**Joe Chaffin**: Hi everyone! Welcome to the Blood Bank Guy Essentials Podcast! I am super excited to welcome to the podcast today Dr. Cassandra Josephson from Emory University. Cassandra, welcome to the podcast!

**Cassandra Josephson:** Thank you, Joe!

**Joe**: It is so great to have you here! I have to tell people a little bit about you and honestly, if any of you out there don't know something about Cassandra Josephson, you're living in a rock somewhere because my goodness, she's really one of the "giants" in our industry today. She's doing so much. She has one of the most unusual combinations of certifications that you will ever find in blood banking/transfusion medicine. She's one of the few people in this country that are trained in not only pediatrics, but also pediatric Heme/Onc, as well as blood banking/transfusion medicine. Cassandra has done so much in terms of publishing, in terms of research, in terms of her work with pediatric transfusion medicine, and that's what we're going to talk about today. Just a little bit about her: She graduated from the University of South Florida College of Medicine. Did her pediatric residency in a place that I know and love; the University of Colorado Health Sciences Center in Children's Hospital in Denver. I was in the Denver area for about 13 years, Cassandra. I don't think we've ever talked about that.

**Cassandra**: No, that's funny!

**Joe**: Yep. She did her pediatric Heme/Onc fellowship at Emory and also, her transfusion medicine fellowship at Emory, and she's boarded in all three of the areas of speciality that I mentioned: blood banking/transfusion medicine, pediatric Heme/Onc, and stem cell transplant, as well as in pediatrics. She's currently a professor in the Department of Pathology in Lab Medicine at Emory, as well as a professor in the Department of Pediatrics at Emory! I'm exhausted, Cassandra! I don't know how you keep up with it all! (laughs)

**Cassandra**: (laughs)

**Joe**: I'm curious, with all that being said, you're someone, obviously, who has a really unique background in transfusion medicine, different than most of the people that I speak with about this. But I'm still really curious to know, what was it about transfusion medicine or what was it when you were training in pediatrics and pediatric hematology/oncology, what drew you to this particular subset and this particular area of medicine?

**Cassandra**: Well, that's a very interesting question because I didn't really know that it was an option to be doing transfusion medicine when I became a pediatrician. Even when I started my pediatric hematology and oncology fellowship, I actually was on course to be a hemostasis and hemophilia doctor. So now, Marilyn Manco-Johnson, did

research with her, and Rachelle Nuss, out in Denver, and then came to work with Pete Lollar and Tom Abshire doing hemophilia at Emory. And after I got into it and kind of was doing more basic science with mice and things like that, I said you know, "I really would rather be working with patients more and doing more consultative coagulation, as well as transfusion." So, Chris Hillyer was at Emory University at the time, and he had the fellowship. And so, Tom Abshire said, "Hey! Why don't you look into that, since that's where you think you want the direction of your career to be more clinically related and clinical research-oriented." And so, after speaking with them, it seemed like the right fit. So, that's how I kind of gravitated towards that. It's an interesting thing because like I said, I didn't even know it it existed!

**Joe**: (laughs) I think, what you're saying is interesting in many ways. I think that, well, put it this way, you and some other folks have published some work describing somewhat of the——I don't want to say, the "paucity" of researchers and workers in pediatric transfusion medicine, but I think that there's a real need out there for more young folks coming up——maybe people that are in the track that you were in pediatrics and pediatric Heme/Onc, to consider working in transfusion medicine because there's a lot of work still to be done, isn't there?

**Cassandra**: Absolutely! I am the Fellowship Director at Emory University in the Pathology Department, but I also have a pediatric transfusion medicine fellowship that I developed out of a K07 grant that was put out by NHLBI and they really wanted the encouragement of more people going into pediatric transfusion medicine. There was really an attrition of people. And the questions that need to be answered are, many, almost everything we do is not evidence based, it's extrapolated from adults. And so, you are right on. The other thing is that you can be an anesthesiologist, you can be internal medicine, you can be a pediatrician, you don't even have to be Heme/Onc to be able to become board-certified in transfusion. So pathology, which was the traditional way to go into transfusion medicine, is not the only path now. And that's been around for quite a while, so the more I can get the word out there, the more we encourage people to go into pediatric transfusion medicine.

**Joe**: Boy, absolutely! I'm really glad you said that, because I don't think that's as widely appreciated as it should be that the American Board of Pathology has opened things up in recent years, for non-pathologists. And I'm a pathologist so I can speak that heresy! It's totally——I mean I love it! Honestly, I love working with transfusion medicine physicians that get the clinical side of things. I spend a little bit of time as a clinician, not a lot, but, enough that I appreciate the clinical side of things and I think that sometimes, I love my "pathology brethren," they're awesome, but sometimes, if all you've done is pathology, it's a little bit harder to understand the clinical side of things.

**Cassandra**: Well, I think there's a good compliment between everybody. The more there are from both disciplines, coming into transfusion medicine, I think there's a big compliment. I work in a department that is made up of both types of tracks; both adult internal medicine, going into transfusion, as well as, AP/CP trained, and then, pediatric Heme/Onc. So, it's really nice to have different, diverse backgrounds of training.

**Joe**: Yeah, that's the key.

**Cassandra**: It enhances the field.

**Joe**: Agreed. That's the key. I certainly didn't mean to slam my "pathology brethren or sisters"

**Cassandra**: No, no! I didn't think you were! But I think it's kinda nice to have all of it and not just from angle.

**Joe**: Yep. Well, you used a phrase, just a couple of moments ago that I think is THE BIGGEST reason that I wanted to talk to you and talk about our topic today, which is, "The Top Five Things That We Want You to Know About Pediatric Transfusion Medicine." And so, just a few moments ago, you used the phrase: "extrapolated from adults." I wrote it down when you said it because that's IT in a nutshell, isn't it?!? I mean, I think that we…I will freely admit to you to having spent my entire career, taking care of adults in terms of transfusion medicine, and not a lot of time in hospitals doing a ton of peds, we have way too much that we're assuming is true in pediatric patients and not enough that we've proven. That's what I hope that were going to explore today.

**Cassandra**: Absolutely, and that's why I picked the topics that I did, because you can kind of see where things have grown and changed, but how things, I'm going to contrast some of what we have found now, that is in sharp contrast to what people sort of thought with regard to some of these topics. So, that's why I picked them, particularly.

**Joe**: Terrific! Well, let's do it! Let's rock n' roll with this then. So, "The Top Five Things You Should Know About Pediatric Transfusion Today." Cassandra, why don't you hit us with #1? What's #1?

**Cassandra**: Okay! "**The Volumes Vary**." This actually pertains to total blood volumes, plasma volumes of pediatric patients/neonatal patients. I bring it up because, especially with neonates, or even up to the age of, let's say 5 yrs, these total blood volumes are much smaller than adults. Interestingly enough, we have quite a bit of trauma in Atlanta, where I am located. We have Level 1 trauma and Level 2 trauma centers at both of the free-standing children hospitals that I'm in charge of the blood banks for, and so, we have set up algorithms to kind of "fit" what those patients have. The importance of that, is that one unit of red cells, let's say, can range between 250 to 320 ml, depending on the anti-coagulative preservative solution, you know, CPDA1 vs. AS-1, for instance. And if you think about a child who is 2 Kg, and you use 80-100 mL/Kg as the total blood volume, right then you get to 200 mL is their total blood volume and their plasma volume is only about 80 mL if you use 40 mL/Kg as a rule of thumb. And so, what ends up happening is, is that, in any places that want to resuscitate a patient, they will just pour red cells into them and a whole unit of red cells immediately is their entire total blood volume. Some of these places forget that we don't transfuse whole blood, so it's missing all the coagulation factors, and the patient's already bleeding, and then they just dilute out the rest of what's there, and before you know it, you have dilutional thrombocytopenia. Basically, you have no platelets and you have no fibrinogen or coag

factors. So, I want to emphasize the point, is that what's really challenging about children is, is that they are **all different sizes**. You can't just say, "70 mL/Kg, you know if you are a woman, you're 45-70 mL/Kg and that's it." And so, we've done some special things to kind of combat this or actually to complement what has been found in the adult literature when it comes to trauma, specifically, because we are all familiar with that 1:1:1 ratio of red cells to platelets to plasma. We want to be able to try to emulate that for children. And so, what we've done is, and we've published this both in "Transfusion" as well as, in the "Journal of Pediatrics," is trying to show that coagulopathy is a problem just like it is in adults, when you have trauma. So, it leads to morbidity and mortality. But we also wanted to show feasibility, that there are algorithms that can be done by your blood bank that "fit" different size/groups, like 1-5 Kg, 6-10 Kg, etc. And that way you can have packages that kind of look like the proper study or things from the "adult world," you can kind of see how that's been scaled back with all the different blood products to be delivered in the right ratios for the right weight. And that was all based on the fact that these patients have smaller total blood volumes and smaller plasma volumes.

**Joe**: So practically speaking, Cassandra, I mean, obviously, we could get really "deep into the weeds" there, but just kind of keeping it practical, how does a blood bank even consider setting up something like that?

**Cassandra**: Well, basically we first of all, met with the trauma surgeons, we've met with everybody, and we have a whole team: anesthesiologists, nurses….we have runners. We have it all coordinated. The next thing we had to do, was we had to have the ability to make these units quickly. And so, we do have thawed AB plasma on the shelf. We do have CRYO packages that are already pooled, that are smaller, like pools of 2, you know, like pools of 5. And then, we actually just make small aliquots at the time, because red cells and plasma are in the first package, so we can get that out and start getting the platelets done. We have to have enough people in the blood bank, to be able to do it, but we also kind of, do a "huddle" and kind of, you know, soon as we get the trauma beeper going and some massive transfusion, they start rockin' & rollin'. And they communicate to us, the weight of the patient by what their guesstimation is, and that get's us rolling on that as well.

**Joe**: So I mean, it sounds like what I always tell people with adult massive transfusion is that the majority of your work is actually done before the event happens. You have to lay the ground work and be ready for stuff like that, otherwise, if you're trying to figure it out on the fly, you're dead.

**Cassandra**: Absolutely! One of the things we try to do is, even before they hit the door, we're trying to know what's going on with the patients. So that's how early the communication is. And as soon as they can get a specimen, we will even get type-specific, doesn't even have to be crossmatch-compatible, because we try to get away from the O's and the AB plasma, as quickly as possible, because inventory-wise, we're not in a large hospital that always has all the O inventory. So we have to give O's to other patients within the hospital who are O. We are very, very cautious about using all of our O inventory, as well.

**Joe**: That's fantastic! You mentioned that you've done some publishing on this and what's kind of your, I guess my feeling with adults, the 1:1:1, while it's widely accepted, that ratio of red cells, plasma and platelets, you know, kind of sort of, if you're talking about whole-blood derived platelets, I should say. But anyway, there is still a little bit of controversy with that in the adult field. Studies that are being interpreted slightly different ways and a little bit of controversy. How do you feel about that in your population in pediatrics?

**Cassandra**: Well, I gotta say that we did two studies: 1) We looked at coagulopathy - this is in the "Journal of Pediatrics," Hendrickson et al 2012. Basically, we looked at 102 of our patients before we did any resuscitation, so we looked at their PT, PTT, fibrinogen and platelet counts up front, and found that PT, PTT, and platelet count were all statistically, significantly bad news if they were abnormal for morbidity and mortality. So we knew up front that there were problems, and there's coagulopathy. We also knew that many of these patients had fibrinogens that were less than 100 and many less than 60 mg/dL. So those were at the greatest at-risk for mortality. We understood that coagulopathy exists like it does in adults. Then the next question was, whether these algorithms really work? Really, we haven't had enough patients to show this 1:1:1 ratio because we just can't get the numbers yet. It was a single center (ours). We are actually looking at an NIH grant with Wash U and Phil Spinella and Nationwide Children's, etc., trying to get the numbers bigger so we can actually demonstrate some benefit. One benefit we do have having the algorithm is that we know that we're keeping up with the resuscitation; meaning that they're not falling so far behind with their coagulopathy. We just don't know if the 30-day mortality is improved and the later mortality is improved in a similar fashion to the way the adult literature is showing. We have found that we had to move up our cryoprecipitate, which is basically our fibrinogen arm, we've had to move it up to the second package (we usually started it in the third), because we are getting coags in the middle of our MTP protocol, and we were seeing that we really weren't compensating enough for the amount of consumptive coagulopathy that's occurring from the trauma. So there may be a slight difference in the consumption of fibrinogen in children than in adults, and especially if they're very small children, because protein C and protein S are way lower until you are about 12 years old. So there may be some hemostatic differences that are playing a role in this coagulopathy. Jury's not out yet.

**Joe**: That's awesome. Since we've got a lot to cover, let's just summarize that. So, the first of the "Top 5 Things" that we need to know is that the volumes vary, and you mentioned your discussion of pediatric and neonatal plasma volumes and how that relates, not only, to regular transfusion, but primarily we talked about massive transfusion and dilution coagulopathy. Is there anything else you want to say about that one, before we move on?

**Cassandra**: Yes, I do. It is about out of group plasma. So, in adults, it seems like it's permissive to give out of group ABO and out of group plasma, around a liter of it. I actually disagree with that, but at least, if you're giving it in adults who weigh 70 (Kg), they have quite a big plasma volume still using that 40 ml, so you've got like 2800 (mL). But I think when you get to these smaller blood volumes, if you give an O platelet, let's say to an A individual and they weigh 15 kilos, and we don't know what our O's have, as

far as, an anti-A titer, because they're all over the map and we don't measure in the United States, then there is a possibility of causing a hemolytic transfusion reaction. I think in 2004 or 2005, there was a pediatric death reported when there was out of group platelets given, an entire apheresis platelet given to a patient. I think this has to be remembered when we are giving out of group plasma to children, that I discourage that. And we should wash or volume-reduce if that need be.

**Joe**: Ok, that's awesome! That is topic #1 of "The Top Five Things that You Should Know About Pediatric Transfusion" - The Volumes Vary. So Cassandra, let's move on. What is #2?

**Cassandra**: #2 is "**Predicting Platelet Effect in Neonates and Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients**." I know that sounds like a REALLY big mouthful! But really platelet effect, and actually bleeding risk are so important and really are very different than adults, in both neonates and children. But there are some similarities between the neonates and the children. Not complete similarities, but I think since we're talking about this and I think it's very, very different than adults, I thought it was worthwhile and there's new literature out about both of these areas, so I thought it was something to mention.

**Joe**: Yeah, cool. Let's go.

**Cassandra**: So, thrombocytopenia, it's associated in both neonates, and I mean very low birth weight and extremely low birth weight infants, that weigh <1500 and <1000 g. Those are the babies I'm talking about. And then in those peds, oncology and transplant patients, thrombocytopenia has been associated with an increased risk of bleeding——that's known. The question is, is that, is giving platelets going to do something about that risk? And it doesn't seem like in either one of these newer publications, that it is going to do anything. *That really the severity or the degree of thrombocytopenia does not influence both, intraventricular hemorrhage, which is the main bleeding outcome they worry about in these very, very, very small babies. And it doesn't seem to change the bleeding outcomes in patients who have hypoproliferative thrombocytopenia*, *secondary to chemotherapy, as far as if they have a 10,000 platelet count or if they have a 50,000 platelet count, the range of platelet count in the thrombocytopenia doesn't matter if you get platelets, they seem to have an increased bleeding risk*. Giving platelets doesn't change that bleeding risk. That's a REALLY big deal, ok?!?

**Joe**: Wow! Yes.

**Cassandra**: Because most people, you know, in the blood banking world, platelets are, that's all they think about in hemostasis. When the newer study that just came out, and I'm talking May 2016, like this month, it was just published in "JAMA Pediatrics." We were a part of it. It was a retrospective study of, it was 6 centers in the United States. We looked at platelet transfusions from 2006-2008 in all the NICU's that were involved. Martha Sola, at Boston's Childrens was a senior author; there were over 900 kids, almost 1000 kids looked at and they were around a gestational age of 28 weeks, and there were over 1000 transfusions given to all these babies. There was about 4 1/2,

plus or minus 6 platelets/transfusion per baby given. What they found is, is just exactly what I told you, that there is an increased risk of intraventricular hemorrhage, which was the main outcome they looked at. But **platelet transfusion did not reduce that risk**.

**Joe**: Wow! That's stunning!

**Cassandra**: It is! It's huge and the hazard ratio there was .92; like it didn't reduce it, at all. So, this is very important because in the United States, platelet transfusions (and this is shown in this paper, and we actually wrote a survey in 2009, Dr. Sola and I, which was in Pediatrics), and it showed that people are transfusing in the United States for platelet counts >50,000; not just in the first 7 days of life of these babies, but even older. In Europe, they go much lower. There still has only been one randomized control trial showing 50,000 vs. 150,000, which is where the 50,000 number comes from, that Andrews did in the late 80's, early 90's, and they showed no difference in intraventricular hemorrhage with that randomized control trial, which was with a very small amount of patients—like 100 patients. So we're geared up right now that we need, because retrospective studies still are wrought with bias and problems, we really need right now, a randomized control trial in the United States, in this age group. We don't have that definitive trial yet, but we have data now for that.

But I just want to underscore that **platelet transfusions are not going to solve this problem of bleeding**, still. Intraventricular hemorrhage probably has pathophysiologic mechanisms of why it's happening, and we aren't stopping it by giving more platelets.

That leads into a similar finding that we found in the secondary analysis of the PLADO Study, which was the "Platelet Dosing Trial." It was in the "New England Journal of Medicine" in 2010, with Cheryl Schlichter as lead author. We did a sub-analysis of all the children and there were around 200 children who were analyzed in that sub-analysis. What we did find similarly to the neonates is, is that the platelet count did not predict (even though there was thrombocytopenia, this is everywhere from a 5000 to an 80,000 platelet count), it didn't predict Grade II or higher bleeding in these patients with cancer or autologous or allogeneic stem cell transplant. But, **children bled a lot more than adults**, at the same wide range of platelet counts, which was a *shocker* to the adult treaters. Another shocker to the adult treaters, and another contrary finding to the New England Journal of Medicine medicine article (we published our findings in "Blood," I was the lead author in that). The findings there, showed that autologous stem cell transplant patients, who are usually 0-5 yrs of age, bled 90% of the time, no matter what platelet dose they got. Platelet dose didn't matter, just like in the big study. But they got autologous stem cell transplants, and they bled **more** than the autologous stem cell transplant adult patients, who are more like multiple myeloma patients.

**Joe**: So when you say, "bleeding," Cassandra, you're just referring to Grade II bleeding?

**Cassandra**: No, Grade II or higher. It could be Grade III or Grade IV.

**Joe**: But not necessarily intracranial hemorrhage?

**Cassandra**: No, no, no! I'm sorry, I didn't mean to confuse you. Yeah, the intracranial would be like in the Grade IV, level IV in an adult…or peds.

**Joe**: Gotcha. I'm easily confused, Cassandra. (laughs)

**Cassandra**: No, no, no, not you! I might be talking too fast! So I apologize.

**Joe**: That's fine!

**Cassandra**: No, in neonates, though, intraventricular and intracranial hemorrhage is the main site of bleeding that is worrisome. That's not the kind of bleeding that they worry as much about. I mean we do worry about intracranial bleeding, but it's a much less observed phenomena in stem cell transplant, pediatrics and adults. Anyways, what I was trying to get at is just the bleeding risk. Again, the platelet count, even though both places, they have thrombocytopenia, there's still a lot of bleeding going on. It is unclear why, and even in the same, what you would say, "autologous stem cell transplants," children are bleeding at a different rate, they're bleeding quicker, actually in the sub-analysis of the kids who had stem cell transplants, the days to bleeding was much quicker than the adults. Like kids 0-5 yrs bled in 3 days, their first bleeding event (even though they were thrombocytopenic), whereas, the 19 yrs. and above kids, the adults, took 11 days for them to bleed. 6-12 yr. olds was about 5 1/2 days and 13-18 yr. olds, it was like 6 days. So children bleed quicker when they are thrombocytopenic, but the severity of that thrombocytopenia doesn't predict when that bleeding is going to happen.

Another big difference that we found in that study between peds and adults is **where** the bleeding happens. It kind of gets to your point with the neonates. Well, pediatric patients, the kids had more oral and nasal bleeding, so they had more nosebleeds, epistaxis and GI bleeding; whereas, adults had more cutaneous and soft tissue bleeding. And that was statistically significantly different in both. The other thing is that kids that were from 0-5 and that were between the ages of 13-18, as compared to adults who were over 19, when they had hemodynamic instability, it was more seen with the *kids*, actually, which is surprising with bleeding than the adults (because kids usually maintain their blood pressure better, even bleeding whenever). But there's something about their vascular integrity which is kind of one of the things we were thinking about, in the discussion of that paper, that seems to be different than the adults. The big difference between adult and pediatric stem cell transplant, and even the cancers that they have that lead up to transplant; the kids are given a lot more intensive chemotherapy than adults are. Especially, sometimes they even do mini-transplants for adults. We don't do anything like that in kids. So, the endothelial cell integrity in the vasculature, may, in fact, be part of why there is so much more bleeding in kids than there seems to be in adults. That's counterintuitive to what everybody thought. People think, "Oh, their vasculature is pristine, they don't have atherosclerotic plaques, blah, blah, blah." But I do think it's the way we're treating them that may be at the bottom. I don't know that for sure, but I hypothesize that may be why.

**Joe**: Right. So, what you're telling me is, I have to admit, frightening!
**Cassandra**: (laughs)

**Joe**: Because we've got a situation where we've got a whole group of patients, from neonates up through pediatric patients that what we have thought traditionally in terms of stuff that we've got on the shelves in the blood bank to help them when they have low platelet counts; turns out it's not going to do a whole lot! So, what are people in your situation, people that are taking care of patients, *do* for those kids that are at risk of bleeding?

**Cassandra**: Well, I think it's a real, you know, as far as the neonates go, I think it's a real conundrum right now. I think people are using more plasma, and that hasn't been shown to work as well. And I think people just are now trying to understand that giving platelets might not be the answer. So, they don't really know what to do. I think there is definitely, this new study is a platform for more study, not just a platelet transfusion trigger study or threshold study, but actually **why** or **what** can we do to combat that kind of bleeding? Neonates have hyporeactive platelets. Their platelets are different than adults, and even pediatric platelets; so, there's a whole bunch of biology that needs to be figured out there.

With regard to the oncology and stem cell transplant pediatric patients, other drugs are being used kind of "off label" and there's some studies going on, there's a study going on right now, the "Treat Study" in the United States. Also, there's a UK study called, "Treat" which is looking at Amicar use, instead of platelet transfusion or in addition to platelet transfusion to kind of try to combat the residual bleeding that's going on, and coming at it from the hemostasis…trying to keep the clot in place for a while by interfering with the plasminogen and the fibrinolysis and kind of stopping that. So, I think that people don't really know, but I think they're looking at other ways to do this. I also think that people are working on other measurements of hemostatic function that include platelets. I know that TEG is out there, but I think we even need better things than that. So I think some novel things are being discussed, they were discussed at the State of the Science Meeting in March 2015, by NHLBI and even there was a pediatric State of the Science Meeting this past April, that again, we need better measurements for: Are the platelets working? How's the hemostatic system functioning in a patient? How do we assess that?

**Joe**: That's awesome. Well, that obviously is a topic we're going to be hearing a whole lot more about, and we should! It has the potential to be revolutionary in terms of how we're thinking about things and how we approach these. But, we have to move on. We're running, we're cruising along, we're doing great, Cassandra! We've got plenty of time, no worries. Topic #1) The Volumes Vary. Topic #2) Our discussion about Predicting the Platelet Affect in Neonates, Pediatric, Heme/Onc and Stem Cell Patients (which is shocking!) And now we're going to #3. What is #3?

**Cassandra**: #3) Is called, "Cleaning House." We're going to look at irradiation and CMV-safe products. I want to just say, that I'm going to go quickly through irradiation because there hasn't been a lot of research done recently about it, but people just need to be reminded of why we do it and there are some special cases in children that it really needs to be remembered what we're doing.

So, irradiation in general, everybody knows you give 25 Gray or 2,500 centiGray to reduce the risk of Transfusion-associated Graft vs Host Disease by cross-linking or deactivating the DNA in the T-cells of the blood donor. And if those T-cells go into an immunocompromised recipient, and they are not deactivated, they are going to cause Transfusion-associated Graft vs Host Disease. Who are those vulnerable groups? Well, in children, they're kids that have suspected congenital immunodeficiencies. They have SCIDS, they have things that are affecting their T-cell immunity, they have diGeorge Syndrome. They are things that aren't necessarily thought about in the adult world. We also have kids that are getting intrauterine transfusions that we end up taking care of, or they get a neonatal exchange transfusion. So again, they are at-risk of having this happen to them, so irradiating those blood products (is) important. Hematopoetic stem cell transplant patients, recipients of blood components that are related blood donors, so directed donation, we're very, very careful about that and that is a big deal, still, in pediatrics. Patients receiving HLA-matched cellular blood components, patients with hematologic malignancies, and those specifically with Hodgkins Lymphoma, and then, cancer patients undergoing intense chemotherapy or fludarabine use, which has been shown to have patients who are susceptible to Transfusion-associated Graft vs. Host Disease.

I think a group that sort of gets left out are neonates, that are <1500 or 1000 grams. You noticed I didn't kind of mention them as a group. But really and truly, I believe that the extreme low birthweight (which is <1,000) and the very low birthweight (which is <1500), that group really should have irradiation. The case reports that are out there are in babies that are 720 g, 25 weeks, 800 g, 1500 g. So, I don't think feel like we should play around with that. There are some people, who feel like our leukoreduction technology is so wonderful, and it is very, very good at these 4th generation filters, that we're really getting rid of everything, so why should we even be irradiating? But I always remind everybody that it only takes ONE. If it's virulent, if it's virile and it's able to go, it's going to make more of itself and it's going to take over. Children or neonates develop their immunologic functioning at different rates. What happens to them in utero, and when they are born prematurely, we don't know who's developing what at what rate. We can't even predict who's going to get NEC or who's going to get other morbidities that belong with prematurity. So I don't think we really understand the neonatal immune system enough to play around and say, "well, we're just going to take a chance." So I would irradiate that group of units. I've heard other countries have stopped. There are places in other countries that just have stopped. So that's what I would say about irradiation. We do have to be careful with how old the blood is sitting on the shelf if we irradiate a unit. Even though there's a 28 day change or, how the expiration date, if it's less than 28 days, stays the same if we irradiate the unit. When we let that unit sit on the shelf, we know that it's aging in general and then we've made it age even worse, and so there is a potassium leak. And I think that there have been plenty of publications of late for pediatric patients that have shown that there are deaths that occur. And that's not even with letting the blood sit that long! **I think that just have to be very cautious, and try to irradiate, if possible, before we are going to give the unit, as opposed to doing it and letting it sit**. Many hospitals don't have irradiators, and they have to order them irradiated from their blood center, and then they have to let them sit. There should be a

discussion if you get past, let's say 24-48 hours when it's been sitting there about the patient you are deciding to give this unit to. What's going on with them? What's going on with their kidneys? Do they only have one line? Is the line only a central line and the tip of it's in the right atrium? There's a lot of things that should be thought about.

**Joe**: Absolutely! Cassandra, let me just interject, that for anyone listening, if you struggle at all with understanding the relationship of irradiation with preventing TA-GVHD, I have about a ten minute video on my web site with some stupid, funny animations, that kind of takes people through it. You can find that on the Blood Bank Guy website. So, that's just a commercial!

**Cassandra**: It's an infomercial! It's good! I like it! (laughs)

**Joe**: (laughs) That's right! It is an infomercial! But it's FREE! Alright, so let's move on and talk about "CMV-safe," because I think that's a big, big deal that we need to talk about.

**Cassandra**: It's totally a big deal, and the one thing I want to say is that ***irradiation does not get rid of CMV***.

**Joe**: Yes!! Say that again, Cassandra!

**Cassandra**: Irradiation does NOT get rid of CMV! Can you hear it?

**Joe**: I get that question all the time.

**Cassandra**: I want to lead in with that. That is a myth, and don't believe anybody that tells you that. As we move on to this topic of CMV, the reason that it is hugely important in premature infants is that CMV in the early 80's KILLED a lot of babies. So, this isn't like, "Oh, this is not a problem." This was a problem, and neonatologists are taught that this is a very big deal, and that it *all* comes from the blood. And so, the reason that neonatologists, if you practice in certain parts of the United States, the reason that neonatologists get all upset about things when we say, "well we only want to give leukoreduced products because they're CMV-safe," is that they've been taught that CMV-negative products are what they should give. The reason is because that's what ended a lot of their problems in their babies in the late 80's, is that by giving CMV-negative blood from CMV-negative donors, they reduced by 30% in many cases the transmission. So, then we came along with leukoreduction, which really does a great job, because CMV harbors itself after the primary infection in the donor or the person, in the monocytes. By leukoreducing, you can get rid of those. If you get less than a million cells after leukoreduction, we feel as a community in blood banking that you have a "CMV-safe" product.

So, with that knowledge, there have been small studies in the 90's and a little bit in the late 80's with different filters than we have now in the 21st century that show that there was promise in just giving leukoreduced products alone to these infants. But the studies were very small, and the confidence intervals were very wide. We just finished a study

that was published in the end of 2014 in JAMA Pediatrics that basically looked at this question of leukoreduction and CMV-seronegative blood going to premature infants that weigh less than 1500 g. The docs would not let us randomize, because they still wanted leukoreduction and CMV-negative, which is what they normally get. We conducted this all in Atlanta, at Northside Hospital which is a private hospital, and Emory University. We enrolled about 539 babies, and 76% of those mothers (there were 462 mothers), were CMV-positive. All the babies received leukoreduced and CMV-seronegative platelets and red cells. We did NAT testing on all the blood, 100% on all the units, both FFP, CRYO, anything they got. We also did flow cytometry looking at residual white cells to make sure there were no leukoreduction failures (because if you have a leukoreduction failure, then you're really not getting rid of CMV from maybe a CMV-positive donor). So we did that, and basically we showed that with that strategy, there were 310 of those 539 babies that were transfused in this, so almost 60% transfusion. We had ZERO, ZERO transmissions! And actually we worked that out; it was less than 1% risk of getting transfusion-transmitted CMV. There were over 2000 transfusions given. There were over 800 units given (now remember, we give small aliquots to babies, and we have dedicated units, so there weren't as many units as you would think with these 2000 transfusions). The *shocker*, though, was we still had CMV in these babies, OK? Almost 7% of the babies still had CMV. We also tested all the breast milk in all the mothers…

**Joe**: Uh-oh!

**Cassandra**: Yep! 27 of the 28 babies that got CMV, and 5 of those had disease, they all got it from the mother! And they had very high, we're talking some of them had 100,000 IU/mL of CMV in their breast milk. And in the babies, they had 9000…there were very high numbers. So, just like blood bankers are always saying, "well, there are other places you can get CMV," this study kind of showed that, yeah! So the cumulative incidence at 12 weeks for CMV breast milk transmission was 15%. The neonatology community has been really concerned about this.

Then, I went on with Megan Delaney in Seattle, at the same time we were doing this study, we embarked on another study which was just published in Transfusion this year (2016, epub ahead right now). We decided to look at leukoreduction only, CMV-untested blood going into these babies. We did the exact same setup that I just described for our study, and we enrolled 20 infants. 8 of the kids got transfused, 43 transfusions, and 60% of the mothers had CMV positivity. None of the transfused units transmitted CMV, and 5 of the transfusions that occurred with these babies came from CMV-positive blood donors. There were no leukoreduction failures; we did all the same thing as with the other study. We had one baby who got CMV, and it was from breast milk. What we basically pulled together with all this for the neonatal world is that, **yes, if you can get CMV-seronegative and leukoreduced blood, then that would be ideal**, because we just showed that with the right-powered study. However, we know there are places that are only giving leukoreduced blood, and it's CMV-untested, and we know that we're getting good filtration. So the question still remains, if you gave blood from a CMV-positive blood donor that was optimally leukoreduced, what is the transmission rate? We couldn't answer that with our study. We think that we should have a comparative

effectiveness study, and that's what the discussion was in the Delaney paper, is that if we looked at 300 more babies where there was leukoreduction with CMV-untested, and we did the exact same study, we probably could understand whether we could just go with leukoreduction alone, which is probably fine, because in our study we had one leukoreduction failure, and it was by ONE CELL (like, literally!). And so, we feel that this is important, because as far as the industry goes, if we could stop doing CMV testing for this population, which in many cases is demanding this, that could save an unbelievable amount of money. Anyway, that's kind of where that goes.

Now, when it comes to oncology patients, the jury is still not really out either. Even in the adult world, there's still controversy as to whether CMV-safe, leukoreduced blood which is optimally leukoreduced really doesn't transmit CMV. So, there's a lot of people still want CMV-negative, some people do. We, for our pediatric patients, say that leukoreduction alone is safe, because we feel like the amount of reduction now, there are so few cells left, that we feel that the transmission is almost nil. Whereas when those other studies were done in the late 90's, they still had 3rd generation leukoreduction filters, it was really different than it is now…

**Joe**: And I think a lot of bedside filtration…

**Cassandra**: Absolutely, there was quite a bit of bedside filtration. And there was a lot of crossover; it was hard to keep everything straight in those studies. So, I think it's easier to say that leukoreduction alone in CMV-untested is OK for pediatric oncology and stem cell transplant patients. That's what we practice.

**Joe**: Excellent! You're 100% right, as you know, that is controversial. I have really variable, in my blood center practice, there are really varying opinions out there. Not just in the pediatric world, but in the adult world as well as you said. This is obviously something, as you said, that more work needs to be done, but I appreciate the work that *you've* done with it. Especially, I'll tell you, when your article came out about the breast milk transmissions, I was like, "Somebody proved it! I've been saying this for awhile, and somebody proved it!" It was awesome…

**Cassandra**: Yay! Well, the nightmare is when they ask you for that lookback. "Go look back at all the units, and see if you can figure out where the CMV came from!" Now I just tell them, "here, we'll test the breast milk!"

**Joe**: There you go. So, we have "cleaned house," I believe! That's outstanding! So let us move on to topic number 4. This is a great one. I think that this is one that there is still controversy about as well (you're picking the hot topics!). So why don't you hit us with number 4?

**Cassandra**: OK, so this near and dear to my heart. It's "**An ounce of prevention makes red cell transfusion possible and lifesaving**." This is really in patients with sickle cell disease. The reason I say that is first of all, just so everybody gets a little background, around 100,000 people in the United States have sickle cell disease. It occurs in about 1 out of every 365 blacks or African-American births. It does happen in

Hispanics; 1 in every 16,000 Hispanic-Americans have sickle cell, and 1 in 13 blacks or African-American babies are born with sickle cell trait. This is a big problem. Before I get to the prevention part, I wanted to say that in sickle cell, there is not a lot of treatment. There's like three major treatments: **Hydroxyurea** is one, which lots of people hear about, and it's a drug and it helps with decreasing some of the anemia. But really the mainstay of therapy is **transfusion** and **stem cell transplant**. And the transplant where it's the best outcomes is for matched sibling transplants. Many, many children do not have a fully matched sibling. There are allotransplants and partial mismatches that are out there, but are matched unrelateds, but they don't do as well, and they still haven't figured out the best scenario there. So, really, we're left with transfusion, and transfusion is used to treat not vaso-occlusive crisis! Nobody should be treating (that) with transfusion! But, for primary and secondary strokes or primary stroke prevention, secondary stroke prevention, acute chest, splenic sequestration, there are many, many things, and they all start in childhood.

**Joe**: Cassandra, can I just stop you for just one second, because you just said something that I want to make sure that my audience doesn't miss, because the topic of treating crisis, sickle cell crisis with transfusion, it's so commonly misunderstood. I know this is slightly off topic of where you want to go, forgive me for that, but it's such a crucial point to make. Could you just spend half a minute on that?

**Cassandra**: Absolutely! Absolutely! So, vaso-occlusive crisis is definitely going to drop the patient's hemoglobin. Many many of these patients live with a hemoglobin of around 7, 6.5, and when they get a crisis, they can go to 4.5, 5. And they still can maintain their oxygen level where they don't require oxygen, but they are in a pain crisis. And if we were to transfuse every time they have this, we might be able to raise their hemoglobin. It doesn't necessarily mean we are going to be able to change the pain crisis' natural history. But we are going to give them iron, and every time we're going to give them iron. So, there is no data to support the fact that during pain crisis, we should be giving this, for acute vaso-occlusive crisis.

**Joe**: Preach it! (laughs)

**Cassandra**: Alright! But the thing that people get confused about is, that acute chest, let's say, IS a vaso-occlusive crisis in the chest. But it's causing a hypoxic problem. As soon as you get hypoxia, which is what we call "symptomatic anemia" in an anemic patient, because these people don't feel good, I mean they always don't feel as much energy and stuff like that, which is different kind of anemia than when you have a person who doesn't have a hemoglobinopathy. So you kind of have to distinguish that. But as soon as they develop that oxygen requirement, it can go downhill very, very quickly when they get a hemoglobin of 4 or whatever, and they're sickling there. And of course, if you're having that same process in your brain: Bad news! So, we want to turn that off as soon as possible, and that's why we will transfuse.

Splenic sequestration, same problem. They can just put all of their blood in their spleen, and they can just drop their blood pressure and they can just die right in front of your face if they get a huge splenic sequestration; it can kill them as well.

So, we've got all this transfusion being important. However, we have this balancing act with iron as a long-term problem that can kill the patient, but the shorter-term thing which is not well understood is why do some people develop antibodies to the red blood cells? I'm talking about the minor red cell antigens. So, Rh, C, E, the Kell system, so for Kell, etc, that's what I'm talking about here. We know that about 25-30% of these patients will develop an antibody, and once they've developed an antibody, whether it's an alloantibody, which means to a foreign protein, or whether it's an autoantibody to those cells, they're going to be at risk of developing even more antibodies. The problem we have is that we don't know which patient is at risk, and this is like the biggest problem we have. So in order to make everybody as safe as we can, we've developed strategies which are not the most practical, not the most cost-effective, but they are the most effective for what we have right now, which is to **match beyond ABO and RhD**. We do that prophylactically, so we're doing it before they develop an antibody, even though we don't know which patients are going to be that developer. And so, in comprehensive sickle cell centers in the United States, many places will test as soon as the person is born, basically, and they come to clinic, we will do what is called the "phenotype" on them. We will look at some of the most clinically significant antigens on the their red cells, that if they developed an antibody to it, they could be in trouble. And those are C, E, Kell, Duffy, Kidd (but there are other clinically significant antibodies that I'm not mentioning, but those are the most common). And so that's what we do the phenotype on, are those first few that I mentioned. And those sit in many people's blood banks, just there, and then if somebody comes in for an acute problem, where they're going to need a transfusion, they can order blood from their blood center that will be antigen-negative for the antigens that the person has that they're antigen-negative for. Plus, they are ABO and RhD-typed. That's what many centers have worked on.

The issue is, and the NIH by the way, has now endorsed at least for C, E, and Kell, in their sickle cell guidelines they say that you can match now prophylactically for C, E, and Kell. So, that's a big step, because before that we didn't have anything except for category 3 evidence (which is still what they used to put that in the guideline, but at least it's there), to show that's what we should be doing. Dr. Vichinsky and colleagues, in 2001, they showed that doing this matching actually reduced transfusion reactions by 90% (like, delayed hemolytic transfusion reactions), and that their alloimmunization rates went from like 3% to 0.5% per unit. So that was a huge, big deal, so that's what we are basing the C, E, and Kell matching on. The issue of this discrepancy, and I don't know if this is too much information, just that the donors who are out there who are supplying most of the blood, their ancestry is a little bit different than the recipients that we have in the United States. That European vs. African ancestry is why we get some of these mismatching if we were just matching for ABO and Rh. We tried very much to go to minority donors and have minority donor collections to be able to get more blood that is similar to the patients that we're treating. So, in the United States, in different states, they have different programs; "Blue Tag" programs, "Partner for Life" programs, the Drew program in Washington University in St Louis. There's all these different ways, but still, that has not thwarted the entire alloimmunization process. So, what's on the horizon, and what is actually now FDA-approved (at least one of the tests are), is genotyping. Can we more cost-effectively test more antigens than 7 or 8 with

phenotyping, which is just looking at the protein on the outside of the red cell with an antibody and identifying it, can we look at their genes and look at their DNA, and look at their projected phenotype based on their genotype? And so what we found is with some of that genotyping; and Dr. Chou and Dr. Westhoff, who I know has done another one of your podcasts, looking at Rh specifically, they found that there is still alloimmunization happening, especially in the Rh part of the gene. That has to do with the fact that when they went down and looked, there are actually variants within the E and the C antigens in the Rh family. And, those variants make it look like, if you only did it with an antibody and looked at the phenotype, they make it look like everybody's protein is the same. But really and truly, it's not, and these unfortunate patients develop antibodies, and they end up that they can't get blood because they can only get these variant blood, and not everybody has these variants.

So, what I'm trying to say is that this prophylaxis and things that we're doing is helping some, because it is getting these patients to adulthood, and they can still be transfused, but we're not completely stopping alloimmunization. One of the things that just got published recently are two very important articles that people should look at. One was published this January in 2016 which was from our group where we talked about the impact of red cell alloimmunization on sickle cell disease mortality [Nickel RS et al. Impact of red blood cell alloimmunization on sickle cell disease mortality: a case series. Transfusion 2016;56(1):107-14.]. So, many, many people don't think about alloimmunization as causing people to die. I mean, if you get a transfusion of a unit that has a mismatch, and you have an antibody, yes, you could have a hemolytic transfusion reaction and die. And sometimes, we're forced, because there are so many antibodies that have developed, that we have to go to that, and somebody could die. We also don't always remember that we can't always *find* antibodies that people have, because they haven't gotten transfused in a while. And so, they get transfused, have a delayed hemolytic transfusion reaction, because they didn't see it on the screen, and they can die from that. But the biggest thing that people miss out on, and this is reported, we have about five cases in here, is people waiting for blood. As we look around the United States, somebody has 6 antibodies, and they need an exchange transfusion, they're having a stroke or they're having some big event; we can't get enough blood for them to do what we properly need to do because we didn't prevent alloimmunization when they were children. Now they're adolescents, they're adults, whatever. So that's actually happened, and it's been sad, and we kind of reported on those.

But another thing that just came out this month in Transfusion (I believe it's this month, but I think it's ahead of print), by Ballas and McLaughlin, it's called the "High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program" [McLaughlin JF and Ballas SK. High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program. Transfusion 2016;56(5):1014-21.]. What I want to say about this is that some of these patients, they go to adulthood and they don't get transfused any more for a myriad of reasons. Sometimes it's about antibodies, and they just say, "you're just too difficult to transfuse." And what they're saying is people who have gotten started on transfusion for whatever the reason when they were children and they don't continue as adults, they're dying.

And it's terrible! So we spend all this time and try to make them have a good quality of life and live a long time. I want to just bring that to everybody's attention, that prevention of alloimmunization will lead to more therapy and more possibilities for people when they become adults, which is what we strive to do for the children.

**Joe**: That's awesome. It's obviously a big, big topic, and there's a whole lot to say about it, and you did that…that was GREAT! Amazing. Can I just pull it back for just one second to ask you one question. You mentioned the strategies, in terms of the prophylactic matching. How would you characterize, and I know it's not universal, I know people have strong opinions about going the "full phenotype" matching, but what is the most common thing that you're seeing out there in terms of how people match prophylactically? Is it that C, E, and K, or is it more than that?

**Cassandra**: Many places will start out with C, E, and K, for people that haven't made antibodies. And if you've made an antibody; this is what we do. We have "category 1" and "category 2" is what we call them. Once you've made an antibody, then we'll match for that, we'll give you antigen-matched units for that antibody, plus C, E, and Kell, plus we will go to $Fy^a$ and $Jk^b$, and that's we'll extend it to, and then sometimes we will go to S. There is a really good "Immunohematology" edition from the Red Cross, I think the last one was put out in 2012 or 2013; it summarizes at least 7 or 8 centers, how they do their prophylactic matching, and Annie Winkler and I wrote our particular one [Winkler AM and Josephson CD. Transfusion practices for patients with sickle cell disease at major academic medical centers participating in the Atlanta Sickle Cell Consortium. Immunohematology 2012;28(1):24-6.]. I think Gerry Meny was the editor. But it's a really good resource. But I think looking at Connie Westhoff and Stella Chou's data on this would be really helpful too, because that's linking the genotyping with the phenotyping, and the prevention as well.

**Joe**: So, you said something that I want to make sure the audience is aware of…Those of you that are listening, if you're listening through iTunes or Stitcher Radio, you can go to the Blood Bank Guy website and go to the show page for this particular episode, which is BBGuy.org/podcast, and you'll find it there. On the show page, Cassandra and I will work together to get a list of references for some of these articles that she's talked about, so you can look them up yourself and have them for your records, because it's really going to help you.

**Cassandra**: Absolutely.

**Joe**: Alright, so that's a great topic, and I'd love to talk to you for another 25 minutes about that, but…

**Cassandra**: We've got one more!

**Joe**: We've got one more. So real quick, before we do that…

1. The volumes vary
2. Predicting the platelet effect, which is a surprisingly little effect in some of the patients that we have discussed today

3. Cleaning house (a discussion about irradiation and CMV-safe products)
4. The ounce of prevention makes red cell transfusion possible and lifesaving

And, Cassandra, I have no doubt that number 5 is going to be just as great, so hit me!

**Cassandra**: Well, thanks, so I'm going to just spend time on a look at hemolytic disease of the fetus and the newborn. I'm going to spend time on what it is; I'm not going to spend so much time on how we transfuse, because it's just such a big topic (unless you want to ask me some questions about that part)…

**Joe**: Well, I just might! We'll see!

**Cassandra**: We'll see. Alright, well we know that we have two different things going on here. We have "hemolytic disease of the newborn," which is when they are out of the womb, and then we have "hemolytic disease of the *fetus* and newborn." I think sometimes they get all kind of jumbled up, so let's talk a little bit about this.

First off is that when it happens to the fetus, it is something that the infant or the fetus is getting is exposing the mom to, and the mom is going to make an antibody. This antibody has to be of the IgG form, otherwise, it won't cross the placenta. It can't happen in the fetus if it doesn't cross the placenta. So, if it's the first sensitization, say to D, which we try to prevent (anti-D is the worst); if the mom gets sensitized, sometimes the first-born baby is not affected or very, very mildly affected. Because that IgG has to have formed after the whole sensitization occurs. But the second baby can be affected and can be immensely affected. Basically, this can happen with D, c, and K most often. Those are the most often ones that can cause hemolytic disease of the fetus. Around 20% if it happens with D are the ones that are seriously affected in utero. So not every baby is going to become "hydropic" (hydropic means where they are going to have such severe anemia that they're just going to become edematous, go into cardiac failure, and die in utero). Those are the kinds that we are worried about in utero, and those are the ones that we give intrauterine transfusions for, when we can detect it, trying to save the baby and then have them come out.

Then we have another type, which is **ABO hemolytic disease of the newborn**, and that really isn't happening in the fetus. It's happening outside, once the baby is born. It's happening with antibodies, they maybe can cross, they kind of cross, but they don't cross in the fetus. They cross a little bit in the fetus in the third trimester, but they don't cross big time like these other ones earlier on, once the patient has been sensitized. So they don't come out super-anemic. It's kind of right at the end, they come out a little bit, where their DAT is positive, and they can be somewhat anemic. But there is antibody that has crossed. It is usually IgG "A,B," and it does cause this insidious hemolysis. Usually in an O mom to an A or a B baby, and it's usually an O to an A that's the worst, and that's because of the antigens that are present on the red cell (there are more A antigens than B antigens). But usually, what happens is that after the baby is born, a DAT will be done for a mother who is O. If the DAT is negative, the expectation is that there's really not going to be a problem. If the DAT is positive, but the hemoglobin hasn't dropped, then there's still a little question of whether there is going to be a problem. But

sometimes there's a baby and they see the hemoglobin which should be around 14 when they are born can be around 10 or 9 or it's lower, then they'll measure a total bilirubin, and they'll see that is going up, and they'll put the patient on some phototherapy, which hopefully with eating and the phototherapy will take care of the bilirubin and get rid of it, because you poop it out and you pee it out!

The reason that babies don't die with the hyperbilirubinemia in utero, just going back a little bit with the hyperbilirubinemia, is that the mothers are able to get rid of bilirubin when they pee and everything, so it isn't until the baby is born, where their system is overloaded, and they can't deal with the conjugating of all the bilirubin and getting rid of it properly that you get this unconjugated hyperbilirubinemia. And if you start to get in the ranges of 17-20 mg/dL, if you get up into those ranges, that's where we start to entertain doing a double volume exchange transfusion on one of these babies. We hope that with phototherapy for the ABO hemolytic disease of the newborn, that you actually can prevent that, not get to that exchange. And then, for the babies that have had hemolytic disease of the *fetus* and newborn, so they have a minor antigen antibody, like the D or the Kell, or any of those, those babies end up remaining anemic even when they've had intrauterine transfusions. They can remain anemic up to 6, 8, 12 weeks after they're born, even though they come to term when they're born. That's because the antibodies from the mother really stay around for quite awhile; 6, 8 weeks. And they actually have been shown in some instances to attack the erythropoietic progenitor cells. So your retic count remains very, very low in these babies. That's why they still continue to require transfusion after they're born. It's not *exchange* transfusion, but they need to be monitored, and many of them require 2, 3, 4 transfusions post. And of course, they still should be antigen-negative for all the things. Then, once the antibody has disappeared in those hemolytic disease of fetus and newborns, they shouldn't need a transfusion, they should be fine, but you don't have to worry because that antibody will be gone forever; it's not from the baby, it's from the mother. And that's what people sometimes forget, is that those antibodies are eventually going to go away. It's just a matter of time.

**Joe**: Got it, and what you mentioned about nailing the precursor cells, that's kind of most famous with anti-K, right?

**Cassandra**: Yes, yes it is.

**Joe**: When I describe that to people and I talk about anti-K HDFN, I typically will say it's not nearly as "hemolytic" as the other possibilities, but it's more of a "suppressive" phenomenon. Is that a fair way to put it?

**Cassandra**: Absolutely. I think that's a fair way to put it. I also think that we're seeing more of the Kell, and I think it's all relative, because we give prophylaxis for D. D was the most common and it was the most severe, but in the United States, people have prenatal care and they get what they're supposed to get, then we've really thwarted the big one. So Kell is the main one out there. We don't have any anti-Kell treatment… "Kell-GAM" or anything like that (LAUGHS)…So, if we did, then we wouldn't even see that. But I do think there is a little different pathophysiology like you are describing.

There's more of a suppressive…and I'm not sure whether that just is the way the affinity of the antibody is for the antigen, or how soon that antigen is formed on the precursor, it might have something to do with that.

**Joe**: The other thing I wanted to ask you about is, with the ABO form of hemolytic disease, as you said, primarily of the *newborn* rather than the fetus and the newborn, what I've found often in my interactions with clinicians about this is that most pediatricians are fairly attuned to this, they're fairly well aware that this is something that can occur. And often, I find that they're more aware of it than some of my pathology residents sometimes! Is that a fair perception?

**Cassandra**: It's a totally fair perception! It's like the very first thing that we're taught! So, when you are a pediatric resident, you always say, "Duffy dies, Kidd kills;" I mean they really talk to us about this, because we are in the nursery and we're seeing all these term babies. And so we will have these moms, and you'll have a list of all the babies you're going to do your physical exams on, and you're going to discharge them all. So, you're looking for ABO incompatibility, you're looking for jaundice, you're looking for all those things, because remember, people aren't staying in the hospital. So you're going to have to set those bilirubin lights up, and do all that phototherapy. The other thing is that we have the moms that are O's, and we're always like, "Oh, this is a set-up." We always know the mother's blood type, and then we're looking to see what the baby's blood type is. And then we look at the DAT. It's kind of drilled into us, to do all that. So, that's why we're aware of it.

**Joe:** That's a good thing!

**Cassandra:** Yeah! A clinical person knowing something about blood bank! (LAUGHS)

**Joe:** It's outstanding! Yes! (LAUGHS) Anything else on that?

**Cassandra:** That was the main thing. The only other thing I want to mention about this is, when you have a baby who is pretty sick, and at the Children's Hospital, we don't always have the moms, but the moms sometimes will come, because that's not where the babies are born, at the Children's Hospital, at least *our* Children's Hospital (CHOP has a maternal ward). But sometimes when you're working on these specimens for these babies, and you need more specimen for their screen, or you're still trying to delineate what is going on, people need to remember that they can get blood from the mother. That they can work on the specimen that way, and that they don't have to keep bleeding these babies. So, they don't have to get all bent out of shape when we call and say, "we need more specimen." We really should be thinking clearly about "where did this antibody come from?", and if we need more to work with, then we need to ask the mother to give us blood.

**Joe:** Great, that is such a great point. Bleeding a baby to anemia or *further* anemia int the face of this is…

**Cassandra:** It's crazy!

**Joe:** …well, it's dumb, isn't it?

**Cassandra:** And nurses have a spaz on the blood bank! I mean, medical technologists get yelled at. "You want ANOTHER specimen? Oh, my God!"

**Joe:** Yeah, well thank God for the nurses!

**Cassandra:** They're being protective!

**Joe:** My wife, by the way (I'm sharing something I've never shared publicly), my wife at one point was a NICU nurse, and she used to tell me all the time that just drove her crazy, when the blood bank wanted *more* specimen. She's like, "STOP IT! No more!" (LAUGHS)

**Cassandra:** (LAUGHS) That's still true that way, and the babies are even smaller.

**Joe:** Well, so we have made a grand tour through a bunch of really cool stuff, Cassandra! I can't tell you how much I appreciate this! I would love, at some point, to have you on again to talk about some things that we haven't been able to discuss; some controversial stuff like age of blood, we haven't gotten to, and I know you've done a lot of work on that, and another one that I know you're working on right now is the association of necrotizing enterocolitis with transfusion.

**Cassandra:** Absolutely!

**Joe:** We've got some more stuff that we can talk about down the line, if I can twist your arm and talk you into coming back onto the podcast.

**Cassandra:** First of all, I'm really honored that you asked me. I enjoy this, and I would love to come back! Yeah, there are so many things; pediatric transfusion medicine is *that* interesting, and THAT COOL! You should go into it! That cool! Yes! (LAUGHS)

**Joe:** (LAUGHS) THAT COOL! Alright, well, we're going to close it for now then. Cassandra, again, thank you so much!

**Cassandra:** Alright. Talk to you soon. Bye-bye.