BBGuy Essentials 040: “Wholly Whole Blood!” with Mark Yazer

Joe Chaffin: You are listening to the Blood Bank Guy Essentials Podcast, episode 040.

[INTRO MUSIC]

Joe: Hi everyone. Welcome back to the Blood Bank Guy Essentials Podcast! I am Joe Chaffin, your host. I have a great interview to share with you today on a topic that actually might first seem "old school" to some of you and might be brand new to others of you. We'll get to that in a second. But Dr. Mark Yazer is back to talk about whole blood in an episode I like to call, "Wholly Whole Blood!"... I could have put a "Batman" on there, on the end, but anyway…

So one thing I need to share with you before we get started with this episode is that many of you are aware with the last episode, Episode 039, we started awarding free Category 1 continuing medical education for physicians, and that was very well received. I'm really grateful for those of you that signed up and went ahead and did that. Now, however, for this episode, we actually have P.A.C.E. contact hours from the American Society for Clinical Laboratory Science available. Again, it's free! You can get up to one contact hour per month, either from CME or from P.A.C.E. So, fantastic news! I'm so excited about it! This is offered through TransfusionNews.com and Wiley Publishing, with generous sponsorship from Bio-Rad (who has no editorial control over the process at all).

[00:01:29] So here's how it works: So you listen to the episode just like you usually do, either (for this episode) BBGuy.org/040 or iTunes, Apple podcasts through iTunes, on your phone, whatever, Google play, wherever you listen to the podcast. There's a transcript and sometimes a quiz available to enhance learning that are available on the show page at again BBGuy.org/040. On the page, you can follow the link to the Transfusion News continuing education page, which is on the Wiley Health Learning site. If you want to go there directly that's fine too. The address is WileyHealthLearning.com/TransfusionNews. No problem. There you'll complete the steps which are really self-explanatory. You have to do a free registration. You'll do a quiz. You'll do an evaluation at the end. And during that evaluation, you'll have to choose either to get continuing medical education if you're a doc or P.A.C.E. contact hours if you're a laboratorian. You do all that, finish the quiz all that, you get your certificate and again it's completely and totally free! I am so happy and so excited about this. I know many of you are are as well.

So here's the legalese for this (we have to make sure that we that we do this properly so that everybody gets credit). And here we go: Funding for this activity was provided by Bio-Rad, who has no editorial control over the content of the

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[00:04:15] OK, on to today's topic! Mark Yazer was my very first guest on the podcast a long time ago (last year) and I'm so honored to have him back for episode 40. Mark is a medical director with the Institute for Transfusion Medicine in Pittsburgh and a professor of pathology at the University of Pittsburgh, and he's here today to tell us why he believes, in his words, "low-titer cold-stored group O whole blood is the ideal pre- and early in-hospital resuscitation fluid." Whole blood's use has declined dramatically over the decades. But Mark believes it's time for whole blood to make a comeback, and he's about to tell us why. By the way, you should stay tuned at the end because I have an update, since there has been an important change by AABB since Mark and I had this conversation that you're about to hear, which was in late August. So here is my interview with Dr. MarK Yazer on whole blood.

Joe: [00:05:09] Well, hey Mark! Welcome back to the Blood Bank Guy Essentials Podcast, my man!

Mark Yazer: Hey, Joe, it's great to be back! I after I kicked it off for you, you had a whole bunch of other really high quality podcasts to come. But surely you always remember your first, right?

Joe: Well, you know my question for you is, how have you handled all the fame that has come as a result of being the first guest on the Blood Bank Guy Essentials Podcast? How's that been for you?

Mark: I've had to get a really long stick to keep them all away. It's been tough. You know we considered some witness protection, but you know I'm learning to deal with it. So it's not so easy. [Laughs]

Joe: I totally understand! That's fantastic! Well Mark, we spoke last year about the use of whole blood-derived platelets, and just from that conversation and just from the many, many times that I've heard you speak over the years, and our e-mail communications, I know that you a little bit revel in the whole...I don't want to say that you're a contrarian, because I don't think you are, but you like to take a look at things and say, "Why have we always done it this way or why we currently doing it this way? Why don't we consider other stuff?" Is that a fair way to put how you look at kind of established "dogmas" in transfusion medicine?

Mark: Yeah, I think that's part of the fun of transfusion is that now we're finally in a position where we can ask these questions. It was only recently, Joe, that we figured out what red cell transfusion thresholds should be for patients who are getting hip surgeries, sepsis, cardiac surgeries. You'd think that we would have had this sorted out years ago, but transfusion's really undergoing a renaissance of investigation and really good studies. So now is a great time to be asking questions about our practice.

Joe: [00:06:59] I completely agree, and this topic that we're going to talk about today I think really fits into that really nicely. So let's set it up a little bit. I want to take you through a little bit on your feelings on this topic, which is, and I'll just read flat out what you sent me as your basic tenet for this discussion. That is, and I'm quoting you, "Whole blood is the ideal pre- and early in-hospital resuscitation fluid." So we're going to get into those details, but we're primarily talking about this today in terms of trauma resuscitation. I've had quite a number of discussions recently on trauma resuscitation, had a emergency medicine critical care doc on not too long ago talking through the logistics from the trauma side, I've talked about massive transfusion, but I'm curious about how you feel about just how you read the trauma resuscitation literature right now. All the stuff that's out there including, obviously, the PROPPR study that came out not too long ago; How do you feel about where we are and how things are looking?

Mark: Again, a real renaissance of studies and of new knowledge that's been brought to light by these studies. You know, I think one of the most important things that we've learned in the resuscitation literature is just how multi-factorial the coagulopathy of trauma is, and how many patients are subject to it when they first arrive in the helicopter or when they come to the door of the emergency department. Depending on the studies you read, you can find upwards of 40% of patients have some degree of coagulopathy, of derangement of their clotting factors when they hit the door (probably a bad pun in talk about trauma, right?). But in in a very real sense we need to understand quickly who those patients are.

But even with our fastest tests that we can do near a patient or at the point of care, we don't know exactly if this patient is that patient with the coagulopathy or is not. And so I think that what we've learned, and what's really important, is the idea of providing plasma early in the resuscitation. And that's not to say that we need to be providing the same quantity of plasma through the entire resuscitation, or that patients should be resuscitated with a certain recipe or fixed ratio for the entire time. But I think that it would be difficult to dispute the need for early intervention with plasma. And I think whole blood is a great way to provide red cells, platelets, and plasma in one one product.

Joe: OK. Well, I have to ask this because I think it's really important, and I fear...I don't know, this may not be the right way to put it, but since PROPPR came out, I have had people more on the trauma resuscitation side, the clinical side, than on the blood bank side, that have said, "Well that answers the question. It's done. There's no need to study it anymore." And I'm not totally sure that it IS done! I'm not sure that we'll be able to do another big study like that, but I'm sure that that completely answered the questions. This is a little bit of a sidebar, I realize, from what we're talking about today, but can I can I ask for your feeling on that?

Mark: [00:10:19] Well, I tell you what, Joe, had I won that Powerball lottery last week, you know with the three quarters of a billion dollars, I would have funded another version of the PROPPR study and probably called something a bit more fun like something to do with my Montreal Canadiens or Ipswich Town or something more interesting. But what I would have done a little differently is I would have had a fixed ratio arm, so pick your ratio, 1:1:1 plasma:red cell:platelet, 1:1:2, pick your fixed ratio. And then I would have had a different arm which would have been anything other than a fixed ratio, so it would have been surgeons intuition it would have been TEG-guided or other point of care or near patient care tested guided arm, something that ISN'T a fixed ratio so that we can actually ask the question, "What IS the ideal way to resuscitate the patients?" To my mind, the PROPPR study evaluated two very similar ratios, and the primary outcome, not surprisingly, was not significantly different between the two. And there were some differences in secondary outcomes: There was less death from bleeding in the higher ratio, and some other secondary outcomes were more favorable in the high ratio group, but those are secondary outcomes. Those generate hypotheses, that don't prove them. So, to my mind I don't think PROPPR has answered the question of, “What is the ideal way of resuscitating patients?” I think it might have asked or at least solved the question of, “If you want to do a ratio, what is the ratio you should use?" But I'm not a believer that the ratio should be started on every patient from the moment they walk in till the minute the bleeding stops. I think a ratio is a good way to think about transfusing blood products to patients early in the resuscitation, because they're going to need platelets, they're going to need plasma, but then we need to get some testing. We need to understand what's wrong with the patient, where is their

defect, and then begin to provide personalized medicine by correcting the defect that the testing tells us that they have.

Joe: [00:12:22] Got it. OK. Well so as we get into our topic for today, which is again. I'll just say what you said, "Whole blood is the ideal pre- and early in-hospital resuscitation fluid," I think that since so many people that are listening to my podcast are learners (I mean we're all learners right?), but people that are early in their careers in the field, as well as people that aren't necessarily totally fluent in blood bank terminology, so let's just talk the basics. You can walk into most transfusion services in the United States, certainly not all, but you can walk into most and you'll see red cells, you'll see platelets, you'll see various forms of frozen plasma; in most places you won't see something that's labeled "whole blood." So what do we mean when we talk about whole blood? Are there different varieties? What's the deal?

Mark: You know, it is what the name says it is. It's everything that comes out of the donor's arm, plus a little bit of anticoagulant and preservative solution. So it's basically what the red cells, platelets, and plasma was before it got manufactured into the red cells, platelets, plasma. So, it comes out of the donor's arm, it comes out in a physiologic concentration. And we put it into a little bit of CPD [NOTE: Citrate Phosphate Dextrose] solution, although it can be put into other things, and we store it for up to 21 days (in CPD of course).

Joe: OK. And are there different versions of whole blood in how long they're stored and how quickly they're used?

Mark: Sure. You know, I think people who've seen recent and historical war movies might be familiar with the idea of what's called a "buddy transfusion." So this is, you know, a very far forward mission, where medevac is going to be hours away. And so the medics, in fact the Rangers will carry with them a transfusion kit, so if someone unfortunately gets injured or needs a transfusion, they'll draw a unit of blood from somebody who isn't injured who is ABO compatible, and they'll give the transfusion right away. So that blood is warm; it's almost as close as you can get to a vein-to-vein transfusion. It's warm, it's fresh. It hasn't been stored for any more than minutes before it gets infused into the injured soldier. And that's whole blood, that's warm fresh whole blood. Now, it's not tested before it's transfused (the soldiers undergo testing before they're deployed). And so, the FDA won't allow us to go to that length in the civilian world, but they will allow us to transfuse whole blood that's been tested and shown to be free from all the usual parasites and viruses, and we store this in the refrigerator. And if it's stored in CPD then it's good for up to 21 days, it does not have to be agitated. And it's never-frozen plasma too, so it hasn't undergone a freeze-thaw cycle.

Joe: OK. So one last question, in terms of, you mentioned some of the regulatory stuff, one last question before we start hitting the advantages that you see for whole blood: Are we limited at all in terms of perhaps standards from AABB or other regulatory organizations in terms of who we can give or how we assess compatibility for whole blood products?

Mark: [00:15:52] Well, Joe, as a matter of fact we are. The current version of the AABB Standards require whole blood to be given in an ABO-identical manner. So it means that a group A recipient has to get a group A unit of whole blood. In that case, obviously, the red cells and the plasma would be fully compatible with that recipient. Technically, you're not supposed to give, let's say, a group O whole blood unit to anybody who isn't group O, because the standards don't permit the transfusion of minor-incompatible plasma (that means plasma that could have some anti-A or anti-B in it that will bind to the recipient's red cells and potentially cause some hemolysis). Of course, we do that anyway with platelets and with some group A plasma that might or might not be low titer, but at the moment the whole blood is meant to be given in an ABO-identical manner. Phil Spinella and I, on behalf of the AAAB and THOR Working Party, are working with the AABB to try and get them to change the standard. We've submitted some comments on the 31st edition of the Standards, and we'll see what happens. We'd like to be able to use low-titer, cold-stored group O whole blood in an uncrossmatched way without worrying about the recipient's ABO group so that we can give it to them early when they're still in the field, or when they first come into the hospital.

Joe: And that gets us to what we're going to talk about today! So, you have been involved in several papers that discuss the use of whole blood in this setting for hemostatic resuscitation of major bleeding, for example, a paper that you did with Phil Spinella in Transfusion in April of 2016, and a more recent one that was in Transfusion Medicine, I believe, also right? In 2016 also?

Mark: That's right.

Joe: [00:17:48] OK, so everyone, I will put the references for both of those papers on the show page, and I would highly recommend that you take a look. But Mark, let's talk first about your first perceived advantage for the use of whole blood or if it is the "perfect" or the "ideal" pre- and early hospital resuscitation fluid, ***advantage number one you mentioned is the long history that we have of doing this***. You kind of alluded to that a little bit ago but why don't you take us through a little bit; where have we been with whole blood?

Mark: Well, whole blood's been with us through almost every battle that we fought in the 20th century. You know, if you think about if you go back to the earliest transfusions, Jean-Baptiste Denis was transfusing whole blood from sheep into people, because the calm spirit of the sheep is going to harm the wild

crazy person down, it's going to get rid of the fever, and nothing could go wrong, right? What could go wrong? When you give a sheep blood to...I mean, we eat sheep, right? So why can't we have a transfusion with their blood?

Both: [Laughing]

Mark: Logical, and it makes a lot of sense...except it doesn't, of course! That was a whole blood transfusion, if you want to go back that far, but if you sort of come to the more modern reasonable approach to whole blood, one of the first blood transfusions was during the Great War where 20 soldiers were transfused with it. And 9 of them survived and that's great news! Whether it was because of the whole blood or the penicillin they were getting, it's unclear but at least at least it provided some very positive momentum, which the U.S. Army built upon greatly during the Vietnam and Korea wars. They were transfusing literally hundreds of thousands of units of low-titer whole blood to their soldiers. And let's face it, it's easier right? It's easy to get a unit of whole blood and just keep it, rather than have to have a centrifuge and spin it and worry about how you're going to get press the plasma off. They were being very pragmatic, and they were using whole blood and transfusing it in enormous quantities with really only a few reports of hemolytic events. One very famous hemolytic event occurred because I think it was a group O recipient got a group A unit of whole blood. So that was a clerical error, right? That should never have happened, and the person hemolyzed. But that's not an intrinsic property of whole blood, that was just basically a screw-up. So can I say that on the...

Joe: You can! You can say "screw up." Absolutely! You can say it four times if you want. That's fine.

Mark: Alright, I'll come back to it then! This is the internet after all.

Joe: Absolutely. Let me interrupt you for just one second because you used a term there that I want to make sure that that the learners listening to this podcast understand. You said specifically "*low-titer* group O whole blood." So again sidebar real quickly for us, what do you mean when you say “low-titer?”

Mark: Right. Thanks Joe. So the problem with whole blood, or well the main drawback to using whole blood is that group O whole blood, which is the group of whole blood that we're going to use when we don't know what the recipient type is, because we can give group O red cells to anybody, it's the universal red cell donor, and the same is kind of true for whole blood. So, a group O whole blood, the red cell part of it will be compatible with everybody. No one has antibodies against group O (well, except the Bombay people). So, group O is the universal donor. The problem with group O whole blood is that it's got some anti-A and anti-B in the plasma part. And so, if you're not group O, if you're group A, B, or

AB, then necessarily, you're going to be getting some incompatible plasma with that group O whole blood. And so by "low-titer," what I mean is that we check the unit, and we make sure that the titer or the concentration or the level of anti-A or anti-B is low. And you want to know what "low" means and I want to know what it means, too!

Joe: Yes.

Mark: There is no standard definition of "low-titer." Just to give a spoiler here, in Pittsburgh we use a titer of less than 50. So, the titer of anti-A and anti-B, the concentration is less than 50. But I know at other civilian hospitals, they use titers of less than 200. And I think that's perfectly fair, I think anything less than 200 should count as a low-titer, and the risk of hemolysis is going to be very low. The way you would pick the titer would depend on your population. We use 50 and we end up excluding about 20% of our donors based on that. I think if you use a higher titer, you would exclude fewer donors. And we can live with excluding 20%, that's fine for us.

Joe: And you mentioned that in the wars in U.S. military experience, that there were hundreds of thousands of those units that were used. Did the military, and I actually I don't know the answer to this question, even though I was IN the military, did they use a standard that was different from anyone else? Or do we know what titer they defined as "low-titer?"

Mark: Yes, I think they used less than 256 as a titer.

Joe: So, much higher than what you're currently using.

Mark: Yes, it's five times higher than what we're using in Pittsburgh. And I think that, like I say, anything that's a reasonable titer, 256, 200, I think less than all of that is perfectly fine.

Joe: OK. So we've talked...

Mark: And you know what, Joe? We're going to find out. Right? I mean if it turns out that 256 really is a bit too high, then fine, we'll dial it back. I think that's part of the learning process that we're going to get with whole blood in this very controlled and very academic experience that we're going to get with it.

Joe: I mentioned that I was in the military, and I will tell you that, before we finished the history part, and I know you know this, let's make sure that our audience does: The use of whole blood did not stop in the military with the end of the wars! We've certainly seen a resurgence in Iraq and Afghanistan. What's your perspective on that?

Mark: Yes indeed there's been...it hasn't stopped. And, again it's been a very pragmatic approach, right? It's difficult to store stuff that's frozen, because it takes a freezer, which takes constant electricity, and it takes a lot of power. And so if you have a walking blood bank, if you have blood stored in the donor until you need it, that's great. Again, it's a very pragmatic approach to providing lifesaving therapy. In the civilian world, it's a little different, because we're expected to have ongoing power, we're expected to be able to test our units before we transfuse them. And so, we're held to a different standard, because we're not in as austere an environment as they are overseas.

Joe: OK. So we've we've established clearly that there's a really long and strong history of using whole blood. Are you ready to move on to your second advantage or is there anything else you wanted to to bring up about historical stuff, Mark?

Mark: No, I think that's great. I think we have a long history of it, and I think that bodes well for us using this going forward.

Joe: [00:25:10] OK so ***your second perceived advantage of whole blood as this ideal resuscitation fluid is that it simplifies the logistics of the resuscitation***. What do you mean by that?

Mark: I'd like to question you on the word "perceived" [Laughs]

Joe: [Laughs] Hey, I'm trying to be open-minded here, buddy. Give me a break! OK. Well at least I wasn't meant to be pejorative. I apologize.

Mark: You know, you talked earlier about the trauma surgeon you had on, and they were talking about the logistics of the resuscitation, right? And I think you know for the trainees who haven't seen a trauma patient or haven't seen a massively bleeding patient getting blood products, if you get a chance to go to the emergency and see it, it's scary! It's scary to see all those people running in and out, all those fluids that are being hung. I think anything that we in the transfusion community can do to help make that easier is going to be a big benefit to our clinical colleagues. And I know that giving them one bag instead of three bags is an advantage. You know, platelets cannot be run through a rapid infuser. There's this idea that platelets get activated, they become less useful if you put them through a rapid infuser, which is a device that can transfuse liters and liters of blood very quickly. And so what you have is red cells and plasma going into the rapid infuser, that's being infused in one line, and then the platelets are going in a different line. And that's in the trauma bay, right? I mean, imagine when you get in the field and you're in the helicopter, and the helicopter's got monitors and beds and people and intubation equipment; do you have room for

three bags? I guess you do. But wouldn't it be better if you could have only one bag and transfuse that one bag which is the same size as a red cell unit that we know how to transport and we know how to store. And the patients will get the plasma up front, which is what many of them need earlier in their resuscitation. So I think this is the biggest advantage that we know of at the moment of whole blood is that is that it makes the trauma surgeons' lives so much easier.

Joe: Do we have any data, Mark...let's put the rubber to the road here, do we have any data to suggest that doing it this way gets people that "balanced resuscitation" more rapidly than doing it with individual products, the so-called "1:1:1?"

Mark: This is an evolving literature. The use of whole blood in the civilian setting, it's really new, right? It really is a new thing. There's some centers in USA doing it, Norway's doing it. So this is kind of the Achilles heel in my argument about the greatness of whole blood is the outcomes data which you've just exploded right up front.

Joe: Sorry!

Mark: But it's true, we don't have a lot of information to say that, yes, resuscitation with whole blood is better, but it's coming. And I can tell you that some preliminary data that we have from our pediatric hospital in Pittsburgh where we're doing whole blood for injured pediatric patients, we showed very statistically significant reduction in the amount of time it takes to get one unit of plasma, platelets, and red cells when the patient is getting whole blood compared to one and getting component therapy. It was often HUNDREDS of minutes faster to give the patient everything in the whole blood than for somebody to think, "OK, well, we're going to give the platelets, we're going to give the plasma, now we're going to give some red cells," because all of that's in the emergency fridge. You've got to think about ordering the platelets. You've got to actually order the platelets if you're not ordering an MTP (massive transfusion protocol). and then you've got to give it. And so up front early on when the patient is coagulopathic and needs these products, they all get in faster with whole blood than with components.

Joe: [00:29:03] Got it. And that's really...I wasn't trying to explode your outcomes data YET, Mark [Laughs], I was more getting to what you were saying, you've shown at least preliminarily that you get that whole blood in faster than than perhaps you might if you're trying to just kind of pick and choose the others and get them all in. So I hear totally what you're saying. We'll come to the outcome stuff. and then we'll have a big fight (I'm kidding, we won't have a big fight). But, let's talk about something that I think is really important. I won't even say that this is a "perceived" advantage, Mark. I think ***this IS a clear advantage, that whole***

blood is more concentrated than components. And this goes to something that is a pet peeve for me, when I hear people talk about the 1:1:1 as "replicating whole blood," it makes me want to scream, because clearly, in my view, it's NOT the same. So I will open up the soap box and allow you to have that discussion.

Mark: Well, you're right, Joe. It's not quite the same. You know when you think of it, we collect the whole blood into 63 mL of CPD solution, and then if it's going to be an "additive red cell," we add 100 mL of additive solution to each red cell. And so by the time you've gotten 5, 6 red cells, you've gotten half a liter of fluid that doesn't transport oxygen, that doesn't get blood to clot. It doesn't do anything other than keep the red cells in a liquid state. So that's basically useless fluid, right?

Joe: Yeah.

Mark: We know that saline is not a good thing to be using in big quantities during a trauma resuscitation. The surgeons want stuff that's yellow, right? "Yellow gold." That's what they want. If it's clear, they don't want too much of that going in. And so, by the time a patient has had, even let's say a traditionally defined "massive transfusion" of 10 units of red cells, that's a liter right there of useless fluid that didn't need to be transfused in the first place. because it's not helping the patient. It's helping the red cells. So the more that we reconstitute whole blood, that is putting a red cell, a platelet, and a plasma back together again, the more that we're compounding the problem of the additive solution and the saline and that's in all of these products that doesn't benefit the patient. So, it's true that you do get an equivalent of a red cell, plasma, or platelet if you reconstitute it. But, if you're using whole blood, you only get a little bit of dilution, because we only have to use 63 or so mL of CPD to dilute it.

Joe: Got it. OK.

Mark: So it's a more concentrated product, comes in one bag, it's easy to transfuse.

Joe: OK.

Mark: I feel like a salesman! I feel like a salesman, like I ought to be getting some royalties every time a unit of whole blood...but that's not what's happening.

Joe: Well, we've got to work on that clearly, Mark! [Laughs] And forgive me, I'm not trying to put you in that kind of a position. I think it's really important to hear this, because so many people have not ever practiced in an environment where whole blood is even on the table necessarily. And realistically, I mean you and I have both been doing this for a while, and I can't say that there have been many

places in my practice outside of the military where whole blood has been something that has been considered. You on the other hand are in a different environment than I am, but I think a lot of people listening to this are going to be going, "wait, whole blood? We can do that?". So it's I think it's really important for you to be the salesman, Mark! We need to hear about this!

Mark: Well then I'll say we can and we should be doing whole blood. I'll tell you a quick story, Joe. I was in London, England, and I wanted to give a presentation at one of the hospitals in London. So I called up a friend I said, "you know, I'm going to be in town. Do you have a forum for me to give rounds?" And she said, "Yeah, sure. Absolutely! What would you like to talk about?" I said, "Well, you know I've got this whole blood..." and just even as the last syllable of "blood" was coming out, She was saying, "Oh, no, no, no! We don't want to hear that, and we're never going to have whole blood in England. It's not on. Next! Move along!" Anyhow, I managed to persuade her to let me give the talk and would you believe, six months later, they were calling me back to ask how to implement whole blood in their helicopters!

Joe: That's awesome!

Mark: Yeah. I felt really good about that.

Joe: [00:33:37] Well, you should. I like it! So, Mark, let's move on and let's do whole blood ***advantage number four***. I love this one because I think it's really important. It brings in discussions that I've had elsewhere into this topic and it's super-important. There is a belief out there and we in the blood bank have kind of fostered this. I think, that when platelets get cold, by God, they don't work anymore. Your premise though is that ***cold-stored platelets might be great***. What do you mean?

Mark: Well that's right. Joe. I remember, and it wasn't that long ago telling residents, "If you put platelets in the refrigerator or the cooler, you've just killed the platelets and you wasted them and the hospital's going to have to pay for that, blah, blah, blah." And while that is the way that the standards are currently written, there is AMPLE in-vitro (so experimental evidence that doesn't involve people) to demonstrate that cold platelets are actually BETTER than the traditional warm-stored platelets. So, when the FDA was deciding how to store platelets, they looked at the recipients, "who's getting the platelets?" And it turns out that the hematology-oncology patients are the ones who are getting the majority of the platelets. So, the decision was made to store platelets in a way that would provide the longest lasting hemostasis, which means to transfuse them or to just store them at room temperature. And so people derive this idea that cold platelets, they change their shape, they become nonfunctional almost instantly. But the truth is, that's NOT true. Cold-stored platelets change the

sugars on their surface receptors, and it exposes some new antigens, and those antigens are very attractive to the macrophages. So when the cold platelets are circulating, they get plucked out very quickly in the matter of a couple of hours after the transfusion. But these in-vitro tests are showing that they're extremely functional. In every in-vitro test that we've done, they've performed better than warm-stored platelets. Now whether that translates into "in-vivo" (like in the person) better activity, that remains to be seen. But at least we have a very solid scientific background to try using cold-stored platelets in patients who don't need five days worth of hemostasis, who just need five *hours* of hemostasis, like the trauma patients.

Joe: Yeah. I think that's an important point. It's not necessarily looking at...whether you're talking cold-stored platelets as a product or cold-stored as part of whole blood, we're not looking at something for long term keeping the count up for long periods of time. We're looking for potentially getting something in there that's going to have an effect *right now* as opposed to down the line.

Mark: That's right. These platelets, if they're cold-stored, in a matter of hours, the surface changes and they're going to be plucked out quickly. BUT they don't go instantly. They circulate, and they can plug holes perhaps even better than warm-stored platelets. That remains to be seen. But, like I say, in-vitro there's some evidence, and there were actually a couple of studies looking at bleeding times in patients who received warm-stored and cold-stored platelets. Cold platelets did better. And there was a study of patients who were cardiac surgery patients who were getting their pump primed with cold-stored platelets. And there appeared to be some benefit to them as well in those in that population. So like I say, we have a very solid basis for thinking that these cold-stored platelets could be excellent for trauma patients. Wouldn't use it in a hematology patient, but certainly in trauma.

Joe: And so I think it's important for those of you that are listening, and those of you that are on the clinical side, before you go calling your blood bank for, you know, refrigerated platelets or before you just start on your own deciding to throw them into a cooler, the standards still do suggest that the storage needs to be 20 to 24C. There are places that have gotten variances, but that's just for study and it's just for immediate resuscitation. Am I summarizing that correctly, Mark?

Mark: That's right. The variance says you can use an apheresis platelet for up to three days unagitated in the fridge. But you can only use it for massive bleeding patients, you can't use it for anyone else.

Joe: Got it. And that variance is not just, "everybody can do it now." People have to apply for that variance, correct?

Mark: Yeah, that's how it works. The variance applies only for those who want it, who've applied for it. But again, you know, if they're making an exception, then that suggests that there's leeway in the way the standards could be written in the future to allow us to do this.

Joe: Got it. One last question on that, and I think this is again important for learners who are who are used to the concept of, to keep platelet function we need to have those platelets on and on an agitator we have to we have to rock them we have to rotate them. Is there is there anything that either in-vitro data or otherwise on whether or not it's necessary to to rock the whole blood?

Mark: You know, it's interesting you say that, because we have that thought, too. When we're storing our whole blood, we thought, "You know, we're using the whole blood in part because of these platelets. We think they could be really functional. Normally, we would rock the platelets. Should we rock the whole blood?" So we did that, and we showed that between day 4 and day 10, there's no difference in platelet function when you analyze it with the thromboelastogram between the unrocked, that is, the whole blood that just sits there, and blood that's rocked (the whole blood that's rocked in three different ways). It did not increase the hemolysis, which was good. So, if you want to rock your whole blood, you can do that, but you don't have to, because it didn't change the thromboelastogram finding.

Joe: Got it. Got it. OK.

Mark: And anyway, let's face it, refrigerators with a three-prong plug on the inside so you can put on an agitator in are super expensive! So, this was very welcome news to everybody except people who make refrigerators!

Joe: [00:39:48] Yeah, they're not happy, but everybody else is good with that! OK. All right, so we've got to get to this one and this is this is ***number five***, Mark, and it is kind of the elephant in the room in many ways, where people are concerned about giving group O as "universal" resuscitation with whole blood because of the concern about hemolysis. So ***your contention is that, and I'm quoting you, "Nobody hemolyzes!"*** How can you support that, Mark? What can you say about that?

Mark: Ha ha! Well, well, well! We changed our practice in Pittsburgh two and a half years ago to use whole blood as the primary resuscitation fluid in trauma patients. And part of that change of practice was that the clinicians would have to draw biochemical markers of hemolysis, LDH, bilirubin, haptoglobin on the day the patient gets the whole blood, and then every day for two days afterwards. And what we wanted to do was we wanted to look at the group O recipients who were not going to hemolyze from the group O blood versus everyone else, so the

A, B, and AB recipients who had potential for hemolysis because group O whole blood has anti-A and anti-B in it. And so when we looked at the differences in these biochemical markers of hemolysis, we found NO DIFFERENCE between the O recipients and everybody else. And that's not to say that all the values were always in the "normal" range. We measure LDH, but we don't specify, "Is this the LDH from red cells or from tissue?" So you can imagine, in a trauma patient, LDH is going to be through the roof. But it wasn't through the CHIMNEY in the non-O recipients, you know what I mean? So, it wasn't higher in the non-O recipients. In fact, it was statistically identical. And we've expanded this, well, we've done this in our 200 patients who we've treated with whole blood, and we're not seeing any differences, any marked differences. Are there small episodes of hemolysis that could be happening that aren't causing any clinical harm? Possibly, but it's nothing that we're detecting with our tests. And I can tell you as kind of a sidebar, you've taken some sidebars, Joe, I'm taking a sidebar now...

Joe: OK. bring it on!

Mark: With Nancy Dunbar and the BEST collaborative, we did the "STAT study," where we retrospectively looked at again trauma patients who are getting group A plasma [NOTE: See BBGuy.org/036 for more on the STAT study]. You know, because no one has enough AB plasma anymore, and so we're starting to use group A plasma in place of AB for trauma patients. And so, with Nancy, we looked at group A recipients of A plasma (so, identical), and then B and AB recipients who were getting plasma that was not compatible. And we looked at early mortality, hospital mortality, length of stay; and we found again no significant difference, not even close, in the patients who got the compatible plasma versus the incompatible plasma. And so, that's a very similar parallel to our whole blood because the B and AB patients in the STAT study were getting 4 units, an average of 3 units of A plasma. and we're in Pittsburgh now using 4 units of whole blood, which is about the same amount of anybody. And in the STAT study, I think it was 72% of the participants did not titer the anti-B in their plasma. So, you know, if ever there was going to be a bad outcome, it would have been here, and we didn't see it. So that tells us that our low-titer whole blood is very safe.

Joe: Well your sidebar works right into my marketing strategy, considering that I had Nancy and Tait Stevens (who was lead author on a similar article published in early August of 2017) talking about talking about STAT and talking about Tait's study as well with Group A. So BBGuy.org/036. You just worked right into there, Mark. That was fantastic!

Mark: Check is in the mail.

Joe: Yes, all right! So if you would, before we get off of this topic; one more time, could you just summarize the characteristics of the products that you're using for

your adult trauma patients in Pittsburgh, including blood type, how you're modifying it, what the criteria you are using to look at it?

Mark: [00:44:07] Super question, Joe. So, for the adults, we use Group O, Rh positive male donors. And we use male donors to mitigate the risk of TRALI, because that's a low risk product if it comes from a male, because we can't get pregnant, and we use Rh positive because we have selected to use this product only in male trauma patients and in female trauma patients who we can identify are over age 50. And that constitutes the vast majority of our trauma patients. We would be expiring a lot of O negative whole blood if we included younger women. So it's O, it's Rh positive, it's male donor. We use an in-line leukoreduction filter that spares the platelets, and so the product is leukoreduced as well. We keep it for 14 days as whole blood, and on day 15, we take it back if we haven't used it, and we spin off the red cell and we transfuse it as an O positive red cell. It helps us to recover a bit of the cost, and we waste almost none of these units because they're O pos, really anybody can get those. And we use a low-titer, less than 50 for both anti-A and anti-B. And for the reference lab people, that's an immediate spin titer with no enhancements and it's just done in saline. There's a little bit of a difference for the pediatric patients who get our whole blood. We use O negative red cells, because there's not a lot of pediatric trauma, and we want to be able to include the girls and so we use O negative whole blood. But we use the same titer of less than 50 and all the other characteristics are the same.

Joe: Got it. One question about the titers, Mark: Do you consider people "once titered, always titered," or do you have to do it every time?

Mark: You know, another good question, Joe. We actually have some data from my colleagues in Denmark. We looked at 56 blood donors and lab volunteers. And what was cool about this study was that from these 56 people, we did a titer on them, an ABO titer quarterly. So we did four titers on them over the course of a year. And they can live their life, right? They can get vaccines, they could have babies, they could do whatever they wanted. They just had to come and have the titer taken every three months. And we showed there was no difference. There was at most like a 1 titer difference between the different titer levels that we did. So that data would support not not having to titer every donor every time, but in Pittsburgh, we do titer every donation every time, and we make sure that they're always low titer, less than 50.

Joe: I'm guessing that you're going to include that data in a report at some point to see whether those donors change.

Mark: I wish we could. There's some technical issues why we can't quite do that, but that would be great. However, to make up for that, again, Nancy Dunbar has another study going with BEST called the "TIPSY study" [NOTE: See http://

bestcollaborative.org/index.php/about-best/best-studies/submission-view/311.html for details] where we're looking at how many how many units of platelets, plasma, or whole blood failed whatever the threshold was. And we're looking to see, is there a variation over the course of the year? So, we're going to be analyzing failures by time of year to see if there's any seasonal variation, like if after the flu shot, everyone's ABO titer goes up or not. And I can tell you having having done almost two years of looking at my whole blood, there doesn't appear to be any sort of periodicity of changing, but that's that sort of a broad population. We want to make sure that every unit is low-titer.

Joe: [00:47:53] So we need to get to ***your last advantage*** and I think this is really, really important, because people are of course going to ask this question. And we've danced around it a little bit, but now I'm gonna pin you to the wall, Mark! ***What do we know about outcomes***? What have you studied so far, what has been studied so far that can give us an idea of whether whole blood does better, worse, or the same?

Mark: You know, so far, what we're getting is that patients don't do worse when they get the whole blood. We published about a dozen different outcome parameters between our control group of male patients who had at least one uncrossmatched red cell in trauma compared to about 50 whole blood patients, and we showed there was no significant difference in any of the length of stay or mortality parameters. And we showed the same thing in our 18 pediatric patients who were treated with whole blood compared to a historical cohort. There was no difference in any of the outcomes. And frankly, that's what we would expect, because we're giving a fairly low dose of whole blood. We're giving now 4 units of whole blood, which really if you think about it, is the equivalent of one adult dose of platelets. It's one dose. So, back in the day when we were giving one and two units of whole blood, you wouldn't really expect to see much of a difference in 24 hour blood product use or hemostasis, because we weren't giving a lot of platelets. Now we're giving 4 units. I have a feeling we'll be moving up to 6 units shortly, because that's what our surgeons want. And I think that's still a reasonable amount to give before we start giving personalized approach to the resuscitation. So now I think when we're giving larger quantities we're going to be able to see if these cold platelets are really “hot stuff”...Hehe.

Joe: [Laughs] You couldn't resist could you? You could not help it!

Mark: I could not, I was waiting all 45 minutes to get to that!

Joe: Fantastic!

Mark: You know, we're going to see. I think now is the time. I think we've shown the safety, which is what we were trying to do initially with 1 and 2 units, was

show, "Can we do it? Yes, we can. Are they going to hemolyze? No, they're not." Now it's the time where we're going to be able to say, "Well, is there any efficacy change here?" And I think now we're going to we're going to be able to see that. And like I say, even in our pediatric population where we give it, by the way to kids who are over 3 years old and more than 15 Kg, so that their ABO expression is a little bit more advanced, and so they can absorb any of the incompatible anybody, we're not seeing any hemolysis. And their outcomes, length of stay, ventilator days, that kind of thing, was not significantly different. But again, we don't have a lot more evidence. Frankly, when when we saw the results of the STAT study, we were overjoyed, because it once again confirmed the safety of the product. But now we need to show efficacy. And frankly I'll tell you this (here comes the salesman again): Is that even if patients don't do better, even if the patients just do as well as the others, if we're making the surgeons' lives easier and the the air ambulance and the helicopter people's lives easier by simplifying their logistics, that's a win. You know, that's worth something, to be able to make their lives easier. And if whole blood does, then I think that justifies using it.

Joe: [00:51:16] OK Mark, so I think that it's important for people listening to understand that in your circumstance in Pittsburgh you guys have a wonderful setup for doing this. You're the blood center, you're the transfusion service in a lot of the hospitals that you serve. In other cases there may be some more logistics that might be involved and it may not be just as simple as a surgeon calling the blood bank and saying, "Give me some whole blood." There's some steps that might have to be taken. So, can you just kind of give us a general idea of things that places that want to consider this might have to think of?

Mark: You know, I think the main limitation will be the supply of the whole blood. If the blood center doesn't provide whole blood...don't forget they COLLECT whole blood, so it's not like the blood doesn't HAVE it! They just turn it into components. I think it's going to be a matter of convincing the blood center of the advantages of using whole blood and of being able to create a business model for why they should start selling it to your hospital. I think that that's going to be the main limiting step is getting the blood center to see the benefits of it and to have a stable and adequate supply of it to keep your program going right.

Joe: Yeah and speaking as someone who currently is medical directing a blood center I think that's correct. I mean, you said it: It's not like we don't make whole blood, we have whole blood. We have whole blood all over the place, it's just that it usually goes on to something else, primarily because of what's been the way transfusion medicine has been practiced in the United States since the 60s and 70s, that component therapy has been considered the standard of care. Let's break the product down and give the patient just what they need. But I think what you what you've made a case for today is that there are certain situations where that is not necessarily the best answer and there are easier ways to do it. And so

you know again I think that's I think it's important to understand that there are logistical things that have to happen but they're not insurmountable logistical things.

Mark: No, by no means. You know, performing an antibody titer is a straightforward thing. The blood center would have to develop a policy for doing it and train people. But none of this is insurmountable. And I think when and if we show that this really does benefit our trauma patients, the blood centers will have to do it, because it'll become the de facto standard of care at that point. And they'll just have to make the policies and do it. Until then, it will require some delicate conversations with blood centers that are more reluctant to get involved in selling it.

Joe: Got it. Got it. Well Mark, I look forward to the data that I know you will be involved in collecting and seeing further evidence going forward. I think you've made a great case for places to consider the use of whole blood. Anything you want to leave us with before we go?

Mark: You know, I think that the other things that a transfusion service starting up a whole program would want to consider would be just just the very basic things, like how long are you going to keep the whole blood in a liquid, as whole blood? Are going to allow it to be used for all 21 days? Do you think the platelets are functional up to 21 days? How many units? Is there going to be a maximum number of units that will allow the surgeons to give to their patients? What patients are you going to let this be used in? Anyone who is having a massive bleed? Are you going to include it in your massive transfusion protocol for trauma? For G.I. bleeding? For obstetrics? For anybody? We just use it for trauma at the moment. A limit of four units for now. And other logistical questions, like where are you going to put it? Are you going to put the whole blood in the emergency room refrigerator like we do (we have four units), or are you going to keep it in the blood bank and the surgeons have to order it and you'll have to figure out how to get it down to the E.R. or to the O.R. quickly? So I think there's a lot of stuff to think about but as you said before none of this is insurmountable. It just takes a plan.

Joe: Yes absolutely. Absolutely. Well Mark, my friend this has been a blast! I'm sorry that you're going to have to bump up your protection after being on the podcast again, but you know that's that's life, buddy!

Mark: I'll get two sticks. Simple as that.

Joe: Thanks so much, Mark!

Mark: Cheers, Joe!

Joe: [00:55:51] Hey guys, this Joe with just a couple of closing thoughts. I love talking to Mark! He's a blast, and I love his take on things. I did promise at the beginning that we have an update on what we talked about. We had kind of danced around the fact that standard 5.15.1 in the current 30th edition of AABB Standards requires whole blood to be administered as an ABO-identical product and Mark had mentioned that they were looking to try and see if that could be adjusted and as it turns out the 31st edition of Standards that will be published online in January 2018 and will become effective in April of 2018 has changed all that. The way the new standard reads is that "recipients shall receive ABO group-compatible red cell components, ABO group-specific whole blood, or low titer group O whole blood for non-group O or for recipients whose ABO group is unknown." It basically allows low-titer group O whole blood to be administered in the same way that group O uncrossmatched red cells are administered. People have to develop their own local policies for how you define low titer, how many units people can get and all that. But that's important and all that is very important, but what this allows is a potential change to the way Mark is describing things. Now the reality is, as a blood supplier, I will tell you that most blood suppliers are not really thinking about supplying whole blood, so it requires some conversations with your blood supplier. It's not like we don't make whole blood. We collect whole blood all the time, it's just that whole blood is generally processed, and so the individual collection centers will have to make decisions on how exactly to do this should trauma centers in particular want to move down this pathway. But it's exciting, it's some interesting information, and it's something I present for your benefit.

So just a reminder: Go to BBGuy.org/040. You get a transcript of this episode and the link to get either P.A.C.E. contact hours or continuing medical education credits. Again, that is completely free, up to one hour per month. My thanks to Mark Yazer for appearing on the podcast. Thanks to each of you for listening and for your feedback. As I've said before, please interact with me through the comment page on BBGuy.org/040. I will absolutely see every one of the comments that are made, and I interact quite often with people in that way you can also find me on Facebook and on Twitter @bloodbankguy. I'm more than happy to interact with you that way as well.

So that is all for today. Thank you again. And as we close, I want to remind you one more time that I hope that as you go through your day, you'll smile, and have fun, and above all, never, EVER stop learning! Thanks a lot. We'll get to next time on the podcast.