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TRANSCRIPT - GR 01 26 24 "***Hepatitis B, a Virus in Evolution***" William Petri, MD PhD, from the University of Virginia

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Internal Medicine Grand Rounds

- Very long introduction plan for John's day. I'll just get the highlights. So Dr. Uva, followed by an internal lens in Residency at Case Western, and unfortunately for all of us, returned to Uva. And then he's concerned here, and the invaluable contributions to the field. As many of us know, he is a highly accomplished researcher here, and beyond research contributions, many prominent appointments, currently research and department of medicine, Uva as well as epidemiology. 2022. He was awarded for Tropical Medicine and hygiene real testament to his exceptional achievements.
- And this actually is really added to a long list of other words and acknowledgements that underscores, outstanding contributions to the field. On personal note, Dr. Features, the attending on service during my last year, and I'll always look back on that in appreciation for having experience work with him. They're on our Smc programs. Many of you know, Dr. Clinician, researcher and role model we are privileged to have here shares, insights and expertise with us. So please join me in extending and welcome to Dr. Petri.
- Thanks, Margo Bangladesh and so it's for a composite interest a case presentation this is out of the literature. It's a real patient, although not a patient here. There's a 28 year old woman history of flu like symptoms.
- She didn't really have any pertinent past medical history. No medications, I think no sick contacts at all, and she, essentially active, is use world contraceptives and she's not traveled outside of the United States the past 5 years. These are also. This is to get into prevent important historical points and interest in time. All the answers are are correct on this, but it helps like to think about very so the fact that she is essentially active and not not using safe sexes. So hepatitis B of the different viruses is the one that's that's most readily sexually transmitted. So that says a hint from her history. Hepatitis E. For reasons I don't understand, is like France, India, Bolivia, and so she hasn't traveled internationally. So hepatitis E. Falls and importance no. Iv drug use things. Hepatitis C are pretty unlikely. And you initiate no sick contacts. And so again, hepatitis A is gonna spread person to person. Probably the best of of the hepatitis viruses cause the fecal world spread. I didn't realize, like how much he would have. It's not unusual to see high hepatitis B super infection. Somebody with hepatitis. B, probably like 2, 5% of the time. Yeah. Hepatitis E is worse and pregnant from which is not pregnant. And
- Apparently she was not back. And because you guys will get into a Us. Infants now, or immunize against both. So and there's no. It's a couple of things that hit some of the other viruses. There's no kind of C virus vaccine, currently, because it's so genetically diverse. So I've had to see as opposed to HIV has been in people for thousands of years. HIV, just for 100. So so genetic diversity. Is enormous in comparison to HIV. So that's vaccine and not unlike HIV, we get quality species. So

this virus is evolving so rapidly, and when you're infected with it, you only have just like one hepatitis cards, you know, with all these species, because the viruses evolve in, you're in fact. And that's what this kind of like fire work, like thing is supposed to show you is from single viruses with how all these new species have evolved. Those are 2 different patients in the you know that. And this is like the point. Hepatitis D is is actually, you know in the in the Us. So yeah, yellow on the map. So we should be so where I work? And then France and Olivia seems to like kind of stand out. Maybe they have like better reporting for So vaccination schedule, you know. None of us repeat Christianity in this room, and so had to look this up. But you get 12 months and 18 months of age those who have children. Now you probably know this better than I do. It's really important to immunize at birth, because if you do that, then you protect the child from acquiring hepatitis B from the mother. And that's key. Because if you get hepatitis B, and for you very, likely to get chronic at the highest speed, which is a problem. We'll get into and I was saying, hepatitis C and D no vaccine and vaccine is. It's been available in China. It's been tested Bangladesh, but it's it hasn't been submitted for FDA approval. I think likely it's not considered. You know enough of a mark, I imagine, for it in the Us.

- But there is a good vaccine. So so back to the patient, then, so she's the word oriented. She's in no distress. Vital signs are free under MoD marketable. She does that and that's about that. And her liver is a little bit enlarged and and tender.
- So here's a laboratory findings. And so, you know, it's like an elevated alt. It's higher than the ast. And so the end. This is one of these medical students. Right is higher than the Asc. And I look to find a reason for that, like I can't. I don't, anybody know but II haven't found a good explanation. Why, that is but it's a good primary, you know, all teach our medical students and so just summarize what I what I just said there. So And these are all true statements. So so we're gonna do like a hepatitis screen in this young woman. So she has surface antigen, that's positive, and she's actively infected. If she has antibody against the surface engine, though, and conversely, she's either been vaccinated and has something else, or she. She's had pass infection with hepatitis. B. The Igm is A is still. We are most useful tests for rolling and hepatitis a and just remember that hepatitis C or not don't show up until almost 2 months into the infection. So then, like hepatitis, c. Viral load is much more useful. So and so here are our hepatitis serologies, and so she surface engine positive. So she has active infection. She'll says Eanagen and she has antibody hepatitis B, and then this is this is just show you the the the time course, and so the very top. This is when you're getting your detectives in the bloodstream right from day one.
- And then these antigens that are produced by the virus start showing up, you know, very, very quickly as well, within the first week or so, that aol elevation is usually about 2 weeks on average, into the illness. And you remember she's been sick, I think, for I think she like that history of 10 days of flu like symptoms. And then this just takes you through the different markers will not dwell on those have nice B. You totally recover from, if you're in fact more likely than not, you are infected with hepatitis. B is in void for the rest of your life. So this is. It stays latent in almost everyone's face. That's not the case for hepatitis a where you actually clear the infection. And very, very similar to hepatitis a hepatitis c and then hepatitis. C. Unfortunately, chronic infection is the rule. There's only about one out of 5 people that's infected with hepatitis C, with their immune system. Be able to clear the virus

and then everyone else goes on to be chronically infected over years and years. And that's probably because of this, you know, ability of the virus to mutate and evolve so rapidly. We, we commonly see, see an HIV, you know, going hand in hand because they can both be transmitted through Iv drug use. So someone brought to look to sort of see what is hepatitis? C evolving slower. And someone who has HIV that has a source even of compromise. So is what's pushing evolution, the immune system. And actually, there was no differences kinda like a disappointing setting. There's probably other things besides our immune response that are driving the evolution, maybe just like adapting to that person. Or, you know, being in the bloodstream most people screening is recommended for for adults, for Hcv. Because of the our ability. That is something that we can cure. So this is this is again kind of a summary of what I just told you so. The fact that she did not have any sick contacts is inconsistent with hepatitis a hepatitis. B, think about that. It's sexually transmitted. Iv drug use hepatitis. C, unfortunately, not really sexually transmitted any you know. Significant extent. But Iv drug use again, important. And then this ability they cause a chronic infection most, but not everyone. And hepatitis D is that that weird virus, and only can replicate. If you have hepatitis outside.

- and then hepatitis, the waterborne people, or and one out of 5 women hepatitis. I think that's an overstate at least based on, like my experience with that involved with that P defined as you have, surface Antigen is detectable on your plasma for 6 months, so that that gives you the diagnosis of chronic hepatitis B, and all the problems that come from that and so the the biggest problem, the versus cirrhosis. And then more rarely have say, like cancer, and it's a treatments.
- Our combination of poly, I think, like all, allows the half life of the interfer to be to be much, much longer, and then a reverse transcriptase inhibitor and DNA virus. But it has an rna intermediate. And so it actually uses reverse transcriptase and I remember, like learning that as a graduate student it never occurred to me like is anti retrovirals for coming out. We should try those out. Many of the Rt. In Hitler's we use for HIV are also active against hepatitis so one can create user treated, based not on how much viruses in the bloodstream, but but how much evidence there is for for chronic active biomarkers. I think there's there's scans, and one can do deliver, to assess, like, how active the diseases, and whether to treat. And just remember, like that. What we like to do, how we prevent this from happening.
- You never get rid of the virus once you have a chronic So this is the situation in the world today for empathy being children under the age of 5. So most of these children are going to have chronic, active advertising. Most of them were infected by exposure to their mother's blood during delivery.
- So and this is an issue, because it's only about half the countries in the world and introduce the first dose vaccine and so this this problem is not gonna go away until we're able to roll that out universally. So and if you compare these 2 things, whereas chronic where children are infected essentially the same thing, so that that that that's our our challenge.
- I'm sort of like a young glass, half full type person. So I think it's great that half the countries in the world are giving the birthdays. We just need to get the other half to do that. So, and something that surprised me until I started like getting into this virus is evolving to, you know. I think of Rna viruses like Hcv. And HIV. To be evolving, because, you know, Rna Polymerases are very error from like reverse transportation, error, every 1,000 basis whereas the DNA Polymerase makes an error every 100,000 pieces so so 100 times better fidelity for DNA. So II didn't think

like that. That might be would evolve to gravitate evolution during an Rna of this virus. And we'll get to is like how the virus is actually able to escape vaccination through evolution. This is another case reporting get like, not out of Uva, but out of the literature. They kind of make this point about viral escape. Try to prevent chronic be number one just to prevent cirrhosis prevent cellular cancer.

- But we also want to, because it's gonna be continued pressure for emergence of viruses that can escape the vaccine. So this is this man. He had chronic kind of high speeds from Laos. He's been diagnosed 2,008. He's never been treated and he been in the Us. Since he was 16, and family history is important because his sister also has chronic medicine, so presumably he and his sister were not vaccinated at birth, and probably have been chronically infected ever since.
- And, as you'd expect for somebody with chronic hepatitis. B. He has hepatitis be surface manager, I'm like, if he had it for 6 months. You're you're defined as having product hepatitis B. He has. He probably would not qualify for therapy, because Lt is not that elevated as far as not that high ordinarily. Well, it it's it's interesting and terrible what what happened? So so he's has chronic. His wife is an Rn. And she has received, you know, his office in this room received to have a nice V vaccine
- and she's been donating blood, you know, pretty consistently, and never been turned back until 3 years ago, and they detected have a nice be surface Antigen in her bloodstream and so, presumably what happened was is is that she acquired events. She escaped from her husband. That. That that, you know.
- unfortunately enable infection to get established in her is despite the fact that she's been effectively vaccinated. And so it's the problem with like chronic viral infection, just an opportunity for the virus to evolve, you know, just like we saw with the with the coronaviruses, you know with with omacron. And basically, it's probably an immunosuppress person for about a year and a half, slowly evolving and pandemic 2 years ago. Now so an example of a viral scheme. So what are we gonna do about improving vaccination? And then I'm also like, I'm a big person, May. And this is a Jim Grant to the late Jim Grant. He was appointed by Jimmy Carter to be unicef director in 1,980 and he was involved with actually realize that, you know, kids really aren't getting vaccinated. You know, that's like, that's like really disillusioning vaccines. What's the point of making a new vaccine if kids are getting vaccinated vaccinated.
- But it's much better than it was in 1980. Because Jim Grant said, Okay, if we're gonna change this first. All we have to measure how many kids are getting vaccinated. So you look for Tetus, because that's you know, that's the easiest you know. Best vaccine any any you know, through multiple times about half the children. We're getting the tetus vaccine.
- So she measure it first, and then you set a goal. So you said the goal said, Okay, like, in 10 years, use that school is to make 90% of children vaccinated against Tedness. And and he succeeded. And this is like the Api. This is the expanded program and immunization. So this continues today.
- See, like the the blue line on the far left there. That's 50 at 50. That's tenness theory that they succeeded in getting that up to 90% from 1980 out to, you know, 2019, and hepatitis B, which is certainly our, our, the topic today, like that pink line. And you can sort of see that that went from nothing until this. We have, you know, over 60% of children.
- So a a wonderful program there's been, you know, every 2 steps forward, one step back with the covid pandemic interfere with childhood vaccination. Also with

instability. Total instability is a big problem like for the countries in Africa had military coups in the last 12 months. So it's yeah, II do work with the World health organization, polio eradication. What W. Joe is that is like you can't work with the

- Director of Health for the country because he or she is probably gonna lose their job like the next turn over the go of the government is what they do. They go one level below, and they work with the person who's in charge, like in in in the Us. Would be like versus trying to help for Virginia, you know, and then kind of that's some way to try to overcome that. But there's there's still like big problems with that saying, Children!
- And so but again, last half full. There's been tremendous advances like the decrease in chronic hepatitis b virus infection with that birth dose of hepatitis. These dramatic decline from about 2.5 million cases to 500,000.
- So that's that's great. And it could be better. And then that's sort of like the focus probably got is it? Really that super is anywhere like 65 to 90% of people will have a protective antibody response. They have vaccine. I wonder if people it's never, ever respond to that vaccine so interesting, how vaccination changes
- HIV vaccine for me. So personal problem. But it's it's it's a big problem. As far as like, you know, we probably gotta get these children 38 years old. I'm gonna go visit him tonight.
- 40 years and the advances, the opportunities to do stuff is just it's just amazing. And so we thought, we're working with Alex Mensur, and so he's at us running on my favorite route. But with Alex we tested this hypothesis. You wanna like have like a hypothesis, something that is testable. But yeah, well, this vaccine's not working very well cause it shows that our responding are genetically different.
- And so how do you go about? Zoom, you know, testing it could be. There's environmental things so that that maybe respond as well. Genetic reason why children are not responding to this vaccine. And so how do you go about doing that? So that take a step back. This is, gonna ask for show of hands, or you're gonna have like, vote on one of 3 choices here about how different, or each of us in this room as humans. And then way, one way you can do that is something called a single nucleotide polymorphism. And so that is your genome like, I might have an A if this position and you know Eric, might have a a T, and that's a step or a single polymorphism. And that's an example of genetic differences between us. And so and I actually asked a room full of geneticists at the same, or institute this question. They got it wrong, so don't feel badly, you know, right? So how many people vote that if we sequence any 2 people in this room that one out of every 1,000 base would be different. So how many 1,000, so one out of 10,000, right in the middle. That's always safe. Right? Okay? Then, we're equally split. It's actually it's one out of a thousand.
- Isn't that amazing? You know, this is how incredibly diverse each of us are. Now, a lot of the snips are probably not important. But you know, just even like, you know, 1% of that is changing our response to the vaccine infection that that's huge. And so how do you go about like looking to sort of see if one of these polymorphism is associated with vaccine response. So we have, like Steve, ratio, we have a set of public health genomics. And so we worked with them and you can like screen through the entire human genome. Looking for these mile markers all the way through the genome you can measure like. Usually we measure about that 8 million of them at once, but they're scattered throughout the genome. So if you find a snip this difference, say, between a child who responded to hepatitis b versus one who

did not. That's pointing you to the right location up toward the restaurant is in the outer banks. That's probably a part of the genome that's important for a a response to this vaccine. And so this is one so called a genome, wide association study.

- And these are like incredibly common today. This is just showing you like the increase in in that have been done, you know, since from 2018 to 2022. It's into almost exponential.
- This one for kidney stones, you know. So you're you're a number of genes for which is a genetic polymorphism that is different between someone with kidney stones without. It's been done for coronary artery disease. As well. And so what we did is to vaccinate a thousand children at birth and when you're age we just measured how much response correlate with anybody sniffs through the through the human genome. And this actually shows up the passage of time here. So 1999 was when I had my first cohort in Bangladesh. I was working in there with Rosh will hop, and then you can see, like almost 25 years later, there's the 2 of us at the infectious disease being in Chicago and the the women that are there are the women. They're visiting children every day these cohorts, and then helping us to do studies like this.
- Sorry I hit the wrong button again. Oh, God, this is this is this video is not gonna work, but just to show you like the environment that we work into this community. We have the field research assistance. Who visit the children twice a week, live in the community. They're college educated. And so you know, it's midnight in Bangladesh right now says that right this moment. But when we're in the office thing children in these communities.
- And so so we have this opportunity because of those field research assistance because of the center of public health genomics because of our semester to ask this question, is there a genetic difference. And yes, it's the answer is, yes. So if you haven't seen us before, on the far left is chrome zone number one all the way through chromosome 22. And what those little dots are those single nucleotide polymorphism, or those mile markers in the human genome and the y-axis is the log of the p-value. The p-value for this association is about 10 to the minus 30.
- You have to have, like a P. Value, but 10 to minus 8 in order for fees significant. You're comparing millions of things.
- One? Just so it's do you have a good anti response or not? Or we're looking at 8 million snaps. So you have to divide your P value by 8 million. So that's why these P guys are so fantastic small. But so you see, each of those little dots is one of those single newly piped polymorphism that we're measuring. So there's a whole region there that's that that's tracking with whether you have a good invite response or not. And, Chris, I was very 6, is very, very interesting as an immunologist, because that's where Hla is.
- And so this is mapping like, right into controlling your vaccine responses. And so you're gonna see something that's different. This is where it would be and not to belabor this. But we have, like 2 different classes of Hoa, and so class one is where antigens are presented to Cdt cells class 2, which is where this polymorphism is, is, we're answers presented to CD, 4 T cells and CD, 4 T. Cells are what help be self to make antibody. And so what we discovered was, a a polymorphism in a class to allele, and you can find, map it, get it down in so-called Vpa allele and
- that this one allele was responsible for the difference in antibody responses that we're seeing. So why could that be? Well, first of all. So you know, Pente being presented from the which is what is going to make be self to make antibody. So it's made sense.

- And then, if you actually looked at the crystal structure, you could sort of see how the the virus peptide could no longer bind in the cleft, and so this again near the end, always give the audience help with the talks almost over, almost over. So but so we have occasions of this ours. The virus has mutated to evade vaccination with this simple vaccine the energy expect seeing all this received.
- And so this is actually present, preventing Peptides process from the being presented on class to to see cells, to make that surface antibody surface management antibody response and through modeling, Alex Mensur was able to see like that. If we could include what's called the Pre as management, we should be able to get around this problem. So what I haven't told you if you would. We look at a those 3 blue bars, the bottom of those blue bars? That's what we all have vaccine with. This is called the short form of the surface, and this is what the but this is what's being used all around the world. The virus has evaded that this to some extent, which is the reason why 20% of the children did not have an antibody response. But you go to the longer ones as we go to the left. That's the medium, then the long size or the Pre. The Pre. S. One antigens. Those would still be predicted to be valid, and to be presented by class to the idea is that if we had a vaccine that instead of the one that uses like the smallest blue box. There it used the biggest one that would be successful. And in fact, we do have that vaccine now. And so since this work has been done. There's not through anything that I've done, but there's a new vaccine called the preheo vaccine, and it has that longer service the Antigen. And if you look at this graph out of the medical letter, you can sort of see, like the now this, the response to the energics vaccine, which is like 76% and someone under 18 years age move goes up to 91. So a solution to the problem of vaccine children prevent chronic hepatitis. B, so and so I'll just kind of close. So this is a picture of the field research assistance that that are in the community every day with my colleague Roger, who leads everything in Bangladesh.
- And then so the last slide here so just like to summarize vaccine that's classically uses is failing about one out of 5 children right now, because these vaccine escape. This is a DNA virus. It's evolving to evade the vaccine.
- And this new generation of hepatitis B vaccines is promising to be more effective. But it's like to do any good vaccine children. And that's like the real challenge, especially in sub-saharan Africa, is just getting children. Vaccines. We're having epidemics and did theory. There's not a much point talking about a new hepatitis b vaccine. So, but if we can prevent medicine, thank you. So thank you for your attention. Questions on Zoom.
- if you ideally have them protected, or also HIV. So I was curious. If this is a presumably healthy cohort of children for the most part. But are there any studies looking at similar things in those populations. Is it a totally different? Is there genetic cases?
- And so I don't know but I would appreciate them would be more effective because you're right raising is issues, environmental reasons that people don't respond to vaccines in addition to genetics or nature and nurture. So I think I actually forget the name of that vaccine that that's like the last one that I got. That also didn't work for me. But Cbg to it might get really like boost in response really become very rational. Now, recognition receptors, we can actually design vaccines, activate like the right pulley receptors. I hope that they'll get rolled out like for, like the patients that you care compromise. And thanks to that question it's difficult. Have one in the chat class to, because that's what presents to T cell help? Really? Well, and any

anything you inject into a child seems to work well. The world vaccines don't work with this as well, but that's because the environmental issues of all the infections these children have. They all map to class to hepatitis. Widest infections. Does.

- Thanks for the talk. I'm great. just a question about
- Why does is it not possible to vaccinate and have any effect on individuals that already have chronic? So certainly prevention is easier. You know it's easier to prevent that infection than they have a therapeutic vaccine but is there any you know any efforts in that direction. Different Antigens, different attributes, or something t to use the vaccine with people there. Chronically great question, and I don't know the answer to that, but it makes a really good sense to try like a therapeutic. Somebody who's got the infection can boost the immune response, you know, generally above this whole field of like using therapy, and that's one of my dreams. We'll be doing just what you described Eric. In the future. Therapeutic vaccines. Give me a modulator set to treat infectious diseases and thank you.
- Forgive me if it's like Tom knows. But the new vaccines that the Pre. Have braille. Are you talking about, are they available? Yeah. And this so like, who gets images? I mean that they're gonna be the new vaccine that everyone gets, is it for 4 non responders, specific indications for the new vaccines as a 2022. So it's been actually yeah, I missed this until teach something, you learn more than anybody else. So so it's been out for, for all you know, over a year now. I imagine that, like everything else, is probably more expensive than the original ones. And so it'll be the reserve for people that are non responders, countries, everything is so like they either. Rotavirus vaccine, for example, made a dollar a dose, India, where it's like hundreds of dollars a dose in the Us. So presumably this technology will get rolled out in in countries like India, so they'll be using for every child better vaccine to be any disadvantage to having all 3. All right. Thanks. Everyone.