BBGuy Essentials 049CE:
Red, White, and Yellow! with Jeff Winters
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Joe Chaffin: This is the Blood Bank Guy Essentials Podcast, episode 049CE!

[INTRO MUSIC]

Joe: Hi, and welcome back to the podcast designed to help you learn the ESSENTIALS of blood banking and transfusion medicine. My name is Joe Chaffin, and I'm your host. I'm super-excited to share my conversation with Dr. Jeff Winters from Mayo Clinic about **cytapheresis**, and why it's important for you even if you aren't actually responsible for it! More on that in a second.

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Now with that out of the way, I had Jeff Winters on last year, and he gave us an excellent overview of therapeutic apheresis, as well as an in-depth look at Thrombotic Thrombocytopenic Purpura. Today, Jeff is back to talk "Red, White, and Yellow!" with me. Confused? Well, "Red" means red cell exchange, "white" is leukocytapheresis, and "yellow" is thrombocytapheresis. These three procedures may need to be done emergently in many, many hospitals, and in fact, those of us in the blood bank may not even be the ones DOING the procedure! However, these procedures impact us in ways we might not even realize, and Jeff wants to share his vast experience and tell you what YOU should know about these procedures. As always with Jeff, we will move fast and give you lots of practical information! So, I don't want to make you wait! Let's go! Here's my interview with Dr. Jeff Winters.

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Joe: Jeff, welcome back to the Blood Bank Guy Essentials Podcast!

Jeff: It's great to be back! I'm looking forward to chatting with you again.

Joe: Honestly, I am always honored when people who have talked to me before are willing to come back, which means you're either just a terrible masochist or we had a good time last time! I'm going to choose to think we had a good time last time. That's what I'm going with!

Jeff: It was a good time! I enjoyed it immensely, and I'm looking forward to chatting again. So, I will put into the good times.

Joe: Okay. Fair enough, thanks. Thank you for not shooting me down there, Jeff. That's cool of you. So everyone, Jeff was with us last year, in 2017, where we talked a lot about the fundamental principles of therapeutic apheresis, that was in episode 25. And we also, in episode 26, took a look at, very specifically, one of the very clear and well-defined uses of therapeutic apheresis, in particular Thrombotic Thrombocytopenia Purpura. Today, I've asked Jeff back to take us through some additional stuff with apheresis, in particular the use of apheresis to remove some cells from the blood (in terms of cytapheresis) and to talk a little bit about red cell exchange, as well. But, Jeff, before we get to that I think we ought to do just a quick thumbnail review. Are you up for that? Just a little quick thumbnail review of what we talked about before?

Jeff: So last time, we focused mostly on plasma exchange or removing plasma, which really is the biggest chunk of apheresis procedures. The stuff we're going to talk about today---removing cells, less common. So, the important thing to remember is that when you do an apheresis procedure, given the definition of apheresis is derived from a Greek word "take away," "to separate," "remove by force." That's what we're doing, we're taking blood components, were separating them, we're returning some back to the patient, and some we're throwing away.

So, the ways that we can separate blood into its various components are essentially two: We can use **filtration**, where we're separating based on size, or we can use **centrifugation**, or separating based on density. Now, last time we talked about plasma exchange; either of those methods could be used for plasma exchange. This time, we're only talking about centrifugation. So blood is going to go into a centrifuge, it's going to be spun, and it's going to layer out according to the density. So the most dense elements, the red cells, are the farthest from the axis of rotation, and the least dense elements, the plasma, are closest to the axis of rotation. And this time, we're talking about removing cells, specifically, we'll start off by talking about removing white cells. They're going to be in the middle band, in the buffy coat. And that's what we're going to focus on.

Joe: Awesome. Okay. And that's a really important thing for everyone to understand. If what Jeff just said to you guys is not making sense, we went into that in a TON more detail in Episode 25. So please, stop this, go back and listen to that if, that was all...I don't want to say "Greek," because apheresis IS a Greek word, right? [laughs]

Jeff: It fits! Yeah!

Joe: So, go back and listen to that if that didn't make sense. But Jeff, one of the other things that we talked about in those two podcasts is something that we're going to use today. And so I think people need to know the very quick "thumbnail descriptions" of the American Society for Apheresis categories and grades of, essentially, how we're using apheresis, and in particular diseases. Could you take us through that?

Jeff: Yep! And I will, as we go on, talk about particular diseases, or particular indications for the cytapheresis and mention those, so that is really important. So first of all, the issue is, there's not much literature, and much of the literature is poor quality. So "ASFA," the American Society of Apheresis, reviews indications for apheresis and assigns each procedure as it's applied to a specific disease an ASFA category and a recommendation grade. So the category is the role of the treatment in the treatment of that disease, okay? So, there are four categories, I through IV, and they're written with Roman numerals (just mentioning that because I see people putting them with Arabic numerals, no, with Roman numerals). **Category I** is a first line therapy, either stand-alone or in conjunction with other therapies. So what that means is, when you see that disease, the first thing you should think of is applying that particular apheresis treatment. The big example is what we spent time talking about, and that's Thrombotic Thrombocytopenic Purpura.

Category II is a second-line therapy, either stand-alone or in conjunction with other therapies. So what a Category II indication means is that you do something first, and if whatever that treatment is that you did first doesn't work, then you can add the apheresis treatment onto that.

Category III: The role of apheresis is uncertain, and essentially you should individualize it. Doesn't mean that apheresis doesn't work; in fact, there IS literature that says it does work. But what you do is, you don't necessarily treat EVERYONE with that disease with the apheresis procedure. So you're going to look at your patient and you're going to make your decision based on characteristics of that particular patient.

And then, the final category is **Category IV**, and basically apheresis doesn't work or is harmful. So, that's the "Don't call me" procedures. They can be done in the context of an IRB-approved research protocol, where you're investigating something. But really, outside of that, the literature does not support the use, and again, it may actually be harmful.

Then, in addition, there is a recommendation grade: "1" is a strong recommendation to do the procedure, a "2" is a weak recommendation to do the procedure. And then with that, you're going to see either an "A," a "B," or a "C." An "A" is high-quality evidence, "B" is moderate-quality evidence, and "C" is low to very low-quality evidence. So, A is randomized controlled trials, B is controlled trials or flawed-randomized controlled trials, and C is case series, case reports, expert opinions from people.

Joe: Okay. So everyone, I'll have a link to the current version of the ASFA guidelines that Jeff was mentioning. Those are out there published for, you can grab a copy of those. They are really truly excellent. As of this recording, the most current one---Jeff, correct me if I'm wrong--- I believe are those from 2016 that are the most up to date right now, is that correct?

Jeff: That is correct. A new edition is published every three years so, look for a new edition June or July of 2019.

Joe: Awesome! Okay, well so, I don't want to spend any more time on that, Jeff, because we need to get on to what we're here to talk about today which is---well, let's start with cytapheresis, with getting rid of some of those cells that you were describing before. What do we want to get rid of first?

Jeff: Let's get rid of white cells first, okay?

Joe: Cool!

Jeff: So, let's talk about "hyperleukocytosis." So really, hyperleukocytosis is an elevated white blood cell count, and usually, a white count greater than 100,000. Now, to be honest with you, 99.9% of the time, this is going to be due to the presence of a leukemia. There are times that you can, and I personally have seen, elevated white counts for other reasons, but they tend to be "zebras," they tend to be pretty rare. Now, when you get these extremely elevated white counts, especially in the setting of AML, Acute Myelogenous Leukemia, you can run into some troubles. And the troubles can be really divided into three categories, and these are: **Hyperviscosity**, **leukostasis**, and **tumor lysis syndrome**. So, when we talk about hyperviscosity, basically there

are so many white cells there circulating through the bloodstream that the blood becomes you know, like well, you know, kind of like "molasses in January here in frosty Minnesota," it's moving REALLY slow, and the end result of that is you're not perfusing end organs.

Similarly, you can have leukostasis where there are such high levels of white blood cells in there, and they're interacting with the endothelium through adhesion molecules, that you're actually occluding the microvasculature. And again, you're leading to end-organ hypoxia. So, we talk about those two, or I talk about those two as being separate entities; they're really hard to distinguish, because they're leading to that same sort of endpoint, which is, you're going to see individuals that are going to have neurologic abnormalities. So they may, for example, have signs and symptoms of stroke or TIA, and they may range from very mild symptoms to complete coma and being completely obtunded.

The other thing that can happen with leukostasis and hyperviscosity is that you can also have such poor flow through the microvasculature of the lungs that these individuals essentially do not oxygenate. There is no oxygen exchange occurring, or there is oxygen, but it's not being delivered. So what's happening is, the oxygen diffuses from the alveolus into the capillary, it's not making it out of the lungs. And in fact, there's so many white cells present that they're consuming all the oxygen. So these people will have these horrible, horrible blood gases. They'll be profoundly hypoxemic, and they can actually have an "alveolar capillary block."

Now, because of the combination of the microvascular occlusion, the neurologic symptoms that can occur, the hypoxia in the tissues, you can also end up with hemorrhage. So you can have bleeding into organs, and the one that we worry about the most is actually bleeding into the brain. So you can see somebody with, not only may their neurologic symptoms be due to HYPOXIA of the brain, but it may be due to actually they're now BLEEDING into the brain because of the damage to the vessels from the hypoxia and subsequent hemorrhage into it. You can see other oddball things; you can see bleeding into the retina and infarction in the retina, and bleeding into other sites, as well.

The tumor lysis syndrome happens when our colleagues, the hematologists and oncologists, show up and they begin to give the chemotherapy. I mean their goal is to kill off these cells, and sometimes, they're too effective! So suddenly, you have massive lysis of white cells throughout the body, and you have the release of the contents of those white cells. And so you're seeing potassium and phosphate and uric acid being released, as well as all these

breakdown fragments of the cells and bits of membrane and things that can trigger the coagulation cascade. And you'll have all of these potentially toxic materials leading to the development of disseminated intravascular coagulation, and leading to renal failure, because of uric acid deposition, for example. As well as electrolyte abnormalities that can cause a myriad of other things such as arrhythmias in the heart...

Joe: So, Jeff, let me interrupt you for just a second, I'm sorry about that. When we go back to leukostasis, for just a moment, you mentioned that the definition of hyperleukocytosis is a white cell count of greater than 100,000. I have seen people, when they're dealing with a leukemic and that white count is above 100,000, that seemed to think that it's automatic that the patients are going to have symptoms. Are there any variables in that? Is it you know, I mean, I know the answer that when you cross 100,000 some switch doesn't automatically flip, but what are the things that people should be thinking about to try and make that evaluation when the count starts getting that high?

Jeff: We'll talk when we get to the end about what the categories say. But the bottom line is, what we really want to treat when we do these procedures is **we want to treat SYMPTOMS**. So in other words, if somebody is symptomatic, I really don't particularly care what their white count is. I want to treat it. Wait a minute: Can people be symptomatic at less than 100,000? The answer is: "Yes!" Because what also determines it is not just the white count, but what types of cells are they, AND, how good's the plumbing? OK? If this is a young female who has the protective effects of estrogen on their vessels with regard to atherosclerosis, they may have no symptoms at an extremely elevated white count, whereas if it's some older gentleman (and I'll put myself in that category), who might have bad atherosclerosis, and has gummed up vessels, and that carotid doesn't look very good as it is, they may have symptoms at a much lower white count. So symptoms really need to drive that.

I alluded to the differences in the cell types. **As a general rule of thumb (note those are general rules; apply them with caution), Acute Myelogenous Leukemia tends to have symptoms at lower white counts, because there are bigger cells with more adhesion molecules expressed and more interaction with the endothelium. So they tend to be that 100,000. "ALL," Acute Lymphoblastic Leukemia, tend to be much smaller cells with fewer adhesion molecules, they tend to have much higher white counts, 500,000, so you know to be honest with you, I don't do the prophylactic reductions until they're hitting MUCH higher counts, in the 500,000 range, if they're ALL**. And then "CML," Chronic Myelogenous Leukemia, in the chronic phase, those people can have incredibly high white counts that are completely

asymptomatic. So, essentially do not treat chronic phase Chronic Myelogenous Leukemia with cytoreductions. On the other hand, if they're "blasting off," if they're developing an acute leukemia out of a chronic, you need to treat them as if you were treating an AML.

Joe: That makes sense. OK, good. Thank you for taking that little sidebar with me. I know we're going to talk more about the specific indications when we get to the section on the ASFA categories. But what do we know about how reducing these white cells actually helps patients, and what does it do for them?

Jeff: What does it do for them? Well you know what? There's good news and there's bad news. And I guess this depends upon whether you're a "cup half-full" or "cup half-empty" sort of person. We know this: That when somebody has a white count greater than 100,000, they have a higher short-term mortality rate than those who have white counts less than 50,000. And that's due predominantly to bleeding into the central nervous system and pulmonary leukostasis, which I mentioned, that sort of alveolar capillaries block. So you'd say, "Oh hey! This is great! We can reduce this white count, right? We could pick these cells out." And interestingly enough, when you apply leukapheresis, you can lessen or reverse symptoms, and it's associated in a number of studies with improved two to three-week mortality; meaning that they survive... in two to three weeks after diagnosis, there's a higher survival. But when you look at their overall mortality, that means, "Did they survive their leukemia?", there is NOT an effect of leukapheresis on overall mortality. That's going to be determined by what type of leukemia they have, what type of "bad cytogenetics," "good cytogenetics," and all the rest of that. How healthy were they before they developed this leukemia? So back to that pessimist-optimist; if you're the "cup half-full" person, and I'm going to be honest with you, I'm a half-full person...

Joe: I would have guessed that [laughs]!

Jeff: When I look at it I say, "Hey, I'm going to do this procedure, because at least I'm going to give them a bit of a fighting chance. I'm going to improve their survival for two to three weeks, and hopefully my colleagues in hematology-oncology can help them." Now if you're the "cup half-empty" person, you're going to say, "It doesn't make a difference in their long-term survival. Don't bother doing the cytoreduction." And there are publications, and there are people that believe strongly about that. And I just throw that out there. I think a little bit of medical judgment and a little bit of medical practice... I'll let the listeners decide for themselves.

Joe: OK, fair enough. I like it! OK, we'll get to the specific recommendations on what to do, but let's talk about the technical stuff for just a minute. And I realize that a lot of the people listening to this podcast are people that may never actually have to deal with the technical aspects, and that's fine. But I think it's important to understand a little bit about it. So, what happens? How's it done?

Jeff: So again, we're back to that centrifugation again, so we're going to go ahead and pump blood into our apheresis device. We're going to spin it around, and we're going to separate it into layers. We are going to have that plasma layer near the axis, red cells outside, and in this case a REALLY large "buffy coat." It's going to be full of all these white cells, these leukemic blasts that have been generated, coming out of the marrow. And what we're going to do is, we're going to go in and we're going to remove, obviously, we're going to try to remove those leukemic blasts to decrease the total white count. And our goal is going to be to decrease that white count so that we can decrease the leukostasis or the hyperviscosity, or that we decrease the total tumor burden, so that when they give the chemo, we don't have the tumor lysis syndrome, or at least we don't have as severe tumor lysis syndrome. So the usual course, is to process somewhere in the neighborhood of 8-10 liters of blood (some people will say, "Well, two blood volumes"), in an attempt to reduce the white count.

Again, **there is NO correlation between the degree of reduction and survival**. So what we really want to do is, we want to look for resolution of symptoms, because again, I already alluded to the fact (and we'll talk a bit more in a moment), we're going to want to focus on treating symptomatic patients. So if that patient comes in, and they're obtunded, we want their mental status to improve. If that patient comes in and they are having a very poor blood gas and poor oxygenation, we want to improve their blood gas and their PO2. So we really want to drive our therapy by following symptoms. So sometimes, I'll get... they will say, "Well, I want you to do THREE of these cytoreductions." Well, you know, if the person gets done and their symptoms are resolved after the very first cytoreduction, we're done! And if the symptoms come back, I'll be there. But I'm not going to go ahead and do another procedure necessarily in an asymptomatic individual.

Joe: So Jeff, one question for you with that, because I think that's a really important point. I have seen people in different places (I've worked in a lot of different places, so I've seen a lot of different approaches to this), but I have seen people that are monitoring the white count, for example, very carefully during the procedure. They'll send CBCs during the procedure to see, "Oh, are we below 'x number' or are we below 'x number'?" So, am I understanding correctly that in your view, that's FAR less important than, "How's the patient doing? What are the symptoms that the patient's having?"

Jeff: You got it, exactly. I mean, I'll be honest with you, there are different ways to "skin the cat," and there are different ways to practice. But again, my goal is, I want resolution of symptoms, because my goal is really in those symptomatic individuals, to treat them until they're gone. In the people that are prophylactic, where they're not symptomatic, but maybe I'm going to have a concern (we'll talk in a moment about that), I may monitor a count, but I'm going to check them post procedure count, because routinely, I can get a 50% reduction in their white count with a procedure where I'm processing that 8-10 liters. And that's talking about AML or potentially an ALL. Now, where that FAILS, in my experience, is if you have somebody with Chronic Myelogenous Leukemia and the AML is arising from that. And basically, what happens there is you debulk their spleen, because they all come in with a big huge spleen. So you will not see the degree of reduction that you would anticipate but their spleen is smaller.

One other thing I want to point out that's REALLY important, really, really important: You gotta shut off PRODUCTION of these cells. You're going to lose, you're not going to be able to beat out those malignant cells in the marrow that are producing the blasts coming out. So our Heme-Once colleagues need to give some form of chemotherapy to begin to shut down production. Otherwise it's a losing game. Now that doesn't need to be there full-course chemo, frequently it's just hydroxyurea. But they need to give something at least shut off or slow down production. If they don't do that, you're going to lose, you're not going to be able to get a significant reduction. You may not be able to get any reduction at all.

Joe: Before we move on, any other technical things about the procedure that some people do, some people don't?

Jeff: The other thing I need to mention is this: There's lot of variability in practice with regard to this, sometimes, especially if there are more mature cells, the density of the white cells, the leukemic cells, is pretty close to that of a red blood cell. And so, you have poor separation of the white cells from the red blood cells, which leads to a poor removal and reduction. And if you can then give **hydroxyethyl starch** [NOTE: "HES"] as part of the procedure, so we'll mix up an anticoagulant that includes hydroxyethyl starch, and this is a sedimenting agent. It basically eliminates the "zeta potential" on that negative charge on the surface of the red blood cells, and leads to rouleaux formation in the red cells. So that clump of red cells is going to be more dense now than that white cell that I'm trying to remove, and you'll have cleaner separation. We did a study through the American Society for Apheresis, retrospective data, but looked at centers that did and did not use HES, and the take-home points for this: One,

we saw a greater degree of reduction in AML if HES was used; we also saw a greater improvement in our pulmonary symptoms when the HES was used.

Joe: OK. So, Jeff, in the interest of time, let's move on and let's talk about what the ASFA categories and recommendations are for this situation.

Jeff: So the ASFA category for leukostasis: Basically **symptomatic leukostasis, symptomatic hyperviscosity, is a category I** (that means a primary treatment modality) with a recommendation grade of "1B." So, a strong recommendation to do it, with "B" category evidence. That means controlled trials, but not randomized controlled trials, so moderate quality evidence. This is, again, treating symptoms; the person's symptomatic, you want to see until the symptoms go away.

Prophylaxis: That means they're not symptomatic, but they have an elevated white count. So, that is a **category III** indication, meaning the optimum role for apheresis is uncertain, and you need individualize it. So again, you're going to look at your patient, you're going to say, "Wow, this is a young person, maybe it's a young woman, very fit, athletic type. No significant other co-morbidities, no coronary disease, and they're at 150,000. Maybe I'm just going to watch them." On the other hand, here's this guy over here, "You've got bad atherosclerotic vascular disease, he's older, he has other co-morbid conditions. I feel uncomfortable. He might stroke on me. I'm going to go ahead and treat this individual." And as a general rule of thumb, the criteria are again 100,000 for AML, 500,000 for ALL. And as I mentioned, CML, we really don't unless they are turning into AML. And I failed to mention CLL, which again, usually we're not treating. By the way, the prophylaxis is a grade 2 recommendation, so it's a weak recommendation, and it's based on "C" quality evidence, so low to very low-quality evidence.

Joe: So Jeff, before we leave cytapheresis, I do want to ask you one more thing, because you hear about this in textbooks and articles sometimes, and that's, is there any FORM of AML that you might want to think twice before doing leukoreduction?

Jeff: Yeah. So, you'll hear people talk about not doing cytoreductions on FAB M3, the promyelocytic leukemias, and the thought there is that you put those cells in the centrifuge and you get them all nice and angry and they degranulate. They kick those Auer rods out, and will lead to that DIC that can occur in the setting there. Now I've got to be honest with you: There are times, in the middle of night, when you did not know WHAT the type of leukemia was.

We did a cytoreduction, and oops, the next day, it's an M3, and nothing happened.

Joe: Right.

Jeff: So, there is that concern. I think if you know coming in, probably avoiding cytoreduction in that setting is reasonable, especially given that you have the retinoic acid analogues, those drugs that can quickly "mature" those cells and basically resolve a lot of the symptoms. Basically, there's another, more effective therapy, I would say, and you avoid this sort of potential complication of development of DIC.

Joe: OK Jeff, so I do have one question before we get into the specific details of the [other] cytapheresis things that we're going to discuss today, and that's this: Many people listening to my podcast are blood bank workers, they're other laboratory technologists and sometimes students, they may be pathologists that are not involved in therapeutic apheresis every day. Obviously, many people that listen, this will directly impact them. But for those that don't necessarily see a reason why they need to know about this, what can you tell us? Why do people need to know about what these things are, what we need to do for them?

Jeff: Well, for those people in the lab, let's say the technologists who are not going to be performing these procedures, they may be SUPPORTING them by setting up blood products for transfusion of these patients, in some instances and we'll talk when we get on to the red cell exchange by actually helping select an appropriate replacement for that red cell exchange. So they have to have some sense of what these procedures are to understand what it is that they're doing to support these procedures and what their role is and why it's important. Obviously physicians, for the trainees and the residents, "somebody" might ask you questions about that on a test somewhere. So that's why you need to know it. But again, you may never know where you're going to end up working, and you may find yourself responsible for helping guide some of these decisions and being in charge of a unit.

Joe: OK Jeff, so thanks for that excellent summary of getting rid of "nasty white cells." So let's talk about something else. Let's talk about platelets! **What happens when we have too many platelets**? What are the things we should be thinking about there?

Jeff: Bad things happen! "Thrombocytosis" is defined as greater than 500,000 platelets. And it can be due to a number of different causes, primary or

secondary. The primary ones are Polycythemia Vera, Agnogenic Myeloid Metaplasia, Essential Thrombasthemia. Things you don't necessarily think about from a secondary standpoint is you know, "Hey, that person that was just in the automobile accident and had to have their spleen removed?" So increase the platelet count post-splenectomy, and interestingly enough, if you have real bad iron deficiency anemia, you can actually bump your platelet count up, because there is some cross reactivity between erythropoietin and thrombopoietin. The body saying, "Make red cells." It can't, so instead it makes platelets.

Jeff: But what can happen is one of two things: **You can either BLEED or you can THROMBOSE**. So if you bleed because you have too many platelets, it's usually muco-cutaneous, so we're talking about nosebleeds, bleeding in the lips, bleeding in the gums, bleeding in the skin. If you thrombose things, it can be "microvascular" or "macrovascular." So you can have thrombosis in the capillaries in the skin, and you can get "erythromelia," this sort of painful purpuric rash, or you can have macrovascular thrombosis, you can thrombosis superior saggital sinus or a bridging vein on the surface your brain. You can thrombose a coronary artery. You can thrombose a vein in your lower extremity and throw off a DVT. So all these are not good for you.

Joe: Jeff, is there any correlation between the... Forgive me for interrupting, I'm sorry, but is there any correlation between the primary and secondary causes of thrombocytosis and the risk for those?

Jeff: Yeah. So the primary causes, back again to our Essential Thrombasthemia, our Polycythemia Vera, they have a MUCH higher frequency, roughly 56% of individuals, when they get that count over 500,000 are going to experience some complication. On the other hand, the secondary causes, pretty uncommon, only 4%. So really, what we end up usually treating are those primary causes. So, what determines whether or not somebody bleeds or somebody clots? So, there are some risk factors. The risk factors for thrombosis are: increasing age, if you've had a previous clot somewhere, and the longer you have the elevation in your platelet count. If you think about it, at least with regard to increasing age and previous thrombotic event, as we all get older vessels get "grungier." If you have a previous thrombotic event, your vessel isn't normal, and so it's the "plumbing is bad." And that's what happens. For bleeding, interestingly enough, if your count is EXTREMELY high, greater than 2,000,000, you're at increased risk of bleeding. What ends up happening is you actually develop sort of an "acquired von Willebrand Disease-like state." Your platelets are slurping up all the von Willebrand's factor in your blood and can't interact appropriately with your endothelium in the presence of injury to

the vessels, and you bleed. The other thing is, somebody looks at your platelet count, and they say, "Ooooh, this is really high! I'd better give them some aspirin so that they won't clot!" And then they bleed. So really, extreme elevations, greater than 2,000,000, and non-steroidal anti-inflammatory drugs; those are the risk factors for bleeding.

Joe: OK. So, Jeff, I'm going to go out on a limb here, and you may cut me off of this limb, but I'm going to go out on it anyway! I'm going to say that since apheresis has been around for a long time, since we've had people with high platelet counts for a long time, that surely, we must have done a ton of really great trials on how well reducing someone's platelet count in these situations works. Am I right?

Jeff: You're wrong! Not at all. There are actually NO controlled trials. So, this is one of these things where really what ended up happening was people said, "Oh look! Their platelet count's high." They treated them, their symptoms improved, and they said, "Wow isn't that wonderful!" And nothing further was done. Think about it; if you were the patient experiencing neurologic symptoms because your platelet count was really high, and I came to you and said, "Hi! I want to enroll you in a randomized trial, and you may either have a stroke, because I'm not going to treat you (I'm going to give you a "sham" procedure), or not have a stroke." Would you agree? Probably wouldn't. So, it's one of those things that we haven't had trials, we probably never WILL have trials in this context, at least randomized controlled trials.

Joe: OK, but I guess we can talk about kind of general practice. But before we get to the technical aspects of this, let me ask you this: Is this somewhat analogous to leukoreduction, in that you're not necessarily treating "magic numbers," but you're treating, in particular, the things that you described: Thrombosis and hemorrhage? Is that a fair way to look at it?

Jeff: Exactly. So, once again, we're going to treat symptoms predominantly, and to be honest with you, once again, I don't really care what somebody's platelet count is, if they are symptomatic from it, and I feel certain that they're symptomatic from it. So, **you'll hear people talk about treating when the platelet count gets greater than 1,000,000**. Well, somebody comes in, their platelet count's 750,000, and they are having what appear to be symptoms related to occlusion of the microvascular, neurologic symptoms because of these platelets, I'm going to treat them. I'm not going to treat a number. There are, and we'll talk in a moment, some people will say, "Well, you know, there is an increased risk of these complications (especially in the primary cases) when

the count's greater than 1,000,000." So, they'll go ahead and do prophylactic treatment in that context, in that setting.

Joe: What aspects do we need to know about how we do it?

Jeff: So again, we process... it depends. People will do **1 to 1.5 blood volumes**, some people will do a fixed time, they'll say, "OK, three hours, we're going to process for three hours," with again, the goal to resolve symptoms, because no correlation between the platelet count and complications. So, if they're symptomatic, you'll want to make those symptoms go away. And as with leukocytapheresis, we've got to do something to shut off the production, because we're going to lose. We're not going to win that battle. We need to shut off the production of the platelets. So that again, tends to be giving them hydroxyurea at the same time that we're initiating the platelet reduction therapy. Again, just like white cells; roughly a 50% reduction. Your mileage may vary depending upon your institution and how you do things, but roughly in that ballpark.

Joe: OK. So, what does that mean for us in terms of our ASFA categories and recommendations?

Jeff: So, for the ASFA categories, "**symptomatic" is currently a category II**, so that's a second line therapy. So theoretically, what you're going to do is you're going to start treating them with medications. Now saying that, usually the medications are not... They don't kick in, they don't shut down the production quick enough. So, you may need to add that. So, category II. Now, we've already told you, there are no randomized controlled trials in this context. So, this is a grade "2C," so a weak recommendation based on low to very low-quality evidence. The **"prophylactic" treatment, that is, "Uh-oh, their platelet count is greater than 1,000,000," or treating individuals who have secondary thrombocytosis (because they rarely have complications), that's a category III**. Again, the optimum role is uncertain, and it should be individualized based on that patient. So, you're going to look at the sum total of the patient. What is there other co-morbid conditions? How healthy are they, etc.? And that again is a recommendation grade "2C." It's a weak recommendation based on low to very low-quality evidence.

You want to hazard a guess as to what the highest platelet count I've ever seen is?

Joe: Oh OK. Let's see...I'm going to say 2,900,000.

Jeff: Ehhh! 7,000,000! It was in a young woman who was an ultra-marathoner and was completely asymptomatic.

Joe: Get out of here! Really?

Jeff: And I'll be honest with you: We looked at her, myself and the Heme-Onc doc, and we scratched our heads and we said, "Do you want to reduce her?" And he said, "Do YOU want to reduce her?" And we both said, "She's asymptomatic." And we said, "7,000,000 is scary!" We reduced her, we cut her in half. She went down to about 3,000,000. We both stared at each other again and we said, "OK, we're good." And we let her sit at 3,000,000, and she did perfectly fine. She had Essential Thrombasthemia.

Joe: Wow! OK so Jeff, we have covered getting rid of "nasty white cells." We have covered getting rid of "nasty platelets" (I'm obviously oversimplifying slightly, but I like putting it that way!). So let us spend the last few minutes talking about what to do for patients who have red cells that need to be exchanged or removed. So why don't we... I'll let you take the lead. What would you like to say about that?

Jeff: Yeah. So, there are actually a number of indications that are pretty rare. We're not going to talk about those, but we'll talk about the common one which is sickle cell anemia. So again, you have this abnormal hemoglobin that polymerizes at a low pH, and in a hypoxic environment, you get these "sickled" red blood cells that occlude the microvasculature and lead to, well, hypoxia, which leads to more sickling, which leads more hypoxia, which leads to more sickling, and you end up with this chronic hemolytic anemia punctuated by these "crises," these crises that are triggered by the sickling.

Jeff: Now, there are a couple of ways you can treat sickle cell anemia. You can give them acute simple transfusions. So, you're just replacing their oxygen carrying capacity by transfusing them. You can give them chronic transfusions, where you chronically transfuse them and try to suppress their marrow production of their hemoglobin S-containing red cells. And then you can do red cell exchange, where you basically remove the evil red cells, those containing hemoglobin S, and replace them with red cells off the blood bank.

Now, you might say, "Well, why in the world even bother doing red cell exchanges? Isn't that complicated? Let's just top them up, right? Let's just give them some red cells." The problem is, that they're endothelium isn't normal. It's been damaged from the sickling. And even the red cells that they have that aren't sickled, let's say they were once sickled and now they're not sickled;

those red cells aren't normal. And so, the red cells are sticky, the endothelium is sticky. And so, what ends up happening is you increase the hematocrit, you start increasing viscosity. Well, what does that do? Decreases oxygen delivery, leading to hypoxia, leading to sickling, leading to more hypoxia, leading to more sickling. So, with acute simple transfusions, you can actually make the situation potentially worse.

So, when you have somebody who has one of these crises, there is, due to the sickling, you can do the red cell exchange and avoid increasing their hematocrit, at least into the realm where you start seeing increased viscosity and hopefully avoid those. You can also do the red cell exchange as the kick-off, the initial part of embarking upon the chronic transfusion protocols to suppress their own marrow productions, because again, you cannot boost their hematocrit up really high that they start having problems with oxygen delivery.

Joe: One of the thoughts behind red cell exchange transfusion versus acute simple transfusion, you mentioned viscosity, I'm totally with you on that. Can you address the iron issue between those two?

Jeff: So, you know, that guy that gets shot and bleeds out 50 units of red cells, and you give him 50 units; his net iron balance is equal. But that's not what's going on here. So, they have a chronic hemolytic anemia. You are addressing their anemia by transfusing them. That iron is going in, but the body does not have an effective mechanism for excreting iron. Basically, it's sloughing your epithelium, and sloughing the lining of your intestine; that's how we get rid of iron (short of bleeding). And so, the simple transfusions will lead to iron overload. Whereas, if you're doing an exchange transfusion, you're putting in what you're taking out. And there are methodologies (which we won't get in to the specifics), there are hemodilution methodologies where you can actually remove red cells at the beginning, so you're removing evil hemoglobin S-containing red cells at the beginning. You're not replacing them, but you're giving them a crystalloid solution to keep them euvolemic. And then you do the red cell exchange part, and what you do then is, you're getting them to that hematocrit you want, you can give fewer red cells to get to that fraction of cells remaining that you want, of less than 30% containing hemoglobin S. You're giving them fewer red cells. So, you're giving them less iron. You can actually start to DEPLETE their iron stores in that setting.

Joe: I think people that are beginning in our field, people that are learners, are often surprised at, when you say, "boosting the hematocrit up," in someone with sickle cell, that number is a LOT LOWER than we might think in someone who doesn't have sickle cell, right?

Jeff: Right, but they're compensated. They're extracting oxygen and they're good to go. So, you know you see those patients with sickle cell anemia wandering around with, let's say, hematocrit of 21, hemoglobin of 7. That's where they live, and they're fine. They're going up and down steps, they're walking down the street. If you and I have that acutely, we'd be flat on our back and probably not conscious! But they live there. And so I've sometimes seen individuals, I've seen physicians maybe who aren't dealing with these patients say, "Oh well, we need transfuse them to a normal range (whatever that is). We need to transfuse them up," and that actually could TRIGGER one of these crises, because they're fine where they're at. They don't need to go higher. But by transfusing them, you suddenly cause them to paradoxically not deliver much oxygen.

Joe: Is there any kind of general rule of thumb, numbers that you want to try and avoid in patients with sickle cell?

Jeff: I usually try, **when I do the red cell exchanges, I try not to get their final hematocrit at the end of the procedure above 30%**, because when you hit that range, you start seeing that paradoxical decrease in oxygen delivery.

Joe: Right. And that's, again, those of you learning this field, it's really important to recognize that this is VASTLY different than other settings where we might be doing red cell exchange (the rare ones that we're not talking about today), but in sickle cell, your target is considerably lower than what we think of another scenarios. So, forgive me for that little sidelight Jeff, I think that's important.

Jeff: I think that's an important... That's the take-home message, that's very important, because I've seen confusion on that topic. There are a number of different crises that can be treated with red cell exchange. I should mention, there are two different types of red cell exchanges: Manual and automated. Manual is basically, drawing a unit of blood out of one arm while you're giving a unit of blood in the other arm. It can be done, it's simple, it's straightforward. It's not as efficient or as effective as doing it automated, where you're hooking up the apheresis machine. But in certain parts of the world where you don't have that spiffy apheresis device, manual exchange is perfectly reasonable. And it also may be appropriate in a setting of people with very small blood volumes like pediatric patients, neonates, and very little people with not much blood volume.

I think probably what we'll do is we'll talk a bit about the different crises when I talk about the ASFA indications at the end. Let's talk a little bit about the technical aspects.

Joe: OK, sure!

Jeff: I mentioned one of them: Our goal, really what we're doing is, we're removing the hemoglobin S-containing red cells, and we're replacing them. And I already alluded to the fact that the usual target is to have a hematocrit of roughly 30%, no greater than that. Sometimes we can't get that high, so you get as close as you can get (basically programming the device, you can't get there). The other thing you try to do is, you hear people talk about the "fraction of cells remaining" (the "**FCR**"), and that is you want the total number of cells, the percent of cells that have hemoglobin S in them at the end of a procedure to be **less than 30%**. ***So, 30/30: 30% hematocrit, less than 30% fraction of cells at the end of the procedure having hemoglobin S in them***. Some people use a little less than 30%. I've seen people use 20%, I've even had people request 10%. Frequently, that's difficult to obtain without using a lot of blood products. Now, the replacement fluids that you're going to give them are red blood cells. That makes sense, right?

Joe: That's pretty simple!

Jeff: Now, a couple of things you need to consider when you're looking at what the replacement fluid is. So first of all, since you're actually, one of your endpoints is to have less than 30% hemoglobin S, you want these cells not to have hemoglobin S in them!

Joe: I can follow that, I think!
Jeff: So, you want to actually TEST; you want to test your cells for hemoglobin S. You say, "Well, wait a minute? Why would they have hemoglobin S in it?" Well, you have to remember that the majority of individuals, obviously, who have Sickle cell anemia are going to be of African ancestry, and their antigen profile on their red cells is going to be different than a Caucasian blood donor. So sometimes these people have antibodies towards those Caucasian antigens, and you're going to select red cells that are negative, and those are going to have a higher probability of being from somebody from African ancestry. And they might have, not sickle cell DISEASE, but they might be a sickle carrier. And so you're going to try to test that. And you're going to measure the amount of hemoglobin S at the end, right, with hemoglobin electrophoresis, to determine, "Did I achieve my goal of less than 30%?" So, test that.

We usually will also use also use a leukocyte-reduced blood product. Why? Well, because these people are going to get a lot of transfusions. If you're not removing the white cells, they're going to be exposed to them, they may develop antibodies to HLA. Really, at this moment, the curative treatment for sickle cell disease is a bone marrow transplant, and if somebody has a bunch of HLA antibodies, that's going to limit donor sources. And, if they run into other problems in the future, you might not be able to transfuse platelets to them because of the HLA antibodies.

And then finally, these people have a chronic hemolytic anemia, they're going to get a LOT of red cells over the years. And so one of the things that we frequently will do, most centers will do, is match for not only those red cell antigens that they might have antibodies to, but they'll match for a subset, match for things to PREVENT them from developing antibodies. So a lot of places will match for C, c, E, e, and Kell (K1). And if you do that, in the "STOP 1" trial [NOTE: See https://clinicaltrials.gov/ct2/show/NCT00000592], basically, they saw a reduction of the rate of alloimmunization from 3% per unit of red cells received to 0.5% per unit received, and a decrease in their frequency of delayed hemolytic transfusion reactions by 90%. If you extend that out, and start matching also for S and Fy^a and Fy^b, because remember, favorite board question: African-Americans, Fy^a neg, Fy^b neg, high percentage, right? But if you go for those, then you're going to even further reduce the rate of alloimmunization.

Joe: And of course, that's balanced with how difficult it may be, depending on the person's antigen profile, to match. That can be a challenge sometimes.

Jeff: Yup, and you and your blood supplier, and what you've got available, and all the rest of that stuff, as well. So again, the type of red cells you use really is not that important, whether you're talking about additive solution or CPDA-1, or what the preservative is on them. You just need to know what the hematocrit is because you've got to program that into the machine. And then, we tend to try to use the freshest ones possible, that is, the rationale being that the fresher they are, the longer they survive, the less likely we're going to have to come back and try this again and do another exchange or do something else.

Joe: Let's hit the highlights, shall we? Because, folks, I've got to tell you, we could have made this ENTIRE podcast about red cell exchange and sickle cell. It's a big, big subject, complicated subject. We wanted to give you this as just some highlights, so Jeff, rock n' roll! What are the take-home points?

Jeff: I want to mention just a few. So there are more than this that the ASFA has categorized, but I just want to hit a few high points. First of all is **acute stroke**. So either prophylaxis for stroke or actually somebody who's experiencing a stroke. So again, these people have bad vessels, they are not delivering oxygen. So **for acute stroke, it's a category I**. So strong recommendation to actually do the procedure, category I, so primary treatment with a grade 1, strong recommendation. Unfortunately based on all low-quality evidence. **Prophylaxis for primary or secondary stroke, so preventing them from having a future stroke, it's a category II** indication. So it's a second line therapy, first line would actually be potentially the chronic transfusions to suppress their own marrow production and decrease that, but again, you may have difficulty with the oxygenation and triggering the sickling crises. So, you can add red cell exchange either as all of the transfusions, or for the first part of that chronic transfusion support. Again, Category II recommendation, grade 1, so strong recommendation, but low-quality evidence.

Acute chest syndrome. Acute chest syndrome is when they have sickling that leads to decreased oxygenation, so sickling in the microvascular in the lungs. Well, if they're hypoxic, they get more sickling, which makes them more hypoxic, which makes them sickle more, and et cetera, et cetera, et cetera. So, **this is a category II** indication, so it's a second-line therapy. You usually try to address the initiator of the acute chest syndrome, which frequently is an infection, it's pneumonia. But if these individuals begin to worsen, and they start getting worse and worse, then you want to intervene with doing the red cell exchange to try to basically abort this circling around the drain. That is a strong recommendation, so grade 1. But again, low quality evidence, category C.

The other one that I want to mention is **prepping people for surgery**. So basically, there have been studies that have shown that really good anesthesia management, that is, avoiding hypoxia, avoiding acidosis during the surgical procedure versus transfusing somebody: They're equivalent. So **this is actually a category III** indication, so the optimum role is uncertain and should be individualized on the patient, with a weak recommendation based on high-quality evidence (that's the trials that have actually looked at this). So, in this setting, if you have anesthesiologists that are used to dealing with these people, you really don't need a red cell exchange. If you have anesthesiologists who aren't used to dealing with these people and there's concern that maybe they might have hypoxemia or acidosis during the procedure, then red cell exchanges may be appropriate. But you're going to want to base that on the patient; not only on the patient, but your facility that you're at.

Joe: Jeff we have hit a LOT in an hour, man! That was a lot of info, but I think you presented it in a way that's not only memorable, but useful for us. So, thank you so much for taking the time to go through all these with us!

Jeff: OK. Well, I appreciate the opportunity, and maybe we'll do something else in the future. I'm willing if you're willing!

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Joe: Thanks for hanging out with Jeff and I for that discussion. I hope that you have a better feel for the “Red, White, and Yellow" therapeutic apheresis procedures we discussed today.

Remember, for continuing education credit, you can directly visit www.wileyhealthlearning.com/TransfusionNews. The other thing I’d love for you to do is give your feedback and comments on the show page at BBGuy.org/049. You can also give your feedback on iTunes, which I would really appreciate, as well.

I hope you’ll join me again in a couple of weeks, when I will have the return of the fabulous Sue Johnson from Blood Center of Wisconsin. She’s one of my favorite people, and she’ll be here for my landmark 50th episode. Sue and I will start a two-part discussion on the essentials of pretransfusion testing (and here’s a little secret: There MIGHT just be a giveaway!). Don’t miss it!

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!