BBGuy Essentials 095CE:
What is Liquid Plasma? with Chris Gresens
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Chris: Hi, this is Dr. Chris Gresens from Vitalant, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, everybody! Welcome back to Blood Bank Guy Essentials, the podcast designed to help everyone learn the essentials of Transfusion Medicine. I am your host, Joe Chaffin, and I am SO happy about the interview I'm about to share with you! It's a discussion on a widely misunderstood blood product known as "Liquid Plasma." A lot of people get confused about this product, and my friend Dr. Chris Gresens from Vitalant is here to help you understand how it might just be the perfect product for your facility!

But first, this IS a continuing education episode. The free continuing education credit is provided by TransfusionNews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into the podcast. This podcast offers a continuing education activity where you can earn two different types of credit: One *AMA PRA Category 1 Credit™*, or one contact hour of ASCLS P.A.C.E.® program credit. This activity also may be used to fulfill Lifelong Learning Continuing Certification requirements for the American Board of Pathology. To receive credit for this activity, to review the accreditation information and related disclosures, you just need to visit www.wileyhealthlearning.com/transfusionnews. One important note: The continuing education credit is no longer available two years after the date this episode was released; in other words, credit for this episode will expire in March of 2024.

When we are transfusing plasma here in the United States, we have really a lot more options than most of you might realize. There is, of course, "Fresh Frozen Plasma," or "FFP," and that is the product that everybody thinks of when they think of giving a patient plasma. You might be surprised, though, to learn that much of what is actually *sent* from transfusion services when FFP is ordered is actually a slightly different product with a horrible but very descriptive name, called "Plasma Frozen Within 24 Hours After Phlebotomy," or "PF24" (check the plasma labels in your blood bank sometime, and you'll see what I mean). There are many, many others, with names like, "Plasma, Cryoprecipitate Reduced," and oh, my personal favorite, "Plasma Frozen Within 24 Hours After Phlebotomy Held at Room Temperature Up To 24 Hours After Phlebotomy," (I know, you think I'm messing with you now, but I'm totally serious! That's an actual blood product!).

Anyway, there is one plasma product that has a very simple name that we are going to discuss today, and that product is called "Liquid Plasma" (you need to note that's a formal name, in other words, the L and the P are capitalized). Liquid Plasma is unique because it is a plasma product that is NEVER frozen, not at all, and there is one very specific use for it. I'm going to discuss that today with my friend Dr. Chris Gresens.

I placed Dr. Gresens' full bio on the show page for this episode at BBGuy.org/095, so I hope you check it out. Chris serves as Vitalant's Medical Director for their North and West Divisions, and he has vast experience counseling hospitals on the best way to use various blood products. He has published on many, many topics, including the one we are going to discuss today, Liquid Plasma. In fact, if you go to BBGuy.org/095, you can download a wonderful two-page pdf on Liquid Plasma that Dr. Gresens wrote with Dr. Marissa Li, formerly of Vitalant and now with Cerus, for the America's Blood Centers organization.

Ok, so with that said, here is my interview with Dr. Chris Gresens called, "What is Liquid Plasma?"

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Joe: Hi, Chris. Welcome to Blood Bank Guy Essentials.

Chris: Thank you, Joe. It's a pleasure to be here.

Joe: I am so jazzed to be able to finally connect with you. You and I go back a long way. We've been friends for a long time, and I do not understand how I have not had you on the podcast before now. What the heck is wrong with me? That's the first question.

Chris: Nothing at all, actually. You had tried in very good faith to get me involved a couple of years ago, and as I recall, there were just a number of competing issues in play and we agreed that we'd find another day soon. So thanks for getting me back.

Joe: I'm super happy that that day has come, my friend. This is, I think, a great opportunity for us to talk about something that I know you have a lot of interest in and a lot of passion for and you've written about in a couple of different settings. One of the things that you did, along with Dr. Marissa Li, was a blood bulletin that was put out by America's Blood Centers. When was that, Chris? A couple years ago? 2019, I think, right?

Chris: Yeah. The purpose, really, was to allow for us to share with our hospital customers. America's Blood Centers, as you know, represent well over 45-50% of the nation's blood supply and customers, so it allows our blood center members to share useful information in small packages that allow for just-in-time learning with our lab and clinical colleagues. That was the purpose of this piece. Two pager to hit the high points.

Joe: Just so people will know what we're talking about, I've already said this in the introduction, but we are talking today about a product that is somewhat misunderstood, I would say, and it's a product that is called "Liquid Plasma." We are going to get into the details of Liquid Plasma in a decent amount of depth.

I want to kind of step back a little bit, Chris, and talk from just the beginning. With the understanding that we both practice in the United States, so some of our international listeners will have to give us a little bit of grace and maybe translate this, not literally, necessarily, but translate this into what is applicable in your individual country, those

of you that are listening from outside of the U.S. But in the U.S., Chris, when we talk about transfusing plasma to people, what are kind of the main options that we have? What are the most prominent and the most frequently used plasma products in the United States?

Chris: I'm so glad you asked this, Joe, so we can set the stage for how Liquid Plasma fits into this. So often, as you know, when plasma's ordered nowadays, it's still ordered as fresh frozen plasma, or FFP. Very often, that is what's being given, but in many cases, it's something a little bit different. Not inferior in most instances, but different.

So of the products, from a very high level perspective, starting with manufacturing, we have several different frozen plasma products, the traditional one being fresh frozen plasma, FFP, which we know is typically frozen within eight hours of collection. For some purposes, six hours, depending upon the means by which it's collected. That is the starting point, if you will. But in not so recent years, it's been determined that there are other options that are similarly useful. Here I'm talking about plasma products that are frozen within 24 hours of collection.

When one thinks about the issues in play for blood collection facilities, oftentimes blood will be collected from distant sites and getting it back to a manufacturing hub where it can be frozen within eight hours is not possible. So having another option, so long as it's similarly effective, is ideal. And again, those are the 24-hour frozen products that go by a couple of names.

In addition, when we talk about frozen products, we talk about what's known sometimes as cryo-poor or cryoprecipitate reduced frozen plasma. This is a product that has had the cryoprecipitate, which is, of course, rich in fibrinogen and factor VIII, Von Willebrand factor, among other constituents, removed from it. Now, this is still an effective product for at least one indication, perhaps others, depending upon the urgency of the situation, but that indication, of course, is for the plasma exchange treatment of TTP patients, patients with thrombotic thrombocytopenic purpura. And a number of fairly reasonable noninferiority or comparison trials have shown that cryo-poor plasma works as well as traditional plasma in this setting.

So those are the biggies as far as the frozen products. Then, of course, we have the liquid state products and there are two ways of looking at them. One is those products that originally were frozen and that are thawed, and I'll talk about that in a moment. And of course, the other one is a product that never has been frozen, what we are calling Liquid Plasma.

Joe: Before we get to LP, if you don't mind, let's just for our learners, is there a difference in terms of the time between when the product is frozen or collected, I should say, and when it can be transfused between, as you mentioned, FFP, fresh frozen plasma, or one of the 24-hour products, the most prominent one being "plasma frozen within 24 hours," or "PF24," as we like to abbreviate it? What's the overall shelf life that we have for those products? Is it the same?

Chris: I'm so glad you asked. The answer is yes, it is. When we freeze under the conditions that most blood centers and hospital transfusion services use, which is less than -18

degrees centigrade, we're talking about a one year frozen lifespan. But then the question becomes what happens after we thaw it. We know that there are a couple of routes we can take. If we wish, and traditionally, although most hospitals now don't take just this option, as I'll explain, we could thaw that product. And here, again, we're talking about FFP, fresh frozen plasma or plasma frozen within 24 hours. We could thaw it and maintain it for 24 hours post-thaw. And for instance, an FFP product treated thusly would be referred to as "thawed fresh frozen plasma." Good for 24 hours.

However, we have learned, based upon studies done both in vitro and, to a less significant extent, in vivo, that the substantial coagulation activity in a Thawed Plasma unit is maintained at a relatively high level with perhaps a little bit of drop off of factor V and factor VIII for at least five days post-thaw. That has allowed, and certainly in my and your career, we've seen an extension by most facilities to the use of a five day thawed product, Thawed Plasma.

So how does that get us so far into the discussion? And are there any other features of this you'd like to explore?

Joe: I think that's really a key distinction and that's something that I think is not as widely understood as it could be. The difference between, and you put it nicely, that in that first 24 hours, that product has a name. It's a quote, unquote, "thawed unit of fresh frozen plasma," or a thawed unit of plasma frozen within 24 hours. Thawed FFP or thawed PF24. To my knowledge, Chris, please correct me if I'm out of date with this, if you just look at FDA regulations, that's pretty much all they talk about in terms of the use of that product once it's thawed.

Chris: Yes.

Joe: But as you said, there is a fairly standard practice that is in *AABB Standards*, and it's in the Circular of Information in the United States, that says that at 24 hours, it gets a new name. Ta-da! But the name sounds like the old name, right?

Chris: Yes.

Joe: That's what confuses people, I think. Can you talk about that distinction a little bit, the distinction between what you call something from the moment you thaw it until 24 hours after, and then from 24 hours out to five days?

Chris: Sure. Part of it, Gertrude Stein might have put, "A rose is a rose is a rose," however, there are some slight differences. When we talk about a thawed FFP or a thawed PF24, to use the vernacular, again, we're talking about a unit that may maintain that name for 24 hours. At which point, if it is still kept in storage, if it isn't transfused or discarded, in other words, it can be maintained for up to five days with a new name, or by it goes as Thawed Plasma.

And again, from a practical purpose, most facilities are using the two products, whether good for 24 hours or up to five days, interchangeably. There are some who believe that if you have a patient who is more likely to need those more labile coagulation factors, that one should skew towards the use of the fresher post-thawed

product. That is debated, though, as we know. I don't really know what the best answer is there, quite frankly. I'd appreciate your opinion.

Joe: Yeah, I think they're interchangeable, Chris, and I think that practice has been... Well, like most things in our world, I can't point to any randomized prospective studies that say they're equal. Right? I wish I could. But I think that's such common practice and pretty much standard practice that it gets used interchangeably, with the one exception that I have personally said if I have somebody that is in a real serious consumptive coagulopathy, I might skew more towards a fresher product in a case like that, a less than 24 hour product.

Chris: I agree entirely, Joe. And not to do digress too much, but you bring up the so important point that so much of what we do our basis for transfusion of plasma is predicated upon historical experience as opposed to hard facts. That's not to say this isn't not a product that in many cases is absolutely life-saving, but had we started with this product in the year 2021, you could be sure the studies would've been so much more rigorous than they actually were.

Joe: What you just said, we could take that sound bite and plug it into just about any blood product we're talking about. Sadly, we just don't have a lot of prospective data for what we do in transfusion medicine. I wish we did. I wish we had more, and I think there are people that are working on that. People smarter than me, for sure.

We were talking about the products, the frozen products that are thawed. And by the way, everyone, for those of you that are learning, just to be clear, we don't just pop it into the oven or whatever. The products are typically thawed, most commonly, in a water bath that goes from roughly 30 to 37 degrees in the transfusion service right before the product is going to be used. If the product is not used, then it goes in the refrigerator, as Chris said, for up to 24 hours under the one name and then up to five days, from two to five days, under the Thawed Plasma name.

And frankly, Chris, this is another place where people tend to get a little confused because when we start talking about liquid plasma and the specific product called Liquid Plasma, I've had so many people say, "Well, isn't that just Thawed Plasma? It's liquid, right?" So why don't you help us and let's define first what is the product that we are talking about today called Liquid Plasma? How do you define that?

Chris: Sure. This is a product that has never been frozen, pure and simple. And there are some other issues in play, that those other products that we just discussed a moment ago, the previously frozen now thawed products, one could refer to as liquid state plasma. But keep that descriptor, state, in play because it's not Liquid Plasma, even if it is liquid. So how's that for a little bit confusing yet at the same time precise?

Joe: Well, I like it. And in fact, Chris, to make it maybe a little more confusing or a little more clear, depending on your perspective, if you look in the US Circular of Information, both Thawed Plasma, Thawed Plasma with a capital P, the 2-5 day product, and Liquid Plasma, the never frozen product, are listed under “Liquid Plasma Components.” So it definitely does. It tends to blend into people's brains. But again, everyone that's listening, I want you to keep this really clear, they are two

different components and Chris just made the first point about it. What we're talking about today is a never frozen product. This never goes in the freezer, never goes into that -18 state. So it never goes by the name FFP or PF24. It's a totally separate product. Okay, Chris, I'll shut up.

Chris: No, this is great.

Joe: So talk to us a little bit more about how we make it.

Chris: Sure. Currently, it's manufactured exclusively from whole blood collections. So that is another issue as opposed to the other more traditional, or maybe not necessarily, but the more used plasma products that can be made either from whole blood or apheresis collections.

Now, that being said, depending upon how you interpret the regulations that describe the starting raw material, some have suggested that there may be a way to use apheresis plasma for this purpose, but we haven't yet explored that option. I won't get into the nitty-gritty of that. In any event, once we manufacture it from whole blood through this typical means that we use to separate plasma from the reds, we then maintain it in, as we said, a liquid state. It's a refrigerated product that's maintained at one to six degrees centigrade during storage conditions. The product, because it's never been frozen, just a brief aside, will have, in some cases, a slightly different look. By that, I mean to say that if one freezes plasma freshly separated from red cells, any red cell contaminant that gets into that frozen plasma product upon it subsequently being thawed, the red cells are lysed and the free hemoglobin just distributes uniformly in the plasma product and you should never see it.

But with Liquid Plasma, because those red cells are never frozen and therefore lysed, in some cases, there may be just enough present, especially upon settling of the product for 12, 24 or longer hours, you might see the layer or you might see upon redistribution as the product's jostled a little bit, a reddish hue. That's certainly nothing to be scared of. The question becomes, does it have any practical impact, and I think we'll discuss that a little later.

Joe: Before we do that, Chris, actually, one thing I want to make sure that we emphasize here, because I think this is an important point. I don't want to lose it before we get... And yes, we absolutely will talk about the implications of that little red blush later on. But I think that unless you're someone who spent a lot of time in blood center world, I think people tend to overestimate how much blood, how many red cells are in something to make it turn a little red. Can you talk a little bit about that? I mean, under our normal circumstances, when we make a product that's going to be frozen, as you said, those few red cells get lysed and they don't have that opportunity in Liquid Plasma. But I mean, are we talking about multiple mls, multiple milliliters of red cells? How much are we talking about?

Chris: Great question. One way to answer that, and we'll backtrack on the napkin as it were the math, is when I trained under Larry Petz and George Garrity, they had referred me to a very nice study demonstrating, for instance, how much hemolysis in a patient

who is freshly hemolyzed would be needed in order to see the hemolysis visually, the first in the plasma or the serum. The first appearance.

This particular study, which I'm sure I could pull up from several decades ago if I took enough time, demonstrated that right around 5 mL per patient, who presumably at the time had about a five liter blood volume, with on the order of three liters being plasma. So right around 5 mL of red cell destruction would be seen in such an instance and then of course would be quickly cleared through the usual in vivo pathways.

Now we're talking about a product here where the free hemoglobin or the red cells in a liquid plasma would be floating in the plasma. So we're talking certainly about less than on the order of 1000th of the volume content, overall the product having red cells until you'd about see it. So for a 200 mL product, we'd be talking, what, about on the order of 0.2 mLs, if that, and probably much, much less. So we're talking about very tiny amounts of red cells.

Joe: Okay, okay. Forgive me for that interjection, Chris, but I think that was important to emphasize. That's a hugely important point. We're talking about a tiny amount of red cells, and we will get back to the implications of that in just a sec. But I interrupted your flow. I think we were at the point where you were going to talk to us about how long this Liquid Plasma product can hang around.

Chris: That's a great question, Joe. The answer is that the expiration date of Liquid Plasma is predicated upon the expiration of the source red cell unit from which it is derived. For example, when one collects whole blood into a collection system that has CPD or a similar citrate phosphate dextrose anticoagulant whereby the red cells themselves, if they were separated pre-addition of any additive solutions, would have a 21 day out date. In this case, the rule is that we can add up to five days to that in this case 21 day out date when we establish the expiration for Liquid Plasma. That is, in fact, what most programs do. They set a 26 day out date. There are some that are more conservative, and that is their right.

Chris: Theoretically, if one were to make Liquid Plasma separated from a CPDA-1 collection, and we know CPDA-1 units have 35 day out dates, we could potentially have 35 + 5; a 40 day Liquid Plasma out date. I'm not aware of anyone who takes it that far though. Does that answer your question?

Joe: It does. That does. So just to be clear, when we're talking about the Liquid Plasma product, that's the topic of our discussion today, the never frozen product, you have the potential to keep that plasma product in your refrigerator for up to 26 days, as opposed to Thawed capital P Plasma, which is a five day product, or even thawed fresh frozen plasma, which is a one day product. So we're talking about a lot longer shelf life, Chris. Is that an accurate way to put it?

Chris: Absolutely. And that is at the risk of making this too mercenary a statement. It's quote, unquote, "selling point." This is a product for which our hospitals, especially hospitals that don't necessarily use plasma every day, can be allowed to have ready to use plasma on their shelves. That can be absolutely critical, as we know, to the

management of severely bleeding, especially massive bleeding patients. So we can certainly talk more about that as we go.

Joe: Absolutely. We will get to massively bleeding patients, because really, that's where the rubber meets the road for this product and we're absolutely going to talk about that. So everyone, hang with us for just a second, but I want to delve into a little bit of the discussion of... Okay, let's be blunt here. So if we're talking about a Thawed capital P Plasma product that's got a five day expiration as opposed to a liquid never frozen plasma product that goes up to 26 days, the question is we talked earlier about the one day versus the five day, or the PF24 versus FFP, are those interchangeable. Well, the obvious next question should be, "Is it interchangeable to consider a five day Thawed capital P Plasma equivalent to a Liquid Plasma at 26 days?" What has the debate and discussion been about that issue, Chris, and about whether or not a Liquid Plasma product can be used just for patients in the hospital that need a plasma product?

Chris: I'm so glad you asked, Joe. The answer is that Liquid Plasma has one and only one indication at the present time, and that's for good reason, the very issues you're bringing up, that this is a product that is stored for substantially longer durations than a one or a five day post-thaw plasma product. Currently, the indication... And I'll go ahead. I don't usually like to read when I'm doing a discussion, but as the package insert, if you will, states, in this case, the Circular of Information, Liquid Plasma is indicated for quote, "the initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhage and who have clinically significant coagulation deficiencies," end quote, full stop.

So to answer your question, what we're looking at is a product that is a single-trick pony. It's a very good single trick and can be absolutely critical in helping to save patients' lives and also to reduce wastage in a facility. We do know, based upon a number of studies that have been performed, that the most important clotting factor function is retained with some diminution, again, of factor VIII and factor V and some other semi-labile substances. However, thus far, it has been shown as a bridging product, and you wouldn't use it for a prolonged period, but for one or two units to get the patient started with yellow stuff going into him or her. It's an ideal product. And then you switch over to the traditional stuff.

Joe: Nice. Okay. Boy, I'm so glad you made that point, Chris, because that's a hugely important point. When I talk to hospitals about implementing Liquid Plasma, I often get that question that, "Well, if this thing is getting to day 24 or day 25 or so, I don't want it to expire. Can I just use it for the patient who has an elevated PT and who's had too much warfarin or whatever?" And my answer to that is always absolutely not. This is not intended for anything other than that urgent use, as you just described, Chris. So I'm super glad you made that point.

And everyone, please don't miss that. One-trick pony is exactly right, what Dr. Gresens just said. So anything else that you might want to use it for, the answer is it's not a good product for that. Doesn't matter what else you want to use it for, the answer is it's not a good product.

Chris: Absolutely. And I might, though, as we continue to consider its pros and cons, I might just share a practical experience I had recently with regard to this at a level two trauma facility that I help support from the clinical side. There was some discussion about plasma wastage. And quite frankly, there was just far too much plasma that was being thawed and never going into patients. Instead, going into the biohazard can.

About six months ago, they chose to invoke the Liquid Plasma option and are now receiving a constitutive number of units currently. In their case, two units per five days. It's meeting their needs very nicely, but they are still occasionally discarding a Liquid Plasma unit because they know if it doesn't go into a patient who has that one indication, they should not use it for other purposes.

So they asked me, "What more can we do to reduce this wastage of Liquid Plasma?" My answer was, "Well, let's look at your overall numbers. There may be some opportunity to change your ordering practices and still support your pay sufficiently, but let's look at what your wastage rate used to be for Thawed Plasma and what it is now. And sure enough, when we looked at their wastage rate for Thawed Plasma before using Liquid Plasma, they were going through, and I won't give a denominator, but this hospital was going through between 5 and about 18 units per month of wasted Thawed Plasma that outdated at five days. Now they're using a relatively nominal amount of Liquid Plasma, bringing in nine or 10 units a month on average. Their wastage rate for Liquid Plasma, unfortunately, they're having a couple units a month that are not being used, but when we also looked at their wasted rate for Thawed Plasma, it had gone practically to zero. So the trade off by far was worth it. They were treating their patients just as effectively, more practically though.

The last thing I'll say just as an aside, when I use the expression wastage, that isn't necessarily fair, because we do understand that there is a purchase price, if you will, to being able to treat patients. And we always have to have a little more than we're ever going to use in order to make sure we're ready. The question becomes how much that little more should be. And if it's just a little, if it's reasonable, that ain't wastage, that's just good planning. Whereas if it's excessively more than that, then I'll use the word wastage. Sorry about that digression.

Joe: No, that's well said. I think that's 100% right. And I think it brings us to what I wanted to make sure that we emphasized, and that's... You just gave the perfect example, Chris, when you talked about what kind of a hospital should be looking at Liquid Plasma.

I've mentioned to you off mic earlier that in my personal practice when I have level one trauma hospitals coming to talk to me, then they bring up Liquid Plasma, I'm really clear with them. I tell them, "This is not the product for you." If you're having major traumas come in on a daily basis, almost certainly, unless you're thawing a whole bunch that you don't need to thaw, it's very unlikely you're going to have a big instance of Thawed Plasma expiring on the shelf."

But for the other hospitals that do trauma, as you just said, every now and then, whether that's once a week, every four or five days, whatever, Liquid Plasma, to me,

is a perfect product because we're going to talk about it in a few minutes. It is incumbent on us in trauma transfusion nowadays to be ready with the yellow stuff. When a trauma comes in, the correct answer is not, "Okay, we'll see in 20 or 30 minutes with some plasma. We've just got to start thawing it." That is not the acceptable answer anymore. So Liquid Plasma might be the perfect product with that 26 day shelf life to serve, as you said, as a bridge to the good stuff, which is that freshly Thawed Plasma. We're still going to freshly thaw stuff, but we've got to get ourselves there in that early transfusion.

So I'm sermonizing now, Chris. Look what you got me started doing there, buddy…

Chris: Well, I appreciate it. Stay on your soapbox, please, and I'll try to join you.

Joe: Oh man, you don't want me to do that.

Chris: Nor I. One analogous situation too, and there's a lot of overlap, is the whole use of group A plasma for emergency transfusions. By the way, just as a spoiler, if you will, when it comes to what ABO type my blood center at my recommendation and that of other experts in our program have promulgated, we almost exclusively make Liquid Plasma off of group A plasma.

The idea here is that as we know, again, during the bridging support of a severely bleeding patient, especially a massive bleeder, that group A plasma, to my mind, even on titer Group A, which is the predominant type being used in the U.S. With some exceptions, is a very appropriate use of resources with minimal risk and also allows for us to save the AB for the patients who really need it.

I've been in that situation recently where you get a patient who can only take AB plasma for, say, a plasma exchange and you ain't got enough AB plasma because a hospital has universally used AB for most of their transfusions. That's not acceptable in the year 2021. So I guess the point I'm making is that Liquid Plasma and group A plasma use have some overlap as to how they're applied, and perhaps we'll talk more about it.

Joe: Perfect. We may hit that a little bit later, but before we get into a real quick discussion on how we're transfusing trauma patients in 2021, I want to just do a couple quick housekeeping things on Liquid Plasma, Chris, because I think these are important to consider.

People that read the U.S. Circular of Information will notice a little blurb in there, a little comment, and you and I both are familiar with the person that at least drafted that comment, because he's your boss, is there's a little comment in there about the fact that there are viable leukocytes, specifically viable T lymphocytes, in units of liquid, never frozen plasma, and that that has the potential to cause Transfusion-Associated Graft Versus Host Disease in a patient.

So we need to talk about this because people are seeing this. What are your feelings on that risk and whether or not it's an important thing to do or at least to consider to irradiate units of Liquid Plasma?

Chris: I'm glad you asked, Joe. My big picture answer is that in most instances for most facilities, I do not believe that the irradiation of Liquid Plasma is required. It's a nicety that one could add on if one wishes, but for most instances, it's not required. And let's think about it from a practical perspective. Who's getting that Liquid Plasma? Well, of course we're talking about severely bleeding patients who typically are trauma patients and most often also getting, or they should if they survive long enough to be treated appropriately, red cells and platelets, both of which are not routinely irradiated prior to transfusion.

So what is the point in most instances for having irradiated plasma to render those T cells incapable of proliferating, causing Transfusion-Associated Graft Versus Host Disease in this instance? Very minimal. Now, I guess you could make the argument that if you were a trauma facility in a region where the patients were at substantially increased risk for Transfusion-Associated Graft Versus Host Disease, it wouldn't hurt to add that belt to the suspenders. But I think in most cases, it's overkill. But I'm wondering though that have... I put myself out there. What is your opinion, Joe?

Joe: Maybe I should just shoot you down just for fun, Chris.

Chris: Please feel free.

Joe: No, I wouldn't do that.

Chris: I don't want people to agree with me all the time, and I know you're so expert in so many areas, I'd love to get your opinion.

Joe: Well, that's overly kind of you to say, but here's what I would say: I've gone both directions on this. When I first saw that statement in the Circular, my initial feeling was, "Well, that seems like a pretty clear statement. Let's go ahead and irradiate it," because my philosophy in general with irradiation is I would far rather over-irradiate than under-irradiate. You and I both know the last thing we ever want to make a diagnosis of is Transfusion-Associated Graft Versus Host Disease, because people die, obviously. There's no getting around that.

But as I've gone along, I've loosened that feeling, frankly, for exactly the reason that you're describing. That realistically, why are we choosing to just irradiate this product when we're not irradiating anything else? Yeah, of course, people that are Heme-Onc patients or patients that have severe immunodeficiencies, they can have trauma too, just like anybody else, but they're getting all these other unirradiated products, why would we specifically irradiate the plasma product? So I'm right there with you, Chris.

Chris: Well, I appreciate that, Joe. By the way, I'm right with you on your progression and I know we have a similar time course of our careers. And I'll tell you, I had done back in the late '90s some very basic research. It wasn't cutting-edge, but it was looking at mitogen stimulation of T cells within frozen and then thawed plasma. We actually, at the time, were able to show that a significant percentage of T cells in frozen and then thawed plasma remained capable of being stimulated by mitogens.

And we had always wanted to do the follow-up corollary, which is to actually try to culture them out and see how well they grow. Our resources were limited at the time.

We never did. But there was a time when working with my prior boss where we actually did recommend for any patient who required Graft Versus Host prevention also to radiate the frozen and then thawed plasma. Which was out there, which was very conservative, but I guess that's taking what we've just discussed to the nth degree.

Now, over time, we let go of that because to my knowledge, there still has never been a case of graft versus host disease associated with the frozen and thawed plasma product. There has, to my knowledge, been one associated with the Liquid Plasma that was never frozen and certainly with other "cellular" quote, unquote, "cellular" blood products. But does an “N of 1” decades ago for Liquid Plasma being associated with graft versus host disease mean that we really have to consider this approach, especially when the indication for Liquid Plasma is so very targeted? So thanks for letting us discuss our backgrounds and evolution.

Joe: Sure. Let me ask you a really basic blood banking question, Chris, before we get into the specifics of that red blush thing that we need to talk about. In general, do blood bankers worry about the Rh issues with plasma products? When we're transfusing previously frozen plasma products, do we worry about Rh?

Chris: In general, we do not take any special approaches to managing the potential for immunization caused by, for instance, Rh positive red cells that are present within a frozen and then thawed plasma unit. The reason for that is number one, the quantity of the red cells is so minuscule. But number two, these red cells are lysed during the manufacturing process.

The question some have is, "Could they still have some immunizing or alloimmunizing potential?" The answer is theoretically it's possible. I'm aware of at least one study that showed in rare cases an association in extremely rare cases of transfusion of Rh positive plasma into Rh negative patients as potentially increased in the risk for anti-D formation. But it certainly has not influenced substantially per act.

Now, the question becomes with Liquid Plasma, could that risk be somewhat greater because the red cells, to a large extent of not been lysed, there might be a little hemolysis over time, but not much, most of them are free floating, could they be more capable of immunizing. The answer is we just don't know.

I could make the argument that if one were truly concerned in a patient for whom this really has importance. And I'm not talking about me, if I, as an O negative patient, were to get a couple units of Rh positive Liquid Plasma, a big deal.

But if it were a young woman of childbearing age who herself is Rh negative, and if a hematologist or an obstetrician or other were to say to me, "Hey Chris, do you think I should give Rh immunoglobulin?" well, I'd still say, "Well, I don't have a strong suggestion that it's indicated." You could also make the argument too that it is very unlikely to hurt and perhaps could help. Consider giving a micro dose, 50 micrograms of Rh immunoglobulin. I don't think would be unreasonable, but just for that very specific indication.

And as we all know, most patients who are going to get Liquid Plasma, when you look at the odds, are going to be men. Those of us who are still stupid enough to do things that put us at risk of trauma and bleeding. And then even of women, we're still talking about fewer than 15% of them being Rh negative. And then a fairly substantial percentage also are going to be old enough that we just don't care anyway. How's that for an answer, non-answer?

Joe: I love that you just threw all of us dudes under the bus. That's what you just did. That's okay though.

Chris: Pretty much.

Joe: It's true though. It's true. Now, I'm right there with you. That's funny. Okay. I guess the short answer is that we don't know for sure, but if someone pushed it in someone who the consequences would be great for making anti-D, such as a childbearing age female, then why not consider giving them Rh immunization. I completely agree with that, Chris.

The one last thing I want to discuss with you, because this is something that if people look at the literature, what they will see is a little bit of... I don't know if it's conflict or not, but there is some debate over after 14 days of storage of a unit of Liquid Plasma, whether or not that product should continue to be used. So the 26-day, generally, shelf life. And I know there's been back and forth on this in the literature. I know there've been some studies that suggest that even though the coag factors are down, that maybe the activity will still be good after that amount of time. I guess what I'm asking is what do you say to the hospitals that you work with in terms of when they come up to you and they say, "Well, Chris, this article said 14 days is probably the max we should do it."? What do you tell them?

Chris: Yeah, I'm glad you asked, because what I tell them is that while of course one major reason why we transfuse plasma is because of the coagulation factor replacement, it's not the only reason, especially in a severely bleeding patient. We know now more and more, although more research still needs to be done, that one reason why plasma transfusions are so important in this population is that there is a correction that occurs to the endotheliopathy that exists during trauma. In other words, we know that the endothelium that lines, of course, blood vessels, becomes compromised in many trauma patients, not because fully of the overt mechanical disruption, but throughout the endothelium, changes can occur that allow tight junctions to be loosened and for both fluid shifts that are problematic for the patient, as well as bleeding into the tissues to occur.

That's a long way of answering that. Certainly, some in vitro studies looking at animals have suggested strongly that the endothelial protecting agents present in plasma are probably good for at least 28 days. So from that perspective, we're looking at a product that probably is going to be helpful there.

And then going back to coag function, yes, there is a drop off in some of the labile factors at 26 days. But the question becomes how significant is that, especially when we know that factor VIII, for instance, is often through acute phase reactant changes

going to be elevated in these patients anyway. And we're really talking about a starting point where we're giving a unit or two before switching over to other products. We're also getting those clotting factors in other products and most especially platelets. And then again, when traditional, thawed frozen products are given. We're not missing much of a beat, if any.

That is my opinion. I think that's based primarily upon evidence basis, but also upon practice. What do you think, Joe?

Joe: I completely agree with you there, Chris. That's almost the identical discussion that I have had with hospital customers. What I often say to folks in hospitals is simply this, "If Liquid Plasma were the *only* plasma product you were ever going to give to a patient, I would agree with you that a 26-day product is probably not what you want." But as we've already beaten to death, this is not the only product. This is just a bridge. This is just to get something in that's going to have some benefit. We know it's not perfect, just like, going back, a five-day "Thawed capital P Plasma" product is not perfect either. They're both bridges. We're both trying to get ourselves to that freshly thawed plasma, which we know, if we're really making the rubber meet the road, that's the secret sauce, right? That's what we're trying to get to people, that freshly thawed product, and we've just got to get there. So I completely agree with what you're saying, Chris. I tell them keep it up to 26 days no problem.

Chris: So well stated. Hey, one other addition too is consider another alternative, the use of crystalloids upfront, or the use of colloids upfront. And obviously, their liquid plasma hands down wins. Now, you can make the argument that I'm setting up a weak straw man or straw woman with those two options, but I think it still holds water.

Joe: I agree. Well, and actually, Chris, that brings us to the last little section that I want to discuss with you. To be clear, I have discussed trauma transfusion on this podcast numerous times, both in terms of general massive transfusion and two separate episodes on trauma whole blood transfusion with the fabulous Dr. Mark Yazer. So if you want a ton of details on trauma transfusion, you can go back and listen to some of those episodes.

But Chris, just in a nutshell, I wonder if you would just walk us through a little bit what we now know, especially in regard to plasma, about trauma transfusion or what's believed, anyway, about trauma transfusion today in 2021 that we didn't know when you and I first started doing this. We won't say how many years ago, but a number of years ago.

Chris: Indeed. The pre-DCR Damage Control Resuscitation approach. In a very small nutshell, we all know that dating back probably to about 2006 when US military experience in Iraq and Afghanistan demonstrated through observational analyses that those patients who got more of the yellow stuff earlier were far more likely to survive and not to bleed to death, we know based upon randomized clinical trials, including an excellent one that came out in the mid teens of this millennium, the PROPPR trial, that getting constitutive ratios of blood products into the patient to approximate as much or as closely as possible whole blood is the ideal.

To this day, it still concerns me, and I know it concerns the clinicians who are involved, when you see a patient who gets 8 or 10 red cell units before getting any other blood product. Unless it's a truly exceptional situation where plasma and platelets are not available, that no longer should happen. The reason for that, it's been proven that the ratio-driven approach also supplemented, as needed by additional transfusions based upon just-in-time coagulation or thromboelastographic testing is standard of care now.

The question becomes, again, how can we most quickly get the yellow stuff into these patients. I think maybe one of the better studies to look at this in the past few years was the PAMPer trial that actually did not use Liquid Plasma, but it used the next closest thing, Thawed Plasma. It was a multi-institutional randomized trial that examined patients in two arms. One is those who were treated traditionally without any plasma. In many cases, they, during air transport from the site of their injuries to the hospitals, would get red cells and certainly other fluids, but no plasma. They compared those to the other arm being patients who got all of the same treatment plus Thawed Plasma. The difference in outcomes was absolutely remarkable. 23% mortality rate in the patients who got the plasma, the extra stuff, versus 33% for those who did not get plasma during transport.

What that means is that of every hundred patients who were treated through the use of plasma versus not during air transport, an extra 10 patients survived because they got plasma on their ways to the hospital. Now, I think that says it all. There was one other trial that came out that year that was a single institution trial out of Denver that didn't show that same difference. But the challenge is that Denver has one of the very best trauma programs, in my opinion, in the world. They so quickly get patients to the hospitals that the use of plasma in transport was not a major factor because the patients didn't take long to get from the site of their injuries to the hospital.

But going back to that PAMPer trial though, even though it was Thawed Plasma that was used, certainly there's every reason to believe that Liquid Plasma would yield similar, if not identical, certainly very similar, comparable outcomes. I think that really says it all as far as the importance of Liquid Plasma in the context of damage control resuscitation. I'll stop there for a moment, Joe, and let you redirect.

Joe: No, I think that's... I don't have a whole lot more to add to that myself, Chris. I think that in the overall context that as you stated so clearly and so well, the old saw that when I was in medical school and I'm sure you were as well, that “the most important thing is to get fluids into these patients as quickly as possible. We don't care if it's clear or not.” I mean, the way trauma transfusion is nowadays is as much avoidance of clear stuff as you possibly can do. That speaks to exactly what we're saying: Let’s consider something else. Let's consider something yellow, platelets, plasma to try and negate some of that ill effect that those clear fluids might have. That, in most cases, don't end up in the vascular system anyway, and you end up with massive third spacing that nobody wants. So what you've said is exactly on point. There is a role for plasma products early in massive and trauma transfusions, and I think Liquid Plasma has a particular role in certain settings, as we've kind of described so far. So I'm right there with you, dude.

Chris: Appreciate that, my friend. By the way, many in the audience, but perhaps not all, know that that complication or set of complications that can be associated with crystalloid infusion is sometimes euphemistically called “CRALI,” or Crystalloid-Related Acute Lung Injury, because some of that extra fluid goes right into the interstitium of the lungs and can cause severe problems. And I'll tell you, actually, as a former heart surgery patient who got a whole lot of crystalloid during my procedure... Appropriately so. I didn't need plasma. I didn't need red cells or any transfusion support. But I'll tell you that it does take a while to clear that fluid. And if you can avoid it in the severely bleeding trauma patient by giving blood products, including plasma, that's just one more benefit.

Joe: Well, Chris, it has been such an honor to have you here today, my friend. I'm so glad we finally got the chance to do this. Thank you for helping us to understand how Liquid Plasma can play a part in modern day trauma transfusion in our world, and thanks for clearing up some of the misconceptions about it. I really appreciate it.

Chris: It's been my pleasure, Joe. And I want to thank you for two things. Number one, for allowing me to join you today. And number two, and this is a big picture thank you, for everything you do to promulgate education regarding transfusion medicine. And I will say this, you can keep it or edit it out, I hope you keep it, that you are one of our foremost educators in this field and I always enjoy sharing links to a number of your different references that I've started to access more and more in the last couple of years with colleagues. Because I know, aside from the fact that they're going to get great information and recommendations, it also saves me time. So thank you so much and it's been a pleasure.

Joe: Happy to help.

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Joe: Hey everybody, it's Joe. I hope you will take a minute to go to BBGuy.org/095 to download the 2 page pdf on Liquid Plasma that I mentioned at the top of the episode. I think you’ll find that stuff really useful.

Remember, if you are a physician or a laboratorian, be sure to go to wileyhealthlearning.com/transfusionnews to get your hour of totally free continuing education credit (you can also get there from the show page at BBGuy.org/095). As always, thanks for the continuing education sponsorship to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as, of course, to Wiley Health Learning.

As always, I hope you will consider going to Apple Podcasts and give this podcast a review and subscribe to it. I’ve appreciated the kind words and learned from the critiques, so please share your review whenever you can.

Next up on the podcast is another continuing education episode. This one is an interview I did with Dr. Claudia Cohn, who is the Chief Medical Officer of the Association for the Advancement of Blood and Biotherapies (yes, in case you missed it, that’s the full name for the organization formerly known just by the initials “AABB”). Dr. Cohn and I talked in depth about blood shortages, including

why they happen, how to deal with them, and what the future might look like. It's a really timely discussion given that we seem to be, right now as I'm recording this in March 2022, coming out of the worst blood shortage I've ever seen in my career.

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