really focuses on one of the chronic forms of Hepatitis. So Hepatitis B, which is a very important topic, but not what we're here to talk about today. And Hepatitis C. The other reason why I make this point is because often when we have

this discussion about elimination, infants, children and pregnant women often aren't part of the discussion. And so when we think about elimination means everyone and so it's really important that we're not leaving any groups of patients behind. Right or wrong way. Okay, so let's start with a few slides to ground our discussion. So we think about epidemiology. Unfortunately, the epidemiology of hep C has been going in the wrong direction. HPV associated deaths have risen from 11,000 per year and 2003 to 19,000. By 2013. It had been the leading indication for adult liver transplant I think we have made some progress in that front. But we still have many people who are infected in this country 4.6 million and last estimate, and 3.5 that actually have chronic infection. There are a significant number of children that also have chronic infection. And these numbers are a bit in flux because they include children who were diagnosed many years ago that have likely aged up into adulthood and may hopefully have been treated Um, as we think about estimates of infants who have actually been exposed and now have chronic infections, our older estimates, were about 1000 new infants per year with vertically transmitted Hep C, in the current era, it's more like 1700. So it's still a significant burden. And we need to address this this challenge. When we think about acquisition, the the now of acquisition really is injection drug use in adults and teens, we're going to come back to this point, and vertical transmission and our infant population. Historically, the risk factors we used to talk about transfusions prior to July 1992. And we have reliable testing, and then some other blood or tissue exposure, this might have been clotting factors, or solid organ transplant or some other tissue transplant, it's important to think about other possible ways to acquire Hep C, sexual transmission is one that's brought up. The studies have shown that if you're thinking about male to female or female to male transmission, that those are actually very low risk events. And so it takes somewhere on the order of one and 300,000 encounters to deck to transmission. Men having sex with men is a different high risk group, it's clear that there have been many Hep C associated outbreaks related to minimum of sex with men. And so this is an important group that we need to make sure that we are communicating with and testing and discussing prevention. There are still a few patients not nearly as many as we used to have, where it's not really clear what their risk factor was. Probably there's some microscopic blood exposure that has happened. But it may be very hard to get at that from a historical standpoint. How do we make the diagnosis of hep C. So we can either look for the presence of antibody, which is indicates either current infection, or at some point previously, and this is the the most common screening test we use, we will then follow that up with what we're really interested in, which is the ACD RNA. This is the indicator for chronic infection. We do this using a real time PCR assay. And the specifics of how it works are not that important. The key attributes that you should be aware of are that this has a very broad dynamic range. So it can detect very low levels and very high levels. It functions very well in that low end range. So it will pick up patients who might just have a few copies of that RNA. And it's also helpful as we track how a patient does over time in response to treatment, or something else. And so the relative quantification is strong as well. All right, so let's dive into the case as I mentioned, okay, so the first one is a 16 year old male. He's admitted to your hospital after an overdose. He admits to using heroin and fentanyl for the last one to two years with some older friends. At admission, he tests positive for hep C antibody and HCV RNA. So our questions related to this case is is this a common scenario? And to how does our current HCV screening strategy address this patient population?

Case too, so a 29 year old woman presents for discreet prenatal care. She denies any prior health problems, but shares it several years ago during what she calls a dark period in her life. She was involved with injection drugs, she had many partners in both injecting and sexual in accordance with screening recommendations that we're going to review. She gets tested for hep C. She tests positive for both antibody and HCV RNA, and she asks you about treatment options during pregnancy. So the question is related to this as are what are you going to tell her about the possibility of transmission to her unborn child? And how do you answer her question about treatment of HCV during pregnancy? Our third cases related to this last case, your case number two patient has now delivered a healthy infant male at 39 weeks and he goes to the normal newborn nursery. The resident team on call calls you to discuss sending off the Rite Aid TV testing for the baby. So your questions related to this case are when is the right time to test infants with a TV exposure? What tests are you're going to send at what time and what are these results mean regarding the long term outcomes for this infant? And the last case we're going to discuss to you here is a four year old infant comes to your clinic. She is healthy, but her mother has had ongoing issues with IV drug use. Her aunt is now her legal guardian. This child has tested positive for hep C and HCV. RNA. The aunt wants her treated now, if possible. And just for as part of your assessment, you see that she's growing well and developing well, her physical exam is normal. Her liver function tests are normal and our HCV RNA is six log six copies per annum. So your question is related to this case are what are the indications for treating a child with chronic ATD? And what are your options for a child at this age? All right, so let's walk through our first case. And we're going to focus specifically on the screening recommendations for HCV in adults and adolescents. So as we talked about the epidemiology of HCV has changed in the last 10 to 15 years, driven by our widespread opioid use an injection drug use HCV has transitioned from what used to be primarily an infection in Baby Boomers to one seen primarily in young adults. And this bimodal distribution of cases is really emblematic of what's happened. The peak to the right is that baby boomer peak, kind of old HCV, if you will, from patients likely infected in the 60s 70s and 80s.

11:22

And whereas the peak on the left is sort of the new ATV, if you will, the young adults who have been infected largely during our recent opioid epidemic. As we think about our old screening policy, we many of you may remember that we were screening people based on age. And so baby boomers were targeted for universal screening, and everyone else was risk based. Now you can imagine looking at this graph that an age based screening would only capture half of this population, and we would miss that whole left handed peak of the graph. And so the change in policy really was warranted. I want to just highlight one other point, which is if you look at the far left part of the graph here, that adolescent cases are not zero. There are adolescents in that group. And it's important to acknowledge that. So what are the new recommendations look like? Or the most up to date ones is all adults should be tested for hep C, at least once. Per CDC, pregnant women should be tested with each pregnancy, I want to highlight that this is actually different than the other universal screening recommendations from the public, US public Preventive Services Task Force, they recommended screening just once in pregnancy, but the CDC guidance is is where I think everyone should be, which is pregnant pregnancy screening

each and every event, okay. But it's important to remember that all adults means starting at age 18. And so the adolescents are not included in these recommendations, unless you happen to know about risk factors. Okay. So what's the problem with that? Well, I want to just review a project that we did a few years ago, with colleagues who are pictured in this photograph, colleagues that I used to work with at the University of North Carolina said Barrett brightly, Monica Schmitt and Tom Ruggie, we used a discharge database called Kid, this is part of a larger discharge database called H cup, which is nationally representative. hospital discharge data. The kid data focuses only on pediatrics and assembles data every three years for, for issue. So using the years 2006 2009 and 2012. We looked for Hepatitis C, and we wanted to look at trends over time in children, we used appendicitis as a control condition. And then we wanted to examine the relationship with substance use in this age population. We were fortunate enough to publish this in the journal Pediatrics now about five years ago or a little more than five years ago. I want to highlight for you that graph panel on the right, which examines the association between substance abuse in children and HCV. And that odds ratio is not a typo. It is 273, which is the certainly the largest one I've ever seen in any project I've been involved with, and I'm not aware of many others like that in the literature. So a staggering Association, the overlap is incredible. So, the other point I want to make is that looking at adolescent testing has been studied and cost effectiveness work. That was sort of laid the groundwork, if you will, for our shift in policy. So this is a group at at Boston University that does a lot of cost effectiveness and economic analyses. And they design their study looking at universal screening. And this particular project started their screening strategy at 15. Okay. And basically what they showed is that including 15 year olds in screening was cost effective that overtime, you picked up more cases. And in fact, it was so strong that if you look at that right hand column, there are several scenarios that are what's called dominated, which means that as soon as you initiated that strategy, that it was so cost effective that you couldn't actually pin a number on it. Okay. And so there are others that fell well below our usual thresholds of about $100,000 per quali. And so, clearly, including adolescence, despite the relatively low numbers in some of the studies would still be cost effective. So what are your takeaways from this or answering the question? So is this a common scenario? I think our data show that this is still all too common. And how does our current HPV screening strategy addresses pay posture patient populations, so we as pediatric providers, the current programs don't include adolescents. And so I think we still need to advocate for inclusion of adolescents and screening programs, and figure out ways to implement this. I did not include it in this part of the talk. But I just want to share that I've been working with some colleagues locally here in Chicago about integrating a TB screening with some of that adolescent screening for HIV and lipid screening. We've shown that this is feasible. And so I envisioned that this is hopefully a future template that we can build on and perhaps implement nationally. Alright, we're gonna move on to the second case, all right. Which is the risk of HCV vertical transmission and the rationale for possible treatment of HCV during pregnancy? All right, so let's review some of the key facts when it comes to vertical transmission. So if you look at the overall rate of transmission, it falls somewhere between three and 15%. And there's a wide range, and it depends on which study, you look at what criteria they use for transmission. When you look at the overall rates of chronic infection, and when I say that, typically we say which what percent of children are still positive by three years. And

that number is much more consistent in that three to 5% range. So you'll see there is a resolution rate early in life, that seems to be higher than what we would see in older children or adults. So there's something that's unique about infants, but still, the risk of chronic infection is there. Can we predict vertical transmission? The short answer is not really. When we look at HCV RNA levels, it doesn't make a difference. If we tried using C section, the way we do with HIV, it doesn't make a difference. There was a genetic marker that predicted the response to interferon therapy called il 28. B, that marker doesn't make a difference. And breastfeeding or the or the absence of breastfeeding doesn't impact transmission. So the only thing that we can really hang our hat on is whether the mom has HCV viremia during pregnancy, okay. I want to just highlight those of you may, if you look at some older literature, read that HIV infection is a strong cofactor for transmission. If you look at those studies, that's very old data from a period before we had effective antiviral antiretroviral therapy. Okay. And so we tend to think that untreated HIV coinfection is associated with increased vertical transmission. But if you have well controlled HIV, the rates come back to similar to what you'd have if you just had Hep C alone, okay. And so if you have welcomed you really are motivation B, get a woman into treatment for her HIV and you will strongly impact the the risks for vertical transmission of hep C. This just highlights a project that I was involved with several years ago, based in Egypt, we were looking at the risk of transmission in women who were screened in a prenatal clinic there in Cairo. And basically this slide illustrates that when you look at the rates of the viral loads at the RNA levels of women who did and didn't transmit, you can see no difference. And I want to just highlight that data point on the right way down at the bottom. So that log two log three level of women who had a child with transmission. So the idea that there is no threshold for transmission that as long as you have RNA you could potentially transmit. When we think about outcomes during pregnancy HCV can lead to preterm delivery, gestational diabetes and potentially lower fertility over time. And if you have advanced HCV during pregnancy with cirrhosis, this is a very high risk scenario for severe bleeding events and or death. And so certainly, you're going to engage your high risk OB and Hepatology colleagues, if you ever were involved in a case like this. We really try to avoid any invasive monitoring fetal scalp monitors and forceps just because of the risk of trauma and blood exposure. But other than that OB care and management really should be dictated by things other than HCV. So whatever else a patient needs during pregnancy, you're going to kind of stick to your routine standard of care, there are not many other custom things you need to do for the Hep C.

21:07

So the main message is that if I tell you that the risk is transmission is three to 5%, that means that the percent of infants who are uninfected is 95 to 97%. Right. So really high, so I try to stress this with my patients when I see them. And also for pregnancy, that there's no specific need to do anything different for the Hep C. But I do want to stress that pregnancy does present us with some new opportunities to address this new wave of HPV infections. So could we use direct acting antivirals, which are the treatments for hep C to treat in pregnancy? And should we do that, um, current recommendation still are to wait until after pregnancy before starting treatment. But many of us think that we sorry for that typo. Many of us think we should consider treating HCV infected pregnant persons while they're still pregnant. So let me offer you some

rationale for doing that. So this is a paper that my colleague Syd Barrett, and I wrote, just comparing and contrasting what we do for HIV and Hepatitis B, and what we do for HCV. So you'll see the risks of transmission for HIV and Hepatitis B are significantly higher than they are for Hepatitis C. And in those groups, we can actually target reliably who is ready and likely to transmit. And for HIV and Hepatitis B, we have designed interventions for HIV, we aggressively treat women for their HIV. And we know that and we target the infants for treatment after delivery. And we know that that has significantly reduced the risk of transmission. For Hepatitis B, we uniformly administer H big and hep B vaccine at birth for all infants with moms who have surface antigen, we've also implemented a secondary risk treatment for women who have very high levels of Hepatitis B DNA where if we treat them with tenofovir and continue that postpartum, that we can strongly impact the risk of breakthrough infection. And so for Hepatitis C, we have not done any of those protocols yet. It's possible that we could use treatment, because as I mentioned, if you can cure the viremia, you could potentially also eliminate the risk of exposure for the infant. Okay. Alright, so just want to reiterate, currently, DEA is are not FDA approved or recommended for use in pregnancy. If you look at the fine details, the pregnancy rating is not that different from most other antivirals, many of which we commonly use during pregnancy like Acyclovir, like oseltamivir, like tenofovir. If you look at the preclinical animal data, there is no suggestion of a notable toxicity. And what's good to consider is that when we look at the pharmacokinetics, there is a wide range where patients can have very varying drug levels and still achieve Hep C care. And so even if pregnancy impacts significantly the distribution of the drug, it's not likely to impact how well they work. So when we think about the potential benefits, when we think about the benefit for the pregnant women, certainly during pregnancy, they have the opportunity to access care, they're coming to see the doctors all the time. So you could cleanly fit in a treatment and observation period within that. You can complete therapy during pregnancy and you can achieve care for that patient. If you delay therapy, then there may be risks during pregnancy and complications and then costs and advancing disease afterwards. For the unborn child or children. Obviously, the potential safety issues we don't observe that days are transgenic. And early studies seem to suggest that and again, cure is achievable for that patient, the absence of HCV at all. The risks of delay therapy are all the complications of pregnancy and risk of transmission that we talked about, for that infant if there's no treatment. And then when we think about broader societal costs, every patient who achieves cure means we're that much closer to eradication, and every patient that is cured, potentially is saved for long term morbidity and potential mortality from their infection. We also would just argue that if patients aren't identified and treated earlier, they may have to get lost to follow up and any patient who is still positive offers some potential risk of transmission to others in the future. So as we started to explore this topic of HIV and pregnancy, one of the questions we wanted to ask was, what do patients really want? And are we as providers the problem in terms of making assumptions so this is a project that I started with several colleagues here at Northwestern and Lurie Children's pictured at the top Seema Shah is a trained bio ethicist, and she had long had an interest in HIV in pregnancy. And so when I gave Grand Rounds a few years ago, she came up to me and we started talking about how we could potentially study some of these factors. And we wanted to really understand how we could study attitudes about pregnancy, and treatment. And so we included Lin Yi, who is maternal fetal medicine specialist,

about a qualitative research project where we could do interviews with patients and providers to really understand where are the barriers and concerns to starting treatment. And Bill grobman, who's pictured below was larger network pi for the maternal fetal medicine team. And we were actually able to obtain a grant from the NIH Office of bioethics to conduct this work. I picture Leo and Patricia, who helped us do these interviews to do the coding. We targeted women of childbearing age who are either currently pregnant recently pregnant, or pregnant in the not too distant past, who had Hep C now or perhaps have been treated in the past. And this was a very Chicago focused project at the time, we targeted OB providers in the Chicagoland area, both general obese, as well as high risk and offense. And we managed to do this study pre and peri COVID. Lockdown from January to August 2020. Ultimately, we included 18 providers and 21 patients in this study. And I want to just highlight some of the themes that came out. So when we talk to providers, there were several things that we learned. So one, they felt like there was still an inadequate evidence base and a lack of professional guidance. And, and one of the sample quotes we included was just this person not knowing about large income outcome trials, or long term fetal effects. And these are the kinds of things that we would want to see before we were comfortable initiating treatment. Another thing they felt like was that they thought the patients actually felt like this would be a burden. There may be issues related to health literacy amongst patients, there may be patients with diagnoses who actually know more about their diagnosis than we do. But still, there may be others who don't have a good understanding of what that is. Many still felt like there were research roadblocks, that there aren't, there isn't enough research going on and pregnant women. And so this is not a priority. They're not big trials looking at pregnant women. Several had issues related to health equity and access. One just mentioned, I have a huge practice, that's Medicaid. But as soon as they're no longer pregnant, they no longer have insurance. So I can frequently be in a position where a patient may be able to afford something when pregnant, but we lose the ability to pay for it after delivery. They admitted they had insufficient knowledge, they felt like they didn't know enough about hep C and pregnancy to address this with patients. And then we'll come back to the safety issues that sort of are pervasive about pregnancy and the risk that if there's no studies there, what if something bad happens? And what would that mean to the patient as well as to the baby. When we talked to patients, there were some significant overlap and also some unique differences. So patients also was concerned about cost and access. They felt like the cost of treatment was so substantial that they didn't even look into it. They weren't sure insurance was going to cover it and they were just really scared of what it might cost. They also felt like providers didn't know enough and that they didn't have the conversation. shins that they want it. And I think it's telling, you know, I wish I would have someone would have been given treatment options. I don't play my OB. I know it's not his or her area of expertise. But I still treatments been out there for a while and it wasn't offered to me. Patients also had safety concerns, they want to know that there, they are going to do fine, and their baby's going to be fine. And they also felt like provider communication and process barriers. Let's say they went to see their GI doctor, their GI doctor didn't talk about treatment during pregnancy. And this one makes me sad, he pretty much shut me down immediately when I had wanted to talk to him about it. He gave me no information and no hope and psychological barriers. I think the trauma

and stigma that comes from prior use and ongoing stigma, I think for patients is real. And I think we as providers need to acknowledge that and and address it and do something about it.

30:58
And then I think the patients want to know what the real rationale is for treatment. If we can't tell them what benefit they're going to achieve, then then certainly they're not going to be motivated to want to get treatment. So we sort of laid this out as this is the overlap. And here are some of the distinct differences between providers and patients. While we were doing this work, we wanted to potentially do some advocacy about treatment during pregnancy and about research during pregnancy and the need to do it. We drafted this commentary piece that was we were lucky was published in hepatology a few years ago, just highlighting the lack of research in this area at all, and some of the ethical and justice issues that come with exclusion of pregnant women from research and treatment programs. And we included the results of a systematic review we did with Swathi on Tala, who was a GI fellow here at Lurie, as well as Peggy Murphy who is our medical information specialist, who basically just show that there has been one paper on this topic at the time, we did a study looking at treatment and during pregnancy, one paper, which again, it's to have such a low number is screams of intentionality of exclusion. This is that study. This was a very small PK study done on nine pregnant patients with what is now the first generation or older regimen, lithosphere and sofosbuvir. year the brand name was Harvoni. They showed excellent safety outcomes, and the PK was comparable to non pregnant patients. And I'm showing you the graph that just basically showed the viral load falling off a cliff as soon as patients started treatment. And everyone who was treated responded and was cured of their Hep C, the Infants who are born during the study were normal and had not had HCV detected. Obviously, these are very small numbers. And this is an old regimen. And there is a current study being done now with the with the pan genotype regimen that we use now most frequently. Since that time, there's been a trickle of other papers, I include this one in particular, this is an open label study published by a group in New York City published last year in November, they set up a cascade of care for hep C screening and treatment during pregnancy. And after a discussion about risks and benefits, they initiated therapy with the current pan genotype regiments. This is what their cascade look like ultimately, of the patients they screened. They filtered down and treated seven during pregnancy, which is that middle bar light law, light green panel, no safety issues were identified during treatment, the challenge they had is very few patients came back up, came back to their clinic to document their viral cure. And so their numbers are still very, very small. And so I would say to you, unfortunately, that treatment during pregnancy doesn't cure some of the underlying social factors that many of these patients have. And so we definitely need to think very holistically about what treatment looks like and how we can facilitate this follow up. So going back to the questions from this case, so what do you tell her about vertical transmission? The risk of transmission is three to 5%. So the odds are good that the baby will be uninfected. And how do you answer her question about treatment of HCV during pregnancy, I would recommend an open discussion about risks and benefits. And we actually have included this sort of shared decision making option in the most recent version of our Hep C guidance during pregnancy. And if this patient is interested in being treated, I

would try to push forward to get treatment approved. Access can vary from state to state. All right, let's move to our thirds. era, which is screening of infants exposed to hep C at birth.

35:11
All right, so the the end result of all these new infections in young adults is that there's been an explosion of hep C detected in women of childbearing age, and subsequently, their infants born. And so this just highlights this is a report from Kentucky, which has been part of the epicenter of the opioid epidemic, just basically highlighting the rates in women across the whole country, and then particularly in Kentucky being just excessive. So how do we test infants? What was the then and what is the now so the prior recommendation we used to use for many years was in the Red Book was using Hep C antibody testing after 18 months, the rationale for 18 months, you many of you are familiar relates to the passage of maternal antibody. And then by 18 months, all of the maternal antibodies disappeared, and any antibody you find should be produced by the infant alone. Given the complicated social circumstances that many of our patients with hep C have, or exposed to hep C, trying to capture them after 18 months was just a challenge. And so when you looked at studies that investigated what our rates were like, they all show that this strategy led to 70 to 90% of infants never getting the testing they needed and being lost to follow up. This is, these two graphs are from two different papers that basically show the same thing. The graph on the left was from the Philadelphia Department of Public Health, they looked at their roster dataset of patients who had been exposed in pregnancy and showed that 84% of the infants never got any testing, and then a significant number. Were inadequately tested. Okay. And very few actually got the appropriate test. The graph on the right, pardon me is from Tennessee data state testing. Again, their rates were a little better 23% got tested, but that big fat number 77% Never got tested at all. Okay, so still major obstacles to appropriate testing. So there's really been a long, long standing interest in other ways to evaluate. People wanted to use PCR, but we're unsure about when to test, our guidance panel, initially had recommended a window between two and six months as sort of a practical window. But actually now we have some good data suggests that this is actually a sound recommendation. So this was a paper that was published now a couple of years ago, from the group at Nationwide Children's Hospital in Columbus, Ohio, they tested 750 infants exposed to hep C, in this two to six month window. what they showed was that all of the kids who tested RNA positive within that window, had follow up PCR testing that was positive. And all of the kids who had negative testing, also tested negative later. Now the challenge with this study, so you'll see it's 100% sensitivity and specificity. But the problem is they still had a pretty big dropout rate. But what's really important and I think that negative state negative relationship means that those patients who you test early and are negative, you can feel really good about telling the family the infant doesn't have HCV and potentially dismissing them from care. So we've adjusted this is what the box recommendation on the HCV guidance website looks like. We have initially we stated, you know testing with HCV RNA assay can be considered as early as two months. We I offer you a spoiler alert, which is that we try to revise this to more strongly recommend testing early so that we don't miss that opportunity. And the AP Redbook recommendation is harmonized notice to to to emphasize that molecular option early. But I want to share some breaking news, which is that CDC has drafted new guidance. So this is a

screenshot from just a few months ago. Just basically highlighting some revised guidance that the CDC is getting ready to issue about stressing the primary option being HCV RNA testing between two and six months. So the public comment actually period ended a few months ago. They're working on revising this, responding to those comments and then finalizing this guidance. They're going to remove mention of that HCV antibody 18 months unless a patient has not been screened before and certainly are her hope is that more proximal testing will increase the number of infants against Green, again, getting us closer to that what we need to do for elimination. So this was just a slideshow screenshot of the the webinar that the CDC team put together to roll out these draft guidance. To lay the stage for this, they performed cost effectiveness analysis, part of the review and identified that universal screening with PCR did increase medical costs, but was cost saving over time because of early diagnosis and rapid referral. And we're going to talk about it later. But we do have treatment options down to h three that made this piece. They also just highlighted that, because of these new recommendations, they hopefully will increase clarity. And this is going to harmonize guidance across all of our sources. And so again, the CDC recommends a TB testing for all infants born and pregnant persons with confirmed or probable HPV infection. And to do that, in that two to six months window, and then there's here are the provisions for catch up testing if a patient didn't get screened earlier. All right. So what are we saying about this infant? And when to screen? So when is the right time to screen? anytime between two and six months of age is fine. What tests do you send at that time? That's that HCV RNA real time PCR? And what are the results mean as far as long term outcome, so if you get the results and they're negative at that time, you're pretty much done. And I think you can reassure the family. And if the results are positive, then I reassure them that the patients are still likely to do well and we're going to follow them until we could potentially treat later on. Alright, let's move to our last scenario, which is treatment of kids with chronic HCV infection. Alright, so basic principles for treating kids with hep C, we don't treat anyone younger than three. And that's because of that window of spontaneous clearance I mentioned, there's still a big percentage of patients who even with high level viremia will get rid of their ATV. Okay. The other reason why we're not necessarily in a rush is because fibrosis and cirrhosis, the the worst complications of HCV are relatively rare in kids. And when they do happen, they really don't happen until the second decade of life at the earliest. And so they're not going to happen in the first year, two years, three years, five years. And so you do have time to wait and consider and see if a patient resolves. The rationale for treatment is less about avoiding the worst outcomes. It's really about curing infection, eliminating future transmission events, and avoiding stigma at school. And unfortunately, still, in the current day, I have patients who say somehow someone found out about my Hep C and now my child is being isolated, either by the school or by other kids. And so I think this is just a tragedy, okay. Young kids actually can take medicine pretty well. And so often that's better than waiting until the teenage years were what I call the teenage makes it a lot more difficult. Okay. I want to just highlight some other work that we were involved in Joe Unwin, who was a grad student at the time we did this work, wanted to look at cost effectiveness of early HCV treatment. At the time, the drugs were approved for teens and preteens. And so we looked at the approved regimen and those that were likely to be approved. And all of the regimens we studied were highly cost effective when we started treatment in those preteens and teens. This is what the rationale look like. And

I just call your attention to that right most column of the dollars per quality. Again, as I mentioned earlier, the threshold usually is around between 50,000 and $100,000 per quali. And you'll see that all of the regimens, we looked at either the ones that were in vogue at the time, or the regimens that are now the state of the art or standard of care. All of them are well below that threshold. So anytime you start training with any agent, it's going to be cost effective over time.

44:30
What options do we have so as of about two years ago now both of the pan genotype regimens are approved for children as young as three years old. So the two that are most commonly used are the soap Bell, the sofosbuvir velpatasvir. The brand name is Epclusa. It's made by Gilead and then glecaprevir and pibrentasvir, which goes by the brand name Maverick, and produced by AFI. These are once daily oral regimens and they cure Just about everyone. And the only reason in pediatric studies that you see a child not cured is because they were lost to follow up. And they need to be classified in the studies as failures. And so it's, it's really amazing and again, argues to the idea that kids with the lack of comorbidities are much more responsive to the treatment, even than adults. We don't do liver biopsies anymore, it's not needed. And for one of the drugs, they actually come in this Microcapsule formulation. And so the key is just to make sure that they're mixed with thicker foods that are not necessarily acidic. So apologies to those of you that might be colorblind. But I put Nutella and green as a good option for for sort of mixing these microcapsules. Peanut butter is also one that's good. But something like applesauce, which is a little bit acidic and more watery and runny. That's not a good option. And so that's in red as a bad option. I've included a link for the ATV guidelines website, which is a great resource. There's a specific page for children under the unique populations tab that I would urge you to access. If you ever have questions about this or looking for guidance. I would just highlight that for those of you in the New York State area, which I think is virtually all of you. New York does pretty well. This is a snapshot from independent group. It's an independent website called state of hep C that that grades each state based on access and restrictions. And so my personal experience is that kids do have access to treatment when we providers advocate for it. And so more and more states are opening the door and lowering restrictions. And so if a provider asked for it, we the state has to provide it. The state policy and many private insurers are following suit. And so now that these drugs are out there, we need to prescribe them more after we've tested the the appropriate people and identified them for treatment. So what are the take comes from this case? So what are the indications for treating a child with chronic HCV? Basically anyone older than three with evidence of chronic infection? So the bottom line is everyone should get treated? What are your options for kids this age, either regimen will work. And typically what happens is the payer will say we will cover this one, and I'll go with that. So I typically don't have a strong preference for one or the other. We'll take what they give us and both are going to work to cure their infection. All right, that's my last slide. I want to thank everyone for your attention. And now I'm happy to take questions. So Lauren, I'm going to stop sharing here.

47:51
What would be your recommendation to discuss screening with teens and their parents?

47:58
So this is a great question. And I think what I would say is that I'll share the experience of our team when we instituted screening. So I think one of the things that happened, I think there was a real concern that parents might push back or kids might push back as the screening was couched as part of our routine maintenance care. And the fact that screening was done at this visit for other things like routine HIV screening and lipid panel screening, which which it is saying that HCV screening is is part of a universal standard and elimination really helped. And the providers were actually surprised that there wasn't, there was hardly any pushback at all. And really, patients and parents were very accepting, especially when it was embedded. If it was a call out test, I think there may have been others. And so this is the strategy I would use is thinking about adolescents, maybe 15. and above. Anytime you're going to have a blood test. And again, I think that the HIV test or lipid panel testing, which most teens get, this is a great opportunity to fold that in, and especially providers in when we think about the geography of hep C. Generally, rural and more suburban areas have been the hotspots for injection drug use, and and so certainly those of you in that area, if you're doing screening, I would highly recommend it. And if you're not doing it, I would strongly encourage you to evaluate Could you do it? I really as I said, I think this is the future. And I this is this is where we would like to go and this is one of the areas that I'm pushing hard on

49:27
call to action. I love it. Next question. This one comes from an audience member about the dogma of maternal Hep C viremia, as being required for perinatal transmission. So they're wondering how good the data are for this and to provide a little bit of background. This participant was surprised recently by a patient, a mother whose third trimester PCR was negative including the day before delivery, but baby's two months PCR is now positive at 16 million.

49:59
That's interest Staying. So studies have. Studies have shown many studies have shown that the viremia is consistent. And that actually, you know, women can have a fluctuation during pregnancy. But usually it's the other way it actually goes up and then can clear later. So this story is very interesting and unusual. We tend not to think about hep C having a reservoir. But it also perhaps underscores the point that we actually don't know when transmission happens. And it's very possible that a transmission event happened at some point earlier in pregnancy. And so I think the point is, this case is very interesting. It's not the norm. It is an unusual scenario. But the good news I would say is that regardless, this infant, one still has a chance that they could resolve. And it's possible that from a genetic standpoint, this infant has favorable characteristics that would lead to that. But even if this child doesn't resolve infection, I would strongly suggest that he she they be tracked each year, and then as soon as they turn three, be targeted for therapy. I've done that for a few patients now with good success.

51:33

Thank you. And this is a related follow up question from a different participants. How many infants who do test positive? I'm talking about real time PCR here clear their infection? And by what age? Is it typical to see the infection cleared?

51:47
Um, yeah, so it sort of can be a steady trickle. So what I would say is the high end of that number, I gave you a three to 15%. That, typically, I'll say that sometimes it's a sort of 5050 proposition. Whereas in adults, we tend to think that progression of chronic illness or chronic infection happens somewhere around 70% of the time. So it's more like a 30% resolution rate. It's much higher in infants, when it happens, I've seen it happen later in the first year, I've seen it happen in years, the second year, and even up into the third year. And so I can't give you a window like this is when it's likely to happen. And it probably has to do with many different factors related to the maturation of the immune system over time. And that is a process that happens over the first year to two years, maturation of the liver. That is actually something that happens over the first three years. So your liver when you're born, the fetal liver looks very different than the adult liver. And that process of maturation happens in terms of changing cell types and, and morphology over that first three years. So it's probably a combination of all those things. So I can't give you a specific timetable. And so I tend not to over test, I will I really see them more to just keep them engaged in care. And I will maybe periodically do an RNA test probably once in that, between so the first test and the three years just to see if that's been a window of resolution. But otherwise, then I'll test them right before we're ready to start treatment.

53:31
Perfect. This one might be a little tricky for you to answer. So apologies in advance, because I know these things vary by state. But we have someone who was wondering if Hep C status is something that is mandatory to report to a school for a child,

53:48
I can say with confidence that you don't you're not mandated to report anything to the school. And I think this stress is a point that I probably should have made more clear, which is making sure that we communicate to our parents and families how Hep C is transmitted, and how it's not transmitted. And so it's really important to stress that any kind of casual contact is not a risk factor for transmission. And so there's no need to divulge anything because you're not putting anyone at risk. The only time you really have to worry about hep C obviously is with any kind of bloody injury. So yes, kids can get hurt, they can fall on everything and so, but we all know that ideally, when daycare or a school or something is dealing with a wound that in this current era, people should be using gloves and and universal precautions in that scenario. And so there's really nothing that's required to divulge. And so I've often told my families if when they're diagnosed, there's nothing there's no need to tell if you have a close confidant let's say if you have a caregiver at home, they should be aware of just because if there's a bloody injury, they know how to deal with it and how to clean up the wound. And the school should be doing the

same for everyone. So there's no need for divulging and That's there are no states that mandate disclosure.

55:05
Two final questions for our last few minutes here, we have someone who was wondering if you can speak to any adverse immunologic effects of DEA treatment.

55:15
So, we have not seen that, you know, I wish I could say obviously, our number of children is much smaller, but still in hundreds. And certainly there's been 10s of 1000s, if not hundreds of 1000s of adults being treated. And we actually see no long term immune effects. And what I would say is actually what we see once patients are treated and cured of their Hep C is that there is actually remarkable healing that happens in their liver. And so the cirrhosis and fibrosis that if it's sort of earlier cirrhosis, and certainly any kind of fibrosis, you can actually see healing pretty quickly over the first few years afterwards. So really, it's it's quite the opposite. You start to allow once you remove the Hep C from the equation, you really allow the body to to begin the healing process. So so we're not seeing long term adverse events.

56:11
Excellent news, final question. And this was coming from our participant with the somewhat complex case, given your response that some kids may clear even at the third year or later, is there any indication to wait beyond age three to treat?

56:25
So that's a good question. I think once you get out to three, I frankly, I've only had one child that resolved after that. So I think the odds of clearance are far lower once you get there. And so I think that if you can get treatment, you I would certainly think about it at that point. If you have a parent, or family who's a little bit apprehensive and wants to wait, I think it's fine to wait a little bit. But I would continue to bring it up. And I think that there is sort of a sweet spot when kids are young. Three might sound like it's young, but actually I got a family I recently worked with felt like they got into a routine pretty quickly. And when you're only talking about eight to 12 weeks of treatment, families really only have to sort of work on a treatment regimen just for a short term. You know, this is not a lifelong thing. And so that's the beautiful thing about these therapies. It's just a short term window longer than our common antibiotics, but but certainly not as much as our chronic medication. And so it really is, I think, pretty easy. You know, I hate to sound like I'm oversimplifying. So there is not a priority. But I think that when we think about the ability to get the medication and working with families to take it. You don't have to rush to do it at three, but I certainly would continue to offer it as an option in the in those early years. You're saying that family after ace three. Thank you so much, Dr. Jhaveri. Again,

[End Transcript]