



**BBGuy Essentials 106CE:
HDFN Essentials with Jen Andrews and Molly Sherwood
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Joe: On this episode of Blood Bank Guy Essentials...

Molly: Well, I think we should be encouraged that we are so lucky that even though this is a rare disease, it is treatable. And so I think having a mindset of expecting survival for these children is huge. And I think it's something that still needs to trickle through the system in some ways, because like we said, only 50 years ago, this was something that many people just assumed to be fatal, and it usually was.

Joe: Hi, everybody. Welcome to the Blood Bank Guy Essentials Podcast. My name is Joe Chaffin, and I am delighted to be your host for this episode, episode 106CE, as well as for this ongoing conversation that we've been having on this podcast for the last 10 years about the Essentials of Transfusion Medicine. I'm so honored that you're paying attention to this podcast and that you're listening to it. And thank you for your feedback. On this particular episode today, we're going to be discussing something that's a very, very important topic. It's hemolytic disease of the fetus and newborn, or HDFN.

My two guests today are extremely passionate about this topic as well. And I think you're going to find their insights to be very illuminating and in many cases kind of personal to them. You can find their full biographies on the show page for this episode. That's at BBGuy.org/106. But in brief, let me tell you about them.

Dr. Jen Andrews is professor of Pathology and Pediatrics at Vanderbilt University Medical Center. She is an expert, board certified, in Pediatrics and Transfusion Medicine and has a lot of interest and expertise in this particular topic today.

My second guest is named Molly Sherwood. Molly is the director of research at the Allo Hope Foundation. Molly works in HDFN research, education, and patient advocacy, and she also has a very personal connection to this disease, which you're going to hear about in just a moment.

Now, I want to be clear, this episode *is* eligible for up to one hour of free, yes, free continuing education credit, and that credit is offered generously through AABB. That credit is available to both physicians and laboratorians and others. Please check either my site at BBGuy.org/CE or directly at AABB.org/BBGuy to claim that free continuing education credit. And just to be clear, AABB has no editorial input into this podcast.

So we have a lot of ground to cover today, and I'm very excited that you're here. I said that before, but I really am. So, here's my conversation with Dr. Jen Andrews and Molly Sherwood.

Joe: Jen Andrews, welcome to the Blood Bank Guy Essentials podcast.

Jen: Thank you. Thanks for having me, Joe.

Joe: It's always great to see you and talk to you. You and I have known each other for a while. Molly Sherwood, you and I have not known each other for all that long, but thank you so much for joining us today.

Molly: Thanks so much for having me.

Joe: It is a wonderful thing to get... one of the great things about doing this podcast is meeting people that are passionate about things that I care about. And I think that you dovetail into that absolutely perfectly, Molly. And I know a little bit about your story, but I wonder if you'd be willing to just share it with our listeners a little bit, to share how what we're talking about today, hemolytic disease of the fetus and newborn and the prevention, the treatment, everything that goes around HDFN and moms who have formed antibodies that can cause HDFN, how has this impacted you? And then how has that impacted what you do professionally and with your organization?

Molly: Well, I pinch myself sometimes. I can't really believe that I was somewhere else completely in my life. And now I am here with you guys having this conversation today. I was actually, my sort of trajectory shifted when I was pregnant with my second son. And I was experiencing some bleeding during that pregnancy. And so I went to the ER to get checked out. And during that time, they were checking my blood type to see if I was going to need Rh immune globulin since I was bleeding. And they said, oh, well, you are O negative. And so since you're Rh-negative, you're going to need Rh immune globulin so you don't develop antibodies. And I said, that is not—that's not possible because I'm O positive. And I am so sure that I'm going to be sassy about it because my last pregnancy, I knew I typed O positive and I never received Rh immune globulin. And so I made them rerun it. Like, how rude is that?

Joe: No, not rude, by the way. That's awesome.

Molly: Well, I sure did. We redrew everything and they ran it again. And then the nurse, I will never forget, the nurse popped his head in the doorway, just popped in and said, well, you're still O-negative, but you do have antibodies. And so that must have been what you were thinking of, which, of course, was not what I was thinking of because I knew nothing about that. And so I left that day knowing only that. I had a paper printed out that just said antibody plus, big circle around it. And I didn't know what antibody or what that meant. But as it turned out, I was typing O positive and O negative because I have a weak D phenotype, which I read about on your website that many years ago, which is so cool. So you have educated me for a very long time. But that was totally unrelated to having red cell antibodies. And so as it turns out, I have anti-S and anti-E antibodies, which kind of cropped up as that pregnancy went on. Through that experience, you know, my background is in research and sort of like clinical strategy.

And so I feel so lucky that I could just dive in and start consuming and consuming about what needs to be done for management of these pregnancies. But I landed in the support group of the Allo Hope Foundation and just learned through my own experiences for the advocacy I needed to do and through the thousands of other women who go through this every day and have to be a really active part of their team

to make sure that their baby is safe. And so there's a lot of work to be done in service to those women. And so I now serve as the director of research at the Allo Hope Foundation. And the foundation does a lot of stuff. We do patient support. We help connect patients to regional experts around the world. We'll do blood drives in rural areas outside of the U.S. And just increase awareness and clinical education, too, for best practices to keep these babies safe.

Joe: That's wonderful. But you skipped one part. Did the pregnancy go okay? Did everything go okay with your baby?

Molly: That's kind of important. I know. I am so lucky. So that pregnancy, he was antigen negative. So even though I had the antibodies, he was not affected. And the next pregnancy, I had another healthy son. And I just was very, very lucky that even though he was antigen positive, he needed very close monitoring but didn't need intervention for his HDFN. And so I'm a very fortunate case. And I know that women deserve the same outcomes that I received.

Joe: Well, Molly, thank you for sharing all that. And we're going to talk a lot to you today about what you and your organization have seen and are seeing in terms of how we can do all this better, how we can what what resources we can apply and how we can make this better for patients who are at risk of HDFN all the way through patients who are affected by HDFN. But Jen, I wonder if you would start us off from your perspective of talking a little bit about. Well, I mean, I've heard you say that HDFN is your favorite topic, which, you know, again, tells what a nerd you and I both are because it's one of mine. As well. But how come? Why is HDFN such a personal and favorite topic for you?

Jen: Yeah, well, I think it's because of how I'm trained. So I'm a pediatric hematologist by training. And then all of you in transfusion medicine are so welcoming that you actually allow us non-pathologists to come do fellowships in transfusion medicine, which is what I did. And you can imagine it's just the perfect marriage, right? Because I understand the hemolysis and the anemia in the pediatric, the neonatal patient. And then I really understand, after nerding out for a year of fellowship, all these minor red blood cell antibodies, which even amongst pathologists, like when I'm teaching brand new interns, for example, you know, maybe they've heard of Rh immunoglobulin, which prevents sensitization against the D antigen, but often they've never heard of any of the other, you know, hundreds of minor red blood cell antibodies. So for me, professionally, it's just a really nice niche that marries two of my fields.

Joe: So it's a little bit of a passion project for you in many ways.

Jen: Yeah, for sure. The best part about it too is if you manage it well and you get the baby through the first couple of months of life, they're quote unquote cured, right? It never comes back. It never recurs. And that's not always a happy story and a happy ending, but usually it is.

Joe: So to be clear, you actually, as a pediatric hematologist, you have actually cared for these babies as a patient-facing physician. You've seen it from all sides.

Jen: Yeah. And it's interesting now because my center has great maternal fetal medicine experts that help care for these infants before they're born, right? So I often now am meeting patients in utero, which how strange is that? Sometimes the This neonatal

intensive care unit like consults me and I say, oh, great. I've been talking to these parents for three months. I'm like, how is that possible?

Joe: Yes, you're a magician, Jen. That's what you are. That's fantastic. I love it. Well, so I think that it's important that we that we kind of set the groundwork for all of this. With that background, I think it's super important to make sure that the learners listening to this podcast have a really clear idea of the basic pathophysiology of this entire process. So when we talk about hemolytic disease of the fetus and newborn, Jen, can you walk us through just kind of the big picture of the pathophysiology of HDFN in terms of what we look for, how it occurs, and just the general overall viewpoint of how HDFN happens? Can you talk us through that?

Jen: Sure. So basically, a woman needs to become sensitized to one of those red blood cell antigens. And so there's a couple of big ways. Molly actually alluded to one, bleeding during a previous pregnancy. So pregnancy itself is often a sensitizing event. Even a non-clinically sort of noticeable bleed, there's often minor blood crossing between mom and baby. So pregnancy is definitely by far a big sensitizing event. And then red cell transfusion itself, don't forget. Lots of healthy people during traumas, for example, might have just a one-time red cell transfusion event. Organ transplants, as we're transplanting more and more patients and they're living and becoming healthy enough to have children of their own, that's a sensitizing event. And then don't forget IV drug use. So really, anytime your blood is mixing with somebody else's blood, that's a potential sensitizing event.

And the problem is the fetus is going to have maternally and paternally inherited red blood cell antigens. So for example, when a previous pregnancy is your sensitizing event, and let's say there's a mismatch between mom and dad, and that same couple goes on to have another baby together, mom makes more of that antibody the next time she's exposed to it. So the subsequent pregnancy, right? And when that titer rises and the antibody is able to bind red blood cell antigens on the fetal side, once they're developed, which typically happens in the second trimester or later, then that fetus is at risk for having anemia. And so what's happening in the fetus is sometimes they're able to keep up with a little bit of red cell loss, but sometimes they're not. And so when it's more severe, they really start reverting back to earlier fetal life and they start making red cells in organs that aren't really responsible for them later in life, like the liver and the spleen.

And so you get this crowding out of the normal hepatocytes with hematopoiesis. And the normal hepatocytes, remember, are making all these really important proteins for oncotic pressure, right? Like albumin. And so when you just can't make enough, you start to have what looks like and what we call still hydrops fetalis, right? And so massive sort of swelling everywhere. And you go into high output cardiac failure if this is not discovered and sort of treated quite quickly. After birth two, if this process continues, the issue becomes sort of twofold, right? So you have that whole thing going on. And then normally in fetal life during hemolysis, when the insides of the red cell are spilling out into the vasculature, not a huge problem in utero. I mean, it's not great, right? But mom's liver can process, for example, unbound bilirubin. But after birth, that fetal liver is really immature, even in term neonates, right?

And so that unbound or unconjugated bilirubin crosses that pretty fragile blood-brain barrier. It's really fragile for the first couple of days after birth. And that bilirubin can actually deposit into the parts of the brainstem that are responsible for movement. And so you can get a really serious illness called kernicterus, which sort of looks like cerebral palsy when you're actually seeing a child with kernicterus. And it's a lifelong disorder. So that can be really serious. So the anemia again, right? The hydrops. And so at that point, you're dealing with an infant who's extremely ill in the ICU. They often need medications to support their blood pressure. They're in high-output cardiac failure. And they really need very careful management. Their fluid status is really tricky to deal with. Hydrops, we don't see a lot in the United States from HDFN, but we certainly see it from other causes. And it's a really tricky illness, sort of end organ pathway illness to deal with.

Joe: We'll swing back around to talking about treatment in just a minute. But Molly, there's something I want to come back to you on that Jen had mentioned that there are several ways for moms to get, potential moms to get alloimmunized. And she, of course, talked about the classic way, what you went through with bleeding during your first pregnancy and exposure during your first pregnancy. But Jen also mentioned other ways of getting immunized. Do you guys have either any data from your experience or any just overall thoughts about learners think about this as it only happens in the second pregnancy? And obviously, one can get a transfusion or IV drug use or the other things that Jen would transplant, the things that Jen was talking about, without having had a pregnancy. What are you guys seeing in terms of how much of a problem this is in first pregnancies for women?

Molly: Yeah, it does happen in first pregnancies, certainly less often. But we have cases where, so for example, our director of development, Katie, who I know Jen knows as well, she found out during a blood donation before becoming pregnant that she had developed anti-D antibodies. But by the time she became pregnant, they were too low to titer. And so throughout that pregnancy, though, it completely ramped up and she still needed four intrauterine transfusions. And so it does happen in first affected pregnancies, not as often as it does in subsequent pregnancies. But it can sometimes ramp up during that process if they've been sensitized early in the pregnancy or through another one of the events that we talked about. And we're also seeing in our group, I do see more moms who are sensitized from transfusion. A lot of times it'll be that they have had a pregnancy before, but they received a transfusion for postpartum hemorrhage at the delivery. And then in those cases, those moms usually have more than one antibody.

And so, you know, it's important to keep in mind that in the U.S., we cross-match really only for ABO and then Rh status. We're not cross-matching for the other major antigens, which some of the other countries do do. They'll cross-match for Kell and C and E, or at least Kell, which I know you've talked about in the past, Joe, but Kell can be more severe for HDFN. And so in those countries, they've been able to reduce sensitization rates by doing that extended crossmatch. But here we're not yet doing that. And so we still see a lot of moms being sensitized from that, too.

Joe: Boy, you are you are hitting a hot button for me. And Jen is about to jump off the screen here. Yeah. Well, you know, I can't help but take that that sidebar for just a second.

Molly: Let's go for it. I'll take it, too.

Joe: I am so, I very much am convinced that we in the United States are, I don't know if it's a disservice that might be too strong, but Jen, I'd love your take on this. For more extended prophylactic matching of patients, I think that what is happening in some countries in Europe, especially as Molly just alluded to, at least for Rh and big K, you know, the Cs and the Es and big K. Can we do a better job of that, Jen? I mean, what would it take to convince people of that, do you think?

Jen: Yeah, I want to know, too. I know. And I'm a believer, just like you guys. I mean, unfortunately, I think it all comes down to cost. It just seems so simple for the big K antigen to match. Yeah, doesn't it? Yeah, any woman less than age 50, right? So, like, we set up things on purpose, right, to catch all these sensitizing events, right? My whole job in the blood bank is to make sure no one has a transfusion reaction from a previous antibody, right, and to prevent HDFN. This would be so easy. And our friends in Europe and Canada have been doing this for a really long time. And sometimes it's just embarrassing to go to international conferences and sort of hang my shame. Like, I know we don't do it in the U.S., but, you know, it all comes down to cost, unfortunately. And so and the other thing is, let's say I decide to do it at my hospital because I just truly think it's the right thing to do. Right.

And let's say my C-suite is like, OK, we're behind you, Jen. We're going to let you match on Kell in addition to ABO and RhD for all women less than 50. Well, what if a patient from my hospital goes to a hospital across town and they don't match, right? And so there's plenty of evidence out there. The AMIGO trial for the learners, you can go read that. Basically showing that like if everyone does it, great. But the problem is there's all these sort of spillage events where women are getting sensitized anyway. A super important one is intrauterine transfusions themselves. So I'm a big advocate of matching mom's minor red blood cell antigens during that therapy. And not all hospitals do that. So that's something your hospital can do if they don't now. Yeah, unfortunately, I think it all comes down to cost. Maybe we'll get there.

Joe: Okay, so let's dive into a couple of things here real fast. Jen, you talked about the pathophysiology. Let's dive into neurodeme a little bit and let's talk about what it requires for one of those antibodies in an allo-immunized mom to get from mom to baby? Because I think our perspective on that has changed over the years. So can you summarize that for us in terms of what antibody types are required and how those antibodies get from mom to baby?

Jen: Oh, super good question. So back to the basics. You're exactly right, Joe. So essentially, remember this from medical school, those big IgM antibodies like the ABO isohemagglutinins, right? They're pentamers. So they cannot cross the placenta. And for the learners listening, IgM, Michigan cold, they usually react at cold temperatures when you're studying for your boards too. I think Joe has a whole podcast on that. And then IgG, warm, Georgia's warm. Those are the Y-shaped, if you're not watching the video that we're recording at the same time, those are the Y-shaped antibodies that

cross the placenta, usually sometime in the second trimester. So not a receptor that does that well during the first trimester. And so it happens later in the pregnancy.

Obviously, there's certain antibodies that are never, by definition, going to cause HDFN. And those that are those that we know are IgM, right? So it's important to kind of say, first off, we think about ABO antibodies as IgM, but they actually, there is a little bit of IgG in those classes. And so the board question is what is the most common cause of HDFN? It's actually ABO incompatibility between mom and fetus, not one of these minor red blood cell antibodies causing HDFN. But why is it not serious? Well, one big reason is the ABO antigen is not well formed on the fetal red cell. And another big reason, especially for the learners, is remember those ABO antigens are on more than just the red cell, right? They're on other endothelial tissues. And so they get quote unquote sopped up when they do cross the placenta. They bind non-RBC ABO antigens. So they don't cause hemolytic disease of the newborn for the most part.

Sometimes they can cause mild disease, and rarely severe disease. And of course, I've seen it because I live in the space. Moms who are originally from Africa, like their ancestry is African. If they are type O and they're having a B—as in the blood group; it doesn't have to be a boy, it can be a girl. But if they're having a B infant, it can be very severe HDFN. There's something about that particular isohemagglutinin, but that's a rare case.

Joe: All right, Molly. So I want to swing back to you and talk a little bit about something that I know that you personally and your organization, Allo Hope are passionate about. And that's how this all should in a perfect world go. In other words, I know we don't live in a perfect world, but under normal circumstances, how should moms normally be monitored from the first time they visit their obstetrician and onward through a pregnancy in terms of what testing should be done? How should we be following these patients to make sure that they're managed appropriately?

Molly: So first of all, I'm very fortunate that I get to say that Jen and I recently were part of a big multidisciplinary consensus panel that published some clinical practice guidelines for pregnancy management of alloimmunization, which was so needed. And I can say hand on heart that with very few exceptions, the children that we have seen die to HDFN would have likely had a different outcome if these protocols were implemented in their pregnancies. So that's been huge for everybody, but really personally so meaningful in our organization. So that came out that JAMA Network Open at the end of 2025. So everything I share is reflective of what those guidelines say. But typically, a mom finds out most often that she has red cell antibodies during her first trimester routine blood work, which is standard of care in developed countries.

And so it'll come back positive for antibodies. And then you guys know it'll ID and usually it should reflexively report on a titer as well. And so at that point, you know, we'll find out that, say, the mom has an anti-E titer of 16 or something like that. So then that's sort of this triage mode of first we have to figure out if the baby is antigen positive. So there's a couple of things we can do to figure that out, because if they're antigen negative, it doesn't matter how high the antibody titer is. The baby is totally unaffected.

But assuming the baby does turn out to be antigen positive, we can figure that out with now non-invasive prenatal testing called NIPT testing that can test the cell-free fetal DNA and can do that for lots of red cell antigens now. So that can be done non-invasively with a blood draw on the mom starting around 10 weeks gestation. But if we don't do that for whatever reason, another option is an amniocentesis, which is sort of like plan B, because the amnio itself, like Jen was even touching on with being sensitized from transfusion, just the invasiveness can mix things up and increase the mom's antibody titer. So not ideal. So the cell-free DNA is great.

Joe: I want to expand on cell-free DNA a little bit because that's something that is reasonably new for us here in the United States. From my perspective, it's such an incredible tool that I've heard about this being in use in other countries. We talked about other stuff that's happening in other countries. I've heard about this for a long time, especially in Europe, being used. So can you expand on that just a little bit? How good is this testing? I mean, can we really rely on it?

Molly: So the Netherlands at Sanquin Labs has been doing this for years. And we used to have moms ship their own samples like FedEx to Sanquin and they would run it for us. I don't think they ever—I don't think those moms ever got a bill. Bless them. So that was really cool. Anyway, so I'm sure Jen and Joe, you probably—you too can speak to it, but it's shown to have extremely high sensitivity and specificity, 99% or more. And to date, you know, we have not seen and we also have talked with a manufacturer about this. No cases of a false negative, which is what you really want to avoid. You never want that. So if there's not enough fetal fraction in the blood draw to actually give you a result, it'll just come back inconclusive. That's what you want it to do. So that's why it's made its way into the clinical recommendations at this point.

Joe: Jen, what's your perspective? What are you hearing from your maternal fetal medicine folks?

Jen: Yeah, so it's become definitely more available in the United States during my career. I would say our friends in Europe and Canada and Australia and other developed countries have been using it a lot longer than we have. And so the data from the Netherlands, for example, is very strong, that the sensitivity and specificity are very high, both above 99%, as long as it's done in the first trimester. and there are some caveats. Like interestingly, we've had some twins and triplet pregnancies at my hospital. It's actually not validated for those kinds of pregnancies, which is really interesting because you don't know which one you're testing, right?

Joe: Sure.

Jen: But it's been available here for a long time. And for those listeners who maybe aren't in medicine, if you're a mom, you go to your OB and you get a triple screen. That's a really common test in pregnancy. And they're now doing that, this cell-free fetal DNA blood draw from you, the mom test, right? So they're looking for trisomy 18, 21, et cetera. But they can do all kinds of testing now, including... So at first, when this was commercially available in the United States, it was just a few minor red cell antigens. There's one large commercial lab on the West Coast that does a lot of the testing. I'm not going to say their name for CME, but it's easily found. But they now offer commercially, and this

is best done around 10 weeks gestation. RhD, all the Es, all the Cs, Kell, MNS, Fy^a, Jk^a, Jk^b, and big U, which I have seen. Wow, wow. But they're doing all of that easily done with just a maternal blood draw at 10 weeks. That's fantastic. It's covered by all the major insurers now, too.

Joe: That's awesome. And I'll just tell you my perspective on this. I have talked with maternal fetal medicine docs who manage their patients who are alloimmunized using that test. And if the baby is negative, they say, OK, have a great pregnancy. See ya. Bye bye. And that's just awesome because I think you mentioned this, Molly, the lack of false negatives allows them to do that. You obviously can't have false negatives in this kind of testing. It would be catastrophic.

Molly: Yeah, for sure. And this is super big for us for multiple reasons. So another thing I didn't touch on yet is that sometimes we will instead have labs drawn on the dad to figure out the dad's antigen phenotype and figure out the likelihood the baby is going to inherit. But, of course, if the dad is heterozygous, we still don't have our answer. We still don't know if baby has it. And we also have cases that we just published on a situation like this recently where the person ordering the lab for dad doesn't really know what they're ordering and they order an antibody screen on the dad instead. And the dad is negative for the antibody screen, but that's not the right lab. And then they proceed as if the baby is not affected. And we've seen deaths simply because of this incorrect ordering.

And so eliminating that risk is also huge. And also being able to find out the antigen status earlier than you would with an amnio allows for the monitoring. And sometimes there are special interventions that can happen for very, very severe disease that can start in the first trimester. And so when you know baby is antigen positive, you can get rolling.

Joe: Okay. So, again, I apologize. I derailed this a little bit, Molly. You were describing the basic structure of how prenatal testing and monitoring is supposed to go. We had gotten to the point where you talked about the antibody has been identified. We're using some of these tools that we potentially have. And we talked about the non-invasive testing. You talked about putting a needle in and actually directly sampling the baby. So let me let you pick it up from there. How is it supposed to go from that point? Let's just say that the baby is potentially affected. How do we manage those babies as we move forward?

Molly: So if the baby is antigen-positive or suspected to be antigen-positive, if for some reason we haven't figured it out for sure, then we follow with titers. And if the titers are staying low, which for us low means under 16, unless it's Kell, which you talked about how Kell has a different mechanism, then under 4 would be a below critical titer. We keep monitoring with titers every four weeks and increasing to every two weeks in the third trimester. But once the titers become critical, then it's important to transition to ultrasound monitoring instead, because a critiKell titer doesn't mean definitively that this baby is going to need treatment for HDFN. It just means that they are in a window of risk where they may require in utero intervention for HDFN. And so then we proceed to middle cerebral artery Doppler ultrasounds, which is assessed by ultrasound through the baby's head.

So we use those ultrasounds, and if the levels are elevated on those ultrasounds, that will tell us that baby is probably anemic and they need an intrauterine blood transfusion as an intervention pretty quickly, like within 24 to 48 hours. With the goal being to do it before hydrops happens and before ascites or hydrops is even visible on ultrasound, that MCA Doppler is our first indicator. And intrauterine transfusions are much more successful when we intervene before ascites or hydrops has developed.

Joe: So Jen, I see you nodding there. Let's talk a little bit about how the use of MCA Doppler has really changed how we look at things and how we manage things. I mean, you and I grew up in an era, I think, when we, probably more me than you, but when we used to stick needles into amniotic sacks and check changes in optical density against a Liley graph and stuff like that. Yep, I remember that curve. Yeah, those are the days, right? Well, I mean, so my perspective is that the use of MCA Doppler has revolutionized care in this setting. Is that yours as well?

Jen: Yeah, it's basically supplanted amniocentesis. Like I would say about 10 years ago, I worked at an institution on the West Coast and we really just saw a precipitous drop in amniocentesis, the procedure itself, to the point where some of the attendings, the obstetricians had never even done one. So I think it's really revolutionized the field. And honestly, I don't really see my MFM group here doing many either because there's so many tests available. We're just talking about one little tiny neonatal disease, right, HDFN. But there's lots of other things that the neonatologists and the MFM doctors are diagnosing in utero via these fancy tests. And so I would say almost no one is doing amniocentesis anymore. And then also one important thing is for the pediatricians out there, they're not doing whole blood exchanges either. When you read about HDFN, you read about sort of what happens when the baby's born and they're bilirubin.

We also have the same curves, those equivalent when you're a human, when you're actually born and you're breathing oxygen out here, they're called Bhutani curves. And you basically plot the same thing. So day or age and life on the X axis and bilirubin on the Y. And you hit sort of this line and you're at really high risk for kernicterus. And so the pediatricians, and even when I was an intern, I used to do this. We used to do whole blood exchanges. And so now They're so rare. Whenever it happens at my hospital, everyone and their mother is texting me. Oh, my gosh, Jen, we have a whole lot of exchange. Right. I almost feel like I have to deliver the cooler myself. Right. So it's such a rare event in a hospital, even a big academic teaching hospital nowadays. So, yeah, really rare. And so the other thing to get sort of get back to, if this is a good time for it, Joe, is titers, because we're still doing titers.

That test is not going to go away. And I think that's really important to say to this audience. Like, cell-free DNA is not going to end all these screening tests that we do. Remember, titers is a screening test for anemia. And so what Molly just shared is once you reach your institution's critical value, I think it's important to say for the audience that 16 is a guideline. And so if you look in the technical manual for the RhD antibody and many of the other RH antibodies, I think the technical manual gives a range somewhere between 8 and 32, right? And so my hospital's critiKell titer for an antibody is 16. And if the medical students and residents go down that rabbit hole of literature, it's actually not very strong for that number.

Joe: Agreed.

Jen: And so when you hit that critical value, then the obstetricians move on to the diagnostic test, the MCA Doppler ultrasound. It's really important for the laboratorians that are listening to also note that each blood bank or labs, titer procedure may be different from another lab. So it's really important that, for example, when there's a pregnant patient in your practice, our doctors tell them you have to come to Vanderbilt, for example, for all your titers. You can't go to Walgreens on the corner and have it sent off to another reference laboratory.

That methodology might be different than mine. And then it's really important that we try to decrease the variability between techs. And so, for example, when a pregnant person shows up and we get their first type in screen and they have an antibody, we identify it, we do the titer, we actually freeze that sample and we keep it because many times during that same pregnancy, we're going to repeat that titer and we're going to do it in parallel to decrease the amount of tech-to-tech variability. So your lab, even in this day and age of cell-free fetal DNA, you still have to have a really strong titer process. And I love that Molly already said it, but just to reiterate, reflexive. For example, the obstetrician's not ordering this test, right?

In my hospital lab, my techs are looking in the medical chart. If we have a new antibody identified and it's a woman less than 50, we're looking to see if they're pregnant and we're titering automatically without the physician trying to figure out how to order that, what's the right test. Because even amongst obstetricians, Maladi already shared with us some really scary stories. There's a lot of misunderstanding between what is an antigen, what is an antibody. So we're the experts in that, in blood banking and transfusion. So we do the right thing for the patient.

Molly: I wanted to also just emphasize how truly important phase is the folks responsible for sharing the diagnosis. It is huge and it sets everybody on the right trajectory, which is sometimes super critical, the window of time that we have, because just to lay out a very common scenario, a woman might not know she has antibodies until she's already 10, 11, 12 weeks pregnant. Say they are already critical. Say they're very high. I perhaps for intravenous immune globulin as a treatment. And that has to start to be most effective in the first trimester. So imagine all the insurance things that have to happen, all the referrals that have to take place, laying out the treatment plan and starting that by the 13th week, and then beginning our ultrasounds as soon as 15, 16 weeks gestation. Some of these doctors are doing intrauterine transfusions in very, very rare but severe cases as early as 15, 16 weeks. And so all of this has to happen with a perfect cascade.

And the ordering provider, to your point, Jen, may not be familiar with this condition at all. And so sometimes they see the positive result, they don't know what it means, and no referral occurs. And so the language that we use when we notify and inform the ordering provider and the patient of the positive result is super important and really impactful.

Jen: A best practice at my institution, for example, is our service and our residents actually write a note when that happens that ends up in the patient's chart. It's not just a little

notation linked to the lab. So for example, with the newest federal law, we now allow patients to look at their records, right? And so you guys are probably familiar with this from your own doctor's office. You can see, oh, my dermatologist said this about me, right? So it's a note. And so you can look it up. And we use really specific language like, This is what it means if you're a woman of childbearing potential. Even if for whatever reason you don't complete this pregnancy, it's a forever thing. Your next pregnancy, you're at risk for this too.

Molly: We are the experts, right? And one more thing I wanted to mention, which we kind of teased a little bit about how Jen does her follow-up at her institution when somebody does have a positive antibody screen. But achieving sort of a national standard for the way that we notify people and their clinicians that they have a positive red cell antibody is super, super important to set them on the right trajectory. And so we actually just put out a commentary in transfusion. I think it was just last month that talks about a potential synoptic reporting output shell that can be implemented at a systems level to try to get that more normalized and set moms on the right trajectory. So we see really good outcomes and immediate referrals.

Jen: I also spend quite a bit of time with my house staff digging through the medical record of every woman who we identify a new antibody because the titers, and this makes, I do not have a scientific explanation for this, but if you've previously had a pregnancy that's already been affected by HDFN, the titer doesn't matter. It has no relationship with fetal anemia, yes or no. So that can also be really easily misunderstood because you're kind of waiting for critical, but it may never reach that level. And the baby could already be hydropic because the mom's already previously had an affected pregnancy. So we need to kind of really get that information. And we go digging into outside hospital records. And sometimes we're calling moms or their obstetrician and saying, like, we really need this information. It's super important for us to be able to give you the correct interpretation of this titer.

Joe: And just so I'm clear on what you're saying, you said this, but I just want to make sure that the listener appreciates this. You're saying that particular thing where the titer doesn't really matter is in a mom who's had a previously affected baby. Is that what you're saying?

Jen: That's correct. And it doesn't necessarily mean a live birth, right? It previously affected pregnancy. Maybe they had an in utero death, unfortunately, right? Because the fetal anemia was so serious. So any previously affected pregnancy, that titer doesn't matter. And so the obstetricians automatically go. So they skip the screening test, right? Because they know this baby's at high risk for disease. And they go to the diagnostic test, which is the MCA Doppler, right? They're looking at that circle of Willis. Remember, we all learned that in medical school. And they're looking at the middle cerebral artery, the blood flow velocity through that particular vessel. And if it's high, they're diagnosing fetal anemia, and then they might need to treat it.

Joe: So, Molly, before we finish this interview, there's a couple of things that I think are really important for us to hit. We need to talk a little bit about the very special and, well, all too common situation of the Rh-negative, the D negative mom, and what special things we do during the pregnancy of a D negative mom. So can you kind of walk us through that?

We've already talked about that and you've outlined the basics of what we're doing for the testing. But what's unique about D-negative moms and how we manage them and assess them and maybe treat them during their pregnancy?

Molly: Actually, not that many years ago, even until the 1960s, we had women who are Rh-negative being exposed to babies who are Rh-positive and developing anti-D antibodies. And this was not a rare disease at that time. And so a lot of people called it RH disease. And many people in older generations will still know it by that name and still know people personally affected who just lose children over and over because they developed anti-D antibodies during a pregnancy with no prevention. And so in the late 60s, Rh immune globulin came out. And so that is an injection. Usually it's an injection, right? Sometimes not. But given to a pregnant woman when she has a bleeding event during pregnancy because that increases the chance of a fetomaternal blood exchange.

And then also, when it first launched, they also gave it within 72 hours of delivery because there's also a big opportunity for exchange of blood there. And they also found that if they additionally give a dose at 28 weeks gestation, then you drop the chances of becoming sensitized to anti-D a little bit more. So normally, if you don't have Rh immune globulin, an Rh-negative mother's chance of developing anti-D is about 16% or so. If we do the dose only right after birth, it drops down to about 1% chance. If we do the dose right after birth and at around 28 weeks gestation, then it drops down to a 0.1% chance. And that is why this is a rare disease now, because having anti-D antibodies was the most prevalent. In some reports, it still is the most prevalent, but we still see the others coming up now to kind of level it out, too, with the anti-Kell and anti-little-c's and so on and the 50 or so others that can cause this disease. But that Rh immune globulin is huge, and it's the reason why this is now rare.

Joe: Jen, can you talk a little bit about RhIG? Do we have any idea how it works?

Jen: No is the short answer. It's sort of like IVIG, right? Yeah, it's a little magic, but the Nobel Prize was given out for that. And the FDA approved Rh immunoglobulin in 1967. And in other countries, I think it's important to note too that, so this is still a biologic. It's made from blood donors' plasma, right? So if you really want to go down a rabbit hole, it's really an interesting story. And the "Man with the Golden Arm" is a really excellent book. And I think they made a movie. And it's about an Australian blood donor who made very high titer anti-D. And personally, through donating decades and decades of anti-D, probably saved millions of children in Australia from having HDFN. Yeah, it really is. And so this is still a big deal in other countries because there is no current Rh immunoglobulin sort of not made from human blood, right?

And so there's just not enough in the world. Like Molly's organization, Allo Hope, does blood drives to get donors out there to possibly make Rh immunoglobulin in certain parts of Africa, for example, where they just don't have it. It's just not available.

Joe: I also think it's important, you guys, that we discuss one other blood group system that we've danced around a little bit, and that's the Kell blood group system. And Jen, I wonder if you could just share a little bit about why Kell system antibodies are so scary.

Jen: Yeah. And the residents and the medical students will sort of know this phrase, "Kell kills." And the reason is the Kell antigen is actually found on not just the mature red cell

in fetal life, but some of the progenitor red cells. And so not only if it's antibody, that's IgG, it's crossing the placenta, attaching to the fetal red cell, it's also attaching to some of the red cell progenitors. So you sort of have this concurrent hemolytic disease of the fetus and newborn. And hypoproliferative anemia, right? And so there's some thought actually that any Kell titer, not just four, so check with your hospital laboratory, is critical. And that probably in the modern era with Rh immunoglobulin, as long as it's being dosed properly and given at two times during pregnancy, like Molly just nicely outlined, that is probably the most common cause of severe HDFN now. And there are labs working and manufacturers working on sort of an anti-D equivalent for Kell, right? But I don't think they've gotten too far. That would be super cool.

Joe: It would be awesome to get to that point. But yes, we're currently not there. So a couple of things as we get towards the end of our time together, you guys, that I think it's important for us to describe for our audience. One is a medication that's currently being used that we've mentioned, and that's intravenous immunoglobulin. And Molly, you've talked a little bit about the importance of starting IVIG earlier than we think we might have to start it. Jen, I'll just throw this to you real quick. I'm going to take a wild guess and that you're going to tell me that we don't have the frigging clue why IVIG works either. Is that accurate?

Jen: That's right. We do not know the mechanism of IVIG. We do a lot of hand waving as clinicians when we prescribe it. Yeah. But we really, truly don't understand. It's a great distractor. I don't really know how to describe it, but it basically, it works for unknown mechanisms for lots of autoimmune diseases with the antibodies. So thank goodness it's in our arsenal.

Joe: Got it. Okay. And you mentioned whole blood exchange, and we also talked about the fact that it's not happening very often anymore. Forgive me, Jen, I'm going to circle back to you on this, but for those taking exams, when we talk about transfusing a baby, either in utero or postpartum with an exchange or just a regular transfusion, one of the things that people get asked about is what are the special requirements for that blood? So I know that's very personal to you because you order blood in these situations. Can you just thumbnail that for us? What are the modifications that we need to do to blood or the things we need to check with red cells in particular before we give them to babies?

Jen: Sure. That's a great question. So at minimum, you're going to give O-negative, right? Because you don't know the blood type of that fetus. Negative for the offending antigen, right? So talking about a mom with an anti-Kell, you're going to make sure that those red cells are Kell negative. And again, there might be multiple. And at my institution, and I think best practice is to give Rh- and Kell-matched for the mother so that the intrauterine transfusion, for example, is not a sensitizing event. That's not a requirement if you're going to give this post-birth. And then in the United States, most blood is leukocyte-reduced, which many consider CMV-negative. But this is a situation where there's not a lot of data. And so conservatively, your hospital might give out CMV-negative in addition, so seronegative. Most hospitals, but not all, will give sickle-negative.

And then also "fresh." And that's because you have to think about an intrauterine transfusion or a whole blood exchange as a massive transfusion event. So whatever

your hospital's mitigation strategy for that might be, like my hospital, which I think is best practice, is to give a unit that's less than five days old.

And then it has to be irradiated because that fetus or neonate is immunocompromised, right? And they're at risk for GVHD. And so we irradiate at the time of issue. And then our expectation is obstetricians are going to give that intrauterine red cell transfusion or whole blood exchange almost immediately when the product gets to the bedside. So it's not sitting there accumulating potassium in the supernatant.

Joe: Molly, I'm going to throw this back to you because one of the things that you as the director of research for your organization and I know Allo Hope is passionate about is some of the newer strategies that we have and potentially some of the non-transfusion type options that we might have. So I wonder if you'd talk just a little bit about a couple of the things that are coming down the line for us, things that are currently in studies. One of them, a medication that's being studied and reported on that's being used to give to moms who are immunized to kind of protect the baby and has some potentially exciting results. So could you talk about that a little bit to start us off?

Molly: There is a treatment in development right now. It's in phase 3 clinical trials called "nipocalimab." And the way it works is you dose the drug IV to the mom weekly, beginning around 16 to 18 weeks gestation throughout the pregnancy. And Jen can probably talk through the mechanism of exactly how it works to block the FcRn receptors. But it has proceeded through phase two trials and the phase two results have been published in the last year or so. And they were super encouraging. So for a trial like that, for a rare disease and for phase two only, you are finding the mothers with just the most severe disease history. And there were 13 moms in that study. What they did was they compared it to their previous pregnancy that was affected by HDFN.

And in those 13 moms' previous pregnancies, none of them had a live birth later than 32 weeks gestation, and only five of them had a live birth at all. And so once they received this intervention, seven of them had a live birth later than 32 weeks gestation, and 12 of the 13 had a live birth. The one fatality was unfortunately due to a complication from intrauterine transfusion. But this is a snapshot of the most severe HDFN, which is very, very rare. And so those results are encouraging. And they're recruiting now for phase three. I think they have like 65 sites around the world. So we will see where that heads.

Joe: Jen, I know you're passionate about nipo. Since I can see you as we're recording, you're like,

Jen: give it to me, give it to me, give it to me. I'm really excited about this. It's sort of like this medication is a game changer and we're going to see a ton of its use in transfusion medicine just in general. So it's a neonatal Fc receptor blocker. And basically what it does is it stops the body from recycling IgG molecules out into the vasculature. And so you give it to the mom and she makes less IgG against this red blood cell antigen, right? So there's less antibody to cross the placenta and cause disease. Molly's right. This was like revolutionary, this phase two trial. It was published in the New England Journal. That's how big of a deal it was in just 13 patients. And the follow-up study was really critical. So I'm a pediatrician by training, right? So I was worried about, well, what about

the other antibodies that mom is making that's protecting the infant from infection, right? And so that was also recently just published.

Molly: It would be a great equalizer. Intrauterine transfusions come with their own share of risks and they're highly technical. And so it can be, sometimes moms cannot reach a referral center that might be multiple states away for a really safe intrauterine transfusion. And so if that could be avoided with therapeutic treatment instead, that would be huge.

Joe: Let's finish this off, Molly, by coming back to you. And at the beginning, we talked about your story and your passion for these moms, obviously in part from your personal experience, but also obviously through the work that you and your organization do. So moving forward, what is your and Allo Hope's perfect world? How can we do this better? Where are the places that, aside from, obviously we've just talked about that particular medication, but what are the other things that you guys see coming down the pike that we can make this entire process better and safer for moms and babies?

Molly: Well, I think we should be encouraged that we are so lucky that even though this is a rare disease, it is treatable. And so I think having a mindset of expecting survival for these children is huge. And I think it's something that still needs to trickle through the system in some ways, because like we said, only 50 years ago, this was something that many people just assumed to be fatal, and it usually was. And so now in the thousands of pregnancies that we've seen, if they were treated with prompt best practice, maybe two would have been really unpreventable losses with just astronomically high titers and extreme situations. And so the goal is to allow every patient to receive that care without having to advocate, without having to relocate, without having to monitor their chart and do their own research. And so I think having to do a lot more interdisciplinary collaboration, which is happening, listening to the patient experience, which is happening. I mean, I'm here today.

I'm on your podcast today. And that is a huge testament to the way that things are shifting. So I think that everybody realizing their piece here when it comes to the diagnosis and informing the ordering provider exactly what the next steps are so we don't lose babies there, referring moms to the maternal fetal care team who has true expertise in doing intrauterine transfusions over and over again and really a highly specialized practice. So the way that we are capturing these moms at the beginning and walking with them through the appropriate treatment, we shouldn't be having babies die to HDFN. So that's the goal. And a global awareness of that expectation is where we need to be. And I think we can.

Joe: It's fantastic. Jen, any closing thoughts for you?

Jen: Yeah, I was just going to tell the listeners too, that there's more guidelines coming. So Molly already talked about the obstetrical care guidelines, but the pediatricians also got together with that same group and their guidelines are going to be published any day now because this is a rare disease, right? And so Molly and the Allo Hope Foundation, they still walk even the babies through care after birth, right? So there's going to be guidance about how often you need to check a CBC, how often you need to check a bilirubin, how you should think about these babies. I've even seen, unfortunately,

pediatricians say like, oh, you're good. If you're a month out, you're fine. Not knowing those antibodies can be around for two, maybe three, maybe even longer. I've seen some infants have that maternal IgG antibody floating around for six months or so, and they might need top-up transfusions for the first couple of months of life.

So there's more guidelines coming. I think Molly summarized it nicely, but this is a disease you're caring for more than just your specialty of patient, right? So the moms who are pregnant, the babies, we've got the blood bank and the titers. We've got all these different cooks in the kitchen, right? And I think it came naturally, but I think we all had to get together and agree on what is best practice. And finally, those publications are coming out. So there's a resource for healthcare providers who might not be as in the know. Even after this podcast, you can see we didn't go down a bunch of really other tangents that we all wanted to do that. That was hard. I know, but there's plenty of resources coming.

Joe: There are,

Jen: for sure.

Joe: Okay, well, you guys, this has been, I think, really helpful, really educational. I think the listeners will gain so much from hearing this. So thank you both so much for being here today on the podcast.

Jen: Thank you, Joe.

Molly: Thank you.

Joe: That was a really fun discussion, and I hope that you learned something from this. Really, I just hope that it made HDFN a little bit less intimidating for you. I think there's a lot of exciting and groundbreaking work that's going on with HDFN, both in prevention and treatment, and we talked about some of that. But there's a lot more that we couldn't talk about. So, I have some references on the show page. I hope you'll check that out; that's at BBGuy.org/106.

There's one more thing I wanted to call your attention to. It's going to seem like a little thing, but I think it's important. A couple of times in this episode, the phrase "anti-Kell" was used, and I should just point out for those of you who are learning, that designation isn't *quite* as precise as I'd like it to be. Most everyone knows what you are trying to say when you say that phrase, but the technically proper phrase would be "anti-Big K" when we are talking about an antibody against the main antigen in the Kell system. Again, I know, it's just a little point, but since this is an educational podcast, we should be as precise in our meanings as we can!

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