Joe Chaffin: Alright everybody! Welcome to episode 007 of the Blood Bank Guy Essentials podcast. I am honored today to have as my guest Dr. Minh-Ha Tran from UC-Irvine. Minh, welcome to the podcast!

Minh-Ha Tran: Hi! Thank you! It's nice being here.

Joe: It's great to have you. I just want to let everyone know a little bit about you. You are an Associate Clinical Professor at the UC Irvine School of Medicine. But you're a little bit different than most of the folks that I talk about, not that that's an insult or anything—you're awesome! But you're in a couple of different departments at UCI. You're in the Department of Pathology and Lab Medicine, and you're also in the Department of Internal Medicine. I want to hear a little more about that in just a second. You're the Associate Medical Director for the Division of Transfusion Medicine and Apheresis. Minh provides medical oversight of the UCI Blood Donor Services and also, does consultation services for patients requiring therapeutic apheresis at UCI. He has an interesting background for those of us in blood banking. It's a little bit different than the so-called "traditional pathway". He did Internal Medicine training at Mercy Hospital in Pittsburgh and then followed that with fellowship training in transfusion medicine at the National Institutes of Health. Minh, how long have you been at UCI?

Minh: Since about July of 2009, about 7 years now.

Joe: Awesome. And you and I have worked together on a couple of occasions, taking care of patients at your institution, just for full disclosure for everyone, which has been fun and that's how I actually got to know you. I would like to, if you don't mind— I mentioned that your background is a little bit "nontraditional," I guess, for those of us that came up as pathologists and moved into blood banking. So why don't you tell us a little bit if you don't mind, what is it that got you interested in blood banking, and how did you set down along this pathway?

Minh: Yeah, the path was an interesting one. Probably one of my most memorable cases when I first started internship was an elderly gentleman with CLL and he had Evans Syndrome. The hematologist/oncologist at the time was very instrumental—-he was like a mentor to me. He would tell me to have the slide ready and he would show up at the microscope and take me through the slide and say, "These are microspherocytes," etc. etc. And I think that started getting me really interested in immunohematology. And then throughout my residency, there have been some interesting cases of coag and other things. As

a senior resident, I was able to do a rotation with Dr. Bontempo over at University of Pittsburgh Institute for Transfusion Medicine, who runs a "Coag rotation" and I didn't even know about blood bank at the time. I showed up to a "coag rotation" and Joe Kiss says to me, "Well you know, the coag rotations are in the afternoons. If you're interested, we'll get you over to the university and do some blood banking in the morning." I was like, "Oh yeah, sure!" So, that's kind of what started it!

Joe: (laughs) You're going, "What's blood banking again?"

Minh: Yeah! (laughs)

Joe: Awesome!

Minh: And then when I got to fellowship, I just found out blood banking encompassed everything about hematology that I was really interested in, without all the really sad oncology stuff. So it was really cool.

Joe: Ah yes, absolutely. Well, I want to thank you because you still keep your hand in hematology I know a little bit, and you actually just finished this past weekend, before we're recording this in the beginning of May of 2016, doing a massive hematology symposium at UCI. I understand that went really well?

Minh: Yeah, yeah! We were really excited! We had a great turnout for our first annual. It was at the Disney Grand California Hotel and we had about 65 people there and we had exhibitors and everything. We just really really had positive feedback. I just got through reading course evaluations and I think it was a nice boost to my ego! (laughs)

Joe: (laughs) Good deal! Well, I know you well enough to know that I'm sure that it was awesome and wish I could have been there!

Today Minh and I are going to discuss—-I guess you could call it a "hot topic"! It's something certainly we've been talking about for quite a while now, and it's something that I think that's **really** important for blood bankers and clinicians to get a really solid handle on as best we can anyway, right now. There's a lot of data that's developing in this field, and we're going to talk about massive transfusion. Massive Transfusion—-no pun intended—-is a *massive* issue for us. Blood banks and blood bankers probably don't have a much more stressful situation that comes up, aside from massive transfusion. It's a big deal. Things happen. People go crazy, in terms of just the amount of product that's needed, for the short time frame that it's needed in. What Minh is going to do for us is just take us through a little bit, how we should be thinking about these things, both from our side as well as what you should work on process-wise with your clinical

staff. So what we're entitling this discussion is "The Who, Where, What, Why, When and How of Massive Transfusion". I think I got that in the right order! (laughs) So "Who, What"…sorry, see I screwed it up! "Who, Where, What, Why, When and How of Massive Transfusion"—-so Minh, why don't you start us off with the "Who," when you say the "who of massive transfusion", who are you talking about? What kind of patient group are we discussing here?

Minh: Sure. So, this is the portion where we define our populations. So massive transfusion, historically, has referred to trauma patients, and **patients fitting into a "massive transfusion criteria" are typically defined as those who receive 10 or more units of red cells, over 24 hours**. Alternatively, they can be defined as patients who receive **more than 4 units over 1 hour** with an anticipated need for continued blood component support or **replacement of greater than 50% of their total blood volume by blood products within 3 hours**. So these definitions, in some regard are retrospective. So you don't know when you've achieved or met the criteria after it's occurred.

Joe: Right…that's a little bit of a problem, right?

Minh: Yeah, it is! Because you kind of want to initiate rapidly. So, I was searching around the literature and I found a paper by Nunez et al. in Journal of Trauma, and they developed this scoring tool called The Assessment of Blood Consumption Score. They have this large retrospective cohort of level 1 adult trauma patients and they were able to look at following scoring parameters:

Penetrating mechanism - Yes or No
Systolic blood pressure of 90 mm or less
Heart Rate 120 or greater
Focus Assessment with Stenography for Trauma scan or FAST scan being positive

So scores of 2 or higher were found to accurately predict those who went on to have a subsequent need for massive transfusion. The sensitivity and specificity were around 75 and 86%. So that's a nice quick way to predict who's going on to get massive transfusion…

Joe: Minh, so let me interrupt you for just on second. I'm sorry about that…

Minh: Sure.

Joe: By the way, for everyone to know that I'll have this reference on the show page for this particular episode, the Nunez paper that Minh just mentioned. But just practically speaking is that something that—-have you seen that be widely used? Is that something—-obviously it's mentioned in a paper and it looks great,

I personally haven't seen anyone talking about using this. Have you seen it used?

Minh: I can't say that, you know, in the trauma bay at the time that these things are occurring, I think I put it in there in response to that idea that if you're waiting until 10 units are transfused in 24 hours—-gosh, the "cat's out of the bag," right? He should have activated by then. I think the trauma surgeons are just very experienced. They probably do this in their head, sort of spontaneously and instantaneously that they are able to evaluate the patient and have extensive experience and this happens probably automatically for them and they just go ahead and activate the massive transfusion protocol…sort of instinctively.

Joe: Right. So maybe, is it fair to say, while they have tools like this, and I'm sure they use it, that for us in the blood bank, maybe massive transfusion is defined as when the trauma surgeon say, "It's massive transfusion!". Is that making it too simple?

Minh: No, that's exactly what it is (laughs)—-Exactly!

Joe: (laughs) Yeah, so functionally speaking, nobody is sitting in the OR probably going, "Ok, well let's see that's six, that's seven…hm, well, we're not to ten yet." It's more of a judgement by the clinicians and more of a "hey, this is a bad situation. This looks like we need to activate the massive transfusion protocol" kind of deal, again, is that fair?

Minh: Exactly, yeah.

Joe: Okay. We keep saying trauma, is it all trauma or are there other situations in the hospital where massive transfusion can occur?

Minh: Yeah. Actually we have a similar massive transfusion protocol that we developed with our OB/GYN colleagues to deal with maternal hemorrhage. I think this sort of, massive transfusion paradigm, it is also being implemented for other, sort of, non-trauma situations where you have exsanguinating bleeding, like massive GI bleeding and things like that. It's a very convenient way to provide massive blood support.

Joe: Okay, excellent! So we'll get more to that in just a few minutes, in terms of the specifics of that blood support. But anything else on the "who"? We've discussed the "who" of massive transfusion, are we missing anything there, Minh?

Minh: I think that's pretty good. (laughs)

Joe: (laughs) Outstanding! Good job us! Yay! So that's the "who" of massive transfusion, let's move on to talk about the "where." I think you already started down this pathway a little bit. Where in the hospital do we typically see these?

Minh: Oh yeah, so the "where" is a complicated issue. We in the blood bank, we're in a fixed site and we're needing to issue blood rapidly and there are many, many players in the massive transfusion scenario. So you have a patient that is brought in from the scene of an accident or something, and they may be shuttled through the ED into the trauma bay, they're assessed by a team of trauma professionals. They may be, at some point, shuttled to the CT scanner, they may go up to the OR, they may go from the OR to interventional radiology if they need something embolized, back to OR, maybe go up to the SICU. So all of these transitions in various sites of care that can happen rapidly are associated frequently with different staff members and people who may not be aware of all the protocols. In addition, specimens are being sent to them from the lab from potentially these different locations, and blood is being requested, potentially to and from these different locations. So the "where" is an important issue because most of the time the blood bank is not—-we're not located in the same location as the resuscitation is occurring and what I always say in hospitals, "you know, these 30 tons of concrete and steel that separate us from the OR or us from the trauma bay," happens— I found that it interferes with the natural clairvoyance that blood bankers have. So we don't know what people are thinking. So this "where" engenders a critical issue of communication, that's like, "tell us what you need and where you need it" and we'll send it to you. And if there's a runner involved, that runner needs to be trained. In fact, some centers actually armed the runner with a cell phone and then the runner always accompanied that patient, or whatever. So the "where" is really important because we don't always know where to send the blood, and if we send the blood to the trauma bay and by the time it gets there, the patient's already in CT scanner, and so on and so forth. You can see it can become really problematic for that patient who needs blood products.

Joe: Boy, you said a couple of things that are super-important there! I've seen you in a lecture that you gave about this. I've seen you kind of diagram that out for blood bankers to try and understand the complexity of that care environment and your diagram is actually hilarious. Can you describe it for me a little bit?

Minh: Oh yeah! I have like these spheres all over the page, and they each represent a location of care. One sphere is the lab and the other sphere is the blood bank and they show these dotted lines that represent specimens going back and forth to each of little area of care and then these straight lines that might represent blood components going back and forth from the blood bank to the various sites where the patient might be at that point in time. So it's meant

to look overly complicated! That's the whole idea is—–that's kind of how real life is. It's not organized as we might want.

Joe: Well, it is, isn't it? Exactly! And I think in blood banks, we are sometimes a little unrealistic about the way our blood products should be handled. We're obviously, we're blood bankers, so we take a very personal interest in our blood products and making sure that they're used appropriately and used in the right places. But we have this very linear thought, sometimes, that "by God, I'm issuing it from here, it's going directly there, one unit at a time and you're going to…", that kind of paradigm—–it really blows up in massive transfusion, doesn't it?

Minh: Yeah, yeah it does.

Joe: For sure. Well, and the other thing that you said, that I want to talk a little bit more about before we leave the "where," is the communication. And I know we'll get to this a little bit more when we talk about the products that we're issuing. But the importance of having that communication, not only at the time this is happening, but a "pre-discussion." Basically, talking about this stuff way before it happens. I don't want to jump ahead, forgive me if I am, Minh, in your "who, where, what," but can you talk a little about that? How, practically speaking, can blood bankers have those kind of conversations, so that when this incredibly complex environment is occurring, that we know what it is that we're supposed to do?

Minh: Yeah, so I think formulating, sitting down with all the key stakeholders. So the trauma service, the ED physicians, the anesthesiologists, runners, peri-operative nursing staff, etc., having them all in the same room and developing a massive transfusion protocol together, so that everybody is on the same page, and recognizing that there are different members of the team. For example, in our center, the trauma surgeons have an expectation for high ratio transfusion when that patient hits the OR. But they're so busy operating that really the true sort of transfusion ordering process of transfusion support becomes the realm of the anesthesiologist. So if the anesthesiologist is not aware of the expectation of the trauma surgeon, the trauma surgeon is, you know, busy operating, then that right there could be what I like to call "the blue drape separating the two teams" as also, a big barrier to communication, that the anesthesiologist may not be aware that massive transfusion was activated on this patient. Because that patient came from the trauma bay to the OR and that communication piece didn't occur, so then the anesthesiologist was like, "Ok, well, here's what the TEE shows, this is what my blood pressure and heart rate show, and here's my hemocue,..". They start doing their own thing, so the communication is really important. Not just between the site of care and the blood bank, but also

between providers so that everybody's on the same page and they know what they want—what the expectation is.

Joe: And you're 100% right. I always tell people in labs where I work, that the work of massive transfusion is largely done—-and this might be over simplifying —-but the work is largely done, the ground work has to be done way before it happens. Because if you're trying to figure out the process while it's occurring, you're dead!

Minh: Yeah! (laughs)

Joe: Way too late for that! I don't mean to over dramatize it but…okay. So, we've talked about the "who," the kind of patients that get massive transfusion and we just covered the "where" and the importance of the complexity of the process, as well as the importance of making sure that communication occurs. So let's move on and talk about the "what." So we've done the "who" the "where" and here's the "what". And the "what", when we talk about massive transfusion what are we talking about? What's considered kind of the standard of how we transfuse these patients that are undergoing massive transfusion?

Minh: Sure. So fixed-ratio transfusion or massive transfusion is an attempt to recapitulate whole blood. So you're using fixed-ratios of usually, red cells, to plasma, to platelets, to try to, in some way, reformulate effectively—whole blood. So traditionally, the fixed-ratio or you know, when people say "1:1" (*NOTE: Read this as "one to one"*) something like that, they're referring to the number of units of plasma to the number of units of red cells and this definition has now, brought into include platelets. Some centers are including CRYO,with every second or third round, or something like that. So the addition of platelets to the definition can lead to confusion. What I like to tell people is depending on where you trade or where you practice, that center might predominantly use whole blood-derived platelets. Whereas, other centers may predominantly use apheresis platelets, so it was a big culture shock for me coming back to California and finding that California is an apheresis platelet state. I always knew it was July when I get an order of 6 units of platelets for a patient, and I'm like, "Whoa, whoa, whoa—-that's like my whole blood bank inventory, dude!" Because they probably trained, understandably, at a center that was accustomed to using 6 packs, right? So obviously, that will affect your ratio. So if you're trying to adhere to, you know when you hear "1:1:1," that's typically referring to the whole blood derived platelets, where you get one whole blood derived platelet per one red cell. So, that's what you would get with whole blood, right? But a center like ours where it's like apheresis platelets, you hear things like "6:4:1" or "6:6:1"—-where you're one apheresis platelets to six units of red cells. So that ratio is referring to the number of red cells, plasma and platelets that you get. And these precise ratios—they vary, between

centers, so every center has its own massive transfusion protocol. And these different ratios may vary between these various centers.

The basic idea is that the clinical team identifies the "who," hopefully they know where they are because it can be sometimes difficult, and then they say, "Ok, this patient needs massive transfusion," they activate the massive transfusion protocol. Presumably, they have a very robust access in place. Something like an introducer in a subclavian vein, and they have these things called "Belmont Rapid Infusers," where you can just dump lots of product into the patient very rapidly. That's a big deal, right? You want to transfuse, but you really need a very robust access first before you start resuscitating these patients. But then the team would say, "Ok, this patient merits massive transfusion." They call the blood bank and say, "We're activating massive transfusion protocol. Send us the first round of product." We send the whole "6:6:1 pack" down to wherever they are. They **transfuse the whole pack**—-everything, and then they reevaluate and say, "You know what? We need another one." So they call us back, request another. We send it. In the meantime, you send it and, the blood bank, because now you're on massive transfusion protocol, is now thawing the next round of plasma, allocating the next apheresis platelet pack, they're preparing the next red cell units and labeling, doing all that stuff so it's ready to go as soon as we get the word from the team.

Joe: Minh, let me stop you there for just a second. That's really important practically speaking, and beginners and people that are early in their blood banking career can kind of miss that. So, as you mentioned——I guess I would say, you mentioned the California center thing, and it's certainly more than California, you happened to do some of your training in Pittsburgh, obviously, which is well known to be a big user of whole blood derived platelets. I had a conversation with Mark Yazer a few episodes ago about that. But in most places around the United States, certainly not all, by any stretch, I would say the majority—-they're using those apheresis platelets. So functionally speaking, a massive transfusion pack in most places, again, is this fair to say that it's usually in the range of six units of red cells in the range of four to six units of plasma and one unit of apheresis platelets? So functionally speaking, that's primarily what we're talking about, right?

Minh: Yes.

Joe: Okay. Being really practical, how does that look? Is it all going out in a big box? I'm sure I know places differ, but how are those put together? When you say a "pack," what are they physically picking up from the blood bank?

Minh: You know, you will have an igloo or something to that nature for the red cells and then some folks will have a different sort of a carrier for the plasma.

Then the unit of platelets will be….so yeah, so you know, the runner will come and have an igloo in one hand and in the other hand, they'll have a plastic bag. All that stuff is sort of mixed in. The idea is that they get to the site of care and it just all goes into the patient simultaneously. So we usually tell them to hang the platelets separately, because often times this is going through a blood warmer so we don't want the platelets to go through the blood warmer. That's usually how it looks. They just come and pick up a bunch of stuff! It's like a shopping trip! (laughs)

Joe: (laughs) Shopping trip where the groceries have been picked out for you already, right?

Minh: Yeah! Exactly!

Joe: Here's pack one, here's pack two—-and that's a key. Because sometimes places can get in trouble when, I don't want to say the anesthesiologists are picking and choosing what their transfusing, but you said something really important. The intent is, you get the pack, you transfuse the pack, you ask for the next pack. Rather than saying, "Ok, I've given all of the red cells but I haven't given the other ones yet. Can you send me more red cells?" Is that sometimes a struggle?

Minh: Yeah, I think that's where sort of the expectations issue is or the communication…if the patient presents in the OR and whoever is managing the transfusion support is unaware or doesn't know that right now we're expected to be following MTP for this patient, then they may just automatically revert to a la carte ordering. So I call it "a la carte." So they say, "Give me two units of red cells and a unit of FFP, and I think we're okay on platelets for now." That might be their automatic, sort of transfusion style. And if they didn't receive the memo that this patient is under massive transfusion, they may not know. The communication is KEY.

Joe: That might be a reoccurring theme, Minh. We might hear that again! (laughs)

Minh: Exactly!

Joe: With that being said, the massive transfusion pack, as it were, that will vary from place to place as you said. Okay, let's do the "why." Why, Why, Why do we do that, Minh? Was there kind of a beginning point to this? I think that most of us have heard this fixed-ratio transfusion, as you mentioned, and the massive transfusion packs have been in widespread use for the last—-I don't know—8-10 years or so. Why did we get there? How did this start?

Minh: So it looks like this originated from a paper by Borgman and colleagues. So what Matthew Borgman and his group did was they performed a retrospective study of 246 patients at Army Combat Support Hospitals, so this is sort of the much touted, "Iraqi combat data." This was a retrospective analysis of data for trauma patients admitted to Combat Support Hospitals in Iraq between November 03 and September 05. The data was derived from the Joint Theater Trauma Registry maintained by the U.S. Army Institute of Surgical Research. So patients were included if they met this criteria of 10 units of red cells over 24 hours and each of those patient's respective medical data were collected. So about 4.6% of the patients or 246 out of 5293 patients admitted met this criteria. So these 246 patients were then divided into groups, based upon the ratio of plasma to RBC units transfused.

So, just as an aside, they were separated out by the transfusion ratios as opposed to trying to find groups of various similar patients or identical patients and then applying an intervention, which is the typical randomized controlled trial. In this case what they did, was they took was, sort of, ratio and let the chips fall where they may regarding the characteristics of those different patient groups. So that's one point to make. So what they found was in terms of mortality, they defined a low-ratio transfusion, if you divide the plasma to red cells, and you get 1:8 so that was the low ratio. So that was a n of 31. Then the medium ratio is 1:2.5, was a n of 53. High ratio was 1:1.4, n of 162. The mortality for these groups was 65%, 34% and 19% respectively…

Joe: And so Minh, again they were— just to clarify on those ratios—-the low ratio ones were people that got a whole lot more red cells than plasma, the high ratio ones that got were roughly, well close to the same number of units of plasma and red cells, right?

Minh: Right, right.

Joe: Okay, go ahead. I'm sorry.

Minh: So what came out of this was, if you look at the outcomes and baseline characteristics of these patients, you find that the **patients in the low ratio group, they tended to die much sooner** than the patients in the other two groups. So in terms of hours, the mean and interquartile range (IQR) for time to death was in the low group was only 2 hours, with an IQR of 1 to 4. The medium ratio group was 4 hours, with an IQR of 2 to 16. But the high ratio group was 38 hours, with an IQR of 4 to 155. Those in the low ratio group more predominately died due to a hemorrhagic death, so it's like 92.5%, 78 and 37%, respectively. In addition, **compared to the medium or high ratio group, patients in the low ratio group were far more severely injured**. So they had a much higher acute injury score for head, neck and thorax. They had a lower presenting hemoglobin and systolic

blood pressure. They had higher presenting heart rates and base deficits and they were more coagulopathic at presentations; so they had a higher INR. So this group was a distinctly different group than what you saw in the high ratio group. But from these data the authors concluded that among combat casualty trauma cases, high ratio transfusion, like 1:1.4 was independently associated with an increased survivor hospital discharge. And they actually recommended that massive transfusion protocols should utilize this high ratio transfusion for trauma patients.

But given that the time to death occurred within 2 hours for the low ratio group, and time to death was 37 hours or more for the high ratio group, what this brings up is an issue of **survival bias**. The more acutely injured, the more ill patients, the more grievously injured individuals, they die before their transfusion support could approach this touted 1:1 type of high ratio criteria. Whereas those patients who were perhaps less severely injured, they survive long enough so that the transfusion support could catch up and achieve this sort of high ratio transfusion. So this is like a survival bias.

Based on this n of 31 of the low ratio, now this sort of fixed-ratio transfusion has sort of become a standard of care. And I'm not arguing with it, by any means. I think it has a lot of merits. For example, I think the fixed-ratio or massive transfusion type of resuscitation allows interdisciplinary collaboration to develop the protocol. It establishes pathways to more rapidly get the product to the patient who's bleeding. It facilitates communication. We in the blood bank, we know when a patient is very, very ill when we hear massive transfusion being activated. It creates a standardized process to minimize confusion. You know, you request it, you get it and you transfuse it. And if you need it, you request it, again. So, I think it has many merits. But it looks like that seems to be the origin of current massive transfusion practices.

Joe: That's a great summary. I think that it's been, my experience as well, that there are so many benefits to the fixed-ratio *process*, but it is important to understand that it was originally based on something that—-I mean, look, I'm an old Army guy and I'm always happy when good stuff comes out of military studies. But quite frankly, this study has had a lot of criticism over the years, and I think the survival bias is the biggest thing. As you mentioned, the people with the high ratios were the ones that died quickly and people argued that just means that they died before you could get them enough plasma. And that's not necessarily the reason that they died. We don't need to beat that to death! Over the years, blood bankers have kind of, I think had mixed feelings about this, I think that's certainly fair for me to say. While there are definitely benefits, I think everybody has been a little worried about the blood bank side especially, well —-let's put it this way—trauma surgeons for the most part have said,"Yay! Good! This works. Standard of care, let's roll! And further, can you get us fresh whole

blood? How about that?" (laughs) But we have been a little more, maybe not necessarily reluctant, but we've wanted a little more data. And I know there have been some recent studies published, as we move into the "when" of massive transfusion. Can you take us through some of the more recent, more prospective-type studies that have looked at this issue that have kind of, hopefully, answered some of these questions, as well as given us an idea of "when" massive transfusion intervention needs to occur?

Minh: Sure, so, there was a paper that was recently published in JAMA by Holcomb and colleagues. This is the "Pragmatic Randomized Optimal Platelet and Plasma Ratios," or "**PROPPR**" study. This study is a multi-center randomized control trial that compared two different ratios, Red cells to plasma to platelets of 1:1:1 vs. 2:1:1. And the study was designed to detect pre specified differences in all-cause mortality of 10% at 24 hours and 12% at 30 days. These numbers are based upon the increased sample size that occurred later in the study of 680 subjects. So importantly, *this is the primary outcome of the study*; the primary outcome that the study was designed to address. **The study found no difference in mortality at either time point whether trauma patients were resuscitated with a 1:1:1 or a 2:1:1 strategy**. For the 1:1:1, 24 hour all-cause mortality was 12.7% vs. 17% for the 2:1:1; the difference was –4.2% with a 95% C.I. of –9.6 to 1.1. So that was less than the 10% difference that the study was designed to detect at that time point. Also, at 30 days, the differences were 22.4% vs 26.1%, with a difference of –3.7%, 95% C.I.'s –10.2 to 2.7. Again, less than the 12% that the study was designed to detect. So, this study found no difference in the primary outcome of 24 or 30 day all-cause mortality whether a 1:1:1 ratio or a 2:1:1 ratio was applied.

So then there was a second study, the "Prospective Observational Multicenter Trauma Transfusion Study," or "**PROMTT**." This is also by Holcomb and colleagues. This was not an interventional study, this was more of an observational study, and I believe that there were ten centers in it, and each were allowed to use whatever ratios they had already established in their respective massive transfusion protocols. The patients studied were adult trauma patients who were analyzed for in-hospital mortality, and this was based on the plasma:RBC and platelets:RBC ratio at multiple intervals between 31 minutes and 6 hours. They had an interval that they studied at 18 hours, and then a 29 day interval (between 24 and 30 days). **So in the first 6 hours, ratios of 1:2 or better, or the so-called "high ratio transfusion," these ratios were independently associated with decreased 6 hour mortality when hemorrhagic death predominated**. **But among survivors at 24 hours and beyond, the subsequent mortality risk at 30 days was no longer linked to the ratios** that were applied. If you look at the graphs and data in this study, you can't help but wonder if these different time points that they were looking at were sort of a microcosm of "survival bias." If you can get the patient through 24 hours they are going to survive no matter what the ratios

are. But in that first, that early period, what happens is if they don't survive, if they die within an hour, then those patients who were very egregiously injured, they drop out of the overall analysis. But they're not accounted for, because you can't possibly re-do the characteristics. So it's sort of like a microcosm in a way of survival bias, is what I would consider it. But I guess that's just my opinion.

So then, the other study that I'd like to point out is the **Riskin et al study**. This is a study at Stanford where they designed and implemented a massive transfusion protocol and an aspect of that massive transfusion protocol was that they would identify the massive transfusion leader, with defined roles for all team members. So this is the communication piece. They would have a defined ratio of 6:4:1 to provide rapid product distribution, and then they would also have four units of thawed plasma available at all times. So it incorporates both communication pieces and operational pieces with an overall impact that they would more rapidly get product to the patient. Their outcome was that, you know, they did a pre/post study, pre-implementation/post-implementation, and they found that **while there was no difference in the ratio of RBC:FFP in the pre/post periods, there *was* a significant reduction in mortality during the post-implementation phase**. So they went from 45% to 19%, and this was attributed to significant improvement in product delivery times.

What I take from this is that, yes, I think we should be adhering to a high ratio transfusion strategy, but that precise makeup I think we still need more research to figure out what that precise makeup is. But perhaps equally important, or maybe even more important, is how rapidly that product is delivered to the patient. That's where you get into the communication pieces, identifying the right patient and having the operational infrastructure in place to rapidly activate and get product to the patient to begin resuscitation as soon as possible.

Joe: A lot of discussion there. That was awesome. That's a great summary of those articles. I think it's fair to say that the authors…that Dr. Holcomb's group probably were hoping for a little bit more of a clear-cut benefit in terms of long term survival, but I think that what you said is important that survival bias and kind of in microcosm. But I think it's important to emphasize that both of those studies, and in fact, in the Stanford study as well, the key that came through was, getting product to the patient rapidly is—-and I know I'm summarizing what you just said—-but getting product to the patient rapidly in whatever exact proportion is really what we're looking at. And that's been for me, the biggest benefit of this entire process. Is that again, fair to say?

Minh: Yeah, the key thing about the PROMTT study is those patients who more rapidly achieved those high ratios in the first 6 hours, that's where that high ratio transfusion benefit came in. So, I think there's definitely some signs out there to

support this trauma-induced coagulopathy premise. Perhaps, achieving these high ratios has that sort of, physiologic benefit of restoring coagulation factors and also, other factors that may be important in aiding in survival.

Joe: Let me throw a curve ball at you, though, Minh. So we talk about—–and you mentioned this phrase at the beginning, kind of recapitulating whole blood. I threw out a word or a blood product that makes blood bankers cringe everywhere. Again, just to let people that are kind of just beginning to understand this, why the heck don't we just use fresh whole blood, for goodness' sake? What stops us from just transfusing fresh whole blood to all these patients and not worrying about artificially creating whole blood?

Minh: I think the premise of component therapy began with the idea that the different components of blood, they each have their own ideal storage characteristics. Fresh whole blood, in the military setting may be okay, I guess because you're walking blood banks running around with uniforms on. But operationally, to sort of have blood for a large population, it becomes very difficult to maintain fresh whole blood which probably I would imagine has a very short shelf life. So, storage of blood at temperatures that might facilitate survival and functionality of platelets, may not be very great for red cells or the clotting factors, some of which are thermolabile and they deteriorate at room temperature storage. And probably you also get a lot of breakdown of cytokines release from leukocytes and things at room temperature that you might not get at refrigerated temperatures. There's the issue of growth of potentially contaminated organisms that may not occur at refrigerated temperatures that do at room temperature or do at a greater rate at room temperature. So, I think the component therapy allows us to have a very robust inventory for a population and your storing these components at their ideal storage temperatures and under the ideal storage conditions for each individual product. So, that's probably why I think, there was that move to component therapy, but please correct me if I'm wrong! (laughs)

Joe: (laughs) I wasn't trying to trick you! You're absolutely right! It's practically speaking, a very challenging thing, outside of the military setting to do a fresh whole blood process. In fact, I often joke that one great way to make a blood banker sweat is to bring up fresh whole blood, and you'll see the immediate reaction, "Ahhhh! No NOT THAT!"

So, we've taken some time to go through the "who, where, what, why and when" but Minh, right here as we finish this out, let's talk a little bit about some of the practical mechanics and we've mentioned some of them already, in terms of the physical packing of units in a pack, etc. I wanted to just touch on one thing, real quick. In terms of blood product choices for ABO, and we don't have to go into this in an enormous extent. I did a long blog post on this not long ago,

on the use of different plasma choices (NOTE: See **http://www.bbguy.org/2016/04/13/breaking-the-rules/**). But can you talk to us just a little bit about what the current state of research is on options, instead of using AB plasma in all these cases when we don't have the patient's blood type. Are their other options or other things that we can do?

Minh: Yeah, so it looks like the industry is moving towards the use of group A plasma as the "universal donor plasma" for emergent resuscitation in this setting, where a patient's ABO is not available. So, this sometimes happens when patients have had severe trauma and perhaps they show up in a very, sort of exsanguinated state, and you try to put needles in and nothing really comes out. This patient is just, I mean, or maybe there's some issue of getting the specimen to the blood bank, or what have you. And you don't immediately have the ABO type. So historically, AB plasma was used, but potentially at the risk of high rates of TRALI, it's a rare blood type, it's hard to keep on the shelves, sometimes the TRALI deferral criteria may need to be relaxed in order to boost AB inventory. So, there's been some movement towards use of group A plasma, there was a small study from Zielinski et al that was published, and it did not show statistically significantly greater rates of mortality or their adverse outcomes in the small number of patients who received incompatible A plasma. And more recently, there was a study published by the Biomedical Excellence for Safer Transfusion Group or BEST Collaborative, and they did a survey of level of trauma services around the country, with a very good response rate. It was actually 50% response rates, 60 of 121 centers. It turns out that 63% of respondents reported use of group A emergency release plasma in the setting of unknown ABO type, and 62% reported no limit on the continuing use of Group A plasma in this group and 79% reported no effort to assess the anti-B titer of these group A units that they had on hand in the event that this situation would arise. So, I guess that's one of the newer things that's emerging right now for resuscitation of these patients.

Joe: Wow, that's fascinating. Especially the 62% that have no limit on continuing use of Group A plasma. From my perspective, that's the only part that would worry me. I mean I think we have good enough data to know that in urgent situations, if you give a Group A plasma to someone who turns out to be either Group B or Group AB, obviously that's an incompatibility. But if they're not using any limit on continuing to pump that plasma in, I guess, I don't know the answer to this, would you assume that that's just due to the fact the patient is continuing to exsanguinate and your pumping in Group O red cells and the A plasma doesn't matter as much?

Minh: Yeah, I think so. You're sort of temporarily converting the patient to a Group O patient.

Joe: It's kind of an immediate urgent exchange transfusion, in a way, I guess. That's really interesting. As I said, I have more information on the Blood Bank Guy website about this, so we won't take anymore time to go into it. So Minh, we've hit a lot of stuff! We've done the "who", the "where", the "what", the "why", the "when" and the "how" of massive transfusion. I know that there's a whole lot more that we could talk about, but we're getting a little short on time. So, I wonder if you wouldn't mind just kind of summarizing for us, your kind of "take home points" for people that are getting ready to or getting ready to have discussions at their local blood bank, or people that are trying to learn about this. What are the key points that people need to remember about massive transfusion?

Minh: Sure!

- Patients who meet massive transfusion criteria, these criteria have been variously defined, but the common definition out there is ten units of red cells in 24 hours.
- Massive transfusion is not just for trauma patients anymore, as we discussed, it's now commonly being applied to OB patients and other patients around the hospital with exsanguinating bleeds may benefit from this as well.
- A recent randomized controlled trial of 1:1:1 vs 2:1:1 found no difference in 24 hours or 30 day mortality between these two different ratios.
- Timing and communication are critical during massive transfusion. Tell us where the patient is, and where you need the blood, and if you need another round of massive transfusion product.
- One of the emerging things is that group A plasma appears to be supplanting AB as universal donor plasma, as demonstrated in the BEST collaborative report, but further research obviously is needed regarding the overall safety and efficacy of that approach.

Joe: Awesome. Well, Minh, I can't tell you how much I appreciate you being my guest today! This has been really interesting and I think you've brought up a lot of really good points for us to think about and understand as we go through this. Is there anything else you'd like to leave us with as we close?

Minh: Congratulations on the Ledin Award that you got at the CBBS meeting this year! You are very deserving!

Joe: That is very nice of you! I appreciate that, my friend! Alright, everyone, that will conclude this podcast. Minh, thank you so much for being here.

Minh: Thank you very much!