BBGuy Essentials 091:
Wholly Whole Blood, the Sequel! with Mark Yazer
Released June 2, 2021

Mark: Hi! It's Mark Yazer from the Universities of Pittsburgh, Southern Denmark, and Tel Aviv, and because whole blood is essential in trauma resuscitation, this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, everyone. Welcome or welcome back to Blood Bank Guy Essentials. This is a podcast where we just have one goal: To try and help you learn the essentials of transfusion medicine. This is episode 091, and my name is Joe Chaffin. I have an interview today, honestly, that is just with one of my favorite people on the planet. The good Dr. Mark Yazer is back on the podcast to discuss whole blood for trauma one more time.

I'm going to tell you more about that in just a second, but first you should know that this particular episode is not a continuing education episode. You can find just a boatload of other episodes where you can get that free continuing education at BBGuy.org/podcast. And the episodes that are eligible for continuing education are labeled with the letters "CE." You can also find them at wileyhealthlearning.com/transfusion news, as well as on any podcast outlet. The continuing education episodes are brought to you courtesy of transfusionnews.com and Transfusion News, by the way, is brought to you by Bio-Rad, who has no editorial input into this podcast.

So back in 2017, Mark Yazer appeared on this podcast, and he was here to discuss the, what was at that time, really exploding interest in Low-titer group O Whole Blood or "LTOWB," for massive transfusions and especially in trauma settings. And you should check out that episode. It's BBGuy.org/040, if you'd like to hear that one first.

Since that time, Mark has continued to be a huge advocate for the use of Low-titer Group O Whole Blood, both in Pittsburgh as well as just internationally through his work with the THOR-AABB Working Group. But since that time of our previous interview, there's been a whole lot more data and a whole lot more experience that are both available now to help guide us in terms of what the best use for Low-titer Group O Whole Blood is, or even whether it should be used in trauma settings. So Mark is here to talk about all that. He's here to update you on everything that's going on.

I should also tell you that this interview was recorded for the California Blood Bank Society Annual Meeting, which was May 21 and 22. I am extremely grateful to CBBS, especially to Elizabeth Cardwell, who's the executive director, Dr. James Burner, who was the president at the time, and Dr. Suchi Pandey, who is the incoming CBBS president, for allowing me to use this recording for an episode of my podcast as well.

By the way, there is one other cool thing about this as a result of being part of that CBBS Annual Meeting, there's a video version of this, just like the last episode,

episode 090. You can go to BBGuy.org/091, and you can watch Mark and I have this conversation, if you'd like to do that. You can also find it on my YouTube channel at youtube.com/bloodbankguy.

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Let me tell you a little bit about Mark. Mark graduated from medical school at the University of Ottawa and did his residency in hematological pathology at the University of Alberta. And Mark is currently a professor of pathology at the University of Pittsburgh, as well as an associate medical director of the centralized transfusion service in Pittsburgh. He's all over the place though! He's an adjunct professor of clinical immunology at the University of Southern Denmark and a visiting professor of pathology at Tel Aviv University. He's published a bazillion, okay, over 250 peer- reviewed papers. And he's an associate editor of both Transfusion Medicine and Hematology journals. He's on the editorial board of multiple other journals. Mark, let's just say this: Mark knows what he's doing, okay? Mark has got a lot going on.

Normally I don't talk a whole heck of a lot about my personal relationships with people that I interview on the podcast, but there is something that I want to share with you about Mark that just lets you know a little bit about him. And since we have a little bit of extra time in this one, the interview is fairly short, I just wanted to share it. So I first met Mark, well, it was over 10 years ago. And it was when Blood Bank Guy the website was, well, it had been around for a while, but I was really just starting to expand it and to increase the amount of educational material that was there.

Well, I was doing something on the direct antiglobulin test, and I came across a figure that Mark had done in an article of his, on the direct antiglobulin test, the DAT, in the Canadian Medical Journal, and I loved it! It was gorgeous, it was wonderful. And so I wanted to use it, and for whatever reason, it just completely slipped my mind to actually ask permission or to even credit him on the website. And I'm horrified to admit that. It was not a shining moment in my career on BBGuy.org.

Mark saw it, and Mark decided rather than, you know, call me up and "flame" me or call me a jerk as he had every right to do, he reached out through a mutual friend with the most grace and kindness you could imagine to say, "Hey, look, I think Joe forgot to do some stuff with this particular figure," and he was 100% right. But that started a communication between Mark and I that at this point has developed into what I think is a really good friendship.

Mark's a great guy and I wish you had the opportunity to know him. I hope you will. If you ever hear Mark speak at a meeting, go up and talk to him. He's really a cool dude. Ask him about hockey! He will never stop talking about hockey.

So anyway, I am extraordinarily excited to bring you this episode, this special episode of Blood Bank Guy Essentials recorded for the California Blood Bank Society Annual Meeting. Here is "Wholly Whole Blood, the Sequel!" with Dr. Mark Yazer.

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Joe: Mark, welcome to the California Blood Bank Society Annual Meeting, dude.

Mark: Hooray, I can feel the heat warming me up already. It's wonderful to get out of the snow, the rain. It's miserable in the Northeast. I'm so happy to be in California, in my mind...

Joe: In your mind, yes.

Mark: At the moment.

Joe: And also welcome back to...

Mark: Isn't that how the song went, "In my mind, I'm going to California..." I think?

Joe: It might have been "Carolina," but that's, who am I to quibble? It's James Taylor, so that's all good. Also, welcome back to the Blood Bank Guy Essentials Podcast, this is a "dual thing."

Mark: Two birds, one stone. Yep, very efficient, that's what would I expect from you, Joe.

Joe: That's exactly right. Well, thanks Mark, I appreciate that. So way back in 2017, you and I got together and did a podcast, and that was, everyone, that's at BBGuy.org/040, that I called "Wholly Whole Blood," with a nice little DC Comics reference there. And Mark, I don't know if I've told you this, but over 5,000 people around the world have listened to that particular episode.

Mark: And I'm sorry. I'm very, very sorry, but 4,999 of those were my mum.

Joe: And mine might've been the other, my step-mom might've been the other. Anyway, we covered a lot when we talked about that in 2017, it's been almost four years, obviously, I can do math. And I wanted to catch up with you a little bit, not just on Low-titer O Whole Blood, but also on some of the new and exciting stuff that's coming out, and that you're deeply involved in, and get a little bit more data perhaps than we had available to us back then.

But I want to start at the beginning, Mark. I want to start at the beginning, and there's something that I want to dispel because I keep hearing this, people keep asking me this, and I know this is something that's near and dear to your heart. The way that this gets phrased to me often is, "I look in my textbooks and I look online at teaching materials and stuff like that, and I see people saying that the initial resuscitation fluid for trauma should be crystalloids. And why are we talking about plasma? Why are we talking about Low-titer O Whole Blood? What's the

deal?" So, you've got the floor for two minutes, Mark. Can you knock that out for us?

Mark: Yeah, well, I think you're reading old textbooks, because the new textbooks would say, "Don't do that, man! We were wrong. We had it wrong." It made a lot of sense, right? I mean, crystalloids, they're dirt cheap, they come in a plastic bag, they don't transmit any diseases, and if you're clever enough to be able to figure out which one is the Ringers, which is the 5% dextrose, and the normal saline, it's not easy, then you can transport it easily, and if it breaks in the ambulance, it's water, who cares? It's not like you have a blood product that spilled out all over the back. And so the thought was, if you could keep the blood pressure up using crystalloid, and then the fairly large reserve of red cell and coagulation factors would get where they have to go and you could sustain the patient until you get to definitive care.

But we've come 180 degrees from that. We don't want to have a high blood pressure, high normal blood pressure anymore. We want a permissive hypotension, right? So we don't need to keep the blood pressure up. And if you look at the constituents of normal saline, there's nothing normal about it. It's a misnomer.

Joe: Right.

Mark: It's like the Maple Leafs is a good hockey team, complete misnomer. It just doesn't make any sense, there's nothing normal about it. And if you have some kidney damage from your trauma, or preexisting, it's even less normal, right? It's like the Boston Bruins, even less normal than the Maple Leafs. And it just doesn't make any sense to be giving people stuff that's acidotic, that does not help to transport oxygen. It doesn't help to heal, to do hemostasis, none of that. Saline doesn't do any of that stuff, and yet they would give it in liter quantities, lots and lots of it, because it didn't transmit diseases, and I think frankly, that's what people were afraid of.

Now we know, with great evidence, we've had evidence for 30 years, the Bickel study in New England I think, showed the patients who had delayed fluid resuscitation, in other words, who weren't blasted with saline from the minute they were picked up in the street til the time they hit the emergency room, in the OR, did better, had longer survival in patients who had a lot of saline administered in those three parts of the resuscitation. And many other studies have shown the same thing. So crystalloids is passe, it's convenient, but it doesn't do your patient any favors.

Joe: Okay. Well, I'm right there with you, and that's the thing I hear repeatedly from trauma surgeons is, "I don't want clear stuff." I mean, to simplify it as much as possible, "Give me stuff that's not clear, avoid that as much as you can." I'm sure you hear the same thing all the time.

Mark: Yeah. And finally, that's great to hear, because that's what's going to be better for the patient. We have so much data that we didn't have back then. Blood products are safer than they were back then, and we have an enhanced understanding of what happens from a endothelial, from a coagulopathy, and a bleeding perspective in patients who are in trauma. And clear stuff doesn't tick any of the boxes.

Joe: Yeah. Well, so with that being said, let's take a step up. So we don't want the clear stuff, I think we got that. What about the yellow stuff? I mean, so there's been a lot of discussion, and you've contributed to that discussion a lot over the years, on using plasma. And perhaps using plasma early, perhaps using plasma in ways that we hadn't thought of before, kind of quote, unquote, breaking some of the ABO rules that we've talked about before. So, let's just get a quick overview of that. What do we know now about giving plasma early to patients?

Mark: You know, I was on a phone call with a bunch of Army surgeons, and one of them called it "Liquid Jesus." And when I realized that half of the Army surgeons were Israeli, I came on and said, "Maybe we should call it the Liquid Abraham." So that's really what we're talking about, you're probably talking about the "PAMPer study," where we looked at patients who were traumatically injured, as if there's any other way to be injured, and transported to the hospital by helicopter, who took 40 minutes to get there, they were seriously injured, they had high mortality rates in the end. A lot of them needed a massive transfusion. These patients were randomized to be supplemented with two units of plasma, could be A or AB plasma, versus whatever the standard of care was. So the plasma was added on to the standard of care, and we showed better mortality, improvement in mortality at 30 days, that was the FDA's favorite endpoint for bleeding studies back then. But if you look on the curve, they started to separate around three hours, which is a much more relevant endpoint for a bleeding study.

So, the high level conclusion of PAMPer was that if it's going to take you a while to get to the hospital, more than 20 minutes, and you're seriously injured, then plasma is going to help to save the day. And we've refined that with secondary analyses to show that this is basically most efficacious for blunt injuries and for patients with traumatic brain injury.

In fact, Jason Sperry and his group have done some really cool stuff with... I'm blanking on the word, but it's the pattern of expression of inflammatory markers. And he's shown that there's a very specific pattern, patients who when they're injured, if they produce this particular pattern of inflammatory markers, are the ones that benefit the most from plasma transfusion. So he's done a really good job of bringing out exactly who is responsible, or who is going to benefit from it. But because it's hard to tell what markers are elevated and in a patient you've just scooped up, if the transport time is long and they're seriously injured, than two units is very helpful.

Joe: Okay. So that being said, Mark, perhaps getting plasma to patients that have undergone trauma as early as possible might make a difference, but one of the

logistical challenges of that, that we've dealt with for years, is that we've lived with the dogma for literally decades, that the only plasma that you can use in those settings is AB plasma. And again, I know you've been involved in some somewhat groundbreaking publications, and especially the "STAT study" that was published in 2017, I believe. And I've talked about that at length with Nancy Dunbar on Episode 36 of this podcast, so everybody BBGuy.org/036 for all the full details. But Mark, can you summarize what was found in the STAT study? And further, what data do you have since then to either support or refute what you found?

Mark: Yeah, and full credit to Nancy for the STAT study, she did an amazing job with it. I was just there. But, well-

Joe: That's half the battle, Mark.

Mark: Well, I think it was about 5% of the battle, and she did the other 95%. You know, we did this with the BEST research collaborative. We asked the question, "Excluding Group O people, where plasma will be compatible for everyone, no matter what group you give, do patients who get incompatible plasma units in the form of plasma do better than patients who get incompatible plasma?"

So we looked at injured Group A people versus B and AB people who received at least one unit of Group A plasma. Didn't have to be low-titer. The Group A could have been just any type of Group A plasma. And what we found at the very highest level was there was no difference in mortality, early mortality, in-hospital mortality. We didn't find any differences in secondary outcomes as well. So what that gave us confidence was that at least at a high level, the Group A plasma, which is so much more available than AB, right? I mean, if we had an unlimited supply of AB plasma, we wouldn't be having this discussion.

Joe: Sure.

Mark: So there is a risk. Yeah. There is a risk, in theory, when you transfuse Group A plasma to someone whose blood type you don't know. Most of the time, of course, they're going to be O or A, that's 85% or more. You get pretty good odds that it's going to be compatible, but it's not everyone. And we have to look out for those other people as well, the Bs and the ABs, and clearly at the high level, we're not causing any harm. Maybe there's some hemolysis that's happening, but it's not translating into mortality, which is really what we care about.

And so we recently redid the study under the code name "MENGO," after the champions of the Brazilian Domestic Soccer League, my team.

Joe: Of course.

Mark: And what we showed in MENGO was basically what we showed in STAT. We looked at all patients, all the blood types, we didn't exclude the group Os. And we looked at all sources of plasma, including the little bit that comes in a red cell, and the little bit that comes in cryo. And we asked the question, "Simply put, do patients who get compatible plasma, so Group Os, or patients who get identical

plasma, so like an A person who gets only A plasma products, do they do better than patients who get incompatible plasma?"

And we looked at what it was, it was a one hour, six hour, 24 hour mortality. And we showed no difference, not even close to any difference amongst the patients who received compatible versus at least one unit of incompatible plasma and the average or the, I guess, the median quantity of incompatible plasma in that study I think it was about 350 mL. So we're almost at about two units of plasma. So it's quite similar to what we were doing in PAMPer. And it reflects the real life practice of how much incompatible plasma patients are getting, at least from the sites that participated. So it wasn't all that much. And we didn't see any evidence of death. We didn't look for hemolysis. We didn't look for any of that. We just looked at death and we didn't find anything.

Joe: Okay. Okay.

Mark: And speaking of hemolysis, just briefly, we've been looking at our whole blood utilization and what happens to patients in trauma who get whole blood, and here we're looking for hemolysis, we're looking for LDH bilirubin, haptoglobin. And we've seen no difference in patients who get at least four units of whole blood with a titer of a hundred, that's our new titer. And again, no difference between the Os and the non-O recipients. So at that level, no adverse event or hemolysis and at the high level, we're not seeing any mortality difference at all. So it confirms the practice.

Joe: So Mark, and that's a great summary. And I think that we're starting to see that in my world, in Southern California, in blood centers, we're starting to see that becoming... I mean, it's just pretty much standard. The use of Group O, excuse me. The use of Group A plasma as the initial plasma resuscitation anyway.

Mark: Joe, just to tell you about a new study that's online early, we surveyed 103 level one trauma centers, level one American trauma centers. And I think 95% of them use Group A plasma in their initial resuscitation. And I can't remember what it was. Maybe it was 10%, only 10% actually titered the plasma. So it's the wild, wild Southwest.

Joe: I like it.

Mark: But it's fine. I mean, this is what we're doing. The practice is very consistent with all the safety data that we're getting. So not all of it is low-titer and luckily the saline's being kicked into touch or made into popsicles or whatever they do with it.

Joe: Okay. Saline popsicles. That sounds really disgusting. I got to tell ya. Oh man.

Mark: For post-op patients.

Joe: Fair enough. All right. So with that being said, we need to wander back into Low-titer O Whole Blood. Because obviously that to me is kind of the next step. And that's, again, just speaking from my personal recent experience. We have several

hospitals here in Southern California that my blood center serves. And I don't serve all the hospitals here nor do I serve all the level one trauma centers in Southern California, but there is a growing interest and, and we are supplying it. My center is supplying it. And what I hear mostly from people is, "How can we get more?"

I think it's pretty safe to say, and I tell people in hospital blood banks this all the time, I think the question is mostly settled in the minds of trauma surgeons. Mostly. Just in general. Obviously, there's more work to do and you're in process of doing that. But I think to a lot of trauma surgeons, it's like, "Great!" They've been wanting whole blood for years. "Super wonderful. Let's rock and roll!"

But what I want to talk to you about, Mark, before we get to some other really important stuff about Rh, is just go back for us for just a second. And I wonder if you would mind just summarizing in your mind, the benefits of using Low-titer O Whole Blood, as opposed to using component therapy, the traditional quote, unquote one to one to one or one to... two to one, whatever, as opposed to that, what do you see as the general high-level benefits of using Low-titer O Whole Blood?

Mark: I would encourage all of the junior colleagues who are on, watching this or listening to go to a trauma resuscitation, right? I mean, we get paged in the blood bank, we send the products down, there's a heightened sense of anxiety in the blood bank. But imagine what it's like in the trauma bay. Go and just be a wallflower and watch it. And you will see organized pandemonium.

And you'll see lines going in and blood products flying all around and people pushing on the chest. I mean, it's a symphony of coordinated action and anything we can do in the blood bank to help those guys resuscitate patients and to make their life easier, I think we ought to be doing. And giving whole blood guarantees that the patient's going to get balanced resuscitation early.

So you don't end up in a situation where they're given 10 red cells and meanwhile, someone's telling about the blood pressure. They forget about the platelets and they don't get any platelets and they get two units of plasma and it's totally imbalanced. And that's not what the patient needs.

The evidence all suggests that some form of early balanced resuscitation is really important until you can get more specific information about what the patients lack. And so if it makes the surgeon's life easier, they're going to yell at us less, which would be great. They might remember to send us a pre-transfusion sample early, that'd be super, and it's going to make their life easier, which probably makes things better for the patients.

So if we simplify the logistics of the resuscitation with easy balanced resuscitation in one bag, that's not much bigger than a red cell, that can go in a blood warmer, that can be administered quickly if necessary, that's great.

There are other benefits, fewer donor exposures. Well, there isn't any additive solution in it. So there's less of this sort of crystalloid-like stuff that's just going to end up in the third space anyway, just like the saline. It doesn't stay intravascular. Most of it doesn't. So there's less of that.

You get the cold platelets, and the evidence that we're accumulating is showing us the cold platelets primed for coagulation activity, you don't get those in room temperature, platelets. So you get a dose of those in, and even if you use a leukoreduction filter, you're still getting a very significant quantity of platelets.

So I think those are some of the main high level benefits where what we're lacking and the notion that the question is answered, is does it do anything for the patient? Is there a better outcome for the patient? I'll just interview myself, Joe.

Joe: Go ahead, yeah. I'll just sit back...

Mark: “So Mark, is there any benefit to the patient of getting the whole blood?” And the answer is, "well probably." And this is what the literature is starting to show. We don't have the randomized trials like we do for plasma or for hemoglobin thresholds. We have great trials for those, because whole blood is a new thing and there are randomized trials that are coming. We have a pilot trial that we finished in Pittsburgh. The Lights Military Network has commissioned a study. Phil Spinella has got a study in cardiac surgery patients. Yeah, it's coming, we know we have to study it. We know we can't make definitive conclusions about its efficacy now. Safety probably, yes, based on our retrospective data. But the efficacy is coming. And what we're seeing are a lot of retrospective studies. And the way I can summarize them is that the patients certainly don't do worse if they get whole blood than if they get components.

Recently a retrospective study from a single center study came out that showed some benefits of whole blood to the patient, fewer transfusions, shorter length of stay. Another study that looked at the T quick, the database, found that although the patients were getting a median of like one unit, there was significant improvements in mortality reductions, in complications. It's hard to think that one unit could be responsible for all of that, but at least the patients aren't doing worse.

We just published a propensity match trial study retrospective, where we looked at trauma patients who were resuscitated with whole blood versus components. And we looked for DVTs, for infections, renal function. We couldn't find any differences. And the trends that were there were all in the favor of whole blood.

So certainly, what we're seeing is that it's a safe thing to do from a hemolytic perspective. Patients don't hemolyze when they're getting it. And two, the outcomes are certainly not worse. And just one word about hemolysis. Here's the thing: So LDH, bilirubin, and haptoglobin change in a trauma patient and they change in exactly the same way that they would in somebody who's having hemolysis.

Joe: Yep.

Mark: So it's difficult to measure, to look at any one patient and say, "Well, is this bilirubin through the roof because of the trauma or because of the hemolysis or is the shock liver causing the haptoglobin to be low?" And so you can't really tell. But you can look at large groups of patients like we've done, like other groups have done, and you just don't see differences, even in trends in these biochemical markers between the O's and the non-O's. So I think for modest quantities of transfusions like we've been doing, four, six, eight units with a titer of less than a hundred, I'm very confident that the safety question is in the bag. The efficacy question, we need the randomized trials to show us that.

Joe: Okay. Well, so you took away several of my questions. Oh, by the way, is it okay if I talk? Is that okay? Do you mind? I'm kidding.

Mark: Oh, do you have anything to add to what I've said? Go ahead.

Joe: You were on a roll, buddy. I didn't want to get in the way. That was fantastic. And it was. So there are a couple of practical questions that people ask about Low-titer O Whole Blood that I want to make sure that we cover. And the first of those is, in your mind, and in the way that you see this going forward, is this an initial resuscitation or is this an ongoing thing? In other words, and you mentioned just a second ago, there's kind of an outer limit for how many that you use. And to be clear, AABB standards requires that centers set a limit of how much incompatible plasma, for example, people get. So there has to be something that people are doing, but how do you transition Mark, I guess is the question, from the Low-titer O Whole Blood to whatever?

Mark: So to be really clear, the standard requires that the hospital sets the maximum amount of whole blood units that a patient can receive. You can set that maximum amount to infinity. You just have to have a policy.

Joe: Right.

Mark: You take everything on the shelf. That would be completely consistent with the policy. Just like incompatible plasma, you just have to have a policy for how you're going to deal with it. The standards correctly don't specify a quantity of whole blood that a patient can receive. The hospital just has to have it in writing what they're going to do. So anything that the hospital comes up with will satisfy that policy. Some policies might be better than others, and that's for anything, but the standards don't dictate the maximum because they're not meant to do that.

And in terms of the transition from whole blood to components, I think that's going to depend on the patient and the extent of the monitoring that's happening. If you're at a center that has near patient testing like thromboelastogram and you're able to get MA back, maybe the patient needs more platelets to supplement what they're receiving. Maybe the patient needs more plasma. I think when you start getting a sense of, is the bleeding slowing down, is there a particular defect that we can correct using components? That's the time to start using a more tailor-

made approach to the resuscitation. But at the beginning, when you don't have any of this back, and they're just bleeding from everywhere, whole blood is the best because it's one bag, you get balanced resuscitation.

Joe: Yep. Okay. And that's fair. But I guess what I'm going for at least as much is, well, first let me devil's advocate for just a second. You're a hundred percent right that according to the way the standard is written, if you set your limit at infinity, that would meet the standard. I might argue that that doesn't necessarily meet the heart of the standard or perhaps the intent of the standard. I mean, and again I don't want to get into a battle with you on this, although it would be fun. We could drop the gloves and go, Mark. Let's do that. But whatever, the facts for me is that, that it seems to me like the intent of the standard saying you need to set a limit is to try and figure out what that limit might be rather than be infinity. But I hear what you're saying and you're right, that that is the way the standard reads. So again, don't want to argue about that.

Mark: Many world leaders have pointed out, you can't go to jail for breaking the spirit of the law.

Joe: That's a good point. You're not wrong there. You are absolutely not wrong.

Mark: And I agree with you, Joe. I agree with you that in the beginning, when those standards came out, virtually nobody was using whole blood and it was new and it was potentially threatening because the cold platelets could be causing clots everywhere, because of the incompatible plasma. So I think there was correct, what you said is right, the intention was to start off in in a sort of really modest way. We started with two units and then work our way up in terms of dosing, as the safety has been demonstrated. And I think that's actually what's happened. I think people started modestly. Those of us who didn't have Army experience, military experience and didn't have experience using it, didn't know. And so we started very slowly and others were pushing us because they'd been there in battle zones and they'd already given 20 units of it and they know it's safe. And so I think what we've now arrived at is the point where the data is ... my computer just turned off, there we go ... where the data is coming to meet the experience of the people that were doing it and knew it was right, because they'd done it. But now we have data to prove that what they were doing was right and safe the whole time.

Joe: Okay, fair enough. So, but back to what I was trying to ask before I got distracted by the dropping the gloves thing, patient comes in, we're resuscitating them aggressively with Low-titer O Whole Blood. We get that pre-sample back, which our ER is kind enough to draw very early in the process and we're very happy. We discover the patient's group B. That's my question. At what point when you get that information, now, I'm assuming it's time to switch over to giving the patient group B. Is that correct? Or do you advocate, or are places considering continuing with whole blood in those settings?

Mark: Well again, I think it depends on what's happening. If the patient's continuing to have an active, unstoppable bleed, then I'd continue with the whole blood in the balance of the resuscitation. I think if the bleeding is slowing down, or if you've identified a specific solitary defect, like they're really hypofibrogenemic then whole blood, which has everything in it, isn't going to correct it as quickly as some cryo or some pharmaceutical will. So I think really the key is how badly is the patient bleeding? What control do we have? And what do we know about the coagulation defect? And if we don't know anything, then I would just continue using whole blood.

Joe: Okay. So I guess the bottom line is that there's probably not a universal thing, a universal rule. It's going to be patient specific. It's going to be situation specific, in other words.

Mark: Look, “eat all you want” means eat everything you want, not eat all that you can. You don't have to give the maximum number of units. There is something between zero and infinity, which is what the patient's going to need. So yeah, if your hospital has a limit of 50 units, you don't have to give 50, but I think hospitals should have a sense of the safety of the whole blood and can implement policies that are consistent with their own comfort level at this point.

Joe: Right. Okay. Well, so Mark, since our time is getting a little short,, there is something that I think we need to talk about, which I think is really important. As you know, when Low-titer O Whole Blood became a thing, and when standards was modified to allow the use of it, I remember talking to you when that happened because it was not long after we had done our episode, if I remember right. As you know, there were some people that said, some really smart people that said, "It's too soon. Why are we putting this in standards? We don't have enough data. We're concerned about this," et cetera. And I'm not here to rehash those arguments. That's not the point. But my point is that not long after that, well, a couple of years after that, you were lead author on an article that kind of blew some minds again and raised some concerns.

As we talked about, Low-titer O Whole Blood... Actually, we didn't mention this, but as we talked about in the last time we discussed this, Low-titer O Whole Blood for most places is O positive. Most blood centers make it as O positive. A few places are making O neg, but most places are making O pos. And because it's O pos, it tends not to be used for childbearing age females on the off chance that they would be RH negative and that they wouldn't induce anti-D and cause problems with pregnancy in the future. So you published this article in 2019 in Transfusion. Everyone, I'll put this on the website. The name of the article is "It's Time To Reconsider The Risks Of Transfusing RhD Negative Females Of Childbearing Potential With RhD Positive Red Cells in Bleeding Emergencies," and I'm guessing you've gotten some feedback on this article, Mark, and some discussions on it. So again, we don't have a ton of time, but what's your basic thesis with this? What do you think moving forward we need to be thinking about in regards to this?

Mark: There were a few things that blew my mind that I felt if they're blowing MY mind, probably others as well, and primarily it was an article I read that showed that from the Dutch Group, because they're the best for HDFN studies, they show that even in women who are sensitized to anti-D and are carrying a D-positive fetus, the rate of fetal demise is 4%. And that blew me away. I thought it was still in the 40% or 50%, like it was before high resolution ultrasound came along. And it got me to thinking about all the different things that have to happen to a D negative woman from the time she's transfused during her trauma resuscitation until the HDFN outcome. And we identified a few important things like surviving the trauma, making anti-D and the D alloimmunization rate could fill a whole other podcast. It ranges in trauma from about 8% to 40% in different studies with the same methodology.

So we picked an intermediate 20%. She's got to get pregnant. She has to carry a D-positive baby. We calculated about a 0.3% risk of fetal death from the woman receiving an Rh-positive red cell unit. If you include other factors like how many pregnancies she's likely to have, when in her life does she have the pregnancies, other societal things, how many partners is she going to have, the risk goes up slightly. And it depends on the age of the patient as well, because the younger the patient is, the longer the pregnancy horizon will be, so the longer the potential. But generally if you're looking at 18, 19 year olds, you're looking at about a 5% fetal any type of HDFN and it drops to about zero after 40%.

So what this told us was that it's not a death sentence for the future fetus if mom gets a D-positive red cell. We know that prehospital transfusions save lives. There's lots of military and civilian data to show that. And we just can't put Rh-negative products where we'd like them to be, because like AB plasma, we don't have enough. So what can we do to improve the care of women of childbearing age who are injured and need a transfusion before they can get to the hospital where Rh negative products might be available? Rh-positive products, including whole blood, carry with them a very low risk of a fetal adverse event, in particular death, and a high risk of saving one's life.

So I think when you look at the absolute risk reductions that come from early transfusion, some studies have shown 14% risk reduction, Sperry's study, the secondary analysis, we showed that in the helicopter, the patients who received plasma and red cells, sounds a bit like whole blood minus the platelets, had better outcomes than the patients who had any one component alone and certainly way better than patients by just saline.

So I think that knowing what we know about how good our obstetrics colleagues are about diagnosing and managing HDFN, that women should not be denied life-saving transfusions in situations such as prehospital transfusions where Rh-negative products aren't available.

Joe: So has this led to a change in your practice, Mark?

Mark: It has. At all of our level one hospitals, adult level one hospitals, we transfuse Rh-positive whole blood to any patient, any adult patient, regardless of their sex. So women and men of Rh type negative or unknown, as they often are in trauma, will get Rh positive products.

We have a program in place where if the patient receives only one unit of Rh positive products, we'll use RhoGAM, well, WinRHO, to neutralize that unit. If she receives more than that, we feel that the extent of the hemolysis would be too severe. And so we have an information sheet and we give it to the patient explaining why she received Rh-positive products. And there's a phone number for the high-risk maternity clinic that they can call if they'd like to have some consultation or advice either now or before the next pregnancy or whenever.

So we have a really good relationship with our obstetrical colleagues, and they're really on board. In fact, the senior author on that paper is the doctor who does the intrauterine transfusions in Pittsburgh. And I was joking with him that maybe he's just trying to gin up some business for himself, but he's not. He truly believes in saving mom's life so she can have a baby. And so it's very confident in their ability to rescue babies from HDFN.

So I think if you have a choice, obviously you would use an Rh-negative product in a childbearing aged woman if you don't know what her Rh type is, but I would not withhold a transfusion if you don't.

Joe: The one last thing Mark, and we really are super short of time. I want to leave time for those on the CBBS meeting to pepper you with questions, but what about using Low-titer O Whole Blood in kids in the pediatric population? What do we know now that we didn't know four years ago?

Mark: Well, again, it's safe from a hemolytic perspective. We use up to 40 mL/Kg of Rh-negative whole blood in the kids, because we haven't quite taken that step to Rh-positive whole blood in our kids. So in the THOR supplement this year, we'll have an article showing the serological safety of transfusing up to 40 mL/Kg of whole blood. Serologically safe. And we're working on a propensity-matched analysis to see what the outcomes are between whole blood recipients and component recipients. And the sneak peek is that certainly, just like the adults, they don't do worse if you get whole blood. We didn't find any increased evidence of adverse reactions in the whole blood recipients. So for what that's worth from a small single center study, it's safe and there's no hemolysis.

Joe: Awesome. Mark, you are the man as always. I always appreciate our time. It's such a blast to talk to you. Fellow hockey fan and friend. So thank you so much for doing this, Mark.

Mark: You bet. Go Habs. Make the playoffs. Don't lose to the Leafs...

Joe: My team's not making the playoffs, dude.

Mark: I know what you mean.

Joe: Take care, Mark. Have a great day.

Mark: Bye. Thanks for inviting me to the meeting.

Joe: Yeah, no problem.

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Joe: Hey everybody, it's Joe. As I mentioned, you can go to BBGuy.org/091 if you really want to watch two guys discussing whole blood and, and a little bit of hockey, you can certainly go there and see the video version of this interview. You can also find references to some of the articles (that's probably more important) that Mark mentioned in this interview.

If you have a chance, I'd really love it if you would do me the favor of going to Apple Podcasts and give this podcast a rating and subscribe. The reason for that is that it just helps the podcast be seen by more people that need to learn. And that's really all I'm trying to do is try and help people learn the essentials of transfusion medicine, as the title says!

My next episode, finally, will be something I've been promising for a while. It is a continuing education episode with Dr. Ruchika Goel. We're going to be talking about transfusion, whether you should or shouldn't, of platelets in ITP, TTP, and heparin-induced thrombocytopenia. So that's a great episode and I'm really looking forward to you hearing it. I've got a lot of really great things coming up as well. And I can't wait for you to hear those throughout the summer and fall of 2021.

But until that time, my friends, I hope that you smile, and have fun, tell the ones that you love that you do, and above all, never, EVER stop learning. Thanks so much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.But until then, my friends, I hope that you smile, and have fun, and above all, never, EVER stop learning. Thank you so much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.