

**BBGuy Essentials 075CE:  
What About Fibrinogen? with Melissa Cushing  
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**Melissa:** Hi, I'm Dr. Melissa Cushing from Weill-Cornell medicine, and this the Blood Bank Guy Essentials Podcast.

**Joe:** Hi everyone. Welcome to episode 75 of the Blood Bank Guy Essentials Podcast, the podcast made just to help you learn the essentials of Transfusion Medicine. My name is Joe Chaffin, and I am your host. Today we are going to be discussing something that I don't think quite gets the attention it deserves, and that's replacing fibrinogen in massively bleeding patients as early as possible. I'm going to talk about that today with my guest, Dr. Melissa Cushing from Weill-Cornell in New York City.

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I think most everyone is aware of the trauma protocols in massive hemorrhage today, and really, in some cases, in other massive hemorrhage protocols as well, where we're moving in the direction of transfusing red cells and plasma and platelets, roughly, in a 1:1:1 ratio. That's been discussed on this podcast before. We're not going to take the time to go into that today (By the way, another alternative to something else we've talked about on this podcast, and that's the use of low-titer group O whole blood). You can see previous episodes for those discussions.

But what I've discovered in the real world (I go out and review a lot of different trauma protocols, and people ask me about trauma protocols on questions that are sent in), a lot of those protocols talk about all those things, but one of the things that gets missed, I think, at least early in the process, is the replacement of fibrinogen. That may actually be a very, very big deal. So I wanted to talk about that with someone who is really an expert in this, and I am very, very grateful to have Dr. Melissa Cushing here today to discuss that very topic.

Melissa has spent has lots of her career studying this issue, and perioperative bleeding in general, and she's here today to outline really why getting fibrinogen in bleeding patients as early as we can really is a big deal. Melissa is a Professor of Pathology and Laboratory Medicine (and Anesthesiology, interestingly enough), at Weill-Cornell Medical College in New York City. She's also the Director of Transfusion Medicine and Cellular Therapy at New York Presbyterian Hospital,

Weill-Cornell campus. Melissa is widely published, well over 75 articles, editorials, book chapters, etc. Studying perioperative bleeding is actually her forte and her area of focus, and she's involved in a lot of cool research, some of which she is going to share with you today.

Melissa has some very strong feelings about this. I think you're really going to enjoy this discussion, and learning a little bit more about why fibrinogen is so important. Here is my interview with Dr. Melissa Cushing from Weill-Cornell, where she asks the really important question: "What about fibrinogen?"

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**Joe:** Hey Melissa, welcome back to the Blood Bank Guy Essentials Podcast.

**Melissa:** Hey Joe, thanks for having me back.

**Joe:** I am so excited to talk to you about fibrinogen replacement, how we can do it better, and what our options are. This is something, as I think you know, that's a little bit of a hot button for me. I love cryoprecipitate, I've done a podcast on cryoprecipitate before, and I'm really excited to hear your thoughts on this. Why don't we start by just asking a really simple question: How did this become what I think it is for you, it's a little bit of a hot button for you as well, how did you get interested in fibrinogen replacement and how we can do it better?

**Melissa:** Yes, Joe, you're definitely right, this is definitely my preferred area of discussion and research, just general clinical interest. I would say that it probably started with my interest in perioperative bleeding. When I first came to Cornell, which was about 12 years ago now, I had asked one of my mentors, Karen King, about what should I focus on? What should my research be on? She basically came back to me and said, "Well figure out what the need is in the hospital where you work, and then figure out the good collaborators you can work with, and that's what you should focus on in your career." Which I thought was really fantastic advice. It became clear very quickly, once I worked at Cornell, that perioperative bleeding was an area that could definitely be improved. There were a lot of people interested in improving it: Our anesthesiologists, our surgeons, other Transfusion Medicine colleagues. So it was an area that I felt was ripe for improvements, not only in our institution, but also in blood products in general.

While getting involved in perioperative bleeding and figuring out why patients in the OR, or even patients that were bleeding on the floor post-op or pre-op, were still continuing to bleed, the idea of giving fibrinogen earlier seemed to be very important. I spent a fair amount of time with European physicians, anesthesiologists, Transfusion Medicine/coag experts. In Europe, they have a very different way of dealing with how they treat perioperative bleeding. That became really interesting to me, the differences between our different countries. Fibrinogen was sort of at the center of that, and how we use fibrinogen because they have a different product in a lot of the European countries versus what we have here, how

that changed the way that they handle perioperative bleeding. That's why I became interested in the topic, and then it just kind of spread out from there.

**Joe:** It's gone to some, I would say, great lengths. Which is great because you have published some recent stuff at the time of this recording, something that's in Early View in Transfusion [NOTE: I said, "Transfusion Medicine," but the paper is in "Transfusion" as referenced at [BBGuy.org/075](http://BBGuy.org/075)], And then another paper earlier in 2019 that really delves in to some of these issues. We're going to talk about both of those as we go along. But specifically, Melissa, I wonder if you'd just give me an overview, just to start us off, on how you view ... I mean, I've made the case that fibrinogen replacement is under-appreciated, and that it's something that I think we're missing that could potentially make a big difference. Do you agree with that statement? If you do, which I hope you do, but if you do, can you tell us maybe why do you think that is? Why do you think we aren't appreciating the need for fibrinogen replacement?

**Melissa:** I think, as we've talked about before, it's been the forgotten factor. A lot of times people just think about red cells, plasma and platelets, and then cryoprecipitate because it's a byproduct of the blood production process. It's stored frozen up until the time we need it. It's less available and less focused on. I think, in terms of the research that's been done as well, until the last probably ten years, people weren't thinking about fibrinogen as much because the tests take a long time to come back. Some of the assays are a little bit finicky, so sometimes places don't have the best possible methods to look at fibrinogen levels, and whether there's a decrease in fibrinogen. I think that's probably why it's not been thought about as much. There was also the focus on the 1:1:1 in whole blood. If you're focusing on that, then you're thinking about the individual components because you're just saying, "Okay, I'm replacing everything," in that model.

We know that fibrinogen does play an essential role in the coagulation process, and more and more studies have been showing that. We also know that in a lot of the massively hemorrhaging patients, the ones who are getting liver transplant ... that have trauma, cardiac surgery, postpartum hemorrhage, that they all have a combination of dilution because they're getting a lot of fluids to maintain their intravascular status. They are losing blood, and then they are consuming as they're trying to clot after the bleeding episode. Then we have fibrinogen levels going to very low levels early on in the process, and we're not thinking about replacing them until much later in the process. Then once you get behind, sometimes it's really hard to catch up. I think the model of thinking about it early and replacing it early can actually save you a lot of time, to get you out of the OR, to get the patient out of that bleeding status very quickly. Also, you can avoid the use of other blood products by treating what's missing earlier.

**Joe:** So Melissa, before we get into some of the specific work that you've done focusing on fibrinogen replacement that I think applies mostly to trauma situations, I know that there are other people listening that may not be involved in trauma resuscitation, such as people that are dealing with ... Well, you mentioned liver transplant, or cardiac surgery, or the other major surgeries where there's dilutional

effects, and of course, obstetric hemorrhage. I wonder if you could just give me your impression, even though your work has, again, somewhat focused on trauma, is this a general thing? Is it applicable to other areas other than trauma?

**Melissa:** Oh yes! Absolutely! Clinically, we do have level I trauma, but I spend a lot of time with cardiac surgery because they definitely have low fibrinogen levels. We perform testing during the OR, as soon as they come off bypass, and they get to very low levels. It's not all of them, but there are some patients, especially the ones that have low fibrinogen going in, that really need early fibrinogen replacement.

We have the same experience with our liver transplants. Sometimes we use a lot of cryo during our liver transplants, and it seems to be, for whatever reason, that patient ... it may be the level of their hepatic dysfunction before they go to surgery, but the only thing that stops their bleeding is when we replace fibrinogen. So yes, we see it. Some of the research I've done is in trauma, but my day to day life, we use it early in a lot of situations.

**Joe:** Okay. That makes total sense. I'm glad to hear that. I don't want those that don't deal with trauma to turn off this podcast because there's so much that you guys are going to learn, oh my goodness!

**Melissa:** Definitely. Yeah, it's perioperative bleeding in general. Of course, you have the use in DIC and other medical ... leukemias and things like that.

**Joe:** Let's talk a little bit about some of the work that you've done. We're going to focus this around a presentation that you've given in the past where, again, it's talking specifically about fibrinogen replacement in trauma, and answer four basic questions. We'll start with the first question, Melissa, and it's this: Do fibrinogen levels become low early during traumatic hemorrhage, and are we replacing fibrinogen early enough? That's a pretty broad question. Maybe we can start with a little bit of an appreciation on what fibrinogen actually does. What's the big deal about fibrinogen? Why are we even talking about it?

**Melissa:** Sure, absolutely. Fibrinogen is critical for hemostasis. It is really the substrate of our clot. It's a precursor to fibrin. You can't have fibrin without fibrinogen. It is produced by the liver, and the liver makes a certain amount every day. It's not an enzyme, so it needs to be produced again in order to have enough of it if we don't replace it. It also has a function in primary hemostasis, so it's a mediator of platelet aggregation as well. It can also attenuate fibrinolysis by binding to thrombin, so that's also helpful because, if given early, it can help to mitigate the effect if you're seeing hyperfibrinolysis.

From a lot of studies, not just trauma but also cardiac and the other areas we've talked about, fibrinogen is one of the first coagulation factors to reach critically low levels. Again, because it's not an enzyme, it has to be made again by the liver, it can reach critically low levels, but the body doesn't really have a great way of compensating for that. That's why it's very important to replace it early.

The other thing that studies have shown is that fibrin strands that form in a low fibrinogen environment will still form, but they're more susceptible to fibrinolysis, so it's important to start with a lot, so you can have a nice, strong clot. And then, in a lot of the settings, if you have low fibrinogen levels and increased fibrinogen breakdown, those are the features of coagulopathies that you'd see in trauma or the coagulopathy that you see after cardiac surgery, places like that.

**Joe:** Is it safe to say that the lower the fibrinogen levels, you almost get a multiplying effect? The levels get low and that's bad, but further, when the levels are low, you get more breakdown and things just don't work as well overall, in the system. Is that a fair way to put it?

**Melissa:** Yes, absolutely. Then you have the problem where the replacement that you're giving doesn't have a lot of fibrinogen in it. A lot of times you're giving fluids to maintain intravascular status. You're giving red blood cells. You're giving plasma usually, at some point, but the levels of fibrinogen in the plasma are not high enough to make up the difference that you have for the amount that you've lost. It's just too dilute a product in terms of fibrinogen.

**Joe:** Do we have any idea of ... for example, in trauma, what kind of trauma patients tend to present with the lowest levels of fibrinogen, or do we know?

**Melissa:** Yeah. There was a study by Rourke, et al, that was from 2012 in the Journal of Thrombosis and Hemostasis. In that study, they found two things that are not that surprising, especially ... I mean, it may have been more surprising in 2012, but today it's kind of a given. The patients with the highest injury severity score tend to have lower levels of fibrinogen. That makes sense because they're bleeding more, they're using up that substrate. The patients that got higher volumes of crystalloid before arriving at the hospital really have lower levels. I think that's something that's universally now avoided. Whether you're in the U.S. or if you're in Europe, there's really a move to try and reduce the amount of crystalloid that's given prior to the hospital setting. I think in the beginning, people wanted to just make sure that you could maintain the blood pressure and things like that. But I think, because it was causing so much harm to the coagulation system, people have really moved away from that.

**Joe:** Yeah, that's something that I've seen over my career. I've hung around a little bit longer than you have, Melissa. So for me, I certainly remember my early days in Transfusion Medicine. The big deal was, "Get that volume in, get that volume in." Now all I hear is, "Avoid the clear stuff. Don't give them any clear stuff." Right?

**Melissa:** Yes.

**Joe:** That is pretty much a mandate that we're seeing. How about any outcome data? Is there any information in trauma about how fibrinogen levels correlate with outcomes?

**Melissa:** Yeah. I think there's a fair amount of studies now that show that if you have higher fibrinogen levels, that there's a decreased chance of mortality and trauma. This



has actually been linked to some of the other areas that we talked about as well. Not just trauma, but postpartum hemorrhage and cardiac surgery, as well. If you can maintain your fibrinogen levels above a certain amount, which we could talk about what that amount should be, then you actually have a decreased chance of mortality or decreased lengths of stay, decreased use of blood products. So yeah, there is a fair amount of information about that. A number of groups have shown that your fibrinogen level is really inversely related to mortality. The higher the fibrinogen level, the lower the risk of mortality.

**Joe:** So if we have this data that says that there is such a correlation, I guess the second part of the question is, are we getting these patients fibrinogen early enough? What information do we have about that? What do we know?

**Melissa:** That's interesting because there have been a number of studies looking at how long it takes to get fibrinogen to the patients that are in trauma, or in other surgical situations where they would have lower fibrinogen, the ones we just talked about. I think there was some good data from the PROMMTT study. The PROMMTT study had looked at the amount of time that it takes to get someone fibrinogen, or cryoprecipitate in the PROMMTT study specifically because it was North America. It was looking at how long that took. Basically, it was 2.7 hours on average before the patient would get fibrinogen replacement, which is a very long time because they always talk about that golden hour of trauma. Now they're saying, "Maybe it's not even an hour. Maybe you have much less than an hour."

**Joe:** Right.

**Melissa:** But if you're not getting fibrinogen until 2.7 hours, then that's definitely not early enough. But if I could just take it a little bit further.

**Joe:** Sure.

**Melissa:** The thing that I found really interesting is that ... There have been a couple studies now that have looked at, in a clinical trial setting, whether we can get a fibrinogen replacement product earlier to patients. One of those was the first study which was done in Canada by Barto Nascimento and Jeannie Callum, their group. In this case, they were trying to give fibrinogen early. Then there was another study that was done by Nicole Curry and Simon Stanworth, that group from the U.K. Oxford, in a number of centers where they were trying to give cryoprecipitate early. The thing I found really interesting about those studies is that they weren't really able to give either product, which is kind of surprising because that was the whole main goal. In the CRYOSTAT-1 study, only 85% of patients got the cryoprecipitate within 90 minutes, and the median time was 60 minutes. Again, if we go back to that, that these were trauma studies ... if you go back to that golden hour where if you haven't taken care of things in an hour, the patient's most likely dead. So that's really not soon enough still.

Some of those things are related to the, you know, they're in a clinical trial, and it's randomized and blinded. You have to take into account the randomization time

and things like that. The actual time to get the product both in the first study, for fibrinogen concentrate and the CRYOSTAT study, for cryo were, I think, really too long.

- Joe:** That's scary. I think before we go any further, Melissa, we should just pause for a second. We're going to get into the details of cryo versus fibrinogen concentrate, which is better? If we can even answer that question, later on. I wonder if you would just set the stage of ... Again, I've already done a podcast previously on cryo, but just give us the thumbnail, if you don't mind: The two main options that we have available in the world right now for fibrinogen replacement. Can you break those down for us?
- Melissa:** Sure, absolutely. Sorry, I got a little bit ahead of myself there, but-
- Joe:** No, you're good. That's fine.
- Melissa:** Yes. So in North America, Canada, and Australia, and a couple other places in Scandinavia and Asia, people mainly use cryoprecipitate, which I know you've talked about in a previous podcast, so I won't get into the details of that product. We mainly use that product now for fibrinogen replacement in those countries. A lot of other places in the world, they use fibrinogen concentrate. In certain places in Europe, such as France, Switzerland, Austria, Germany, they actually don't use cryoprecipitate at all, and it's not a licensed product there. In fact, they're not allowed to use it. It's a really different take on it versus the U.S., but they find that because it's a pooled product and there's no pathogen reduction technology used on it at all, that they think it's ... I think I've heard it called a "dirty product," meaning that there's still infectious disease risk, but it's pooled. So they had made the decision a long time ago to move to fibrinogen concentrate. They feel strongly that it's a better product. I think in the U.S., we tend to like cryo, but I think that both products could potentially have improvements made to them. That's generally what the landscape looks like.
- Joe:** Again, for those that don't feel like going back and listening to that cryo podcast, there are other things in cryo other than fibrinogen, but is there really any use for cryo other than fibrinogen replacement in the U.S. and those countries that are still using it?
- Melissa:** When I talk to the residents, I always give a slide, and I put all the components of cryo, and then I actually link them up. So every single thing in cryo has a factor concentrate that's pathogen inactivated associated with it. If you look at the factor XIII, there's a factor XIII concentrate that's super expensive, but it is available in a lot of countries, including the U.S. von Willebrand factor, there's multiple options for a concentrate that has von Willebrand's factor. Factor VIII, of course, we've had factor concentrates for factor VIII for a very long time. For fibronectin there isn't, but fibronectin we're not really sure exactly what its role is in coagulation. We know it has a role in the innate immune response and potentially wound healing, but we don't really understand if it's helping or if it's not when we're talking about treating a bleeding patient.

- Joe:** Before we leave this overall global question ... our first question about fibrinogen levels and whether we're replacing them early enough, I wonder if you have any either general idea or is there any data on whether or not cryo or any other fibrinogen replacement is actually being used in massive transfusion protocols?
- Melissa:** Yes. My general impression is, from looking at the massive transfusion protocols of other institutions participating in a couple studies, that people usually do have cryoprecipitate in their massive transfusion protocols, but they tend to come later, and that's for really practical reasons. But the actual use of cryo in the MTP also is known to be variable by center. If you look at the data from the PROMMTT study, the cryoprecipitate use varied by center from 7% to 82% of the massive transfusion patients that they were treating. Even if you look within my institution or other institutions, there's a lot of variability. A lot of the variability has to do with how much they're bleeding. We have massive transfusion, or massive hemorrhage protocols that are called, but they tend to use less than one cooler or one cooler. The ones that tend to have massive hemorrhage, that we're talking 80, 90, 100 units, fortunately, those are few and far between, but they tend to all get cryo.
- Joe:** I think we've pretty clearly answered the question of, do fibrinogen levels become low early during traumatic hemorrhage? Yes. Are we replacing fibrinogen early enough? No. Let's move on to the second question. I think this is a really important and practical question, and that's this: What is the best target fibrinogen level to use for traumatic hemorrhage, and is it possible to give that fibrinogen replacement earlier? So it's a two-part question. Let's talk about the target levels. What should we be shooting for in these patients?
- Melissa:** I think there isn't ... Again, this is one of those areas where we don't know 100%. I've always been slightly disappointed that we don't have more studies that have clinical trials where we say, "Okay, let's try replacing at this level versus this level versus this level." Because otherwise, we're kind of guessing or we're left to look at retrospective observational trial. There was one by Hagamo in Critical Care in 2014 where they did look ... it was a retrospective, it was an observational study. They were trying to figure out what the critical fibrinogen was where you could decrease mortality. What they found, it was almost like a U-shaped curve. When you had very low levels of fibrinogen, there was much higher mortality. At some point, there is a point where it goes the other direction, where as you replace fibrinogen or your fibrinogen levels are higher, you have less and less mortality, but then when you get to a certain level of fibrinogen, the mortality actually goes up slightly again. In that study, they found that the "sweet spot," I guess you could call it, was a critical fibrinogen concentration of 2.29 g/L, or 229 mg/dL for those of us in the U.S.
- I think that's one of the few studies that have looked at that. We do have some guidelines from different groups or organizations worldwide. I think that's something that we've seen change again in the last ten years, where if you asked someone probably ten, fifteen years ago about what the critical level of fibrinogen is to replace, somebody might say 100 mg/dL. I think that was, in hematology, the level that we thought about for at first congenital patients, and things like that. As



we've looked at more studies, we've kind of adjusted our acceptance level of low fibrinogen. Now if you look at the European Guideline in trauma, they suggest replacing with fibrinogen concentrate or cryo when the plasma fibrinogen level gets to be less than 1.5 to 2 g/L. If you look at the American College of Surgery guidelines, they suggest using cryo or fibrinogen concentrate for a fibrinogen level that's less than 1.8 g/L (180 mg/dL).

So, that definitely has changed. If you look at the other anesthesiology guidelines, the European Society of Anesthesiology or the ASA, they've also increased. Sometimes it's 1-1.5, 1.5-2. Everything's kind of in that range around 1.5, I would say.

- Joe:** Gotcha. Okay. And as you said, I think that's important to recognize that the old days ... again, I keep referring to myself as this "old dude," I don't feel that old, but whatever...
- Melissa:** You don't seem old.
- Joe:** Back in "the day," as we like to say in the cool circles, we used to focus on that 100 mg/dL or 1 g/L measurement as, "Boy, you've got to get it above that." But that seems to be very clearly too low, based on current data. I'm right there with you.
- Melissa:** Yes. The only thing I would say is that whenever we talk about those guidelines, and when I'm talking about it as well, it's in bleeding patients. I just want to make that kind of clear, because they're all specifically saying "bleeding patients."
- Joe:** It seems pretty clear, from those studies anyway, that it's difficult to give fibrinogen replacement as early as we do red cells and plasma in trauma situations. Is that a fair way to assess the data that's available so far?
- Melissa:** Yeah. Definitely, I agree with you. As I mentioned, the first study and the E-FIT 1 and the CRYOSTAT-1, all of them found that it's hard to give it both of those products, either fibrinogen concentrate or cryo, earlier than an hour. I think a lot of that has to do with the product itself. I think there's a lot of focus on how we can potentially improve those products so we can get fibrinogen to people earlier. I think most of us, we're working in a transfusion service, whether we're dealing with trauma, or cardiac surgery, or postpartum hemorrhage, liver transplant, would really love to be able to get that product to them sooner, but there's practical reasons with each product that we can't.
- Joe:** Let's really "rubber meets the road" here on the next question, Melissa, and that's: What is the BETTER product to replace fibrinogen in trauma, cryo or fibrinogen concentrate? I know you've had some public debates about this, which is awesome, with a former podcast guest, the magnificent Dr. Jeannie Callum. I'm not gonna ask whether you won those debates or not, but let's kind of just talk through... I personally wouldn't want to go against Jeannie. She would kill me.

- Melissa:** There are a lot of people that told me that after, like, "Oh my gosh, I would never want to go against Jeannie." She's a really nice, fun person actually, but she's a serious debater.
- Joe:** Oh yeah. She's amazing, and so are you though, so I'm sure you held your ground. Let's talk about this. What is the better product? How do we go about assessing this? You've already mentioned that cryo is primarily used in North America, Australia, I believe the U.K. still as well. Is that right?
- Melissa:** Yeah, sorry. Yeah, the U.K. still, definitely.
- Joe:** Okay. And then fibrinogen concentrate primarily in other parts of Europe, et cetera. I don't think we need to go over that again, but let's just talk a little bit about how do we compare these things? What's the deal?
- Melissa:** I guess I could start a little bit with the weaknesses of each product. One of the main problems that I previously spoke about is that when we identify that fibrinogen is low, we want to give the product immediately. Just because we have platelets, we can give them when we see a low platelet count, if we see a coagulopathy, we can give plasma pretty quickly because we can keep that thawed in the shelf. But with cryoprecipitate, because of the current state of that product, when we need it, it's sitting in a freezer in the blood bank, and the OR wants to give it immediately. The problem with cryo is that it's not available when you need it.
- Part of the reason that we have to keep it in the freezer is that once it's thawed, it only can be used for four hours if it's a product that was pooled in a non-sterile manner, or six hours if it was pre-pooled in a sterile manner. But that's really not enough time, because if somebody told me tomorrow, "OK, I have a huge cardiac surgery that's a re-op and there's a lot of scar tissue. We know we're going to get to the point where we have low fibrinogen. Can you just keep it thawed for me?" Maybe in a one-off setting like that I could, but I can't on a regular basis keep thawed cryo because I'd be wasting it all the time, and then we'd have shortages. I think we're also not very good at predicting who is going to have low fibrinogen. I don't really get those calls very often, where I say, "I think we're gonna really need it."
- The other problem with cryo is that they're in surgery, they've sent their lab test. We could talk about what lab tests there are available, if you want, for fibrinogen. They've sent it, it takes time. So they're already behind because they've waited for the test to come back. The patient's rapidly bleeding. They can't just sit there and say, "I'm just gonna twiddle my thumbs while I'm waiting for the labs." While the surgeon is screaming, "Oh my God, there's blood everywhere. It's not surgical. You have to treat this coagulopathy." In the meantime, we end up giving a lot of other products - plasma, platelets, a lot of red cells - and then sometimes, if you give enough, you can actually stop the bleeding, an antifibrinolytic. Then the product that they've ordered 45 minutes to an hour ago arrives.

They're like, "Well, we only give" ... I think most only give a blood product if the patient's bleeding in the OR. At that point, it just gets sent back to the blood bank, and we often waste it because we don't have another patient to give it to within the six hours that we have before it expires. That's a major weakness in cryo.

The other major weakness I already alluded to when I talked about why Europe doesn't like cryo, but it is a pooled product. It's not pathogen inactivated. I think in this country, we're more comfortable with that, and we have a lot of other products that are not pathogen inactivated. We're willing to deal with it, but I think that would be a nice thing to have, a product that was pathogen activated to avoid the multiple donors.

For fibrinogen concentrate, there are also weaknesses. One of the things that I really like about cryo is that in some of my studies, I have looked at this, is that the other components of cryo can actually be useful, especially the factor XIII. Factor XIII is again, if we're talking about forgotten factors in our blood, factor XIII is something that is important. We don't use the concentrated factor in this country, because I think it's thousands and thousands of dollars if you were going to treat with. But it does have an important role, and I think of the most important roles is it does improve the clot stability, and it can strengthen the fibrin molecule by the cross-linking. Also, it has effect in mitigating hyperfibrinolysis. That is a useful thing that is in cryo, and in certain of the factor concentrates for fibrinogen, it's lower.

There is a new factor concentrate that's available now that has higher levels of factor XIII in it. I haven't seen those two products compared directly, cryo and the new fibrinogen with more factor XIII, to see which one's higher. But when I do calculations based on studies we've done and studies in the literature, it seems like that new product has factor XIII levels that are approaching what are those in cryo. That kind of evens that out a little bit.

The other problem that you have with fibrinogen concentrate is, again, it's not in a readily usable state. I think this is something people tend to underestimate about that product, but you still have to reconstitute it. In our institution, we're a hemophilia center, so we give out factor products a lot. We see a fair amount of wastage because people don't know how to reconstitute them properly. One of the problems with the fibrinogen concentrates is that they tend to "foam." If you try and reconstitute too quickly, it gets foamy and bubbly. Then when you're pulling up your syringe to get the product out of the vial once it's reconstituted, if you can't really look at it clearly, you can't tell if everything's in solution, and it doesn't go into solution perfectly. So you really have to ... if you want to do it carefully to get the exact dose that you're looking for, you have to reconstitute it very carefully. I think when people think about fibrinogen concentrate, they say, "Oh, it's automatically gonna be faster."

I mean, I think it can be faster because it could be stored up in the OR. That can make things a lot faster, just not having to have a transaction with the blood bank, not having to send pick up slips, and all that makes it faster. I think those are some of the drawbacks to each of those products.

**Joe:** So Melissa, I think with all that being said, there's one other important factor that we really have to consider. I think, in this day and age, it's kind of the "elephant in the room," and that's how much do these suckers cost? Relative cost between cryoprecipitate and fibrinogen concentrate. Certainly on the surface, it's easy to look at fibrinogen concentrate and say, "God, that costs much more than cryo." But what do we know about it?

**Melissa:** Right. So yeah, absolutely, when you look head-to-head the products, fibrinogen concentrate is definitely more expensive. There have been some analysis of this. We did an internal analysis a couple years ago to decide if we should be thinking about moving to fibrinogen concentrate or if we should continue to use cryoprecipitate. There was a nice study published by Okerberg et al, which was...also Yossi Schwartz and Huy Pham on that publication. What everyone's found is that fibrinogen concentrate is more expensive than cryoprecipitate. Again, all of our analyses have been from the United States. In the Okerberg study, they found that fibrinogen concentrate was much more expensive, and that you needed to consider ... even if you did consider the fact that we waste 27%, approximately, of the cryo that's used in our institution, and the fact that we have additional time for the blood bank to maintain and thaw that product and issue that product, if you look at the technologist's time, still it's much more expensive in their analysis.

We found a similar analysis in our institution. When we looked at it, the fibrinogen concentrate product, which is now somewhere between \$800 and \$1000 a gram, would have to drop to approximately \$300 to \$400 a gram in order to be cost neutral (so the product's costing about the same). When I talk to my colleagues in Europe and I ask them about their price of fibrinogen concentrate, they say "No, it's much cheaper there." I think that price difference is always one that we see in factor concentrates in Europe versus the U.S., and some of that has to do with the clinical trials that are necessary to get FDA approval and things like that. So that can drive up cost. They generally have the fibrinogen concentrate for about \$200 to \$400 per gram.

**Joe:** Oh wow.

**Melissa:** So it's significantly less expensive there. When you're talking to them about why we still use cryo here, they're always like, "But fibrinogen is not that expensive." But then when we come back and say, "It IS that expensive."

The other thing I really should mention, because it has to be mentioned in this discussion, is that in the U.S., the FDA currently only has approved fibrinogen concentrate, again, there are two that are available here, but they're both only approved for congenital hypofibrinogenemia. If we use those products, and a lot of hospitals do this, it's an "off-label use." That comes with consequences in terms of reimbursement and risk, and things like that.

I think there are studies that are ongoing right now that are designed to prove to the FDA that the products, cryo and fibrinogen concentrate, are either equivalent or maybe one's superior versus the other. But I think, in the current stage in 2019,

fibrinogen concentrate products are only approved for the congenital. It's kind of a really interesting ... I don't know, what's the word for it without being judgmental? It's like a double standard. If you tried to use cryo for congenital hypofibrinogenemia, it would be contraindicated for safety reasons. On the other hand, we can't use it for acquired hypofibrinogenemia. The same product that we have to use for congenitals, we can't use for acquired hypofibrinogenemia. So it's almost an interesting situation.

**Joe:** It is. That actually brings me to my next question, which is ... I mean, the overall question, which is what is the better product? You've done a great job of talking us through some of the weaknesses of both cryo and fibrinogen concentrate. You wrote an article, you and Thorsten Haas, in *Transfusion* earlier this year. Earlier in 2019, I believe it was in the May edition of *Transfusion*, where you talk about what we can learn from the clinical trials on fibrinogen concentrate. I wonder if you'd just summarize your conclusions from that. Because I'll be honest with you, I read your article, and my first thought was, "Hmm, that's sadly a little disappointing."

**Melissa:** It is disappointing. Yeah.

**Joe:** Am I wrong in that? Yeah...

**Melissa:** Right, it is disappointing because we just spent the previous 40 minutes talking about why fibrinogen is important to give early. If we don't give it, then the mortality and other outcomes are not good. But overall, the clinical trials in fibrinogen concentrate, and in our study we looked at the 21 major randomized controlled trials that had been published, up to date. Only 60% of the studies in which fibrinogen concentrate was used showed decreased bleeding tendency and decreased transfusion requirements versus the comparator. The comparators differed. Sometimes they were plasma, sometimes they were platelets, sometimes they were just a placebo. There was only one where the comparator was cryoprecipitate. Overall, that's not that impressive that only 60% responded.

I think what we were trying to tease out in that rapid review for *Transfusion* was that you have to look at the studies specifically. We tried to do a clinical trial in our institution, trying to look at cryo versus fibrinogen concentrate, and we got really caught up in the details of the clinical trial in terms of predicting who's going to need fibrinogen is really hard. In the design of the clinical trials, that comes into play. I think what they decided to do in some of these trials is to allow patients that they suspect of hypofibrinogenemia but they didn't have laboratory levels into the trials. That meant that a certain amount of the patients in the trials did not have significant hypofibrinogenemia. They didn't need those guidelines that I talked about. Some of them over 2 g/L. Some of them are over 3 g/L, that were in the study.

The one thing that I can say after I looking at all those clinical trials, is that there were over 700 patients that received fibrinogen concentrate between them. There was no increase in the rate of perioperative thrombosis in the fibrinogen arm versus the comparator arm. There have been some other studies that were more



retrospective observational studies that have said the same thing, but I think the risk for thrombosis for fibrinogen concentrate can be said is pretty low. There have been some exciting trials that are recently completed in this area, and they're all comparing cryo versus fibrinogen concentrate head to head. They've all been presented at various meetings that I've been at in the last couple months. All of them have had a higher rate of thrombosis for cryo versus fibrinogen concentrate. I think only one of them was statistically significant, and it's not a huge difference. But definitely, if you're comparing it to cryo, it's not more thrombotic than cryo, which I think is something people might worry about with this product.

**Joe:** Do we have any idea right now how cryo use in the U.S. is changing? Is it going up? Is it going down? Do we have any concept of that?

**Melissa:** So, we DO have an idea. We have a number of studies that have been published that have looked at the utilization of blood over time, over the last 10, 20 years, and we have some big data that we can look at for that. Overall, we've seen ... I think you've had people on your show that have talked about we have decreasing utilization of red cells, platelets and plasma. But we've seen, in the studies that have looked at it, that the use of cryoprecipitate has gone up. The AABB recently released, within the last week I think, the 2016 AABB Blood Survey fact sheet. In that, they showed that overall, all blood products were going down, except cryo increased from 2015 to 2016 in terms of production of cryo at a blood center by over 40%. The distribution of cryo increased by about 30%. Then when they looked at the transfusion service data from the hospitals, they found that there was a 22% increase in the number of cryo units from 2016, compared to 2015.

At the same time, they saw a decrease in plasma transfusions by about 10%. So we see that cryo is going in the opposite direction of the other products. I think a lot of that has to do with the increased recognition of low fibrinogen. I think people are thinking about it more. As we talked about before, there are more studies showing that we should be thinking about it. But I think also, there's been a trend worldwide, the U.S. as well, to start using point of care viscoelastic testing in the OR. That tells you much more quickly because it's in the OR, it's a rapid test, you can get results for fibrinogen within five to ten minutes. I think we're seeing the low fibrinogen earlier, so we're able to react to it earlier. So there's a greater need for cryo.

**Joe:** That brings me to a little more of our fabulous crystal ball. One of the things that you've been involved in, in the work that you've done and the work that you've published recently, and everyone I'm going to refer you to some of the things that Melissa has published on the show page for this episode at [BBGuy.org/075](http://BBGuy.org/075). One of the things that you published, again earlier this year, was on the efficacy of a new pathogen reduced cryoprecipitate product. I wonder if you'd just take us through a little bit of the background on that. In particular, if this is a product that is going to be useful in the future, how does it compare to "regular" cryoprecipitate? What are the problems with regular cryoprecipitate that led you to think that maybe this new product might be helpful?

**Melissa:** Great question. I think we touched on these a little bit, but just to summarize. Cryo: Currently stored frozen, so it's not readily available when we need to use it. We need to wait 45 minutes to an hour to thaw and issue it. Then the infusion takes another 10 to 20 minutes after that. Then that short storage time also causes increased wastage because it's called for when it's needed, but by the time it gets there, often it's too late. So we have a high wastage rate. Thirdly, we have the infectious disease transmission risk. It's a pooled product that's not pathogen reduced.

So if I were to use my crystal ball, I would say that we would ... Or if I were to actually just say, "What do I need to improve the treatment of bleeding in my hospital?" We need a product that has an extended storage time. We don't need a product that's stored in the freezer. We need something that's stored at room temperature, potentially refrigerated. We need something that can last longer than just four to six hours. We need something that can be stored, thawed, and available for closer to what we use thawed plasma at, for five days, or even maybe longer. Then, of course, we need something that we don't have to worry about the microbial contamination if we do decide to store it at room temperature for five days to two weeks, or something like that.

So there have been a fair number of studies now. There's probably one published every year that's looked at cryo. If you let it sit either at room temperature or refrigerated temperatures for ... I think there was originally, people looked at 24 hours, then people started looking at a week. More recently, there was a study that was published by Andre Cap's group that looked at keeping it for 35 days. They looked at it both in refrigerated and room temperature. They found that, really, the fibrinogen levels didn't drop off in terms of the function of fibrinogen until about 14 days.

For us, the storage temperature is a question. We've had an experience where we have not been able to get cryo back into the solution once its sitting at refrigerated temperatures, so it precipitates out. That's the nature of it.

**Joe:** Right. Kind of the definition of it, right?

**Melissa:** Yeah, exactly. Yeah, that's how it works. I think, when I talked to Andre about this, he said he had had a little bit better time at getting it back into the solution. They mentioned that in their study that was published this year. For me, I think having it at room temperature is even better, because any time we can give a room temperature product to a patient that's already cold and not give a chilled product is even better. You also don't have to worry about ... it would be very inconvenient to have to drop the cryo product that was sitting in the refrigerator back into your plasma thawer and then issue it. So it's great if it's "grab and go." You just grab the product off the shelf and then you give it to the OR, or you have it available in the OR in a controlled temperature setting.

This all could work if we could just ... what's stopping us from doing that right now, I guess, is that the FDA has only approved it for those four to six hours. Why is it

only approved for four to six hours if we're showing that the fibrinogen is stable for longer? Then it's the microbial contamination. It's a pooled product. Could bacteria be growing in there? I think there have been some nice spiking studies that were done that showed that bacteria can grow in there if it's not done sterilely we ... assuming it's done in a sterile manner. So it should be okay.

But that brings you to the point, should it be pathogen reduced? If it's pathogen reduced at the time, then you don't have to worry about a microbe from a patient causing a problem. It's lower risk anyway because you're freezing that product. No matter what, you'd be freezing the product. During shipment to the hospital, it would be frozen. Then you'd use it probably more like you'd used thawed plasma, where you'd thaw a certain amount per week. Because again, you still don't want to have wastage if you thaw it too early. You'd thaw a certain amount, and then during your ... when the OR's open, you'd have thawed cryo just sitting on your shelf, thawed PR cryo. In the past, some of the PR cryo that's been attempted, methylene blue, amotosalen, and other types of pathogen reduced cryo, have actually had lower levels of fibrinogen due to the pathogen reduction technology, or pathogen inactivation technology.

The study that you talked about that we did earlier this year was actually looking at a new product that was created to actually increase the amount of fibrinogen, so the pools are actually higher in that product than a standard product. What that allows is that you have higher concentrations of fibrinogen. So if you lose a little bit during the pathogen reduction process, you still have an equivalent or slightly higher level of fibrinogen to the old product for cryo.

What we were doing in our study, it was an in vitro study. We took healthy donors and we drew whole blood from. Then we diluted their whole blood to induce a dilutional hypofibrinogenemia, and then we compared three products. We compared PR cryo and we compared regular cryo that was thawed immediately, and then we compared fibrinogen concentrate. The PR cryo had been thawed five days before, so it was a five-day thawed PR cryo product that had been stored at room temperature.

What we saw is that when we looked at all three products ... we used rotational thromboelastometry, or ROTEM, which is a point of care viscoelastic test. We also looked at factor levels in that study. What we found is when we looked at overall clot stability, which is the EXTEM test, they all were able to restore the viscoelastic strength of the clot to a similar level. Actually, PR cryo, because of the way it was manufactured, actually looked slightly better than the regular cryo.

**Joe:** Just to be clear Melissa, this was an in vitro study, correct? So this was not in people?

**Melissa:** Yes, in vitro. Not in patients, not in patient specimens. It was healthy donors that came in. We phlebotomized them, and then we took their specimen and diluted it 50%, so it was an induced hypofibrinogenemia through dilution.

**Joe:** The second question is, just to be clear, people can't call their local blood centers tomorrow and say, "Hey, give me some of that PR cryo." Correct?

**Melissa:** No. It is a product that's in development right now, and I think at least one company is talking to the FDA about this product to potentially get approval. What is approved right now in this country in pathogen reduced plasma, and pathogen reduced cryo is made from pathogen reduced plasma. That's the starting material is pathogen reduced plasma. That is approved in this country, and it's not widely used yet.

**Joe:** That's exciting information, and it has the potential to open things up to maybe allow us, down the line, to do a better job of replacing fibrinogen as early as possible.

Melissa, as we close our time here, I wonder if you'd just take us through your overall thoughts on where we've been, where we're going with fibrinogen replacement in these situations, and maybe ... what are your favorite take-homes from this particular topic?

**Melissa:** Sure. I would say, in terms of the first question, where were we and where have we gotten today? I think 10, 15 years ago, we were under-recognizing the effect of hypofibrinogenemia on hemostasis. I think we've made a lot of progress in the last 10, 15 years with the increased recognition that we need to look to see if fibrinogen is low in our bleeding patients. When it's low, we need to replace as quickly as possible.

In terms of the products we use, there's a lot of discussion about this. As I said, there's going to be three randomized controlled trials that are probably published by the end of 2019. They're comparing our two options for fibrinogen replacement head-to-head. So that's exciting. I can't wait. I mean, I've heard preliminary results on each of them at meetings, but I think it would be great to see those published. That will tell us a lot more about, if you're comparing cryoprecipitate to fibrinogen concentrate head-to-head, is one superior? Should we be using one? And our country is going to change their approach to how they replace fibrinogen because of these results.

I think my final point is that if we're going to ... say we find out that cryo is equivalent in terms of efficacy, then we want to think about we can improve cryo so that we have cryoprecipitate available when it's needed for our bleeding patients. So are there ways we can allow it to be stored at room temperature so that the product becomes grab and go? We can take it to the OR and then give it right when it's needed, and try and reduce our wastage at the same time. I think probably for that to happen, it'll require a pathogen reduced product because it is a pooled product and now we'd be storing it at room temperature.

So I think all those things are extremely exciting for the field. We keep talking about the crystal ball, but if we look five years in the future, I have a feeling that our practice is going to be dramatically different for fibrinogen replacement than it

is currently in 2019. I think probably the pendulum will switch towards one of those products versus the other based on a lot of clinical trials that we're going to be seeing in the next couple years. So it's an exciting time for fibrinogen.

**Joe:** That's awesome. Well Melissa, thank you so very much for sharing your thoughts and your time with us. This has been really, really useful and helpful. So thanks again.

**Melissa:** You're very welcome. It was a pleasure.

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**Joe:** Hey, this is Joe with just a couple of quick closing thoughts. My biggest and most important thought is a simple one, and it's, "Thank you so much!" As I mentioned at the beginning, this is episode 75 of the Blood Bank Guy Essentials Podcast. You know, when I started this whole thing in 2016, I really had no idea what kind of an impact it would have. Well, as it turns out, we just crossed 300,000 episode downloads in countries all around the world since we started. I'm just flabbergasted by that! So thank you all so much. My goal has always been and will always be to bring you the essentials of Transfusion Medicine in as meaningful and manageable a way as possible, and I hope that that's been the case for you.

I do want to mention again, this is a continuing education activity, so if you are a physician or a laboratorian, don't forget to visit [wileyhealthlearning.com/transfusionnews](http://wileyhealthlearning.com/transfusionnews), and get your hour of totally free continuing education credit. My thanks for that as always to Transfusion News, to Bio-Rad who brings you Transfusion News, and to Wiley Health Learning.

I also want to thank Transfusion News assistant editor, Dr. Daniela Hermelin from St. Louis University. Daniela, as has become her habit, has written the continuing education materials for this episode, and she's wonderful. I encourage you to check those out.

The next episode is coming in a couple of weeks, and I'm very excited about it. It's an interview with one of the inventors of pathogen reduction technology, which is amazing. His name is Dr. Ray Goodrich. Ray and I have known each other for a long time, and I'm excited to share his insights with you.

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