BBGuy Essentials 047CE:
I See CMV! with John Roback
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Joe Chaffin: This is the Blood Bank Guy Essentials Podcast, episode 047CE!

[INTRO MUSIC]

Joe: Welcome back to the podcast designed to help you understand the essentials of blood banking and transfusion medicine! I'm Joe Chaffin, your host.

Today we are taking an in-depth look at a controversial topic: Transfusion-transmitted cytomegalovirus (CMV) infection. There are many opinions and thoughts about TT-CMV, and I'm going to explore them with an expert in the field, Dr. John Roback from Emory University.

Before that, here's some housekeeping: Continuing education credit for this episode is provided by Transfusion News (TransfusionNews.com), with generous sponsorship from Bio-Rad (who has no editorial input). The big news I have for you is that this and all of my previous CE episodes now qualify as Self-Assessment Modules ("SAMs") for the American Board of Pathology! You can find all of them at BBGuy.org/podcast, as well as iTunes and Google Play (look for titles ending in the letters "CE"). If you've already received CME for any of those episodes, you should have already received updated certificates by email (let me know if you have not).

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OK, back to today's topic: At the AABB Annual Meeting in October 2017, recently retired UCLA blood banker Dr. Dennis Goldfinger received the Emily Cooley Memorial Award. In his remarks, Dennis made what some might consider a "heretical" statement. I wrote it down so I wouldn't mess it up. He said: "You can't get CMV from a blood transfusion!" Now, I'm sure that not everyone believes that, but I wanted to repeat it so you would know that what we are going to talk about today, transfusion-transmitted

cytomegalovirus infection, is FAR from a settled subject. You have people who believe and practice in a wide variety of ways, and I can tell you that here in the U.S., nothing *at all* is settled!

My guest today is Dr. John Roback, Professor of Pathology at Emory University and a 2017 AABB President's Award winner. John was also senior author on a *truly unsatisfying* 2016 AABB Committee Report on TT-CMV that I wanted to discuss with him (don't worry, he agrees with that assessment!). The report really illustrated the challenges we have in coming to a concrete conclusion about the "best" way to prevent TT-CMV. As we talked, I realized that we actually have slightly different opinions on the subject! That's ok, because again, it just shows that well-meaning people can have different interpretations of the "best" way to do something (I'll talk more about that at the end of the episode).

I'm excited for you to hear this interview, so let's get started! Here's my conversation with Dr. John Roback about transfusion-transmitted CMV.

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Joe: Hey John! Welcome to the Blood Bank Guy Essentials Podcast!

John Roback: It's great to be here. Thank you so much for inviting me. You know, like I mentioned when you first contacted me, it must have been like 20 years ago that I was one of the students at your Osler review course, and it was awesome! So, I think it's great that I can actually help you do some teaching now.

Joe: Well, thank you for making me feel old right off the top of the bat, John! That's fantastic! I think this interview is going to go *great*! [laughs] Well, that's very kind of you to say, and I really appreciate that. You have gone on to do great things in blood banking and transfusion medicine, and I'm really, really honored that you're here to talk to me today about transfusion-transmitted CMV, a topic that I think both you and I have wrestled with over the years. You have been involved in not only some groundbreaking research, but also some committee reports and statements from AABB that we're going to get into. It's one of those things that I think we WISH we could close the door on and say, "Oh great! We figured this all out! We're done!" BUT, transfusion-transmitted cytomegalovirus, John, I think you and I would agree that we're not where we would like to be in terms of having definitive answers. Is that a fair way to put it?

John: You know, absolutely! It's one of those situations where down the line when we have, let's say, “pathogen-reduction" methodologies that are approved for use on *all* blood components, and are being universally applied, we'll never worry about transfusion-transmitted CMV again. But until then, we're left with these conundrums of, given our current approaches to prevent it, what's the best way to do it or what's the best combination of ways to put together to produce the safest blood product for our patients?

Joe: Absolutely, well, so let us go down that path, John. But before we get to those options, I really want to take us back to the start, and let's talk about cytomegalovirus and what it is, what makes it unique, and why do we care about it so much in transfusion medicine? So, if you would, just start us from the beginning. Just give us some basics about CMV. What is this virus?

John: So, CMV is a beta-herpes virus and like other herpes viruses, it can establish lifelong latency in the host. So, you get that initial transient infection, and if you're an immunocompetent recipient, you quickly bring the virus under control, but it persists, and it actually persists in, one of the main reservoirs is in **monocytes** in the peripheral blood. So, if you transfuse blood to another individual and that blood has CMV-infected monocytes in it, then, theoretically the virus can reactivate in transfused monocytes and infect the recipient.

So, one of the reasons, I think, why this particular herpes virus is so interesting, and why it still presents these conundrums to transfusion medicine practitioners, is because, first of all, it does remain latent in peripheral blood white cells, so it can be transfused. And secondly, we have a pretty good match between the percentage of the population that is “CMV-naïve” (that's never seen the virus and so has no immunologic response to it), and the proportion of the population who harbors CMV. Depending on the part of the country you live in, somewhere between, let's say, 40 and 70% of the donors will be CMV-seropositive, will have previously seen the virus, but about an equal proportion will be naïve to the virus. So, if you contrast that, for example, with Epstein Barr virus (EBV), one of the reasons we don't worry about transfusion-transmitted EBV (or don't worry about it much), is because 95% of the adult recipient population is immune, (you know, has already seen the virus--already made antibodies). But here in the case of CMV, we have a population, a large population of adult recipients who are naïve to the virus. So, if that population of recipients, if they're not only naïve to the virus, but they're immunocompromised, once they SEE the virus, they don't mount a good immune response, and now this opportunistic infection can cause significant morbidity and mortality in the recipient. It's a very challenging virus from that perspective.

Joe: Well, let's step back for just a second from that before we get into some of those details, John. Have we worked out, is there science that tells us now what the stages of it or if there are stages of infection for CMV? Are there different steps in the infection for say, someone who's in the community and gets a CMV infection? Can you talk us through that a little bit?

John: Typically what happens then, is after the viral infection, **there's a phase in which you can find CMV, both in peripheral blood white cells and then also though, as free infectious virus in the plasma**. And, you know, as with many viral infections, you have this so-called "seronegative window phase." So, by the time these recipients typically have made an antibody---by the time your serology turns positive saying, "This person's been infected"---you've already had a few days to maybe up to a week or more, where there's been free virus in the plasma and/or CMV in peripheral blood white cells. So, then you have that window phase. Now, that window phase occurs before the viral levels peak, so after seroconversion, in most of these healthy immunocompetent recipients, you still see an increase in CMV viral loads, either free virus in the plasma or in the white cells, which then slowly goes away, but that can take several weeks to months, in some cases.

Joe: I think that's really important to make sure that the audience is really clear on that. We have this tendency to think of CMV as a “white cell virus,” and it is, right? But I think that the CMV being free in the plasma is something that is not always appreciated. There's not really a question there, John, I just wanted to re-emphasize it. I think that's important for people to get!

John: That's absolutely important because if it were only a white cell-associated virus, we may not be having this conversation now! You do leukoreduction, and in the US, you know, where...some other countries are 100% leukoreduced. In the US, we're approaching that, but that would mean that doing a very efficient leukoreduction would eliminate the problem. But I think it's that free virus which can cause issues. I did a literature search recently, wasn't able to find anything, but early on in my career as a transfusion medicine physician, we actually did a couple "quick and dirty studies" and found that if we take a sort of a purified viral preparation and then put it through a leukoreduction filter, a lot of the virus makes it through the other side. So, at least those older generation leukoreduction filters were not very good at efficiently removing free virus.

Joe: Can you talk a little bit about, symptomatically, what does that mean for an immunocompetent person? Is that person who doesn't have some issue

with their immune system, are they going to know that they have CMV or are they going to be wiped out? How does that work?

John: I think a large segment of the seropositive community (at least this is what I teach the residents and fellows), a large segment of the seropositive community, probably never realized that they were infected. It was probably a relatively benign infection. Maybe they thought that it was just some kind of strange viral syndrome they had that quickly went away. It's complicated, it has some sophisticated ways of evading the immune system, but by and large it's kind of, I would use the term a "wimpy virus," in the sense that if you have an immune system that is functioning normally, the virus does not really represent much of a challenge to the immune system, and the immune system clears it pretty fast.

Joe: All right, so we've talked about the people that are immunocompetent and get CMV, and for our perspective for this discussion, we're going to consider those in the "donor group," the potential blood donor group, because we're talking about transfusion-transmitted CMV. So, let's talk about the other end, the patients that are receiving blood potentially from a donor who is CMV infected. What can you tell us about the spectrum of things that can happen to someone who RECEIVES CMV from a blood transfusion?

John: Right. Well, once again, if the recipient has a normally functioning immune system, if they're immunocompetent, then the risks are pretty low. They may have a transient infection, they may seroconvert, but not really a lot of concern. But on the other hand, if they're immunocompromised, if their immune system is not able to deal with this opportunistic infection, then there can be quite severe sequelae up to and including death. I think we'll talk a little bit later about a study that we were recently involved in, looking at CMV transmission in low-birth weight infants who were "immuno-immature" I would say, so their immune system had not fully developed, but we saw a substantial amount of morbidity in that study, including infant deaths that were attributed to CMV. The same thing can happen in adult immunocompromised populations.

Joe: And can you be specific with us, John? What adult populations are we worried about? What kind of patient groups should we be most worried about with CMV?

John: Well, in adults, the population that we normally get asked about is the **bone marrow transplant** population, and specifically, we're talking about cases where neither the donor NOR the recipient has been previously

exposed to CMV. So, if you're talking about autologous transplants, then the recipient who is actually also the donor is CMV seronegative, but if it's allogeneic transplants, then it's a situation where both the recipient and the donor are seronegative. So, in adults, that's the main population that we're concerned about. You know, a smaller population would be, for example, **patients with significant deficits in cell-mediated immunity**. Normally, we discuss those with congenital defects in cell-mediated immunity, although, there could be some concern for example, that patients with AIDS, for example, that have an acquired deficit in cell-mediated immunity, could also be at risk, although, that I don't think has been as well-defined. And then, as we talk about groups that are immuno-immature, either **very low-birth weight infants, or in addition, cases of *in-utero* transfusions**. So, there you have the ultimate immuno-immature recipient. It's interesting, if you're doing in-utero transfusions, that's a scenario where even a number of transfusion medicine practitioners who say, "Oh, it's not a situation we have to worry about," kind of pause a little bit and say, "Well, MAYBE for in-utero transfusions we have to do something special to prevent CMV transmission." So, that's probably one area where most everybody agrees.

Joe: And one last thing before we move on from that, because we need to get to how we're testing our patients and donors and how we're trying to *prevent* CMV transmission. But before we leave this topic, I have heard the argument made, in some cases from the stage at AABB Annual Meetings, that that we are, oh, how shall I put it? That "freaking out" about CMV is less of an issue than it used to be, or we shouldn't be so concerned about it because, for example, in bone marrow transplant and organ transplant recipients, those patients are being monitored incredibly closely for evidence of CMV infection. So, you know, why are we even worrying about it from the transfusion perspective? And I just wanted to get your take on that in particular with...yeah, that's probably true for bone marrow transplant, but is it true for ALL patients that could get CMV?

John: I would say it's NOT true for all patients, and even in the case of bone marrow transplant recipients, it might be true at some sites but not at other sites. So, for example, if you are monitoring your patients really closely, if every week you're testing for CMV infection, for example, and you're able to, as soon as you see a blip suggesting that the recipient has been exposed to CMV (either a blip up in CMV plasma DNA or whatever method you're using), and if you're ready to jump on that immediately with antivirals [*NOTE: "anti<u>retro</u>virals" was said inadvertently*], then I think that you know you probably don't have much of a problem. And a few years ago, when I was talking with some people from "the Hutch" [*NOTE: Fred Hutchinson Cancer*

Research Center, Seattle, WA], that's basically what they do. And they're one of the biggest proponents of saying, "Let's just use leukoreduced blood and we'll be fine and we have nothing to worry about." And it's that combination, I think, in their population of using leukoreduction plus using really active monitoring, where were they dealt with the situation. But if your particular center is not monitoring that actively, or if you're concerned about other patient populations like low birth weight neonates, for example, then I think it is something that still needs to be considered. I can tell you, in the case of some of our big obstetrical practices in the Atlanta area, that they're very wed to the practice of using both seronegative AND leukoreduced blood, just because they're so concerned about any of their patients contracting CMV infection from transfusion.

Joe: When we are testing blood donors for CMV, what kind of test or tests are we doing?

John: So right now, when we're testing, *essentially the only test we have to identify a donor who might be high risk versus low risk is serology*. So, what we're looking for in that case is, we're looking for the presence of **antibodies against CMV**, indicating that individual's previously been exposed to CMV. Now of course there are nucleic acid-based tests to detect CMV, and those tests are used a lot, for example, in organ transplant recipients. But those tests have not been applied widely to the blood donor population in order to identify donors who are relatively higher risk or relatively lower risk. That's something presumably that *could* be done. I've heard some discussions about doing the studies, but at this point, it's not something that's really *been* done. So if you if you turned to your blood center, for example, they'll be able to get you CMV-seronegative blood, but if you ask them for "CMV DNA-negative blood," they just laugh, because is not routinely available.

Joe: Okay! So is it fair to say that when you get a unit of "CMV-seronegative blood," there are several possibilities for that donor in terms of what their actual status is?

John: Absolutely. If somebody is CMV-seronegative, and this is just a classic example of the viral "window period," and this is the same thing that applies to, for example, the window period for HIV or Hep C, or any of the other viruses, which is that the virus is there and it's circulating BEFORE the recipient has actually mounted a measurable immune response. So somebody who is CMV-seronegative could: 1) truly never have been exposed to the virus, or 2) they could have been exposed to the virus relatively recently and they could have free virus, potentially infectious virus, in their

plasma, or 3) they could have viral DNA in their white cells ready to replicate before they've actually made the anti-CMV antibodies. So that would be the window period when the patient or the donor is infectious but has not yet mounted an antibody response.

Joe: And so, for everyone listening, I am going to do everything I can to get an image that John and Cassandra Josephson (another friend of the podcast) put in in their editorial from 2013 in *Transfusion* that shows what John is describing so super well! I'm going to do everything I can to get that on the website [*NOTE: It IS on the website at* BBGuy.org/047]. So, I've said this to you before, John, but I think that is perhaps the BEST illustration I've ever seen to make it clear to people trying to learn how CMV works. So great job on that!

John: Well thank you, I appreciate that. The one thing I would mention to students and residents, other trainees out there, is if you look at that figure and if you just delete the dotted curve in that figure for white cell-associated CMV, then it could apply to virtually any other virus that we're worried about in transfusion medicine. The thing that's a little bit different about this is we also have that period of white cell viremia.

Joe: Okay so that brings us, John, to the time when we need to we need to lay out some alternatives. So I will lay this wide open for however you want to approach it. But there have been at least a couple of different approaches, potentially three, I guess, if you if you include BOTH of those approaches, but take us through: What are the options to try and protect those vulnerable recipients from transfusion-transmitted CMV?

John: Right. Well, there's really three approaches that are in standard use in the U.S. One of them is **serology**; so order units that are CMV-seronegative. The caveat there is you may have some "window period" donors among the seronegative. The second option is to order **leukoreduced** units. And that's also highly effective, although the caveat with leukoreduced units, as I had mentioned earlier, at least when we looked at it before, the filters don't do a great job removing the free viral particles. And so, if you have a big spike in CMV virus, and you leukoreduce, you might still get some virus making it through. And then, there's also a concern (although we think it may not be as big a concern in this day and age), there's also concern about filter failures and whether you might have a donor where the filter failed, you got a lot more white cells into the product than you thought you would, and some of those white cells have latent CMV that can reactivate. So there is leukoreduced units. And then there's what some people have described as the "belt and

suspenders approach" of using **BOTH seronegative and leukoreduced** units.

Joe: And I guess John kind of by default, if you're practicing in a country that does “universal leukoreduction,” if you get a unit that's seronegative, you're probably doing that [*last one*], whether you're ordering it that way or not!

John: Exactly. That's exactly right.

Joe: I want to make sure that people understand something really, really important here, and you hit that really well. You've got potential issues with seronegative units with "window period" type infections, you've got potential issues with leukocyte-reduced units, of a plasma CMV viremia that would not filter out, or potentially filter failures (which I agree is less of a concern but still potentially there). But John, what you're telling me, and I want to make sure that I'm understanding this and our audience is, that neither method is *perfect*. Is that true?

John: I do believe that's true. So, for example, if you look at it from the perspective of serology, I mean, that's generally accepted that **the seroconversion happens after there's already CMV in the [donor] blood**. Now the leukoreduction failure is a little bit harder to pin down. Because, in the days when most experts quoted the risk of CMV transmission by either leukoreduction or serology used separately, they typically quoted at 1 to 3%. And the reason that we thought at that point that there were significant episodes of filter failure is just because if you look at the data from sort of the classic randomized control trial by Bowden (which was published in the 90s in *Blood*), that's kind of the rate that they were seeing. But, what's important to remember about that is back in that day and age, first of all, the blood filter technology was kind of in its infancy, and a lot of filtration happened at the bedside. So, you were dependent on nurses, for example, some of whom may not have been well-trained in how to put the filters together. You were dependent on the nurses actually doing the filtration. So, back then I think that there was more of a concern. You know, we talked a little bit about the study I was involved in, I guess we'll be talking about that more, but in that study, we did a very detailed analysis of the possibility of failure failure. And it's an extremely, extremely rare event. In fact, we didn't really find anything that we would call an "overt filter failure" in that study.

Joe: OK. Well so we will...you've teased that twice, so we will get to that. I swear we will! Give me just give me a minute, we'll get there!

John: [LAUGHS]

Joe: But before that, John, I think it's important for everyone to understand that...And ok, I'll be slightly "tongue in cheek" here, and I'm going to poke at you a little bit so forgive me...that in 2016, you were a senior author on an article published in *Transfusion* that was titled, "AABB Committee Report: Reducing Transfusion-transmitted CMV Infections," and I daresay, John, that has answered EVERY question that we might have. Is that...right?

John: I would say actually it pretty much answered NONE of the questions!

Joe: [LAUGHS]

John: In fact, what was interesting about this study is that...right, that was 2016 in *Transfusion*...What was interesting is that the AABB leadership said to our committee, the Clinical Transfusion Medicine Committee or “CTMC,” they said, "You know, you guys did a great job putting together practice guidelines for plasma transfusion, for red cell transfusion, for platelet transfusion. Why don't you guys go ahead and tackle prevention of CMV transmission?" And once we started looking at the data, we basically said the data comparing leukoreduction with serology to prevent CMV transmission were of poor quality, there were no studies of significant size that had been performed in at least 10 years, that there was extremely wide variation in practice, and that there were other approaches that could be used that hadn't been tested. And so we said, "You know, we just don't think it's worth AABB's effort to put together clinical practice guidelines, because they'd be of VERY low quality." So, rather than that we just put together this committee report to tell you what we thought the state of the art was for understanding a transfusion-transmitted CMV infection, and that the state of the art was pretty poor.

Joe: By the way, I tease you, but I would actually highly recommend to folks to get a copy of that, if they have not seen it, simply in order to get, as you said, the state of current practice, because I think there's a ton of great information there. I don't mean to mess with you too much, John!

John: No, no, no, you're absolutely correct. I mean, once we started looking at it, we said, "You know, we won't be able to produce guidelines that will help any practitioner at all!"

Joe: What exactly *is* the problem that we see now with some of those older studies regarding leukocyte reduction versus CMV-seronegative?

John: The main problems with the old studies, as I see them, are the technology being used. Back then, the leukoreduction technology was not quite as sophisticated as we use now. For example, some of those studies, they were still using “bedside” leukoreduction. And also, as you look at some of those studies, they described the leukoreduction filters they use as "3 Log" filters, and now we're now at least a log or more beyond that. So, we're getting rid of tenfold more white cells, at least, in the current day and age than we were back then. So that's in terms of leukoreduction. Then, in terms of the serology, many of the studies back then utilized things like particle agglutination or hemagglutination. And now we have much better ELISA-based assays. So, I think that in some of these older studies, there were probably, in terms of the serology problems, with false negatives, maybe false positives and just generally less reliable assays than we currently have access to.

Joe: I don't know that I want to *challenge* you on it, but I want to at least get your thoughts on, your feelings on the study that was published in 2011 in *Transfusion*, from Thiele, et al, that looked at a population of stem cell transplant recipients who got purely leukoreduced blood products (not tested for CMV). And their conclusion was that it worked really well. I wondered if you had any thoughts on that particular study, and how much that study went into your committee report discussion?

John: So, we did talk about that study, which was a prospective observational study. And the conclusions from that study, I think, were pretty strong. In that study we had 23 CMV-seronegative BMT recipients who received transplants from CMV-seronegative allogeneic donors, and in total, those 23 patients received 1800 blood products, and none of them developed CMV-associated clinical complications, none had detectable CMV DNA, which led to a calculated risk of TT-CMV of 0.0% in their study, which with a 95 percent confidence interval of 0-0.12%. So once again, it was a well-done study. And if a practitioner wanted to look at that study and essentially say, "You know, there's no risk with the transfusion of leukoreduced, non-serologically tested blood products," I think you could use that study to defend it. It is only one patient population, so it doesn't address other at-risk patients, and so I think that is an issue.

The other thing to keep in mind with this study and I don't have any really good data to argue one way or another on this, but these patients received a LOT of blood products in this study. And along with those blood products, they received a lot of passive CMV IgG antibody. So that, in some ways could

have been protective. In fact, more protective than, for example, if you used this methodology, just leukoreduction, not serology, if you were to use this methodology for other patient populations that may only receive one or two blood products. Maybe in that setting, if you transmitted CMV in the absence of antibody, you could get a different result. That's just something to consider, but clearly for a heavily transfused population of immunocompromised BMT patients at risk for CMV transmission, this study suggested that just using leukoreduced units was highly effective.

Joe: OK. So, I would like to move on from here because I think you've made a ton of excellent points, and all the details that you've given are great. I would like to move into some of the more recent stuff that has been done and I am FINALLY going to let you talk about your paper that was published I believe in *JAMA Pediatrics* in November of 2014…

John: That's correct.

Joe: …again, Cassandra Josephson was the first author and you were the senior author on this paper. So, take us through it, John. Who were you looking at, and what were you guys trying to do?

John: Right. So, in this particular paper, we wanted to study transfusion-transmitted CMV infection in one of the high-risk populations I talked about, in this case, very low birth weight infants. And initially, when we started designing this study, our hope was to sort of replicate the "Bowden study": Have two arms…make it a randomized control trial…have two arms, one where the babies received just seronegative blood, the other one where they received just leukoreduced blood. The problems that we encountered doing that, though, were first of all, the study was going to have to be quite large. And so, in order to do that, we actually had to recruit three separate hospitals in the Atlanta metro area. And so we had to go to those three hospitals, and one thing we found out right the beginning (and you know, Cassandra did just an unbelievable job organizing this study), is two of the hospitals said, "We are using leukoreduced and seronegative blood, and there's NO WAY we're changing for your study." So that quickly eliminated the possibility of doing a randomized control trial of any sort of meaningful size. So, what we did then is we pivoted a little bit and said, "Well, if we can't do that, then why don't we do an observational cohort prospective study, and look at what happens if all of the very low birth weight infants at all of the sites received seronegative and leukoreduced blood?" So that's what we ended up doing.

Now one of the things that was interesting about this study is that it was designed very rigorously to try to track every single avenue of potential CMV transmission. So, for example, all these babies were in the NICU. And so, one of the things when you look at the old studies, if you're so inclined to pull up some of the older studies looking at the rate of transfusion-transmitted CMV, even the ones in a bone marrow transplant population, it was very difficult in those studies, because a lot of the patients were followed after they left the hospital, it was very difficult to quantify "community-acquired CMV," which is a real risk. In our study, because the babies that were on study spend most of their time in the NICU, we think we did a pretty good job of eliminating the risks of community-acquired CMV infection.

The other thing we did in this population is that we carefully tracked CMV transmission by breast milk. So we got samples of breast milk that was fed to the babies, and all that breast milk was tested for CMV by PCR. So we looked at our breastmilk transmission. And then all of the blood products that were transfused to the babies were tested both for residual white cells to try to rule out filter failure and then they were also tested by PCR to try to identify cases of CMV virus in the plasma.

So that was the general framework for the study. We ended up, at the end, we had 541 very low birthweight infants that were accrued into the study. 310 of them, or 58%, received at least one transfusion. There were a total of just over 1000 blood products used for transfusion. And as you know, those of you that have worked in pediatric hospitals, or studied transfusion on the OB services, in many cases, the products come from the blood center and then the blood banks split them into smaller products. So those just about 1000 cellular blood products were actually divided up into just over 2000 different transfusions. There were about 1500 red cell transfusions, 380 platelet transfusions, 130 FFP transfusions. So, we really tracked all of this closely. I talked about filter failures; we only had one case of all these units that were transfused from 1000 cellular blood products, we only had one case where you would technically have to call it a filter failure. That's why I sort of hedged on, when you asked me that question earlier, do filter failures still exist? Pretty rare with our current methodologies.

Joe: Got it. So what did you find John in terms of the babies that did get CMV? Was there a particular theme to how that actually happened? Are we able to figure that out?

John: Yes, absolutely! What we found was that 29 of the infants we enrolled in the study became infected with CMV. And interestingly, **all of them were**

born to CMV-seropositive mothers. So **of the 127 seronegative mothers in our study, none of the infants born to them contracted CMV**. So what that said to us was, there were essentially no cases of community-acquired CMV infection, no cases of transfusion-transmitted CMV infection in that population and obviously, no cases of breast milk transmission. But all 29 cases happened in seropositive mothers, and there were about 412 seropositive mothers, so that was an incidence of about 9% CMV infections in babies born to seropositive mothers. And that indicated that, in this population, the key pathway, if you will, or key method of CMV infection was via "vertical transmission," either transplacental or breast milk. But then we tested all of these babies right after birth for CMV infection. And in almost every case we ruled out transplacental transmission, we only had one example of that. So we think that almost every case, 27 of the 29 cases, were due to breast milk transmission, and that was based on not only our ability to identify CMV in the breast milk, but also to rule out the presence of CMV in these other sources. So the conclusions from this study were that we saw no cases of transfusion-transmitted CMV infection when the infants were uniformly given seronegative and leukoreduced units. So, one of our conclusions was, from the transfusion medicine perspective, that the use of seronegative and leukoreduced units is highly, highly safe when it's being used for a susceptible patient population.

Joe: So the devil's advocate in me says, "Ok, John that's great! Is anyone taking that forward and looking purely at leukoreduction without the seronegative, or is that a study you can do?

John: So it is a study that one could do. It would, I think, be a very large study, and in fact Cassandra and Meghan Delaney published a paper in *Transfusion* just recently which was a pilot for that kind of a comparative effectiveness study. And you know, Meghan is out there at the University of Washington, where they're big proponents of using “leukoreduced only” for their bone marrow transplant populations, so that could be one site where one might be able to do the same kind of study on very low birth weight neonates.

Joe: Got it. So we said from the beginning that there is no absolute standard anywhere. But let me let me ask you this, and just so everyone will know, what I'm about to ask Dr. Roback is not for John to say, “Everyone should do it this way,” but in your personal practice, John, at Emory, how do you handle very low birth weight babies and CMV prevention?

John: So what we do is, with **very low birth weight babies**, we do use both seronegative and leukoreduced units. Now that has to do with the fact that these babies are not monitored on a very intensive basis for CMV infection, and there are some risks using antiviral medications in this population. So for those babies, that's what we do. So my personal approach, and this is, once again, very individualized, but for the adult recipients, if it's a, say, either a **bone marrow transplant patient or a solid organ transplant patient**, even and including cardiac and lung transplant recipients if either the donor or the recipient is CMV seropositive, then we just give them leukoreduced units, and if they ask for both seronegative and leukoreduced, we talk with the clinicians, we explain these data, and we say, "If your patient were to contract CMV infection, it would come from either the recipient of the transplant or the donor, but it would be highly unlikely to come from the blood product." And in most cases, they say, "Okay, thanks," and they go ahead with the leukoreduced units. However, in those populations, if we have a transplant individual where both the recipient AND the donor are seronegative, and if the clinicians ask specifically for seronegative units, then we do give them both seronegative and leukoreduced units. And I typically cite this data and say, "You know, I'd like to be able to say, it would really make my life a lot simpler to say that I'm sure leukoreduced units are plenty fine, but the data we have only tells us that units that are both seronegative and leukoreduced are highly safe." And so, for our most at-risk patients, that's what I would give as a "CMV-safe unit."

Joe: Okay, so let's continue with the scenario. Let's imagine that you're in that situation, and you know as we're recording this, it's January 2018, the East Coast is in the middle of horrible snowstorms and terrible weather. There's flu all over the country. Donations are down, We're in a a fairly significant "crisis mode" right now. I think you know where I'm going with this, John. So suddenly, you're in that situation, and CMV-negative units are not available. What do you tell your clinicians then?

John: And so what I would do is, I would go through the same kind of explanation we've just gone through, and I'd say, "You know, under ideal circumstances, I would try to obtain for your recipient units that are seronegative and leukoreduced. Obviously, with the weather, with the donations down, we're not in ideal circumstances. You know a lot of the data suggests that leukoreduced units are still very, very safe. You and I really need to discuss how urgently the patient needs transfusion. If they need blood “soon,” the next 12 hours, 24 hours before we could reasonably expect to get seronegative and leukoreduced units, then I would say, no question, let's transfuse them with leukoreduced units, because the risks of them

foregoing transfusion are a lot greater than the risks of contracting CMV from a leukoreduced unit. But you know, if you can wait, and we have a reasonable expectation that we'll get leukoreduced and seronegative units in the timeframe you can wait through, you know, 12 hours, 24 hours, whatever, then go ahead and wait. When we get those units in, we'll give them to your patient. And if we reach that point, and the units still haven't arrived for whatever reason, then we'll revisit the discussion." But I certainly wouldn't forego transfusion waiting on seronegative units.

Joe: Right. OK. I really appreciate that perspective. I think that to those of you that are listening and are sitting there right now going, "Give me rules! Give me specific hard and fast things to follow!" John, I'm pretty sure I can speak for you when I say that, "You know what? Each facility has to decide, has to look at the data, has to talk with your clinicians and decide exactly how you want to handle this." Is that a fair way to put it?

John: That is absolutely true. I mean there's there's a big gray area here, but there are gray areas in many of the questions that we deal with in transfusion medicine. When I enter those gray areas, that's when I really like to pick up the phone, talk to the clinician, make sure they understand my perspective. I want to understand their perspective, and then collectively, we'll reach a decision.

Joe: All right John, before we go, I think we've covered so many details and it's awesome, I would like to just hear from you a little bit on the way that some other people are handling this, potentially like in other countries, or different approaches that have been defined other than our kind of three "traditional" ones, and just get your take on some of those. So the first one that I want to make sure we cover, and you can go from here to wherever you want, but there's an approach that's been out there that people have talked about, using specifically SEROPOSITIVE units in donors that have been positive for a long time, like a year or more. Can you talk through that a little bit and how that might work in the United States?

John: Sure. So this came out of a study that was performed by Ziemann and colleagues, published in *Transfusion* in 2013. And what they did is they turned the whole problem on its head, and they basically said, "OK, so if we look at serology and we realize that right after somebody seroconverts, they still have a ways to go: Several weeks, even a couple months where they're going to have CMV viremia, either virus in the plasma or viral DNA in their white cells. But then, if we wait long enough (and what Ziemann did is they waited a year), if we wait long enough, then that initial phase of viremia has

been cleared. And now that donor should have little or no CMV DNA remaining in their blood. And, in fact, what Ziemann postulated at that point was that the only risk would be transient reactivation of the virus. So what they proposed doing then, was waiting a year after seroconversion, and then accepting all donors who had seroconverted a year or more previously as being "CMV-safe." And I've heard that's an approach that is being used in some other countries. And it will be interesting to see what impact that has on the risk of transfusion-transmitted CMV in those countries. The problem is that you would have to operationalize that into your blood center processes. And what I can tell you is if you called up your blood center someplace in the U.S. and said, "Hey, I want a blood product from a donor who seroconverted at least a year ago, and I want that blood product leukoreduced," they would have no mechanism for finding such a donor.

Joe: We would stare at you blankly! That's what we would do. [LAUGHS]

John: Exactly! It's just it hasn't been operationalized, and there's no really good way to do it. So, in theory, I think it's a really interesting approach that could be explored further in the U.S., but it's just not something that we're capable of implementing in this day and age. There are other things we can look at too. You know we could look at adding CMV NAT on top of serology, or adding CMV NAT to leukoreduction, or adding CMV NAT to the Ziemann approach; There's a lot of different potential combinatorial ways that we could look at this. And if you're able to either get that figure we talked about earlier up on the web site, or at least put a link to the editorial, then I think that the listeners can go and look at that article and see some of the interesting ways that these methodologies could be explored to further provide CMV-safe units for the at-risk patients.

Joe: And I guess we could close by saying, John, what you said earlier: That once pathogen reduction technology is in place for all products (and to be clear everyone, at this point we can do it for plasma we can do it for platelets in the United States, but we can't do it for red blood cells), but once that is in place, then this whole discussion goes away, right?

John: Absolutely. The virus is *extremely* susceptible to inactivation using those methodologies. So, once we get pathogen reduction that can be applied to all blood products, then the problem goes away. But until then, it still provides fodder for these kinds of discussions.

Joe: All right, John, it's just been an amazing discussion, and I really appreciate you taking on this topic that I guess I'm sad to say for both of us

that there are no definitive, clear answers yet. But nonetheless I think you've done a great job at talking us through the possibilities. So thank you so much for being with me!

John: My pleasure. I mean, I sincerely wish I could have given the people listening a clear-cut answer but in the absence of that, the best I could do is explain that data as I know them and let let people make their own conclusions.

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Joe: I mentioned at the top of the podcast that John and I have slightly different views on TT-CMV prevention. As you heard, John generally thinks that CMV-seronegative AND leukocyte-reduced is the best option, while I have stated multiple times (including most recently in episode 044CE during my discussion with Pat Kopko) my belief that modern prestorage leukocyte-reduction is sufficient to call a product “CMV-safe.” As I said, just because we differ somewhat doesn’t make me right and John wrong (or, I hope, vice versa!). It just shows where we are, as illustrated by the lack of conclusive evidence in the literature. Remember, I started this with a quote from a highly honored transfusion medicine physician who said, “you can’t even GET CMV from a blood transfusion!”

If you are looking for continuing education credit, you can directly visit www.wileyhealthlearning.com/TransfusionNews. Please give your feedback and comments on the show page at BBGuy.org/047, as well, or through iTunes, or even using the direct email comment@bbguy.org.

I’ve got some great interviews coming up, including the next episode, 048, which is an interview with Dr. Steve Frank from Johns Hopkins on Bloodless Medicine. After that, Dr. Jeff Winters from Mayo Clinic returns to discuss more therapeutic apheresis topics, and then Sue Johnson from BloodCenters of Wisconsin will thoroughly explain pretransfusion testing. Remember, my goal is always to help you understand the essentials of blood banking and transfusion medicine!

So, until we meet again, my hope is that you’ll smile, and have fun, and above all, never EVER stop learning! Catch you next time on the podcast!