



**BBGuy Essentials 055CE:
2017 Critical Developments with Claudia Cohn and Melissa Cushing
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Joe: Hello, everyone. Welcome to Blood Bank Guy Essentials, the podcast designed to help you learn the essentials of transfusion medicine. This is episode 055CE. My name is Joe Chaffin. Today's episode is designed to help get you up-to-date on recent developments in transfusion medicine that you might have missed.

I'm going to tell you more about that and my guests, Claudia Cohn and Melissa Cushing, in just a second, but you should know that this IS a continuing education episode. Hurray! Continuing education credit is provided by TransfusionNews.com, and Transfusion News is brought to you by Bio-Rad (who has no editorial input). This podcast offers a continuing education activity where you can earn the following types of credit: (you ready?) One AMA PRA Category 1 Credit, one contact hour of ASCLS P.A.C.E. Program credit, and American Board of Pathology self-assessment modules (SAMs) for Continuing Certification (CC), formally known as "MOC." To receive credit for this activity, to review the accreditation information and related disclosures, just visit www.wileyhealthlearning.com/transfusionnews.

I hear all the time from people, "I don't know how you keep up with all the stuff that gets published, Joe." I've got a little news flash for you: I don't. I'm not sure if anybody really can, right? If you've ever felt like the flood of new information is just impossible for you to wrap your arms around, today's episode is just for you. Dr. Claudia Cohn from the University of Minnesota and Dr. Melissa Cushing from Cornell are here to talk about a paper that they were involved in that was published in April 2018 in the journal, Transfusion. The paper was called "Critical Developments of 2017," and it's really just a summary of the literature from late 2016 into 2017 written by an all-star cast, I'm not kidding, an all-star cast of Transfusion Medicine geniuses. Claudia and Melissa are representing the AABB Clinical Transfusion Medicine Committee, and they're the ones that did this paper. Honestly, I just can't wait for you to hear it. Are you ready catch up? I know I am. You ready? Here we go. Here is my interview with Claudia Cohn and Melissa Cushing.

Joe: Everyone, I am so honored to have two tremendous guests here today with me on the Blood Bank Guy Essentials Podcast. Let me introduce them one by one. First, I have Dr. Claudia Cohn from the University of Minnesota. Claudia, welcome.

Claudia: Thank you, Joe. Honored to be here.

Joe: It's such a pleasure to have you. I really appreciate you being here. I also have Dr. Melissa Cushing from New York Presbyterian Hospital and Cornell. Melissa, welcome.

Melissa: Thanks, Joe. Excited to be here.

Joe: It is very cool to have you as well. You guys, I'm really jazzed to talk about this paper today and this whole process, because I'll be frank, when I saw this paper come out, and I saw it before the journal actually was published, before the April version of *Transfusion* was published, but when I'm looking through *Transfusion*, oftentimes I go, "Oh, yeah, well, there's that. Oh, yeah, there's that. I've seen something like that before" (this is what happens when you get old). But when I saw this paper, I was like, "Wait, a minute, I haven't seen anything like this before, this is cool!" I am so glad that you guys agreed to talk to me about this.

The paper, everyone, just so you'll know, is "Critical Developments of 2017: A review of the literature from selected topics in transfusion." It's a committee report from the AABB Clinical Transfusion Medicine Committee. Now, that's a mouthful for a paper. But Claudia, I wanted to start with getting just a little bit background from you on how all this came about. How did this project come into play, how did you become involved in this project, and why are we seeing this in *Transfusion* now?

Claudia: Sure. This is part of the charge of the Clinical Transfusion Medicine Committee (I'm just going to call it "CTMC" to keep the mouthful down). The CTMC is asked every year to come up with 8 to 10 topics that are covered in the literature that are exciting, or new, or if there are interesting developments, and look at all the literature on that topic for the year, write a synopsis or a review of that literature. This isn't a systematic review, this is just a generalized review of the literature from that year, with potentially background material as well. And, this is for the board. We take these 8 topics, 10 topics, write it all up and give it to the board because the board of the AABB is composed of people from a lot of different specialties. There are people from blood centers, from hospitals, people who are specialists in molecular or immunohematology, etc., so they can't cover all the information that's in the field of transfusion, but they need to be aware of it.

So, for years (I'm not sure how many years), the CTMC has been producing this synopsis, this critical development report for the board. We'd write this 40 or 50-page report and send it off to the board, and we never heard anything about it. A few years ago, a few of us in the CTMC began talking about how we could make this more widely available to the readers of *Transfusion* or to the transfusion community in general. A few ideas were kicked around, and one of them was, "what if we just published the whole thing in *Transfusion*?" We approached Paul Ness, who was editor of the journal at the time, and he said, "If you can knock it down into publishable form, that is, something that's roughly 5,000 words or fewer, then yes, [they'd] be happy to publish it." We formed a subcommittee last year of people who would not only help to write the critical development report, but also then take the 40 or 50-page whole piece and edit it down to roughly 5,000 words. Melissa was a key part of that process. I was part of that process. We had a few other people helping us, the editors on the project. That's how it came about. I've already spoken to the new editor of *Transfusion*, Rick Kaufman, and he said that they would welcome it again this year, so we're very excited about that.

Joe: It's a big, big project. Before I talk to you, Melissa, about how you got involved in this, Claudia, I just want to make sure, is the big version of this ... Obviously, the

synopsis is available in the April 2018 Transfusion, is the BIG version of this available anywhere?

- Claudia:** It should be as a link in the article itself, on PubMed certainly, and within the article, that was the idea.
- Joe:** That one I actually can report on. I was able to download the "beastie." I'm going to call it like all kinds of insulting things! I don't mean that, because it's amazing, but I'm silly that way, so it makes me laugh. My apologies for that.
- Melissa:** "Beast" in a good way.
- Joe:** Beast in a good way. Exactly.
- Claudia:** I like that. It's the beast.
- Joe:** That's for sure. Melissa, from your perspective, from the committee's perspective, how do you guys hope this project, this summary, gets used by people?
- Melissa:** Joe, that's a great question. We thought about this a lot in the committee, and I think we all have a problem keeping up with all the literature in transfusion medicine. Even though it's a very specialized field, we are fortunate to have tons of research being published every year. Sometimes it's still hard to keep up with everything, and you can occasionally miss things. The main purpose of the manuscript was to make sure that people are aware of all the critical progress over the previous year. Then most of us who are transfusion medicine experts read Transfusion regularly, but we don't read every journal for every other specialty, surgery, hematology, anesthesiologists. A lot of big developments can be published in those journals as well. We want to make sure that all transfusion medicine experts are aware of what's happening when clinicians are talking about it.
- Another reason is for clinicians that are interacting with our field frequently; anesthesiologists, hematologists, it gives them a snapshot of everything that happened during the year, and keeps them up-to-date. The beauty of this being part of a large committee for AABB is that, as Claudia mentioned, we have a huge number of people on the committee, and everyone on the committee reviews it. If somebody misses something in one of the sections, a committee member will step up and say, "Oh, did you see this paper that was in the New England Journal or this paper that was in Lancet?" I think it gives you a broad, very thorough look at what happened. Then, of course, finally, for our trainees, it's really important, our TM fellows, our residents who are interested in going into transfusion medicine to be aware of how the field is moving.
- Joe:** That's great. I think it really serves all those purposes really, really well. We've got a lot to talk about today. Folks, as I said, this article is published in the April 2018 edition of the journal, Transfusion. You can find it there, you can read through. I will have the link available on the show page for this episode. Just go to bbguy.org/podcast, find this episode [Note: BBGuy.org/055], and you'll see the link there. There are seven big areas that you guys covered in the synopsis. I would like to start if I could with ... We're not going to go quite in order, by the way, of the paper, everyone. We're going to start actually with Melissa.

REVERSAL OF BLEEDING IN HEMOPHILIA AND FOR PATIENTS ON DIRECT ORAL ANTICOAGULANTS:

Joe: Melissa, we're going to have you discuss the topic that has the heading of "Reversal of bleeding in hemophilia and for patients on direct oral anticoagulants." Melissa, with that really long preamble, what did you find?

Melissa: Okay. Thanks, Joe. I just want to say that this section was worked on by myself, Monica Pagano, and Julie Karp. All of us reviewed the literature that it happened between 2016 and 2017. This is an area that I felt had really a lot of exciting critical developments. To me, it was almost more than any other area. There were huge improvements in both sections, or ability to reverse bleeding for hemophilia, as well as direct oral anticoagulant reversal. I'm going to highlight the article that I thought was probably the most exciting for the reversal of bleeding in hemophilia, which is the emicizumab study. Everyone that I'm talking about today has a really hard to pronounce name, so please bear with me as I get these maybe wrong.

This article was in the New England Journal of Medicine. The first author is named Oldenburg, and it was in August of 2017. It's looking at a drug called "emicizumab," which is a brand-new drug that's gotten a lot of press and interest, especially in the hemophilia world, in the last couple years. I think it's moved really quickly through the FDA, and is now approved after only having a few trials. Emicizumab, just as a little bit of background, is a recombinant, humanized, bispecific monoclonal antibody. It bridges the factor IX and the factor X molecules. What that allows it to do is to restore the missing function of factor VIII for hemophilia patients. That's really useful for patients with factor VIII alloantibodies, also known as inhibitors, because those inhibitors can make factor VIII replacement ineffective, and about 30% of hemophilia patients have those inhibitors.

This trial was looking at the reversal of bleeding in patients with hemophilia using this drug. In this situation, they're looking at episodic treatment rather than prophylactic. There have been some other trials in this area that'd been more looking at prophylactic treatment for patients with hemophilia. In this case, the patients were randomly assigned to receive subcutaneous emicizumab at a dose of 3 milligrams per kilogram weekly for four weeks and then followed with 1.5 milligrams per kilogram after that. I just want to emphasize what I just said about it being subcutaneous because this is also revolutionary for hemophilia patients. We are used to having IV infusions, which means they have to go into the clinic. Subcutaneous means they can do it at home, which can really improve their quality of life, so that's really important.

The study primary endpoint was looking at the difference in the rate of treated bleeding events. They had a total of 109 male patients, because they were hemophilia. The annualized bleeding rate for patients that were getting the emicizumab treatment was 2.9 events per year versus 23.3 bleeding events for patients who did not get the drug in the control. It was a very successful study. Again, this is changing the game in hemophilia treatment. But I did want to point out a couple of things about it. Emicizumab, since this trial was published, has now been approved by the FDA for patients with hemophilia who have developed

resistance to other treatments. That was in November of 2017. Even more recently, in April of 2018, it's now approved under the "breakthrough therapy" designation by the FDA for patients with hemophilia A who have NOT developed resistance to other treatment. It can be used for most hemophilia patients now.

But there are some risks associated with this drug. The brand name is called "Hemlibra." There have been an association with thromboembolic events if you're using emicizumab with an activated PCC, which it's frequently done for patients with hemophilia and inhibitors. Then there's also an association with thrombotic microangiopathies, again, if you're using emicizumab with an activated PCC. But overall, this is an amazing study that has really changed the face of hemophilia. There's been a lot of developments in the world of hemophilia, with long-acting factor VIIIs and things like that, but this one, I think, is probably the most cutting edge.

Joe: That's awesome. Like you said, that is game-changing stuff. That's fantastic. Okay. In the interest of time...that one, I can tell, is sweet spot for you, Melissa... [LAUGHS]

Melissa: I do like that study!

Joe: I can tell! That's for sure.

Melissa: Very interesting.

Joe: There were some other things that you guys talked about in terms of the new oral anticoagulants and reversal of that. What would you like to summarize for that?

Melissa: Right. There were three big studies that we talked about for the reversal of the "DOACs" or the direct oral anticoagulants. There was one on andexanet alfa for the reversal of bleeding in patients on DOACs. That one was an interim report in New England Journal of Medicine in 2016 of an ongoing study. That was an open-label study looking at people who had had acute major bleeding after edoxaban. Then, the drug was given and they showed, again, excellent results where they had clinical hemostasis adjudicated as excellent or good in 79% of patients that were getting that reversal agent. Interestingly, since that study was published, the FDA has now granted approval for andexanet alfa, or the brand name is "Andexxa," for patients that have been treated with factor Xa or direct oral anticoagulants of that category in May of 2018. That was another big study that's ongoing. The full report is not published yet, but it's already been FDA-approved. That was another big one.

There was a study looking at idarucizumab for dabigatran reversal. Again, idarucizumab has now been approved by the FDA, its brand name is "Praxbind." That study was called the "RE-VERSE AD" clinical trial, and it was in New England Journal in 2017 [<https://www.nejm.org/doi/10.1056/NEJMoa1707278>]. In this study, an interim result had previously been published in 2015, but the one we focused on in our report was the full cohort analysis. It was a multicenter prospective, open-label trial to determine whether idarucizumab could reverse the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding or were about to undergo a procedure. They enrolled over 500 patients and found that idarucizumab could rapidly, and durably, and safely reverse that

anticoagulation effect which was, again, this is a new drug that everybody ... I think, most hospitals are now starting to use this. I know our pharmacy stocks it, and that's how we now reverse dabigatran, which is great because we didn't really have a good option before that.

Joe: That was the problem, yes. That's all very, very interesting for those of us that deal with that on a near-daily basis, it feels like. But, as you said, it's nice to have potential options coming down the road for these direct oral anticoagulants that have been a real challenge for us since they've been introduced. I really appreciate you taking us through that.

DURATION OF RBC STORAGE:

Joe: We need to move on and talk with Claudia about the duration of RBC storage. I think, Claudia, most of us in blood banking world have ... I'm going to speak for myself ... perhaps we've gotten a little bit of "age of blood fatigue" over the last few years, because there's been a lot of discussion, a lot of talk. I'm going to open the floor to you to just take this wherever you want to go. In terms of what you guys summarized in this article, what did you guys find?

Claudia: Sure, Joe. I understand why you might have had some fatigue over this subject. It's been in the news and a big deal since about 2008 when Colleen Koch came out with, I think, the first major article on this topic in the New England Journal of Medicine. She had done a retrospective review of about 6,000 cardiac surgery patients, and she found that those patients who had received blood that had been stored, red blood cells that had been stored longer than 14 days had higher risks of major postoperative complications and greater short and long-term mortality. This created a maelstrom. People became very concerned that "older blood" was dangerous. This was a retrospective study, and all retrospective studies, no matter how well done, have their limitations. This launched a number of better designed prospective, randomized, controlled trials. In the critical developments, Nancy Heddle was the author, and she did a great job putting together a review of the available evidence that was published in 2016 and 2017. She outlined what the clinical relevance of the red blood cell storage lesion was.

I'd like to just begin with a brief review of the red blood cell storage lesion. As soon as the red blood cells leave the body and enter the bag, they begin to age and they develop the "storage lesion," and it progressively gets worse, so that the cells become less deformable and stiffer so that, theoretically, they cannot enter the microcapillary beds as easily to release oxygen. There's a lot of biochemical changes as well, such as the 2,3-DPG level goes down. That's a molecule that's critical for releasing oxygen at appropriate moments in the body. As soon as the red blood cells enter the body again, the 2,3-DPG level is corrected, it's replenished and equilibrated. But we don't know what the rest of the storage lesion has done to the red blood cells that might affect their clinical ability to carry and deliver oxygen.

So, what is the clinical relevance of the storage lesion? I will begin with the "INFORM trial" first. INFORM is an acronym for "INforming Fresh versus Old Red cell Management." It's nice that Nancy Heddle wrote this clinical development, because she was the lead author for this. It was published in the New England Journal in 2016, and it was a multinational trial. There were three Canadian

hospitals, one from the US, one from Australia, and one from Israel. The interesting thing, I think, about this trial is that patients were unselected. It wasn't a specific population, other than the fact that they were all adults. Any patient who was admitted to one of these hospitals who received a red blood cell transfusion, all of these patients were enrolled and randomized to receive either standard-issue red blood cells, which were based on regular inventory control on a blood bank, the oldest unit on the shelf, or they received the freshest blood that was in inventory.

They ended up enrolling 31,000 patients. The oldest blood tended to be, the average was 23.6 days old, whereas the freshest unit were 13 days old on average, and so they did achieve their 10-day separation. The final results: In-hospital mortality in the fresh arm was 9.1% while in the standard-issue arm, the older arm, the mortality was 8.7%. So, 9.1 for fresh and 8.7 for new. Statistically, that means that there was no difference between the two arms. The older units were not causing more harm. The fresh blood cells did not decrease in-hospital mortality compared to standard-issue red blood cells. Naturally, they did subgroup analysis. They looked at high-risk populations such as patients who had undergone cardiovascular surgery, patients in the ICU, patients with cancer, and they found no significant differences. They also looked at those patients that received the very oldest units. Patients who received units that were between 36 days and 42 days old, and they found that there was no difference either. There was no evidence of harm from these older units.

Joe: If I can interject there, Claudia, I think that was the initial criticism of INFORM, was in its first version, people said, "Well, 13 days versus 26, whoopee-doo. We want to know about the 35 to 42." As you said, that sub-analysis helps with that.

Claudia: Yes. I'd like you to hold on to the fact that in the FRESH arm, even though there was no statistically significant difference between the 9.1% and the 8.7%, the fact is 9.1 is a larger number than 8.7. I'll be returning to this fact a little bit later.

Now, let's move on to the "TRANSFUSE trial." This was another massive trial that was led by Dr. Cooper from Monash University in Melbourne, Australia. There were 59 centers that participated from Australia, Saudi Arabia, New Zealand, Finland, and Ireland, so really multinational. These were patients who were admitted to the ICU. The trial design was very similar to INFORM, young versus old units. The primary endpoint was 90-day mortality. The patients were all adults, and they were enrolled in the trial if they're expected to stay in the ICU for at least 24 hours and were supposed to receive red blood cell transfusion.

They also had a good separation in the age of the red blood cells. The short-term group, the younger group, the mean age of the red blood cells was 11.8 days, versus the older red blood cells were 22.4 days. Again, they got at least the 10-day separation. When they compared the two groups, they were similar about many things. They received roughly the same number of red blood cells. They received roughly the same number of other components. The final result, at 90 days after randomization, death had occurred in 24.8% of the short-term group and 24.1% in the long-term group, so just a 0.7% difference, and that was, statistically speaking, no difference whatsoever. Again, same sort of conclusion as in the INFORM trial.

They also went back and looked at the patients that received the oldest units, those stored from 35 to 42 days. Just like in the INFORM group, they found no differences in outcome. However, they do mention in "limitations in the study" that there were very few patients who received those older units, so they can't really comment on this in any significant way. They also looked at severely ill patients, those with APACHE scores of 3, which is a way of grading clinically ill patients. They found that these patients who are critically ill, who had received the freshest available red blood cells, had a higher mortality rate than those who received older units. This was a trend, it wasn't a significant finding. But, as I said, I'm going to come back to this.

This brings us, if there's time, to the meta-analysis. Nancy Heddle reviewed a paper that she was a part of, and this meta-analysis looked at 14 trials of older versus younger blood. The lead author on this, I'm going to butcher the person's name, Dr. Chai-Adisaksopha. If they're listening, please pardon me for that. As I said, they analyzed 14 studies, and when they included the TRANSFUSE trial, it brought it up to 15 trials. They found that there was no difference. **The transfusion of fresher blood does not reduce mortality compared to blood stored for longer periods.** Hopefully, this puts an end to all the questions about this, but it brings up a new question. That is, they found that in 10 of the 15 trials, there was a trend towards higher mortality when fresh blood is transfused [laughs]. I think it's pretty ironic that this all started with older units, and now they're finding some harm with younger units.

I want to end by saying red blood cell transfusions are really, really safe. If you go to a hospital and you happen to receive some fresher units, you're probably okay, too. These findings are small. So far, they're not statistically significant, but maybe they'll be able to design a trial and make it large enough to actually pick out and see if this is a true difference, or maybe this will be a big data study with retrospective data. I don't know, but I think it's really exciting.

Joe: That's awesome. Everyone listening, I talked on this podcast right when the INFORM trial came out. I did an interview with Nancy Heddle about it. If you want to hear more about INFORM, which Claudia just summarized beautifully, you can go to BBGuy.org/e022 and you can find out more information directly from Nancy Heddle on the INFORM trial. Claudia, that's awesome. Thank you so much for that. We are going to move back to our friend Melissa who's been patiently waiting. Melissa, you with us?

Melissa: Yes, I'm here.

PATHOGEN INACTIVATION/REDUCTION:

Joe: All right. Fair enough. Melissa, you get to talk about something that ... It feels like we've been kicking around pathogen inactivation for a very long time as well. I want to set the stage a little bit by saying I think everyone thinks that ... well, most everyone thinks that pathogen inactivation as an idea is a really good idea, the idea of treating blood to, I don't want to say "sterilize it," because that's not correct, but to at least reduce the risk of infectious diseases being transmitted. But I think there's also been some questions about what that treatment does to the blood, and I think that this section described some of that stuff. Again, I will leave the floor open to you. What did you guys find about pathogen inactivation?

Melissa: Yeah. Thanks, Joe. I couldn't agree more about your previous statement that every time we have an intervention, a manipulation of a product, there's always benefits, but then there are also drawbacks. Some of trials that I'm going to be discussing really focus on those.

First, I just wanted to briefly discuss the "Allain trial," which was in Lancet in 2016. This is really interesting trial because it really gives you information about how countries with significant cost restraints that can't do all the testing that we do in the US can really use pathogen inactivated products to have safer transfusions. In this one, it was a randomized, double-blind, parallel-group clinical trial that was looking at the use of whole blood pathogen reduction technology to prevent the transmission of malaria. It took place where it should in sub-Saharan Africa, in Ghana, in an academic hospital there. In that country, malaria is endemic, and there's a huge portion of the donors who are asymptomatic carriers of malaria. It's really important to think about a way to make their transfusions safer. They had a shockingly high prevalence of parasitemia in their blood donors of around 50%, which is just really fascinating. It shows how this product can help there. Most hospitals don't really have a great way to look at the product. Some of them may examine the product by microscopy to see if there's malaria, but we know that's not the most efficient process, and a lot of countries don't even have the resources to do that. This trial was really useful from that perspective.

What they did was they used Mirasol units, which is whole blood that's been treated with UV light and riboflavin [vitamin B2], to reduce the pathogen load and inactivate the white blood cells. Their primary endpoint was the incidence of transfusion-transmitted malaria in non-parasitemic recipients who were exposed to parasitemic whole blood. They found that the incidence of transfusion-transmitted malaria was 4% for treated blood in that category and 22% for untreated blood. I'm not sure we've mentioned the table 1 yet in our critical developments report, but for readers who just want to get the key points about what we discussed in this overview, there's a nice table that has key points, and for each section, we talked about what those are. For the pathogen inactivation section, we really talk about the fact that pathogen-reduced platelets can mitigate the residual risk of septic transfusion reactions and reduce the risk of other transfusion-transmitted diseases, but there are some downsides to that.

The three clinical trials that are discussed here that were all published between 2016 and 2017 in addition to a meta-analysis that was ... Lead author there was Estcourt. They all highlight the same points. The three clinical trials were very similar, which is interesting because they were all conducted by different countries, they're all multicenter, but they all used a similar approach. They all had primary endpoint of percent of patients who developed the WHO, or World Health Organization, Grade 2 bleeding or more. They all had slightly different descriptions of what ... They were all inferiority studies, so they all had a slightly different description of what the inferiority margin should be to be called "equivalent," but they also had similar findings. I think just to be a little bit more concise, I'm just going to mention the name of the trials and then discuss them as a group instead of going into them if that's okay with you.

There was the "Rebulla trial," which was in Transfusion in 2017. That was an interesting one because the two main manufacturers of pathogen-reduced platelets worked together with the Italian Ministry of Health and conducted that trial. They didn't compare directly to each other, but the study design was the same for both. Then there was the "PREPAREs study" which was by Van Der Meer, and that was again a multicenter trial in multiple countries, including some centers in United States. Then the last one was the "EFFIPAP study" which was funded by the French Ministry of Health and, again, have the same primary endpoint as the other two.

Just to summarize all of them, they were all conducted in hematology patients with thrombocytopenia, so most with heme malignancies. As I said, the primary endpoint for all was WHO Grade 2 bleeding. Rebulla et al. found that there was more Grade 2 or higher bleeding for both Intercept and for Mirasol versus standard platelets. However, they found that this was not statistically significant. But unfortunately, that study did not achieve the power that they needed, so we can't really draw any conclusions from that information. The PREPAREs study only found a 3% difference in Grade 2 or greater bleeding in their intention to treat protocol, and that was not a significant difference. But when they looked at the per protocol group, they found a significant difference of 8% between the two groups.

Then EFFIPAP found that, for the per protocol assessment, there was higher Grade 2 bleeding for ... They actually had three groups in there. They had a group that had pathogen reduction in PAS [Note: Platelet Additive Solution] platelets, versus standard platelets, versus platelets just in PAS. What they found was for the per protocol assessment, there was higher Grade 2 bleeding for the PR PAS platelets than standard platelets. But the PR platelets were equivalent to platelets in PAS, so there may be some effect of the PAS itself, and not just the pathogen-reduced process. These are interesting studies. The other main study we should compare this to was the SPRINT trial, which is McCullough et al. in Blood in 2004. In that study, they reported non-inferiority between the level of Grade 2 or higher bleeding. But in that study, they did find more mean days with Grade 2 bleeding. However, that's really been controversial whether that's actually true or not.

I think what this tells us is that we really need to think carefully about the pros and cons when we're implementing a process that we know reduces the risk of bacterial contamination, for example, but also **the meta-analysis that we present in the paper also looks at whether these patients could potentially be more platelet refractory and have less good of an increment.** Then the thing we worry about the most is do they have more bleeding, because that's really the main point of our platelet, is to try and prevent that.

Joe: You take the good sometimes with the maybe not so good, and you have to figure out what works best, and ultimately make a decision on that.

Melissa: Right. Yeah. I mean, I think that's the challenge of a transfusion committee in a hospital, the medical director of the blood bank. You have to all discuss that, make sure everybody is aware of the pros and cons, and then make your

decision. There's also, I didn't mention, the financial impact, but that also needs to be considered.

Joe: Yes. As someone who's directing a blood center right now, I can tell you that when we talk about pathogen-reduced products with our hospitals, when the discussion gets to that point, eyebrows are raised and there's a little bit of surprise. "Oh, there's a cost difference? Oh, okay." It changes things for sure.

Melissa: Someone has to pay for it, right?

Joe: Exactly.

Melissa: Yes.

BLOOD DONOR CHARACTERISTICS AND PATIENT OUTCOMES:

Joe: Okay. Melissa, thank you so much for that summary. That's outstanding. We are going to head back to Claudia. Claudia, you get to do one that, as I said, I direct a blood center right now, so I'm fascinated by the advances that have been made and the discoveries that have been made, and some of which we're not sure what they mean yet in terms of blood donor characteristics and patient outcome. Why don't you take us through that?

Claudia: In a nutshell, the authors of these different studies looked at quality data from blood centers and asked, "Is there a difference in blood donor characteristics that would create a clinically relevant change in the quality of the red blood cells that are delivered?" What they found seems to suggest that in some cases, all red blood cell products are not created equal. We always knew that women have lower hemoglobin than men, and so male donors tend to have higher hematocrits and higher total hemoglobin. We've also found, of course, that multiparous women giving plasma, that can lead to TRALI. We know that there are essential differences and risks based on gender, or based on the specific donor. But there are other things that maybe you don't expect, such as male donor-derived products, they consistently have higher levels of hemolytic compared to units from females, and this is true regardless of processing methods.

In 2010, researchers decided that they were going to look at a large database from Scandinavia, the Scandinavian Donation and Transfusion Database also known as the "SCANDAT," and they did what was called the PLASMA study. They said, "We know that plasma causes TRALI, so what other things might be going on?" They looked at plasma preparation methods and storage time, and what they found, I think, surprised even them. They found that recipients of female plasma, plasma derived from female donors, had higher short-term mortality than those receiving male plasma. They looked at 93,000 patients, and 8.85% of the recipients were dead within 14 days of receiving a plasma transfusion from a female compared to 7.53% who received plasma from males.

What's going on here? Does this have wider implications? That, of course, led to the next study, which was in 2011 and that was out of the Netherlands. The Dutch, they also had a huge cohort, not as large as the SCANDAT but they looked at 11,000 patients and 96,000 transfusions. Overall, looking at all 96,000 transfusions, transfusions from female donors were not associated with

increased mortality, that sounds like a relief. But when they analyzed the single-donor recipient cohort, mortality was increased in male recipients of female blood. This effect was significant, statistically significant, at one month follow-up. They could also see that at a five-year follow-up, it was no longer statistically significant. It was a weaker signal, but they found the converse wasn't true. Females receiving male blood did no worse. Retrospective study, large cohort, a lot of limitations but, of course, it led to more studies.

2016, three more studies came out that were all in cardiovascular surgery patients. Two were from Sweden, one was from France. One of the Swedish studies found increased mortality. But there was a sex mismatched transfusion, male to female or female to male. But the French study and the second Swedish study did not find anything. Then we go to the next study, which is even larger. In 2016, Chasse et al. came out with a retrospective study of 30,000 transfused patients who'd receive over 188,000 red blood cell transfusions. This study found that for each additional transfusion from a female donor, it was associated with a small but statistically significant increase in the risk of mortality. They also found that the same sort of increased significant risk was, if you got blood from younger donors, if the blood came from a donor 17 to 19 or just shy of 20, the risk was highest. But if it came from a donor 20 to just shy of 30 years old, the effect was weaker, but still could be seen. They also found that blood from older donors was not protective.

Let's sum this up with the last study, which is the largest yet, and that came out in 2017. This was Edgren et al., and they went back to the SCANDAT database and they said, "Let's just pull it all and see what happens." Using the SCANDAT database, they pulled data from **968,264** recipients. Holy cow. They found that **donor age and sex were NOT associated with recipient mortality in patients receiving red blood cell transfusions**. Is this the final word? I doubt it. There was a meta-analysis in 2016 by Chasse, the same author that came out with the study I referred to just before, and they found that there was increased overall... looking at all the different trials or retrospective data close as they could, that there was an increased 90-day and 6-month mortality for males receiving blood for females. But the quality of evidence was low to very low, so they really couldn't make any conclusions based on the meta-analysis, but there it is. There seems to be a signal out there, and it's left up to researchers to figure out if it's real, and if so, why.

Joe: Got it. That's really fascinating. There's a lot more I know that you could have gone into there, but in the interest of time, we should move on and just leave it at that. But thank you so much for that. That's really cool stuff and a little bit frustrating stuff. I will have to admit that.

Claudia: I agree completely.

Melissa: Yes.

PEDIATRIC TRANSFUSION MEDICINE:

Joe: Melissa, you get to bring us something that I always find interesting and exciting. I think that pediatric transfusion medicine, in general, for a lot of us that don't practice it every day, it sometimes feels a little out of the comfort zone. I mean,

I've had multiple conversations with people like Cassandra Josephson who tells me that you can't just translate what you know about adults into little babies necessarily. I'm really interested to hear what we found in your look at 2016 and 2017 in pediatric transfusion medicine.

Melissa: Yeah. Thanks, Joe. That's a great segue into this section. I just wanted to acknowledge that this section was written by Ruchika Goel, Ajay Perumbeti, Phil Spinella, and David Friedman. They did a great job providing a lot of information in this section. I'm just going to talk about a couple of the interesting ones that they presented. The first one I wanted to talk about was the "CHILL study." This study has not been fully published yet. It was published in the AABB oral abstracts, and it was presented at the 2017 meeting by Bryan Spencer. The CHILL study stands for "Comparison of History of donation and Iron Levels in teen blood donors." I think that really illustrates your point well. Can we apply everything we do for adult blood donors directly to our pediatric high school blood donors who make up 10% of our blood supplies? We really need them, because they provide us a lot of blood. But should we be treating them differently?

This interesting study looked at the ferritin levels in high school blood drives from 2015 to 2016. They did have some adults in those blood drives and then they had the population they compared to, which is the 16- to 18-year-olds. They found that the 16- to 18-year-olds had a 28.6% rate of having low ferritin, and the teen blood donors were 3.3 to 4.7 times more likely to have ferritin levels less than 26 than the adult blood donors, who were aged 19 to 49 in that category, or in those collections. The pediatric donors were 2.1 to 2.6 times more likely to have absent iron stores, which they defined as less than 12 ng/mL in that study. What was interesting was, you might say, "Okay, are we depleting them and is that why they have low iron?" But many of the teen donors were iron-depleted even at the first blood donation, so that may reflect more the age, their diet, things like that than actually being related to the blood donations.

What do we do about that? There's also another study presented at the AABB meeting last year where Ralph Vassallo reported a Blood Systems study that looked at an intervention in teen donors with low ferritin. For those, they advised taking some iron for 60 days after the diagnosis or having longer deferrals for females and males that are in that teen donor category. Those, we're waiting for the final publications to come out to find out their final conclusions, but those are interesting things that we need to be thinking about. As a field, are we being cognizant of this problem that we found in pediatric donors, and are we treating it appropriately? That's information that we'll still find coming, but super-important. That was the CHILL study.

There was a great meta-analysis by Amy Keir and Simon Stanworth on the adverse events of red cell transfusions in neonates. They provide great information for those of us with a pediatric patient blood management program. There's no evidence that rates of mortality differ between restrictive and liberal transfusion strategies for red cell transfusion. They found that a liberal strategy was not superior to restrictive in terms of rates of retinopathy, of prematurity, chronic lung disease, or intraventricular hemorrhage. That's great data to have. I know we struggle in our patient blood management programs, specifically with pediatrics, because there's just not as much evidence out there. As you said, a

lot of people are ... They feel that kids should be transfused more just because they're kids and they're a vulnerable population, but there's really not much evidence to support that, either. I think for a lot of us that struggle with pediatric PBM, this is a nice study that we can go to and say, "Okay, here's some evidence for neonates," because sometimes we have them requesting transfusions for sky-high hemoglobin, and then it's a tricky one.

The other one I wanted to discuss is the British Committee for Standards in Haematology published a very nice set of guidelines on transfusion in neonates and older children in December 2016. This is a revision of their previous work from 2004. This is especially useful because we don't really have that many guidelines for pediatric transfusion medicine. Again, this is a help for PBM committees. There was a nice guidelines published by Roseff back in 2002, but this has been many, many years since that was published, so it's nice to have something fresh and new that we can use to refer to our clinicians. That was the highlights I have for pediatric.

Joe: Excellent. Everyone, on the show page for this episode, I will make sure that there's a link to that British Committee for Standards in Haematology guidance that Melissa just mentioned. I agree with you. I thought that was really, really good and very, very useful. Okay. Awesome.

TRANSFUSION APPROACH TO HEMORRHAGIC SHOCK:

Joe: Claudia, we are back to you. You know what, this could be a big topic, but we'll see where you go with it. This is on the transfusion approach to hemorrhagic shock. What did we find there?

Claudia: This section was put together by Phil Spinella and Ruchika Goel. It covers many aspects of transfusion support for patients in hemorrhagic shock. But in the interest of time, I'm going to keep it fairly narrow and just give an overview of what was presented. They began with a review of the major trials that have been done in this field. That includes the "CRASH-2 trial" and the "PROPPR trial." CRASH-2, I don't know what these acronyms stand for, but it was an international trial. It was huge, 48 countries, 224 hospitals. It looked at tranexamic acid use in massive transfusion protocols. It's an antifibrinolytic agent. Patients were randomized to either receive tranexamic acid or a placebo. The primary outcome was in-hospital mortality within four weeks of injury. They found that all-cause mortality was significantly reduced with tranexamic acid when it was given early in treatment. Now, there have been other trials since then on tranexamic acid. But, again, on the interest of time, I'm not going to discuss those.

Claudia: The PROPPR trial was another very important trial in the massive transfusion literature. They were trying to determine, the authors were trying to determine, the efficacy and safety of transfusing patients with severe trauma and major bleeding using different ratios of plasma, platelets, and red blood cells. They compared a 1:1:1 ratio of those three components for resuscitation versus a 1:1:2 ratio. Either you had equivalent amounts of plasma and red blood cells, or you had half that amount of plasma as you had to red blood cells. PROPPR had 680 patients. The primary outcomes were 24-hour and 30-day all-cause mortality. Basically, in a nutshell, because there is controversy over the interpretation of this data, so I'm just going to stick with the major version, and that is there was

no significant difference in mortality between the 1:1:1 group and the 1:1:2 group. Neither offered advantage over the other. That could be detected in this trial. That was an introduction for this section, too, where the literature was. Then they went on to talk about the Trauma and Hemostasis Oxygenation Research group, or THOR.

Joe: [SHOUTS] THOR!

Melissa: THOR!

Joe: I cannot let that be said without raising my arms, imagining a hammer in my hand or something. It's horrifying. I'm sorry. [LAUGHS]

Claudia: I think the group likes that, too. THOR is dedicated to exploring the best techniques and materials to use to resuscitate hemorrhaging patients. There's a ton of interesting stuff that they're doing in THOR. They're looking at cold whole blood for trauma patients. They're looking at freeze-dried plasma, cryopreserved platelets, avenues that the US military and other militaries around the world are very interested in because it might lead to better resuscitation, quicker resuscitation, and also easier to transport materials on the front line. I think more and more interesting stuff is going to come out of the THOR group.

But one of the things that's really interesting is whole blood, the use of whole blood in resuscitation. I think it's kind of fun that in the '70s, we were using whole blood, or maybe before the '70s, we were using whole blood to resuscitate patients in hemorrhagic shock. Then that went out and was replaced with a combination of crystalloids and blood components, and now we're swinging back again to whole blood. In the critical developments, they cover this topic with a focus on the comparative efficacy of whole blood for resuscitation. They focus on the properties and differences between platelet products that were stored at four degrees C versus platelet-containing products that were stored at 22 degrees C, or room temperature. They found that, in essence, if you have a platelet in the cold, it becomes activated. That was the original thinking of why you shouldn't store the platelets in the cold. You don't want a pre-activated platelet.

But people started saying, "Well, maybe you actually DO want a pre-activated platelet for trauma patients who are liberally bleeding, and the bleeding needs to be stopped as quickly as possible, as opposed to, say, patients receiving prophylactic transfusions for platelets if they're heme-onc patients." They're looking into this and trying to understand whether cold-stored platelets or cold-stored whole blood would be a better component for patients who are bleeding from trauma. They also, in the critical development, include material on trying to debunk various misconceptions, according to them, that are associated with whole blood. They go over the fact that whole blood actually can be leukoreduced. Apparently, there's a belief that it cannot be. They also say that whole blood, group O whole blood, if it has a low titer of anti-A and anti-B, can be used as a universal component. They're trying to say that there are wider applications for whole blood, and trying to interest the general population in using it more frequently.

I'm going to close with the last paper that was gone over in the critical developments in this section, and that was it was published initially as an

abstract, but now it's a paper by Meyer et al. called "Every Minute Counts." This was published in 2017. They used 680 patients, which I think is the same number in the PROPPR trial. This might have been a re-look at that data. They looked at the increase in the time to massive transfusion activation and the time to arrival of the first cooler, and whether the delays were associated with problems. What they found that whenever there is an increase in time, it was associated with a prolonged time to achieving hemostasis. This was statistically significant. They found that if there was an increase in time in a massive transfusion activation and the time for the first cooler to arrive that there was an increase in mortality. They also found that increase in time to arrival of the first cooler was associated with increased mortality at 24 hours and at 30 days.

The title says it all, "Every Minute Counts." The faster you can get the blood to the patient, the better off the patient will be. No matter whether it's in a 1:1:1, or 1:1:2, or whole blood, faster is better. That's it for that section.

Joe: That's a great summary. Like with many of these things, we could go into a lot more there, especially that last paper, as well as the whole blood stuff. But we've got to move on. We got to finish this up.

THERAPEUTIC APHERESIS AND EXTRACORPOREAL PHOTOPHERESIS:

Joe: Melissa, we don't have a ton of time left, but I wonder if you'll take us through whatever you think is either the most critical or one of the most critical things in the therapeutic apheresis and extracorporeal photopheresis section?

Melissa: Yeah. Absolutely, Joe. I just want to say that this section was written by Ellen Klapper, Monica Pagano, and Yossi Schwartz. I'm just going to focus on one but, again, there's a lot of good stuff in there, so people should come back and read everything. But the caplacizumab study has the potential to change the way we treat TTP, so I want to just discuss that, the pros and cons of that study. It's really an interesting study. It's not actually focused on therapeutic plasma exchange. It's really focusing on a supplement to TPE for treating TTP. The drug is caplacizumab, which is a humanized anti-von Willebrand factor immunoglobulin.

This was a phase II randomized controlled trial to evaluate the use of this antibody to inhibit interaction between ultra-large von Willebrand factor multimers and platelets to treat newly diagnosed TTP. The study was in the New England Journal in 2016, and the lead author was Flora Peyvandi. The primary endpoint of this study was to look at the response to TTP. Then the secondary endpoint was to look at the exacerbation of TTP disease and relapse. Unfortunately, the study ended early due to recruitment challenges, but I think there's still things we can learn from it. The authors found that the time to response to TTP treatment was significantly reduced by 39%, the median time. These are all patients that were treated with both TPE and then they were randomized to either get caplacizumab or to get placebo. Therapeutic plasma exchange or TPE was definitely part of it for all 75 patients that were enrolled in the study. They did find that the time to response was reduced by 39%, which is great.

The interesting thing, or the downside of the drugs in this study, was that after the cessation of caplacizumab, the relapse rates at 1 month and at 12 months were more frequent in the caplacizumab group. But the authors also point out in the

discussion that these patients had persistently low levels of ADAMTS13, and that suggests that perhaps the relapse might have been related to the underlying autoimmune disease, so I think we really ... This is just 75 patients, so we really need to get more information on that.

They did publish a follow-up study in July of 2017, which was not included because this was after the time that we did our review. But in that study, they showed that caplacizumab reduced the frequency of major thromboembolic events, exacerbations, and death in patients with acquired TTP. That one was the same first author in the Journal of Thrombosis and Haemostasis. This drug really has the potential to make major improvements in the treatment of TTP, but we're waiting to see. The drug is not yet available and approved, at least in the US by the FDA, but hopefully, we'll be seeing more of it and learn more information about it.

- Joe:** You guys, man, so much great information. In many ways, this is like a 2016-2017 journal club. You guys have really done a great job with taking us through this. I wonder, just as a last question to both of you, you mentioned that you're starting to put together next year's version of this. Either based on that or based on what you're thinking and seeing so far, I'll throw it to both of you. If you could pull out your crystal ball, what do you think we might be talking about this time next year when we're talking about the new developments?
- Claudia:** That's a great question, Joe. We have a list of topics that we are developing right now, and they include blood donor characteristics and patient outcomes (again), transfusion therapy and coagulation, transfusion approach to hemorrhagic shock and mass casualties, platelet transfusion and pathogen inactivation, pediatric transfusion medicine, apheresis, and extracorporeal photopheresis. Here are some new ones: Emerging infections and testing, cellular therapies (which is not strictly our territory, so we're still thinking about that, but there's a lot in that area). Then this is Nancy Heddle's baby, I think: Big data applications in transfusion medicine. I think that will be a really exciting topic. I think all of them will be, but-
- Melissa:** Yeah, I would agree. I think that if we're covering cell therapy, the CAR-T is definitely going to be a focus on that because there have been so much progress we've made with the CAR-T-cells this year.
- Claudia:** I think that topic is what prompted many of the committee members to say, "We really need to include this this year."
- Melissa:** Potentially blood banks may start getting involved in it because it's not the same level of processing that we do on our cell therapy labs. It may be, at some point in the future, that the product moves into a blood bank if they don't have their own cell therapy labs. I think it's very relevant for transfusion medicine, as well as cell therapy.
- Joe:** That's fascinating. I'll tell you from my perspective, my little crystal ball, which is really foggy most of the time, but my little crystal ball is sitting here, based on the questions that I am getting asked... as I mentioned, I'm currently working in the Blood Donor Center environment, though I work with a ton of clinical hospitals, what I'm hearing about all the time is cold-stored whole blood in trauma. I mean, it is a constant drumbeat of "what are we doing about this?" "What's going to

happen?" I know that Phil Spinella and Mark Yazer and those guys are doing more and more studies. I suspect we're going to hear more about that in the coming year.

Claudia: Phil is on the committee and a very active member. Of course, he's a member of THOR.

Joe: [SHOUTS] THOR!

Claudia: I'm excited to have him right more on that topic.

Joe: For sure. For sure. Okay, you guys. Thank you so very much, Claudia Cohn, Melissa Cushing; You guys have been fantastic. I really, really appreciate you being with me on the podcast.

Claudia: I enjoyed it thoroughly, Joe. Thank you.

Melissa: Thank you, Joe. We enjoyed it.

Joe: Thanks for hanging out. If you are getting continuing education credit for this episode, you have *earned* it. Congratulations! Don't forget, go to www.wileyhealthlearning.com/transfusionnews to get that free, totally free continuing education credit. You can also find references and other stuff on the show page for this episode, that's at BBGuy.org/055. If you have a chance, go to Apple Podcasts and find this podcast and give it a review. I would really, really appreciate that. The previous episode, which was an interview with Dr. Nicole Draper on ABO discrepancies, is proving to be very, very popular. I hope you've checked it out. If you haven't, go to BBGuy.org/054.

Finally, the next episode, which is coming in a couple of weeks, will be another continuing education episode, believe it or not, featuring the return of the brilliant Dr. Jeannie Callum. She and I will discuss the often confounding topic of transfusion in patients with liver disease. That's coming, as I said, in a couple of weeks.

But until then, as always, I hope that you smile, and have fun, and above all, never, EVER stop learning! Thanks so much for being here. We'll catch you next time on the Blood Bank Guy Essentials Podcast.