BBGuy Essentials 101CE:
"Look Before You Leap" with Rich Haspel
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Rich: Hi, I'm Rich Haspel from Beth Israel Deaconess Medical Center and Harvard Medical School, and this is the Blood Bank Guy Essentials Podcast.

Joe: Oh yes! New theme music! I am so happy right now. Hi everybody. This is episode 101CE of Blood Bank Guy Essentials, and my name is Joe Chaffin. I am your host. That new music, by the way, is from my friend Tommy Walker. Go to the website BBGuy.org/101 to get links to more of Tommy's music.

So I am thrilled to be back with you and to be bringing you an interview today, um, with Dr. Rich Haspel from Beth Israel Deaconess Medical Center, and I'm really excited for you to hear what he has to say.

But first, this IS a continuing education episode. The free continuing education credit is provided by TransfusionNews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into the podcast. This podcast offers a continuing education activity where you can earn two different types of credit: One AMA PRA Category 1 Credit™, or one contact hour of ASCLS P.A.C.E.® program credit. This activity also may be used to fulfill Lifelong Learning Continuing Certification requirements for the American Board of Pathology. To receive credit for this activity, to review the accreditation information and related disclosures, you just need to visit www.wileyhealthlearning.com/transfusionnews. Finally, don't forget: The continuing education credit is no longer available for this episode two years after the date it was released. In other words, if you are listening to this episode later than May 4, 2025, the continuing education credit will have already expired.

Okay, back to this episode. You know, I think we are all very, very well aware that new information in transfusion medicine, really new medical information in general, just comes flying at us at an amazing rate, and it really, really is hard to keep up. And I think further though, A lot of us had no great training in how to really interpret or evaluate the literature in, in a critical way.

So I'll speak for myself. I'm not a "research guy," and I will tell you that there have been times when I'm looking at new stuff and it sometimes can be a little bit hard for me to just get past the abstract. I'm admitting the quiet part out loud, but it's true. There's just so much, it can be really hard to keep up.

Well, my guest today, Dr. Rich Haspel from Beth Israel Deaconess Medical Center and Harvard Medical School, has made it his goal to help us move to a place where we are better following the evidence. Now Rich has been with me before. He was, he joined me back in 2017 for episode 42 of Blood Bank Guy Essentials, where we discussed some educational things and some initiatives that he was actually, that I ended up helping him with a little bit to evaluate the medical knowledge or the knowledge of transfusion medicine in different medical specialties today.

I asked him to join me to do two things. Number one, to give us a basic approach and some tools for how a learner can actually start to critically evaluate the medical literature. And that really is about the first half of this interview. And it's, it's really, really important listening, and I hope all of you that our learners will take the time to hear and, and apply what Dr. Haspel has to say, but further the second half of the interview, I wanted him to use that approach to discuss what's really become a hot button topic right now, and that's Low-titer Group O Whole Blood.

Now, if you've listened to this podcast at all, you will probably be aware that I've talked about Low-titer Group O Whole Blood primarily with Dr. Mark Yazer on two different occasions: Episode 040 in 2017, episode 091 in 2021. And you can find links for both of those on the show page for the for this episode at BBGuy.org/101. And I even discussed with how one hospital implemented low titer group O whole blood with Drs. David Oh and Mike Goodman from Cincinnati in 2019. That's episode 073.

Well, again, unless you've had your head under a rock, you're probably very clear that Low-titer Group O Whole Blood is something that's really being asked about and talked about a lot. I worked in a blood center for a long time…well, most of my career I've worked in blood centers, and in the last few years I've been amazed to see the amount of interest there's been in this particular product. Well, Dr. Haspel believes that there are some weaknesses in the current evidence for that, that may kind of belie the rush to using Low-titer Group O Whole Blood.

And he's spoken about that publicly, including the fact that he's gone to an AABB Annual Meeting a few years ago and in a session that was full of people that were totally on board with Low-titer Group O Whole Blood. He was the counterpoint. He served as the counter. To kind of say, “Hey, hang on a second. I think that there are some problems with this!”

I want to be clear, this is not intended to be an “anti-Whole Blood” episode. You know, if you pushed me and you really asked me, I would probably tell you that I personally believe that Low-titer Group O Whole Blood is gonna turn out to be a good thing. But if you pushed me again, I would also admit that the evidence is probably not as strong right now as we would like it to be. And that is Dr. Haspel's point, and he walks us through really why feels that way. Not to berate anyone or belittle anyone, but just to illustrate his approach to evaluating evidence. And you know, again, he feels fairly strongly about the way he feels about Low-titer Group O Whole Blood.

So I really enjoyed this discussion and I hope that you will too. You may not agree with every point. That's totally fine. But the approach is interesting. The tools that Dr. Haspel gives us are fascinating and useful, I believe, and I just hope that you'll listen and learn from it.

So here is “Look Before You Leap; Thoughts on Evidence-based Transfusion Medicine,” with Dr. Rich Haspel.

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Joe: Hey Rich, welcome back to Blood Bank Guy Essentials. Thanks so much for being here, man.

Rich: Thanks so much for having me. It's great to be back.

Joe: Well, it's been a while, my friend, and you and I have actually worked on a couple of different projects since we last talked, specifically with assessing transfusion medicine knowledge, and I want to thank you again for your leadership in that. The one that I participated in with you looked at pediatric residents, and looking at their knowledge of transfusion medicine. I'm curious, I know you've published on that. Did anything jump out to you during that particular study?

Rich: I think it was interesting to see just how certain topics that were more important for pediatrics. But what was probably more interesting is how much overlap there is between the different specialties, and how the deficits, regardless of specialty are still pretty significant. So I would say there's more similarities than differences between some of the other studies, but it's important to look at each area, and also in each area, like pediatrics versus adult, find those specific topics, like hemolytic disease in a newborn is not really a topic for the adults, so more similarities, but thank you for participating. We don't do it, unless we have people participating, so thank you.

Joe: I didn't actually plan on talking to you about this, but it just popped into my head. I will tell you that the results of that, when the results came out, the pediatric teaching staff at the facility where I'm currently working at Loma Linda, said, "Hey, what can we do about this?" And I said, "Oh, what can we do about it? Are you interested in having some further education in transfusion medicine?" They said, "We are. It seems clear that we need it." And I said, "Great, let's go." So it's actually led to a lot of really good discussion with my colleague, Dr. Tait Stevens and myself at Loma Linda. Again, a side benefit. Right?

Rich: Well, actually, I'm glad you brought that up. That's the whole reason we're doing this, to get people to start teaching and recognizing there's a deficit. And if people are interested, if they go to the articles or they can email me, I can send them the exam, if they want to do it locally. But thank you for sharing, and it's really the goal. It's one thing we'll do an exam and show there's a need, but to use it as a tool to get people to realize, "Hey, we need you to teach. So that's great. I'm glad that happened."

Joe: As a teacher, and I know we share this, as a teacher, that is something that just warms the heart when they say, "Hey, we want to learn. Can you teach?" "Hello? Absolutely. No problem. All day every day." I am so glad to have you back on the podcast, Rich. As I said, obviously we've been in communication from time to time since the last time you were on, but one of the things that's kind of happened in that timeframe is something that I have found really, really interesting.

I think it's pretty fair to say that we live in an era where information just seems to be flying at us with ever-increasing speed, and new things come out in the literature, and new ways to practice and new considerations. Sometimes with callbacks to old ways to practice, just it feels like to me come flying at us with ever-increasing pace. And I think

that that has happened, that pace has even accelerated to some extent during the pandemic, with so much information that needs to be evaluated.

You have found yourself in a really interesting position, and I want to give you the chance to explore this a little bit, in that with one particular topic that we're going to spend some time on today. But just in general, what I've seen from you over the last few years, is something where you have been willing to publicly say, "Okay, hang on just a second. Let's evaluate this and let's make sure that we're looking at this the right way." Whatever the topic is. Again, specifically the topic we're talking about today on whole blood versus components and trauma. But I wonder, is this something that's kind of been true for your whole career, Rich, is this way of looking at things, how is that manifested in your career?

Rich: Well thanks for the kind words. I try to be very data-driven. I think it stems from, I don't do basic research anymore, but I did an MD/PhD program, and part of the thing about PhD is learning how to critically analyze the literature. And we had a journal club, when I was getting my PhD. The challenge was... so I would bring up a paper and you'd try to rip it apart. You'd really try to be very critical, not just to insult... The person who wrote it wasn't there. But it's not just to be difficult, but to really say, "Is this strong data?" And that became, as a PhD student, that was a very big focus.

And when I did my blood bank fellowship, I was fortunate enough to work with Sunny Dzik over at MGH, who was also very, very data-driven. And I learned how to apply some of that approach. So clinical studies, because what I'd previously done was more basic research, but the overall principles are very similar. And so going forward, I've just always been very interested in reading the literature, not just the abstract, but really looking at the data and learning ways to critically assess it.

And there are good papers out there, and there are not so good. And just because it's in a really famous journal, it doesn't mean it's necessarily good either. And so that's why going forward I try to help to teach our trainees about how to critically review the literature, and I feel when the topic comes up, I like to weigh in about stuff like that.

Joe: Yeah, I think that experience and that idea of how to look at something critically, if we can just kind of delve into that a little bit, I think it would be really helpful for my audience, Rich. Because, as you know, a lot of people that listen to this podcast are people that are just getting going in their practice, both on the laboratorian side as well as on the medicine side. And so, I think that there's a lot of value for us to learn from you.

So let's put yourself in a situation where, and I know this would never happen, where you're sitting in your office and suddenly some clinician comes into your office and is hot to trot about the latest cool thing that they've learned at a meeting, let's just say, of people in their specialty, and they're just, they're ready to go.

They're like, "Okay, Dr. Haspel, this is clearly the way that the world is going, and this is what is happening out there. We're going to get behind the times, Dr. Haspel, we're going to be behind the times if we don't implement this yesterday." So, could you just walk us through your process, how do you go about evaluating this "hot new thing."

Rich: Well, the first thing is, get the literature, get the papers, look at the papers, and try to see, reading them critically. And part of the issue is, with training today, I mean my ClinEpi course, or my statistics was literally first year of medical school. So about a t-test, like it didn't really teach you how to critically evaluate a paper, and I was fortunate from people I've worked with, I learned more. And it's something you practice, and you also learn actually reading letters to the editor, or a good way to understand.

But don't just read an abstract, read the whole paper. So I'll get the paper. And the thing is, you're not going to have randomized controlled trials for everything. So, when we teach this, and I'll just give a little plug. We do a journal club, we do a transfusion journal club with our evidence-based journal club, but it's papers I've picked, where it's two papers that reach absolute conclusion on the same transfusion topic.

And we had published that a while ago. So if people are interested in those papers we use, because a good example is CMV for local reduction versus CMV-negative. And we look at the literature on that side by side. So it's something you can practice. But if someone comes to me, I'm going to look at the literature. And like I said, you can't always have randomized trials. So the example I bring up when I'm teaching sort of in this journal club, is smoking.

So I asked, "Well, there's never been a randomized controlled trial for smoking. There isn't going to be a randomized trial for smoking, we're not going to randomize for this one. But do you believe that smoking causes lung cancer?" And of course people say, "Yes." So then we start delving into, "Well, why do you believe that?" And there's certain things, there's, it's reproducible the data, right? There's strong P-values in the observational studies. There's biological plausibility. We know that there are carcinogens in smoke. There's a dose response, the more you smoke, the higher the risk. There's also reversibility.

If you stop smoking, your risk goes away. So what I've basically just listed are some of the things that are called, the Hill criteria, where a guy named Hill, who was an epidemiologist, came up with this list of things to say, "How do I take observational data and try to see, is it true cause and effect if I stop smoking, will it actually lower lung cancer, or is it just an association with no cause and effect?" And what's interesting, Hill, one of his studies, one of the first observational studies to look at smoking and lung cancer, was actually done in physicians.

Joe: Wow, interesting.

Rich: But the idea is thinking of... And people can bring those up without knowing those are the Hill criteria, but it's nice... There's some other ones. So, how do you take that observational data and translate it? So that's the first thing, how do I look at that data to see if there's cause and effect?

Another thing to keep in mind, and you can learn about this and read about it, is what are biases that are associated with trials, or with studies? And there's a ton of different biases that are out there, but to understand some of the more common ones, especially ones in transfusion medicine, are very, very, it's important to understand those things.

So I'll just mention a classic one in the transfusion literature. The trauma literature was the whole one-to-one plasma to red cells.

So the initial studies came out and said, "Hey, look, people who got more plasma with their red cells did better." So if they had five to one red cells to plasma, people with one to one did better. No one's going to argue when you start going to 10 to one red cells to plasma, that's a bad idea. But the idea that three to one versus, so when you look at that data, it's really hampered by something called, survivor or survivor treatment bias. So is it that, because what would people get when they're injured? They get red cells, right?

Then if they survive for the first hour, then you're starting to give them plasma. So was it that the plasma helped them survive, or did they survive long enough to start getting plasma? And in fact, there's a very great study which showed what they control for that bias, the benefit at this one hospital or they controlled for that bias, the benefit of high plasma ratios went away. So, that's a good example of the type of bias that you have to be aware of.

There are treatment biases, there are selection biases, but the idea is to learn a little bit about those different biases, and then have they been addressed in that paper? And then the last thing is, once you about the biases and the Hill criteria, how have the authors tried to maybe address those biases, or how can I see if those biases exist? So what I usually tell people is, table 1 in any study is critical. How comparable are the groups? Even in a randomized trial, right? Because if you have randomized trial with 100 people, if you flip a coin 100 times, you don't get 50 heads and 50 tails.

Joe: Right, of course.

Rich: You want to make sure, looking at table 1, you want to make sure how well-matched those groups are, and then if they're not well-matched, did the authors do something like multi-variable analysis to try to control for those confounders? Now, people might say, "Hey, I'm not a statistician. I don't know how to do multi-variable analysis." I don't know how to do multi-variable analysis either! Well, I do know enough about blood banking to be like...

One of my classic examples I love is, people say, "Transfusion causes death." Right? In all of those studies, the more you get transfusions, and I'm not pushing, "Give everyone transfusions," but there's a huge confounder there. Sicker people get transfused. And it's amazing when you look at the literature, some studies do not control for that.

Rich: So, again, to have then controlled for those confounders by looking at how similar are the two groups. The other thing you want to be very cautious of, are secondary outcomes. So there's a reason why you define a primary outcome. Well, there's a couple of reasons. The first one is, you have to figure out sample size. Right? So if getting hives is more common, obviously, fortunately, than dying from an allergic reaction from transfusion, if my outcome is getting hives for some intervention, I'm going to need a lot less patients than seeing if they died from an allergic reaction, right?

Joe: Sure, yeah.

Rich: So it's for sample size. But the other reason you have to declare a primary outcome, is because the more statistical tests you do, the more likely you're going to find a P-value less than 0.05. Because again, the 0.05 says there's a 5% probability that this happened due to chance. So if I do more tests, there's going to be a more probability I'm going to find something less than 0.05. An analogy is with reference ranges for lab tests. We use 95% confidence intervals.

So for each test you do, 5% of perfectly healthy people are going to fall outside the reference range. So when you do some math, what you find out is, if you do 20 tests, like a chem-20, there's an over 60% chance that one of those tests is going to be outside the reference range. Well, in a similar way, 95% confidence interval, 5%. P-value, less than 5%. If I do 20 statistical tests for my study, there's a 60% chance one of those is going to give me a P-value less than 0.05.

So, that's why it's incredibly critical that the primary outcome is declared. And I'm not saying that you can't look at secondary outcomes, they still can be important, but they should be declared upfront. If it looks like this was just added on ad hoc, you have to wonder, "Were they just looking for something?"

And in fact, there's a whole literature now on how bad the literature is on that. I think it was in JAMA, there was a paper to say, you're supposed to register your trials with your primary outcome. And one of the main reasons for that, is so you can't play games, and shift the primary outcome to now something that gives you a good P-value. And they found a pretty high percentage, I don't remember the exact, of studies, that the primary outcome they declared on clinicaltrials.gov, is different than what they actually use.

So, look at secondary outcomes, don't ignore them, but be aware, if they do 30 other tests and one of them has a P-value less than 0.05, and they make a big deal about it, that's kind of a problem. And also, if they didn't declare them upfront, that's also a problem. So those are just a few of the things that when I'm looking at a paper I try to keep in mind.

Joe: If someone were sitting here listening to this, Rich, and they're going, "That all sounds good. I have no great idea about how to get experience with that." You talked about journal clubs that you've participated in, and are there places that you would suggest learners to go to kind of get, not necessarily training, but at least some exposure to evaluating these things?

Rich: Yeah. Unfortunately, it's not super easy, especially when you're... It depends what's local, right?

But if you go to meetings, listen in. What I tell people is, just read it, and go to someone of your faculty who, if you want to talk about a paper, you'll talk about it. Also, read the letters to the editor, because often those are critiques about the paper, and those could be helpful in thinking, "Oh hey, I missed that. Now maybe I won't miss it." You know what I mean?

And it's all about practice, and then going to meetings and reading the letters. And it's a skill that you can just build up. And especially, as you're more in the field, you see something that was observational data, then get disproved by randomized trials. That's

why some of our data we look at, is we compare an observational versus a randomized trial in our evidence-based journal club. Because, what happens? What are the issues?

It's not in transfusion, but an example I bring up, there were all these observational studies saying, "Vitamins prevent cancer," or do all the... Well, if they were all observational. With the randomized trials, it didn't work out. And there was probably, even though no matter how hard they tried to control, people taking vitamins were probably healthier overall.

So there are things like that, like I mentioned that survivor by it. There are things like that in blood banking. Now, and you don't have to be a statistician to know, sicker people are going to get blood, so why don't control for that? Well, just think, what are the things that could affect this outcome, and have they controlled for that? And you don't have to be a statistician to do that.

Joe: Awesome. So, I mean, what I'm hearing is, it's a process, it's experience, it's looking at all the resources you can, utilizing local resources from people that are more experienced than you are, with stuff like that, and building up your skills over time. Is that a fair summary, Rich, of what you told me?

Rich: I think that captures it.

Joe: Okay.

Rich: It's practice, and having at least somewhere to go, even if it's the letters to the editor where you can see, where my critiques, even there, or learn about how to critique an outcome. Well, I will add, Transfusion Medicine Reviews has a journal club, where people... A little bit of conflict of interest I guess, I was one of the journal club editors, and I'm on their editorial board now.

But what the people who did a journal club, and what I used to do is basically try to take apart a paper, and not just necessarily pick a paper that's wonderful but really try to critique. So that's another very useful resource I think for trainees. And it's not like 400 pages, its just, you can look at those. And it also tells you what's kind of hot. I think there's now also something in transfusion itself, that looks at things in the literature, that also gives more of a, it's not just saying, "Wow, super." It's trying to critique it a bit, and see.

Joe: Right. I'm really glad you brought up the Transfusion Medicine Reviews journal club. I learned personally from the critiques that when you were writing, and I think Sunny used to write them as well, and I still look at them from time to time. There's a lot of value there for learners. Just one other thing I would mention, I'm not sure, you're probably aware of this, Rich, but I know they started, the editors of the journal, Transfusion, have started a podcast where they actually break down, I think they take one article that's in a current edition of Transfusion, and then they discussed some of the background and some of the mechanics of it, that again, could potentially be useful for a learner as well.

Rich: I wasn't aware of that, but that sounds like a great opportunity too. What's a podcast though? I don't know what that…

Joe: What's a podcast? Oh, man, let me just pull that knife out of my back, Rich, you're hurting me!

We need to move on. In the time we have left, I want to explore how you utilized some of the resources and some of the approaches that you've been talking about and describing. In one very specific situation that I was really fascinated to see you become a part of. I think most everyone that listens to this podcast is aware that I've had Dr. Mark Yazer on a couple of times, talking about using whole blood in trauma situations, specifically cold stored, low-titer group O whole blood.

And what really was interesting to me, is to watch some of the interactions that I've seen between you and Mark and other folks in, see, I don't want to paint it as pro whole blood, anti-whole blood, but you have been someone who's been willing to engage on the topic and to say, "Let's look at what the literature actually says."

And in fact, I have to tell you, Rich, I really admire this. You went into the lion's den in 2019, in the THOR meeting at the AABB, and listeners, if you're not familiar with THOR, it's basically a pre-AABB meeting, and in recent years it's been largely devoted to discussions about whole blood among a variety of other critical care and trauma type transfusion interventions.

But in any way, you went in and were willing to talk about, I think you called it the “Case for Components” in 2019, when you discussed this in that setting. Well, so before we talk about your specific things to think about with this discussion about using whole blood versus components in trauma, how did you get involved in this discussion?

Rich: It goes back a ways, I don't remember all the details, but I know some of the people who were involved with THOR, on a personal level, very nice people. And I probably had spoken up at other meetings that we've all attended. And even though most of the people in that room probably were not those that would agree with me, it was great that they invited me, and were very courteous about it.

And I think that's really important, to be able to talk about that stuff. So I think part of it was, I knew some of the people through other mechanisms, and then also just like you noticed that I would get up and say, "What's going on here?" Or, "Let's talk about it a little bit. Let's look at the data and see." And part of my reason for this is, Joe, not to make you too old, like me, but I'm sure you remember the whole recombinant VIIa.

Joe: Oh, yes.

Rich: So, when I was in training, they would use it like water, in terms of someone bleeding, they would give VIIa. And it was sort of observational, a case report data, and people just jumped on the bandwagon, because they're like, "Oh, they're going to die from that." But the danger of jumping on the bandwagon, what eventually happen is, they did the randomized trials and trauma and other things, they showed no benefit, because VIIa is really for hemophiliacs with inhibitors. But someone said, "Oh, we're giving more VIIa, it'll help." So when they finally did the randomized trials, it showed no benefit.

And worse, when they start collecting more data, people are getting all these clots that probably caused more harm than good. So, that's also sort of, a kind of motivation for

me, because it's something I lived through, and you always have to think about when you make an intervention, "Yeah, there are benefits, but what are the harms of changing current practice?" And I think that is a really, to me, that's a very strong example. But to answer your question, I think I just kind of knew people and I would speak up, and they kindly invited me to talk a little bit about it.

Joe: You and Yazer didn't step outside after the THOR meeting and "go fisticuffs?"

Rich: No, he's a very nice guy. And while we disagree on certain things, he's really very nice, and we've even gotten a beer sometimes together, believe it or not.

Joe: There you go. Aside from him being a hockey fan of the Montreal Canadiens, aside from that, he and I get along pretty well.

Rich: What's your team then, Joe?

Joe: I'm from Detroit, so I'm a Red Wings fan.

Rich: Oh, okay, I didn't realize you're from Detroit, how about that? Okay.

Joe: Yep. All right, let's take that example, Rich, and let's talk through this. Just in light of, again, the structure that you've talked about or the manner of evaluating new data. Because I can tell you from my personal experience, not just from having been involved with Mark on this podcast and talking to him about low-titer group O whole blood, but just in my previous practice as a blood center chief medical officer, I can't tell you the number of times that people would come to me from hospitals saying, "We've got to have this, and we've got to have it now!" Because, as I said before, "we're going to get behind, if we're going to do this, everybody's doing it."

So let's, again, not necessarily to make the anti-whole blood case, but just for the case of let's look at what the data is, can you walk us through, I know you had kind of summarized, as I recall, you gave three key claims that we'll kind of use as the framework of the rest of our time together to talk about what the data shows. Could you walk us through those key claims first?

Rich: Yeah. So I try to divide things up into sort of, sort of the bullet points people use, but unfortunately things aren't always as simple as just a bullet point. So one of the first ones I like to talk about is people say things like, "well, whole blood is what people are losing, so that's what we should be transfusing." But the problem with that is what's in a bag of whole blood is not the same as what people are losing. There are additives, it's being stored, and so it's not the same.

And I think a really good example of that is some of the studies looking at hemoglobin thresholds, like 7 versus 10, 7 versus 8, because what we find is a restrictive threshold is just as good. And you would think if what we're transfusing is, you know, the same as what people are losing, we should shoot for a threshold of, you know, 11, 12 hemoglobin. But it isn't the same because there are harms.

And a really good example of some of those harms was a study looking at GI bleeds and the, I can't remember the exact thresholds. It was like 7 versus 8 or 7 versus 9, but the restrictive was better, and they actually found harm with the higher threshold. And it

might have been due to the fact that some of these patients having the upper GI bleeds had cirrhosis, had high portal pressures, and you were increasing their portal pressure, making more bleeding. But there was actually, I believe, a mortality difference.

So if we were transfusing exactly the same as what people are losing, then I wouldn't expect all these restrictive thresholds to be so wonderful.

And on a related note, things like platelets and plasma; so cold platelets, we still don't know how pure good they are. And whole blood would have cold platelets. You also lose factor V in the plasma when you store things.

So what's interesting, there was a study done during Vietnam when they were using Whole Blood. This study, done in the early seventies, I think, or late sixties, was the first to show about dilutional coagulopathy in massive transfusion, and they were using whole blood. And you know, you get about 15 units, 10 to 20 units around there, that's when your INR starts going up and your platelets start to drop. And this was with whole blood. So the idea is that this study, using Whole Blood, showed a dilutional coagulopathy.

And what's interesting, they repeated a study like that about 20 or so years later in the OR, you know, in a civilian hospital using mainly red cell units, packed red cells, and guess what? About 10 to 20 red cells is when you start seeing the platelet count getting to a place where you start to worry maybe about, you know, 50,000 or so and you start to see the INR start creeping up.

So what's interesting, whether you use whole blood or packed red cells, you hit a dilutional coagulopathy at the same point because what is in a bag of stored whole blood is not the same as what a person is losing.

The other sort of related point here, so you might say, "well, how can you get 10 units of red cells and not really impact certain things?" Well, fortunately we evolved to have a lot of excess in our platelet counts, in our clotting factors. So we can tolerate losing some of them and that's why it's readily accepted, right? Those guidelines, we know in oncology we can go down to 10,000 for prophylaxis, or you know, a commonly accepted, you know, 50,000 in surgery based mainly on empirical data. But people feel comfortable with that.

So the idea is if you are losing blood that I have to get the platelets and the plasma in them right away. No, that doesn't make sense. And even a little saline is not, I mean, I don't wanna give gallons and gallons, but there is some wiggle room there. You don't need the platelets and plasma front, and also to me, the most important thing isn't the platelets and plasma. It's whether you can oxygenate your tissues. So to me the first thing is red cells.

So the bottom line is with that claim, "people are losing whole blood. That's what they should be getting," first, what's in the bag is not the same. And we have evidence from some of the, especially hemoglobin trials or like I said, you still get a dilutional coagulopathy that's similar to giving pure red cells. You get the same one with whole blood. And then on top of it, we have to remember, we have this huge surplus of red cells too, right? You lose a couple units of red cells, you don't die. So the idea is we

don't need to give everything back right away. So I think that's really how I look at that key claim.

Joe: So let me ask you this, Rich, I think this point is really important. I'm pretty sure we share this feeling. There's a misconception out there about, and you've alluded to this earlier, when you look at the one-to-one, to-one studies, and the previous stuff that was primarily observational. And to my knowledge, there's only been one really big randomized study to actually look at the benefit of one-to-one, to one, the proper study from a few years ago.

I have had so many people come to me and say, "Well, PROPPR clearly showed such benefit to patients. So clearly if PROPPR works and that ratio works, then clearly whole blood's going to work." I'd love your thoughts on PROPPR, because I'm not sure I read it that way.

Rich: I'm glad you asked that, because just a little bit, to go back on the history. I had mentioned that there were these observational studies showing higher plasma ratios, seemed better, but there was that whole survivor bias issue. Right? And so we were waiting for that randomized controlled trial. The primary outcome in PROPPR, I believe was a mortality benefit. It didn't meet the primary outcome.

It met a couple of secondary outcomes, but the secondary outcomes was like death from exsanguination. Which, one, is kind of subjective. Two, would be adjudicated after the blinding was over. I don't really, I mean I care that people died, but whether they died of exsanguination. I mean the outcomes, or another one was I think achieving hemostasis, those outcomes were secondary.

And the point is mortality, who are you... So PROPPR was a negative study, because I can find all sorts of secondary outcomes that will... We talked about the P-value issue, and you do enough studies. So PROPPR to me showed, that a two-to-one is just as good as a one-to-one. All right? But people look like those secondary outcomes, somehow that's the big thing, but it actually was negative.

And then we haven't had really data on whole blood. There has been no randomized trial. And when you talk about the Hill criteria and things like that, you want reproducibility, the data's been very varied in terms of an advantage. And when you look at some of those studies. I think there was a recent study that came out claiming, saying whole blood is better. It was looking at hospitalized patients. But when you look at it a little bit closely, I'd mentioned table one, you have to see how are the two groups.

So the first thing, there were only a third of the people in that... So there was the whole blood group and the component. The component group was a third of the size of the whole blood. So you have to ask yourself, why was it so much smaller? Was there some sort of bias to why someone got components? One idea might be, is it maybe futility? So the idea is no whole blood is very valuable, it's hard to collect, right? Because if we use whole blood, we don't have plasma, we don't have, well, the other stuff.

So where the clinician's saying, "This person isn't going to do well, I'm not going to use whole blood on them." Right?

Joe: Yeah.

Rich: Well, when you look, while they did control for certain things, the Glasgow Coma Scale was much worse in the component group, and they didn't control for that, in the multi-variable analysis. So that's an example of, I still think the papers like that are important. But right there are some issues where I'm wondering, are these two groups really comparable?

And going back to the Hill criteria, in some of these studies with, well, if you look at with whole blood, they got what, two units of whole blood, how is that biologically plausible, that getting one or two units of whole blood saved their life, when they got other components?

So again, it's applying, and I'm totally for doing this in, people can make their own decisions, and there should be more research. I think there are a couple of randomized trials going on now. But for me, what are the downsides? Well, first of all, this whole idea of low-titer, it's all over the place. I don't know if you've looked at absolute phase of titering.

Joe: Oh, my gosh, they're horrible.

Rich: We don't know what a safe titer is. And I don't have a problem giving, or when you give someone, you use a plasma as your emergency release plasma. Yeah, we give incompatible platelets, and it's okay.

But even then sometimes you get hemolysis, but I'm less worried about a couple of units, I'm worried, these people are getting 10 units or more of incompatible plasma or whole blood. We don't know what the threshold is. And what's interesting, the military, when they were using a lot of whole blood back in World War II in Vietnam, one, they would do a minor cross-match. And there was a policy that if you got O whole blood and you were an A, you couldn't get A units for at least two weeks, or until your minor cross-match cleared.

And we know even giving someone a bag the platelets, it trends people getting hemolysis with higher titers. But we have people who have it at lower titers. It also depends, if you're doing IgM versus IgG. And to me, one of the biggest, scary things, I'll be honest, this is scary to me. Based on the data for whole blood, which I don't think is there, and besides the titer issue, the fact that now we don't get more bang for our buck from a product, was also the issue of people are talking about giving women, for patients of childbearing potential, D-positive units.

Because it's very hard to get D-negative whole blood, and there's papers out there saying, "No, no, hemolytic disease of the fetus and newborn, we can now do intrauterine transfusions. People don't die from that anymore." Well, that to me is very scary, because why do we collect Rh-negative blood? For with the patients of childbearing potential, there hasn't been proved to me, there's really not the data there. There's no randomized trials, the observational data is all over the place.

I pointed out some issues with those trials. So if you're going to take a woman of childbearing potential and give her a unit of whole blood that's Rh-positive. If you know

they're Rh-negative or Rh unknown, because you think whole blood is better than components? That to me, with the idea of HDFN, no, people still, babies still die, fetuses still die from intrauterine transfusion. And even if it's gotten less, there's significant morbidity associated with anti-D. That's why we give her RhoGAM.

So people have to understand, look at the literature, but then look at the harms. And I bring back to the VIIa thing. I don't want to stand in the way of progress, but let's really think, weighing the risks and benefits, is it worth it at this time giving a woman whose Rh-negative, or we don't know her Rh type, O Rh-positive whole blood for a benefit, at most one or two units, because that's all we're going to have? When there was a very good, actually, Dr. Mark Yazer published a really important study, in trauma, one unit of Rh-positive blood, 30%, got alloimmunized.

And as I mentioned, you can't always predict who's massively transfused. So we're now going to give that blood, they might not even have that many more units, now they're going to get sensitized. So I think it's very important to really consider what the studies are showing about benefits. And to me, with the PROPPR trial, I agree it's not whole blood, that was arguing one-to-one, I'd also by extrapolation whole blood is, I'm not convinced, let's put it that way.

Joe: Just a quick little, aside here, what you just said in particular about the perception that it's no big deal to give an Rh-negative woman of childbearing age an Rh-positive unit. I actually recall, I don't know if you'll remember this, but it may have been the last AABB meeting, annual meeting, that was live. But I remember in a session, which I won't say which session it was, it doesn't matter, but that opinion article had just come out, and someone kind of mentioned that from the stage.

And again, Rich, I don't know if you remember, but I recall like it was yesterday, you getting to the microphone about as fast as I've ever seen anyone move. And you very politely, I don't want to mischaracterize what you said, but you very politely said, "I think that it's a mistake to look at this in a cavalier manner. I think that it's a mistake to consider this a settled issue because of an article that was published about this." Do you remember that?

Rich: I think I remember that one. There were a few that, I think that year that... Well, and I think it's important, because again, not everyone feels comfortable speaking up and stuff. And I'm more than welcome for people to disagree with me. But I'm also saying, I don't mean to minimize the difficulties of getting Rh-negative blood in general. Sometimes you have to be a really good steward of that. But to me, the answer is maybe then, well there's a whole pre-hospital transfusion, right? That's a whole other area where I'm not sure that the data really backs it up.

So the idea that we're going to give Rh-positive blood to women of childbearing, it's one thing if it's proven that whole blood or pre-hospital transfusion really saves lives. But now we're taking a true risk of LOD with a, to my opinion, not proven benefit. Just to be clear, I'm saying we have to be good stewards of Rh-negative. Well I'm not sure the place to do that is by giving patients of childbearing potential Rh-positive whole blood.

Joe: I understand what you're saying. That leaves me with one more kind of big picture question for you on this, Rich, and that's, you've walked through a little bit. And everyone, just to summarize, the things that Dr. Haspel had mentioned, is kind of the three key claims were that whole blood is what patients are losing, so that's what we should transfuse. The second was, that there is ample data now that whole blood is safe and better than components. And then the third is, even if we're not 100 percent sure that whole blood is better, what's the harm?

And you've kind of walked through and talked about all those points, I'm not going to make you go through them again. I guess the question for me is, from your perspective, where do we go now? Is the work that's being done now from what you've been able to glean of the studies that are going on now, are those things that appear that they will at least try to answer some of those questions that you've raised?

Rich: Yeah, I think as we get more data, we'll learn more. The refill study just came out, which I think is important. Again, that study wasn't perfect, there was a dual outcome. One of them was lactate level, which isn't the most important outcome, but it definitely did not show a benefit, if there was going to be a huge benefit in regards to survival. And that was definitely, whole blood and they were giving lyophilized plasma. But as we get more data, I think also we had talked a little bit in our prep for this, just like, "Well, what do you do locally?"

And I think the key thing is, you mentioned that story. Someone walks into your office or they give you a call or sends you an email. It's, take a deep breath and say, "Let's get the people, the experts in your hospital involved, and let's talk about this." Whether it's transfusion committee, and I'll give you an example just to show, like when all the one-to-one stuff was coming out, one of our surgeons contacted me and said, "Should we consider this?" And we had a really good meeting, but what I recognized is, actually our first cooler didn't have any plasma, and they already had some red cells from the ED.

So we didn't agree that we had to give a ton of plasma upfront, but we did change our protocol to make sure there was more plasma early, right? So it's not like I'm dogmatic about it, but meet with people and invoke, have the trauma surgeons come, have an ICU person come, have a hematologist potentially come when you're discussing these things. And be prepared, talk about the literature, not in these sound bites of like, "Well, they're losing whole blood."

And make sure, that's the other thing, a lot of the people, and again, I freely admit I am not the one doing the surgery or things like that, but the people doing that, we see all the harms of blood, what we see, transfusion reactions or things. So they might not be as aware of some of the harms from this, that what might arise. So, I think it's very important to build relationships wherever you work, but have a discussion, and be prepared to have looked at the literature and reach out.

I reach out sometimes outside to people to get their thoughts, but I do feel strongly that, I was joking to Joe earlier, from Austin Powers. I didn't go to evil medical school to be called Mr. Evil, you know what I mean? Like we're physicians, we have a perspective, we have something to add, and I don't think blood banks should be “have it your way."

And it doesn't mean to be like, "No, no, no." But it's about discussion. And I think that's also why I'm glad there are things like the AABB meeting. They invited me to THOR that weekend, at least talk about it, and think about it in that regard. So does that make some sense?

Joe: It does. I think it's really important to have as clear a perspective as we can on what's going on right now, and I think you've really helped us with that. Thanks for giving us a way to at least think through things before we jump too fast. So, thank you, my friend.

Rich: Thank you so much for having me. As always, it's been a pleasure. Thanks so much.

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Joe: Hey everybody, it's Joe. Just a couple of thoughts before I let you go, and I hope you listen to this. This is important. I found myself in, I guess I would describe it as a little bit of an awkward position in this interview, because I have two people that I consider friends, Dr. Haspel and Dr. Mark Yazer, who was mentioned several times in this interview, who have very diametrically opposite feelings on this particular issue. And I mentioned at the top, if I were to really be pushed, I am probably, well no more than probably, I am more pro-low titer O whole blood than I think Dr. Haspel is. But that's okay.

So here's what I hope you take away from this interview: Whether you listened to this and you, and you totally agreed with Dr. Haspel or you didn't totally agree with Dr. Haspel, I think what is most important is that we evaluate the data and the evidence as dispassionately as we can and try and figure out what's the best thing for patients, right? That's really what we're all about, and that's why I wanted to have this discussion with Dr. Haspel. Simply, he looks at things in a different manner than I do. It's a more sophisticated manner than I do, and I'm not embarrassed by that. He has more skills in these areas in terms of evaluating the literature than I do.

But as I said, there are differences of opinion and what I feel doesn't matter. Really what Dr. Haspel feels and what Dr. Yazer feels, doesn't matter all that much. What matters is what the evidence shows. And again, I hope you take from this just the feeling that we should be looking at things as dispassionately as we can in figuring out what the best things for patients might be.

I just wanted to remind you that Dr. Haspel has been kind enough to share several links to kind of take you further in your understanding of what he talked about today. You can find that on the show page at BBGuy.org/101. One of the links in particular is to an article that he was senior author on that was published in January, 2023 in the journal “Transfusion,” talking about some of the same things about whole blood that he mentioned in the interview.

I do want to mention that while you're at BBGuy.org/101, you can also link to or go directly to wileyhealthlearning.com/transfusionnews to get your hour of totally and completely free continuing education. As always, thank you for the continuing education sponsorship to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as of course to Wiley Health Learning.

Also, if you can, please go to Apple Podcasts and give this podcast a rating, review and subscribe. That will help other people find it.

Just so you'll know, moving forward, I think I mentioned before that the odd numbered episodes such as this one, number 101, are going to be primarily continuing education episodes, while most of the even numbered episodes, including the one that's coming very soon, will be of practical educational value. Some of those will be teaching, some of them will be talking about things related to education, and that's actually what's happening with the next episode: "So You Want to Be a Blood Banker."

I have more fun episodes coming as I continue to… well, you guys know me. All I'm trying to do is fulfill the mission of this podcast and my professional life, which is to teach the essentials of transfusion medicine to learners everywhere.

I can't wait to share all that with you, but until then, my friends, I hope that you smile, have fun, tell the ones that you love just how much you do, and above all, never, ever stop learning! Thanks so much for hanging out with me. I'll catch you next time on the Blood Bank Guy Essentials Podcast.