[MUSIC PLAYING]

NAUDIA JONASSAINT: So I'm going to talk a little bit about viral hepatitis. And I've given part of this talk before. I just want to warn you all, I'm not going to talk anything about specific treatments for viral hepatitis, but a little bit about kind of our overall thinking in regards to viral hepatitis. And today, I'm going to talk about hepatitis C first, and then I'm going to talk a little bit about hepatitis B, because there's just some fresh off the press literature in regards to this-- in regards to this issue.

So I don't have any financial disclosures. I just want to say this, because I think everyone in the room knows it, is that the liver has no bridge. And the reason why I became a hepatologist is exactly that reason, because I felt like studying an organ that basically has no replacement. I can argue, beacause I see RJ in the back, small bowel also would be on the list.

But essentially, for everything else, for kidney you have dialysis, for the heart, you have the VAD. You can use insulin for the pancreas. All of these things have somewhat of a bridge, something that if it's not functioning you could essentially use, but the liver does not fundamentally have that.

With that in mind, realize that hepatitis C still is the leading cause for transplantation in the United States. And I think over the next 10 to 20 years, we're going to be talking about something very different. And I'll tell you some of the overall predictors of how hepatitis C could become a rare disease if handled properly and treated properly in the United States. But for right now, hepatitis C still is kind of our biggest issue when we consider what the indications for transplantation in the United States are. And I think that this is going to be overcome quite certainly by NASH in the future. And alcohol is trying to run quickly behind that.

So when we think about the burden of hepatitis C, it causes a significant burden on the health system in the United States. It's the leading cause for transplantation in the United States, but in addition, it affects 1% to 5% of the population. And they will eventually die from complications of either cirrhosis and/or liver cancer.

It is thought that the total cost is expected to rise from 2012 being $6.5 billion to $9.1 billion in 2024. And I think that those are old predictors. When we think about the cost of hepatitis C and those people, both in the general population and disenfranchised marginal populations that have hepatitis C, I think that our costs of the disease is going to be much, much higher than that.

So just to refresh our memories, remember that the progression to cirrhosis in hepatitis C happens over decades. So for us, when we see someone in clinic that's 25 or 30, we very rarely are running to treat their hepatitis C. Certainly, from a public health perspective and a population health perspective, this is very important. But most of the time, was sure certainty, we can tell that person, unless they've been using IV drugs or they've had an exposure from the time of birth that they're unlikely to be cirrhotic in that scenario.

If I see a 25-year-old who's only been using for five years, it's very unlikely that that person is going to have cirrhosis at the time that I'm seeing them in clinic. So what we're trying to prevent from happening is this natural progression of disease from hepatitis C to chronic hepatitis, and then cirrhosis, and then people going on to develop decompensated cirrhosis and very, very complex end stage liver disease and HCC, for which a lot of these patients have probably a 2% to 3% per year risk of developing HCC once they get to the cirrhotic endpoint. Just remember, just as something quick, the 80-20 rule in medicine normally applies.

So 80% of those people who are exposed to hepatitis C in their lifetime are going to go on to develop chronic disease, and 20% of those people are going to spontaneously clear. So whenever you see hepatitis C in clinic, remember, a hepatitis C antibody does not connotate active disease. That really suggests that you've been exposed.

80% of those people will have chronic disease meaning they have virus in their blood. But the other 20%, maybe even up to 40%, has spontaneously cleared the virus on their own. So that's just something important to remember.

So what we're trying to do in essentially treating hepatitis C is we're trying to remove the idea that you would ever develop cirrhosis or ever develop the end stage complications of liver disease, but instead, kind of reverse your process and take you back to what could even be a normal liver parenchyma in this setting. What we know from studies is that liver fibrosis certainly regresses with hepatitis C treatment. So we tell people that you may have F2 fibrosis the day that I'm seeing you in clinic. You may be exposed to eight to 12 weeks of medication, and your fibrosis may regress.

And what we know from various studies done across the literature is that those people who have F0, so no fibrosis, to middle stage fibrosis in the F2 region, once those people have achieved SVR 12, meaning that they have a sustained viral response 12 weeks after finishing their last pill, those people can be discharged from therapy. Those people with more advanced fibrosis, meaning F3, F4 fibrosis, we don't know. So those people are really supposed to stay in care for the remainder of their lives. I think over the next five to 10 years we will be able to tell what the overall risk for those people progressing to HCC or end stage liver disease is despite the absence of virus, but I think we're going to find out that our original inclination was right, and that those people with no fibrosis don't need to be in treatment. And maybe even those people with F3 actually are going to experience some regression and not need to be surveyed, not need to undergo HCC surveillance long-term.

So just to remind ourselves, there has been a revolution of hepatitis C treatment over time. When I was in residency, we were still treating people with peginterferon and ribavirin. And over time that, has just been completely revolutionized to the point now where we have one to three pills once a day regiments that people take for between eight to 12 weeks and achieve cure. So that's been a true revolution for the treatment of hepatitis C over the course of-- over the course of our lifetimes.

This study that was published in the *Annals of Internal Medicine*-- and actually Alison Foulkes, who's not here anymore, was actually one of the co-authors on-- looked at whether or not in the setting of DAAs, what would happen to hepatitis C over time. And as you can see at the bottom line, that is if we treated people with the DAAs and they were maximally effective, somewhere in the 90% range, which most of the DAAs are-- nearly all of them because we don't accept anything really less than 95% efficacy for these medications-- that hepatitis C in 2050 would be classified as a rare disease.

So that's you know something just crazy to think about over a lifetime. Meaning that four to six million Americans probably had this disease. And 30 years from now, this would be considered something rare. In the realm of what I think it was Tevar saying he hasn't transplanted anybody with chronic hep B for probably a decade because in our minds, that's something that really doesn't even happen. And to think that this would happen with hepatitis C is pretty amazing.

But there's one thing that stands in between the possibility of that happening. And that's the opioid epidemic. And unfortunately for us in Western Pennsylvania, this is pretty profound. And has a pretty profound effect on the way that we practice medicine. But in addition, I think it has profound effects on what this means for transplantation for our patients in this region.

So just to remind you, when we look at the causes of death in the United States, overdose from drugs has basically increased 500% since 1990, which is just phenomenal to think about. This has had a profound impact on what this means for the people that are entering the donor pool in regions throughout the United States. Particularly in the rural United States, which we kind of have on many sides of us when we talk about southwestern Pennsylvania.

So just to kind of put this to the forefront of our minds is that every day in the commonwealth of Pennsylvania, 13 people die of overdose. 17 young people contract hepatitis C. And that the women infected with hepatitis C who don't know their status are constantly giving birth. So there is a huge push from the ASLD and the Infectious Disease Societies of America for ACOG, which basically dictates whether or not women, young women, are screened for hepatitis C. Which they are screened for hepatitis B because we know the vertical transmission of hepatitis B to children is about 5% or maybe a little bit higher to push the national guidelines such that young women are actually being screened for hepatitis C

And I'm actually part of a trial that's going on that's actually providing immediate treatment for women that deliver. They are getting their hepatitis C medication as they leave the hospital, and continuing hep C treatment with us in their suboxone replacement, clinics, et cetera. Because that is the most likely time for these women to be caught in care. And we know from some of the studies that are out of the New York centers, that people actually, and I know this is going to sound weird, but actually will use conscientiously even after cured of hepatitis C.

So women will say sero-segregate. Men and women will sero-segregate if they know they've been cleared of a viral disease, and they're going to use. Pennsylvania is not that liberal when it comes to clean needle use, needle exchange, and all of these other things. And I think we have a lot of work to do particularly in Pittsburgh in regards to our thoughts about drug use, and those other things, and trying to think about the public health implications of that.

The other thing that's interesting and has a great effect on us when we think about the donor pool is the age group in which people are actually being diagnosed. So we know that the age group, that 0 to 35 age group, people who would otherwise wise be young and have no other comorbid disease is actually increasing over time. So when you look at the blue bar, you actually see the increase in death across these groups. You're talking about-- sorry. An HCV presentation across this group. And that younger population is growing over time, and that's going to mean something significant in regards to the donor pool.

You can see here when you look at southwestern Pennsylvania and you look overall at the reported cases of hepatitis C in the group 15 to 35, that there is a profound cluster around both Pittsburgh and Philadelphia. And those are going to be areas that are going to be quite affected by the opioid epidemic and again the donor pool as it relates to hepatitis C. In addition, on this chart, and can't really see it very well. But believe me when I say that the counties most affected by overdose deaths are the ones that are right in and around Pittsburgh. So the ones Westmoreland County, butler, all of those areas are greatly affected by this.

So then the question becomes not only its role in transplantation, but what do we do? So I'm only going to briefly talk about medication. And only because in the realm in which we were really considering hepatitis C treatment two or three years ago, it changed the way we thought about things. And that was really of about three *New England Journal Medicine* papers that came out in the same December, 31, 2015 *New England Journal of Medicine,* which was the first pan-genotypic medication called Sofosbuvir-Velpatasvir. Or what we know from his trade name Epclusa.

And for the first time, we were seeing greater than 99% SVR in patients with and without compensated cirrhosis in all of the genotypes. So people were starting to think, OK, well we can treat hepatitis C. We can really get over this thing. This is something that's going to be reasonable. And we can start even doing these things without knowing the genotype. And I think since this time, other medications have come out that are also pan-genotypic. And give us the confidence that we're going to be able to tackle this. But the opioid epidemic still stands in our way.

This I just wanted to show you briefly as I move forward in regards to thinking about how does hepatitis C, the donor pool, and all of those things converge on what we do and the decisions that we make in regards to our patients on a daily basis. And this is really looking at the kidney list to say that we know people who are staying on the wait list are more likely to die if we let them stay on the waitlist rather than transplanting them with a HCV positive organ. So if you ask me as a hepatologist if I had cirrhosis, and I would want to HCV positive organ, you can sign me up 25 times. Because based on what I've already told you, this is more than a treatable disease.

And what you can't get over and what you can't reverse is death on the waiting list from that process. OK. So everything started really rolling pretty quickly because on the front of the *Boston Globe* was actually one of my med school classmates, Parsia, on the left when this young man that was being seen at MJH decided that he wanted to accept a hepatitis c liver positive liver transplant as opposed to continue to deteriorate from PSC. And they decided to do this transplant. And he was treated with 12 weeks of medication, and became hep C negative fairly quickly.

So this kind of got people thinking, well, why wouldn't we do this? It's ironic because some people feel very conflicted about this. And we give people CMV. We expose people to CMV. Something that we can't cure, and can stay around for a very long period of time, and be a pain in our behinds post transplantation. But have a very, very hard time accepting the idea that we would give someone hepatitis C during the course of transplantation. Remember this is a curable disease. And I think we have to get over the natural stigma that goes with how people might have actually gotten the disease process, and understand that these organs provide a possibility of cure. And in addition to that, the patient can be cured after transplantation.

And notice, it's interesting because even still they're saying hepatitis C tainted liver. I mean, just the connotation of that has some negative connotation with it. So that started the ball rolling, and people just started to say, well, if my patients are otherwise going to die, let's just start doing this thing. So people started doing this in heart. People started doing it in lungs. And this is just another paper from 2017 where they decided to essentially use a hepatitis C donor for patient that was otherwise going to die on the heart transplant list.

So many papers would come out after this kind of questioning the idea of whether or not we should use hep C positive disease liver donors in response to essentially organ shortage. And we talked about allocation and reallocation in the concentric circles, which are going to really limit what we can do in regards to deceased donor transplantation in our region. And this is just something that needs to be heavily considered. So the American Society Of Transplantation came out in a consensus conference and said certainly we should be doing this. And some of the things are going to end up being institution specific. But this is something that we should consider doing for our patients because now we know that this is part of what is going to extend the donor pool, and end up being like a lifesaving measure.

So I think this is going to be probably the last thing that I discuss in regards to hepatitis c. But fresh off the press from two weeks ago was a large trial that was done at Harvard. Again, which I referred to before, in regard to that first *Boston Globe* article. And they looked at heart and lungs. And it was pretty interesting because they actually-- and this doesn't transmit great here. But they used four weeks of medication. Four weeks of medication in order to treat these patients. And the patients end up doing quite well.

When you look at it really plotted out, unfortunately how exactly heart and lung patients are lost to follow up I'm not exactly sure. But when you look, the majority of the patients that they see at follow up actually have SVR six months after being treated with four weeks of these medications. So remember, your treating day one after transplantation. You are not allowing the viral kinetics to overcome. And your treating almost immediately.

Remember also though there is one caveat here, which is this is a non-hepatotropic organ. Hep C is hepatotropic. It's going to essentially live in the liver. So again, the likelihood of transmission, these are all net positive. Meaning there is actual virus in the blood. So you are going to probably get positivity in all of these patients. But just remember when you're dealing with hepatotropic organs it's slightly different because we know that typically when we have NAT positive livers the likelihood that we're going to transmit that virus to somebody is 100%.

There is I think one reported case in the literature of someone actually getting a NAT positive organ, and actually not becoming viremic. So I just want to put a plug out there, which is across all organs, UPMC has decided to as part of our care across kidney, liver, heart, and lung to provide hepatitis C positive organs for those patients who are interested in signing up for this. Tivar is basically heading the PI portion of this study from the kidney standpoint. There's already been I think four hearts done. There was one done last week. And there's one set to be done probably in the next couple of-- probably is going to come up in the next couple of days. Again, someone was recently listed and is pretty sick. And I think two lungs have already been done. And we're starting to get going on the liver kidney portion of the trial.

So if you have any patients that you think might be interested, or you're seeing in clinic, please let me know. And I'm happy to talk to them. We are going to be having two educational sessions for patients to possibly sign up for their interest in this. Because I've talked about hepatitis C so many times before in the past, what was more interesting to me kind of was hepatitis B.

The role of hepatitis b in transplantation and using organs that have been exposed to hepatitis B in the past is pretty controversial. And there is a very, very wide variation about how institutions handle this. Our typical historic-- from a historic standpoint-- we did not use core antibody positive livers, and people who are not immune. Meaning for patients who are not surface antibody positive unless it was an emergency.

The institution that I came from, that was not the case. So I was actually interested and had been interested looking at this liver partly because I've been asked about this before and accepted core antibody positive livers for people who are not surface antibody positive. And the question is whether or not this is something that we should consider. And whether or not this is even controversial anymore.

So to date, there's been a lot of conflicting data regarding the use of hepatitis B core antibody positive livers in non-immune recipients. I'm hoping that I'm going to make an argument to you today that this is not that controversial anymore. That in order to extend the donor pool, we should be considering this. And there is a possibility, I think, in the next five to 10 years that we might be pushing this envelope a little bit further in order to continue to save the lives of our patients.

So this was a systematic review that was actually done in 2010 and published in the *Journal of Hepatology* looking at liver grafts that were hepatitis B core antibody positive. And looking at how patients responded, and how they did when they were hepatitis B naive. And whether or not those people developed de Novo hepatitis B. The one thing that I want to point out to you that may not be obvious to everybody in the crowd is that acute hepatitis B kills people. And acute hepatitis C does not. So you can have essentially what we would call acute or fulminant liver failure presentation from hepatitis B. And that almost is never going to happen as a reportable incident in the setting of hepatitis C.

So it's just very important to understand that in the background even though we can suppress hepatitis B, the reactivation or de novo hepatitis B could be a real killer in someone because in fact it can happen in a healthy population if you acquire hepatitis B acutely. So when they looked at patients who had essentially received a hepatitis B core antibody positive liver and they looked at people who were hepatitis B naive-- meaning they had never been exposed to hepatitis B in their lifetime-- this is really the overall percentage of people who develop de novo Hepatitis B. And you're talking about 48% of the population.

Now remember, these were the people essentially that didn't receive any prophylaxis after transplantation. So to say 48% of people who had never been exposed to hepatitis B, I would have actually probably predicted it was going to be a little bit higher in those people who received no prophylaxis. Meaning you did not get hepatitis B immunoglobulin, and you did not get any type of suppressive therapy meaning tenofovir, entecavir, or lamivudine in this population. So those are the people who actually did-- the percentage of people who actually develop the de novo hepatitis B after exposure to hepatitis b core organ.

When we look at those people then that received post-liver transplant prophylaxis, and we look at those people who are essentially hepatitis B naive, we're talking about 12% of the population. As opposed to those people who are surface antibody positive. And those are the people that we concern ourselves the most with at UPMC on the far-- what is going to be your far right. Those people who have some immunity. So essentially, we're being very safe. Right?

Zero people who had surface antibody, and then were further protected in some way, and got some type of prophylaxis after transplant developed de novo hepatitis. But what's important, if you just look at the surface of this study then it looks, OK, like this is pretty catastrophic. But remember this is a systematic review. So they're looking at a number of different studies. Very heterogeneous. And the population is a little bit different when you dive down into it.

So in 14 studies that looked at hepatitis B core to naive recipients, about 48% of patients, as I showed you before, developed de novo hepatitis B. More importantly though, when we look at all the studies across the board, surface antibody status really had no bearing on the probability of developing de novo hepatitis B. None of the studies looked at in that 2010 systematic review use the modern nucleocide. So there's no entecavir or tenacavir to be spoken of. All of these people either received a HBIG plus or minus lamivudine or HBIG alone, or lamivudine alone. OK. Or vaccination.

And then in addition to that, naive recipients that use Lam prophylaxis, none of them developed de novo hepatitis B unless they discontinued antiviral therapy. So when you really break down and look at the heterogeneity of the study, it's really to suggest that the surface antibody itself, in and of itself, does not per say protect against de novo hepatitis B when exposed to a core antibody positive liver. And in addition to that, there might be some other considerations that we might need to make in the future. And I'm going to talk a little bit more after I go through a couple of other studies.

So this was a study that was actually published in liver transplantation in 2015. And this there was a study done in children. And this looked at essentially de novo hepatitis B prophylaxis again with either hepatitis B vaccinations or HBIG in a pediatric population that, again, received core antibody livers. So when you look at de novo hepatitis B prophylaxis-- and this was mainly, again, done with vaccination and HBIG. So you're not even doing viral suppressive therapy. And you look at what people's overall status was. There was essentially not a humongous difference in that population of patients depending on what their antibody status was before they were exposed to the hepatitis B core antibody liver.

In addition to that, there are six people that somehow dropped off and did not receive any prophylaxis. And when you looked at those six people who received no prophylaxis-- again, they were not protected against the development of a de novo hepatitis B by vaccination, HBIG administration, which is immunoglobulin, or antiviral therapy. Three of them developed. So half of them developed de novo hepatitis B. Two of them were treated with lamivudine after the fact. And they negatively sero converted.

So no hepatitis B. All viral suppression in the blood. And then one of them essentially received Entecavir, and did great. And still had their graft at 18 years. One person was actually prophylaxed with vaccination in the second year after transplantation. And that patient also did very, very well for 17 years. And ended up having to be re-transplanted for portal vein thrombosis after 17 years of graft survival.

So the last study that I'm going to talk about-- which I think is very, very interesting-- this is actually has not been published yet. And is going to come out in the *Journal of Hematology* probably in the next couple of weeks is a retrospective study looking at these patients. So hepatitis B core antibodies going into core negative recipients. Realizing that the entire population, again, is not homogeneous.

So they did 548 core negatives and 416 core positive transplants. 108 of those went into hepatitis B surface antigen negative recipients. And they received, again, a core positive liver. When you look at on antiviral monotherapy prophylaxis alone with no HBIG use, only three of these patients developed hepatitis B infection, which is a risk of about 2.8%. And there is no significant difference in graft in patient survival when they looked across a 10 year time. So about a 10 year 80% survival in this patient population.

So when you look at it further broken down, you can see that there is hepatitis B surface antigen negative recipients, surface antigen positive recipients. So let's kind of consider ourselves the surface antibody positive recipients. Let's ignore them. They've been exposed to hepatitis B in their lifetime. And you might think, OK, well those people will naturally be protected. We would transplant them. The question remains in this side of the surface antigen negative recipients. And then further, not only those people that are surface antigen negative, but we also want to look at those people who are an anti-hepatitis B surface antibody negative.

So that's going to be if you go all the way over. You actually want to go to the negative negative patients. So all the way onto the far right side of the slide. So those 24 patients. And as you can see, in those people who are surface antigen negative, don't have the disease, have no protection, and have never been exposed, they have equal chance of getting de novo hepatitis B post transplantation.

So I think, again, this argues that because we didn't have such powerful drugs before-- we didn't have the tenofovirs of years we didn't have the entecavirs before. This may have been something that we may not have realized. That the risk might be reasonable for this population. So when you further look at this, and you just look at this from a patient's survival and a graft survival standpoint, looking 10 years out you can see that the survival is near 80% in both populations. And that the lines essentially cross and are not different.

When you look at those people who did develop. So the patients in that 2.8% of the population who did in fact develop de novo hepatitis B, you can see that all of those patients were treated with lamivudine. So again, we don't typically use lamivudine anymore in hepatitis B treatment because we know after about five years of treatment, a lot of people have break through. The resistance profile of lamivudine is suboptimal in the treatment of chronic hepatitis B. And a lot of people will have resistance, will develop resistance, and break through lamivudine over time.

We do sometimes continue people on it when they've been on it for a long period of time. And we sometimes will use some of these older medications when cost is prohibitive to patients affording tenofovir or entecavir therapy. But with entecavir becoming essentially generic and tenofovir also having a generic formulation, this should no longer be an issue.

So the last thing I'm going to talk about is something that I think is really truly pushing the envelope. And that is the idea that it might be safe to use people hepatitis B surface antigen positive donors in liver transplantation. And that gets extremely obviously extremely controversial because you're talking about this person has active disease. This is the person we would call an active disease carrier. And you're talking about giving this person a liver.

So they were a little bit ginger here. And they were provocative in the title. But when you really break it down, the majority of these patients hadn't been exposed to hepatitis B over their lifetime. So the majority of the patients who are receiving hepatitis B surface antigen positive livers had actually either been transplanted for chronic hepatitis B cirrhosis. Meaning they had been exposed to hepatitis B before, and might have had viral suppression. Or they had an HCC related to chronic hepatitis B. So obviously these studies are being done in the east where hepatitis B is essentially endemic in the population.

But what you will note is that there are some people in this population who are not hepatitis B positive. So when you look on the on the left hand side-- the second column after the titles, in the end you can see hepatitis B related diseases, yes. 90.5%. But there is a very, very small population of patients, 9.5% of these patients who had never been exposed to hepatitis B before in the past.

And then when you again look at patients survival, and you look at graft survival, those lines do not cross to suggest those patients seem to do just as well as the patients who had previously been exposed to hepatitis B before in the past. If we kind of really, really drill down and we look at what we care about the most, which is are you able to suppress virus after you transplant these people? Because what you fear is I can't suppress virus and that person ends up with something catastrophic like acute hepatitis B or fibrosing cholestatic hepatitis. And that just doesn't seem to be the case. Because when you look at long term follow up, and you look at that last follow up area, no one's viremic. Meaning there's all zeros in there hepatitis B DNA positive category.

So everyone's virus is suppressed when you look at them. And that doesn't matter what the mismatch is in regards to the donor and the recipient. So from a conclusion standpoint, hepatitis C remains the leading cause for liver transplantation in United States. And I think the pan-genotypic drugs have really just made standard difficult to treat disease very, very easy to treat.

The only thing standing in between us and hepatitis C being a rare disease is the opioid epidemic. And I think obviously the nation is aware, and people are really trying to try to stamp this out as an issue. The study of a solid organ transplantation and this idea that we would give hepatitis C positive organs to people who are hepatitis C negative, at most institutions in the country is going to become standard of care. So this is something that we're going to do as people are more accepting of this idea that hepatitis C is curable.

And I think in the upcoming years patients will continue to be faced with this question of whether or not they want to accept hepatitis C positive organs in the setting of stigma, which is something I feel like we should we should get over at this time because these are really lifesaving measures. And when faced with death, hepatitis C seems pretty appealing.

In regards to hepatitis B, I'm hoping that in what I've shown you at least in the new data, that the use of hepatitis B core antibody positive donors is safe. No matter what the antibody status. Those people who develop de novo hepatitis B did so after prophylaxis with lamivudine, which is kind of an outdated medication that we use only under certain circumstances. And the postulate there was really that people were likely to have this circular close covalent DNA. This cccDNA that's living in the liver. And then when lamivudine resistance profile is as low it is, you're having breakthrough virus.

There were no de novo hepatitis B cases in those patients in these studies that received entecavir. And there was no difference in de novo HCC. That simply seems to correlate with the development of cirrhosis in the population, regardless of what type of organ you received. So what I would suggest is that we continue to think about how to push the envelope. Start making sure that we extend the donor pool. And accept hepatitis B core antibody positive livers for patients. Realizing that really the thing that was previously standing between us and doing this safely was really the quality of the medications. And with tenofovir and entecavir, that has dramatically changed the landscape. That's all I have. Thank you.