BBGuy Essentials 074:
Radioactive! with Chris Tormey
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Chris: This is Chris Tormey and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, and welcome to Blood Bank Guy Essentials, the podcast made just to help *you* learn the essentials of Transfusion Medicine. I'm Joe Chaffin, and I am your host. Today's episode is a discussion of irradiation of blood products, which really sounds simple but has more nuances than you might think, with the great Dr. Chris Tormey from Yale.

But first, you should know that 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 several different types of credit, including: One *AMA PRA Category 1 Credit™*, one contact hour of ASCLS P.A.C.E.® program credit, or one American Board of Pathology Self-Assessment Module for Continuing Certification. To receive credit for this activity, to review the accreditation information and related disclosures, please visit www.wileyhealthlearning.com/transfusionnews.

So, earlier this year, in my "day job" as Chief Medical Officer for LifeStream Blood Bank in Southern California, I was looking really hard for a concise article or irradiation to send to a doctor at one of the hospitals my center serves. Honestly, I couldn't find much at first! However, I stumbled across an article written by Drs. Burak Bahar and Chris Tormey that did such an amazing job describing the whole entire issue that I had to ask Chris to join me today to discuss irradiation. The article was published in Archives of Pathology and Lab Medicine in May 2018, and it's truly terrific. You can go to the show page for this episode, at BBGuy.org/074, and find a link to the article.

You should listen to this episode if you are a learner, because it is full of information that you will need to know for exams. You should also listen if you are NOT a learner, because I'll bet you will learn some things you didn't know! I love episodes like this, where the whole idea is to take a simple topic in Transfusion Medicine and really break it down, and Chris Tormey is just the right guy to do it! Chris is is a pathologist who is board-certified in Clinical Pathology as well as Blood Banking/Transfusion Medicine. He is an Associate Professor in the Department of Laboratory Medicine at Yale University in New Haven, CT. He serves as Medical Director of Transfusion Services at both Yale-New Haven Hospital in New Haven, CT and VA Connecticut Healthcare in West Haven, CT. Chris is the Director of the Transfusion Medicine fellowship program at Yale, and teaches students, residents, and fellows at the Yale School of Medicine. He is widely published, and has won several awards for his research and teaching efforts.

So get ready for an in-depth, “essential” look at irradiation of blood products. Here’s my interview called, “Radioactive!” with Chris Tormey.

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Joe: Chris, my man! Welcome back to the podcast!

Chris: I'm very happy to be here, Joe. Thanks for having me.

Joe: I'm really very excited to talk to you about this article you did with Dr Bahar, who was your fellow at the time; I understand he is now faculty at Yale?

Chris: That's correct.

Joe: Why don't you tell me if you don't mind a little bit about, what led you to do this? What was the motivation behind doing this article?

Chris: Joe, it's I think very similar to the motivation you discussed earlier. We get frequent questions at the two hospitals I cover, which are Yale New Haven hospital and VA Connecticut. Our residents and fellows are actually involved in the pipeline for irradiation requests. So if a patient has not had radiated products before, our residents and fellows are involved as a first-line triage for this. And I really recognized there wasn't the one go to resource. You and I chatted a little bit before the podcast. I didn't really have any educational materials myself that I could give to folks; it was typically one slide in a PowerPoint that explained, you know, maybe guidelines to irradiation. So with all that in mind and having a very, very willing fellow, as you mentioned, Dr. Bahar, he did a wonderful literature review and we thought this would be useful not only internally for folks, but since we had this concern and this desire for information in this area, we thought others would as well.

Joe: So Chris, let us rock into this. So we're going to talk about TA-GVHD and irradiation's role in it. And I think it really behooves us to start kind of the way you started it in the article, to talk about, where did this whole thing come from? How did we get to the point where we're irradiating blood products?

Chris: Yes, it's an interesting story and it's one that actually I did not know much about. And, our fellow, as I mentioned, the current faculty, Burak Bahar, he had found these really interesting initial resources that were published that really is a result of the radiation poisoning that came out of World War II and use of atomic weapons. So, lots of experiments were done in mouse models looking at what were the effects of radiation, and transplantation as a way to try and recover for folks who had severe or lethal-dose radiation exposure. And they found one of the number of these animal models that if they would do transplantation after lethal irradiation, that they'd get sort of a systematic illness and die, and that, if products were then subsequently irradiated, it actually prevented a lot of the graft-versus-host disease that they were seeing.

And it wasn't even called "graft versus host disease" at that time. It was like a "reactivity syndrome." And then over time I think is folks began to understand it's something in the product we're giving itself. And in that case it was the cell therapy products, but something in the products themselves, which are driving a reaction against recipients. And then there were a number of studies that were subsequently published showing that this was happening with blood products themselves.

Joe: Let's talk about that specifically, Chris. What is that interaction? What is kind of the "guts" of TA-GVHD, if you will, no pun intended. What happens to cause something in this transfused product to attack those recipients?

Chris: You got it, Joe. So, I think it's a question we're still grappling to understand completely. But as we reviewed in the article, I think the current day understanding is that most often it's an immunosuppressed recipient. So typically in immunosuppression, you know, I think we throw the around very lightly and very, very commonly in medicine in general. In the case of transfusion, what we're really talking about is individuals who have a cellular immunodeficiency, and in particular a T-cellular immunodeficiency. And it's those individuals that are probably at highest risk for this.

In normal day to day practice transfusion medicine, if you're transfusing an immunocompetent host, someone who has normal cellular immunity, but maybe say it's an individual with something like sickle cell disease where there isn't an immune deficiency, the lymphocytes that come across from the blood product, whether it be a red cell product or platelet product, those are usually targeted for immediate clearance by the recipient's immune system. They recognize that there's a different HLA coming across and those cells are targeted for destruction and ultimately destroyed. Now if you take someone who's severely immunosuppressed, particularly again, maybe they've gotten a severe chemotherapy regimen that's depleted their own lymphocytes, or maybe they were born that way. One of the most common severe cellular immune deficiency disorders we see is something called "DiGeorge Syndrome," another called "Severe Combined Immunodeficiency," where patients just do not have generation of normal T-cells, normal cellular immunity. These individuals cannot fight back.

So, when they see the donor lymphocytes coming across, their immune system can't do much with it, and then those lymphocytes really kind of take over. They engraft in lymphoid organs, they engraft in bone marrow, and then they start attacking everything that they deem as foreign, which is the host tissues. So a lot of manifestations of graft-versus-host disease are similar to *transfusion-associated* graft-versus-host disease. So folks think about the common things that happen with organ transplants. Well, we see that in severe immunosuppressed individuals who get transfusion.

And one of the first people I ever learned from said, "Think about transfusions as not unlike a transplant. We're just transplanting blood." And what ends up happening is that those lymphocytes get into bone marrow, they cause severe

deficiencies of red cells and platelets. So patients have severe cytopenias. It's kind of a hallmark of transfusion-associated graft-versus-host disease, which makes it different than many of the forms of GVHD. The gut gets attacked. As you alluded to earlier, these patients have severe lymphoid aggregates, severe disease of their gut. They have severe skin rashes. They have chronic fevers. And over time, usually over the course of about one week to about eight weeks, if there's not an immediate treatment, really this does, this is almost a uniformly fatal type of reaction. So it's something very serious. It's something we worry about a lot in the transfusion community. Obviously we're giving lots of blood to patients who could potentially have immunodeficiency disorders. And on top of all that, Joe, the other concern is that there are reports out there that you don't necessarily even have to be immunosuppressed for this reaction to happen to you, and we can get into more details on that. So hopefully that's kind of a ground-level overview of what we're dealing with, with transfusion-associated graft-versus-host disease.

Joe: I want to explore that just a little bit because learners in my experience are often really confused by why family members, HLA-matched transfusions, immunocompetent patients are at risk for TA-GVHD. So why don't we take just a second if you don't mind, and just kind of nail that down. What do we know about that? Why would that be a risk, If you get blood from somebody who's close to you?

Chris: Right Joe. And I think that's currently the thinking is that those are probably the highest risk individuals right now. So if you're donating for a family member who's getting cancer therapy or stem cell transplant, the problem is, is that the immune system can be somewhat easily fooled in this regard.

And probably the easiest way to think about this is that let's say as a donor, your HLA haplotype is “AX BX” and you're homozygous. So you only express AX BX as a donor, as someone who's, you know, doing an altruistic thing by trying to donate for a family member. And, most likely if you're donating for a parent or a first degree or secondary relative, they're going to share some, but not necessarily all of your HLA haplotypes. So if they see your AX BX homozygosity and they share one of those haplotypes, let's say they're “AX BY,” their immune system may not recognize that as foreign. So they'll...it's almost permissive. It's like the gates are open, allowing for those cells to engraft. But then once those cells and graph they recognize again these being the donor cells, they recognize the small difference between themselves and the recipient, and then they mediate a very severe form of graft-versus-host disease like we just discussed. Really taking advantage of the fact that there is that that one haplotype difference or one allele difference in one of the HLAs.

And kind of what we alluded to earlier in the introduction: If you're "AX BX", and the recipient is "AZ BL" (Again, just throwing those out there, these are all hypothetical terms, these are not real HLA types), but there's enough heterogeneity there that if you're an immunocompetent individual, we think the vast majority of the time, your immune system is going to recognize those cells and target them for immediate deletion. But if there's enough similarity there

between the donor and the recipient, and again most often that similarity is going to be seen from first or second degree individuals, that does...It's almost like a "Trojan horse," in some respects. It allows for "the enemy" to get in. It doesn't get recognized. And then once the enemy has engrafted itself, it's going to mediate severe graft-versus-host disease against any cells that look even slightly different from it from an HLA, or an antigen standpoint.

Joe: So, it's basically a scenario where the recipient may have a perfectly wonderful and fantastic immune system, but as you said, there's some degree of "fooling" that recipient and the recipient just essentially *chooses* not to counteract that attack.

Chris: That's exactly correct. And, like we said earlier, the most likely scenario, so in a big diverse place like the US, the most likely scenario where this kind of Trojan horse attack's going to happen is where individuals...you're getting blood from someone who likely shares at least some of the genetic profile that you do. Again, a first or second degree relative. But in some countries that have less HLA diversity, you may encounter a random individual, random allogeneic donor who has similar HLA types to you. So in certain countries, the risk for GVHD is significantly higher.

I always point to Japan...I think a lot of really good studies have come out of Japan, and that's where even a first or second relative doesn't necessarily have to be your donor, but because of the somewhat more homogeneous HLA nature of the Japanese population, as an example, there's potentially a high risk for a transfusion-associated graft versus host disease in that population as well.

Joe: Before we leave the discussion and the description of TA-GVHD, could you go over just one more time again, what clinically and laboratory-wise we should expect to see in a patient with TA-GVHD?

Chris: Right. So, uh, clinically...And I think the other thing that's important to point out here, Joe, is that I'm not sure about your experience. Fortunately, I've never actually seen one of these in my career...

Joe: Thank God, me either.

Chris: Yeah. So it's not the kind of reaction that we're, I think used to seeing. So I think if we're not thinking about it, and we're not thinking about the signs, it could be something that could easily brushed off as, "Oh, it's a viral infection. Oh, it's some complication of chemotherapy." So that's where I think it's important from a blood bank consultant standpoint to be aware of these things. So if you're discussing patients, you might want to raise the possibility, particularly for immunosuppressed individuals, that you might be dealing with a GVHD.

So, to your question, probably clinically is the way these patients will be recognized first. The timeframe from infusion of an implicated product to symptoms, people have reported about one to seven weeks is the timeframe, some as quickly as one week, some as late as eight weeks after the exposure. And usually clinically this is how they're going to come to attention: So, these

patients are going to have very, very red, what are described as "erythematous" rashes over time as those lymphocytes engraft in the bone marrow. And again, this makes transfusion-associated graft-versus-host disease particularly unique is that in most other forms of organ transplant graft-versus-host disease do not involve the bone marrow. These patients with TA-GVHD, which is the transfusion-associated form, bone marrow *is* going to be involved.

So they're going to have cytopenias, perhaps worse anemia than initially before their transfusion. Certainly leukopenia (reduced white cells), thrombocytopenia (reduced platelets), and almost an intractable cytopenia. These cytopenias won't improve. These patients will have fevers. We discussed the rashes. They'll often have GI complications, so watery diarrhea, malabsorption, things of that nature. And then, constitutional symptoms that are a little bit vague and nonspecific, like fevers, cough, things of that nature.

And then, from a laboratory standpoint, we already discussed some of the cytopenias that we can detect. If you suspect something like a transfusion associated graft-versus-host disease, really the way to cinch the diagnosis from a laboratory standpoint is to look for essentially two populations of lymphocytes in the patient's blood. And, we can accomplish this the same way we accomplish monitoring patients post-transplant. We can do something called "chimerism studies," where we use molecular analysis to determine, using very, very unique aspects of the genome, we can look to say, "Oh, it looks like there are two different populations of cells in the patient's peripheral blood or bone marrow," like you would see status-post a stem cell transplant, but in this case, this is an unwanted second chimerism or second population. That's really the way the lab diagnosis is formally, I would say cinched or completed.

Joe: Again, my suspicion is that some learners out there are listening to this and they're going, "Okay, irradiation, TA-GVHD, blah, blah, blah, blah, blah." Let's be really clear about the consequences of this diagnosis, and you and I have just said, we're both really happy that we've never actually seen a case. How badly do patients do when they get the diagnosis of TA-GVHD, Chris?

Chris: Yeah. So when we originally wrote the article (and I think the data have not really changed), that was written about two years ago, it's a greater than 90% mortality rate. So, versus virtually every other form of transfusion reaction we can see, this is probably the most deadly. And part of the issue is that it does not have a straightforward treatment regimen.

So, if someone has TRALI, transfusion-related acute lung injury, or hemolysis, you kind of know what you're dealing with. It's often an acute reaction. And while those can have high morbidity and mortality, at least there's often a clear treatment plan for those with something like a transfusion associated graft-versus-host disease. Really the only treatment is stem cell transplant for those individuals. And most patients are just not in a position, by the time this disease is recognized, they often have other comorbidities, which is why they were probably being transfused to begin with. They're just not in a position where you can actually turn the corner

and get these patients to definitive treatment, which is a stem cell transplant. So yeah, high morbidity, high mortality, not easily treated, and just something you really want to AVOID, which is why we've been from… the paradigm of transfusion medicine is we can't really treat these. So of course the best thing to do is to try and prevent them.

Joe: And we will get to that in just a second as we really dive into irradiation. One more question, Chris, before we leave TA-GVHD, do we have any idea of how often it happens? I mean with national and international reporting, is there any data out there that you're aware of that suggests the frequency with which TA-GVHD occurs?

Chris: I think in the U.S., we're much more biased toward looking at fatalities. So, as many of the listeners likely know in the U.S. if you have a fatality due to a transfusion reaction, that has to be reported to the FDA. And they're actually fairly rarely reported to the FDA, on the order of less than five over the last about five or six years, when you look at the accumulated data that's available on the FDA website.

But the problem is that A, there's probably under recognition of these, and B, if someone actually did survive, if they're the lucky 10% that did survive this, it probably wouldn't be recorded there. There's fairly inconsistent reporting. I'm sure again that our listeners know that the U.S. CDC has set up a hemovigilance database. Not every hospital participates in that. So, you're not necessarily getting data from all of U.S. hospitals. I think we have to kind of look abroad, and when you look at the UK where they really encourage reporting to the UK's hemovigilance database, not only fatalities but near misses, as well as the Canadian study you talked about earlier, we're talking about probably a rare reaction.

Joe: Let's dive into irradiation, Chris and, I'm just going to hit you with the crux of the matter, right from the start. So, what do we know or what do we think we know anyway about WHY irradiation prevents TA-GVHD?

Chris: Yeah, it's a great question Joe. And I can tell you just as a kind of setting the table for this, one of the reasons why we have this as a consult at the hospitals I covered is that folks see that as an option in our electronic medical ordering system. They will check it off because they think it's providing better products, but it's often not doing what they think it is doing! So, I think that's why it's worthwhile to have it available as a consult if you can.

So, the way we think this works Joe, and again I think it ties very nicely to the pathophysiology of the disorder we just talked about, is that if lymphocytes, particularly T-cells, are the problem, if they're going to be the mediators of this disease in either an immunocompetent or an immunosuppressant individual, then you want to have a process by which you can essentially deactivate those cells. And that's really the crux of what we think irradiation is doing. That by giving a dose of irradiation to a product bag, you're basically *killing* the proliferative

potential of the lymphocytes there. Essentially, causing DNA damage, DNA breakdown that's irreparable, such that while the lymphocyte may be still there and intact as a cell, if it gets into the circulation of the recipient, it's not going to be able to proliferate. It's not going to be able to basically activate or mediate any of its downstream effects, to cause graft-versus-host disease. So, and that's, that's really the fundamental crux of it, that we're giving a high enough dose to kill those cells, but not fundamentally damage or alter any other aspects of the cells that are present there, the red cells or the platelets or even granulocytes for those who are still doing granulocyte transfusions.

Joe: I raised my hand on that one. I am still giving granulocytes!

Chris: You know, there's clear interest in that still in the modern day.

Joe: Yup. So, and that actually, again, let's take advantage of having the captive audience on this for just a moment. As you said, sometimes people think it does what it doesn't do. So let's be clear: Does it kill anything else? Does it kill "bugs in the bag?" Does it sterilize the product? Is there any other benefit that you get from a radiation?

Chris: There really is not. And we make that very clear to our folks who call us and say, you know, I have a patient who's got a Gi bleed and you know, they're completely immunocompetent and they're just taking aspirin. They have a GI bleed and they want to give a platelet transfusion or red cell transfusion. Then they want irradiated products and we say, "This is not a safer product. This is not a better product. In fact, it comes with some damage actually!" that we can also get into a little bit later. So, it's not necessarily for everyone. But it really doesn't do anything but inhibit lymphocyte proliferation. That's essentially what we're doing. Like you were saying, it's not more sterile. It doesn't kill virus. It doesn't kill bacteria. It's really just essentially inhibiting proliferation of those white cells.

Joe: And, one last question before we talk about how we do that. Again, learners listening to this podcast, especially those of you that are pathology residents and in fact those of you that are studying for SBB or your clinical lab scientists exams will need to be aware, certainly at least in the United States, what dosage are we talking about Chris? What is, what is the recommended minimum dosage?

Chris: Yeah, Joe. So, a quick anecdote. When I was a medical student, I was told that there are certain things that if you're awakened at 4:00 AM and someone shined a flashlight in your eyes and said, “You HAVE to know this!” So, if you're a pathology resident or a blood bank fellow, this is just something you have to know. You're going to see it on board exams, RISE exams until the end of time.

So, what is generally recommended, actually, I can even give some hints and tricks away. People try and trick you on those exams. So, what the U.S. FDA and what other guidelines essentially mandate is that you need to deliver a minimum dose of 25 gray [NOTE: Abbreviated “25 Gy”] to the center of the blood container with any area outside the center getting a dose of at least 15 Gy. The way this can

sometimes be asked in a tricky format is that sometimes people use the "centigray" unit and therefore the doses then become 2,500 centigray [NOTE: Abbreviated “2500 cGy.” Also note that “centigray” is the same as “rad,” an older term still used on exams] to the center of the bag and 1500 cGy to anything outside the center of the bag. Those being, again, the minimal doses, so they will try and fool you by changing the units there. So, keep in mind it's “gray” if there's, essentially it's a double digit number, like 25 or 15, and it's “centigray” if you're talking about a number, like 2500 or 1500.

Joe: I understand that dosage is somewhat higher than other countries, is that correct?

Chris: That's right. So, most countries would say that you want sort of minimal 25 Gy to anywhere in the bag, not to exceed 50 Gy. So the, for instance, the UK guidelines recommend that. So slight differences. I think the bottom line though is that as long as you're getting that at least 25 Gy to the center of the bag, that's going to be more than sufficient to inhibit lymphocyte proliferation downstream. And actually, you probably don't want to exceed the 50 Gy, because that can actually start to cause damage. There's some concern that you could actually, again, if it's a red cell unit, you can cause significant damage to the red cell membrane. You can cause significant potassium leak. There's even sometimes concern that you could actually damage the plasticizers that line the bags and you may get contamination of, because you're giving a fairly high dose of radiation to that unit. So, some institutions will say, you know, minimally 25 Gy everywhere, not to exceed 50 Gy. The U.S. is I think a little bit more conservative in that regard. With the idea that the doses that were giving as long as they're in that 15 - 25 Gy ballpark really should be more than sufficient to inhibit lymphocyte proliferation.

Joe: Okay. So how do we do that, Chris? What are the pathways that we have available to us to expose a unit to those levels of irradiation?

Chris: Right. So, in the U.S. right now, there are, at least I'm aware of, Joe, just two FDA-approved…again, if we go kind of to the bare basics without using company names, there are really just two FDA-approved platforms or approaches. **One is to use a radioactive source**. And most commonly the reactive sources that we're using in the U.S. are a cesium source, so a reactive cesium source. Cobalt 60 would be the other one that is used, but not very frequently used in the US as far as we could tell from our research. So that's kind of pathway/platform one.

And then **pathway/platform two**, which is actually becoming more popular, and I can tell you that at my facilities we're using cesium sources now, but we're really looking very closely at this other platform, which is **x-ray**. And again, it's very similar to that, you're taking your component, your package, you're exposing it to an x ray dose of the similar 25 Gy in the center of the bag, and the x-rays also do a completely appropriate job in inhibiting lymphocyte proliferation.

Joe: So why would someone choose one over the other, Chris?

Chris: It's a great question, Joe, and I can tell you that, for those of you who have this experience of having cesium sources in your hospital, they're not the easiest things to deal with. There's always security concerns with them. So, the cesium source itself, could be, from a security standpoint, there's always concerns that that could be, you know, somehow accessed by people who want to do bad things, and disseminated and really could do some damage. As a result of that, a huge amount of security needs to go into these. So, really, really have to protect these cesium irradiators quite well. So practically speaking, at least one of the hospitals I cover, we have to keep it in an isolated room with a steel reinforced floor, in a cage with retinal scanners to actually access these radiators. They're not the easiest things to have in a bustling laboratory, as you can imagine.

And the other major problem with them is that if we think back to our physics, and I am no by no means a physicist! I am a physician, not a physicist, but the one thing of course that we always have to remember with a radioactive source that the, the strength of the rate act of signal has a half-life and the strength of the reactive signal decays over time. So we have at least one of the hospitals I cover, I think the youngest cesium source was from 2005. So it's getting on near 15 years old, and as the cesium source wanes in strength, as it decays, in order to achieve that minimum dose that we had discussed earlier, you need to expose the products for longer and longer and longer periods of time, which again, logistically is not the best for hospitals that are trying to turn these blood products out in a meaningful timeframe.

So those are probably the two biggest disadvantages to a cesium source. And the x ray sources don't have those problems. So x-rays cannot be disseminated. You can't do terrorist type of activities with x-ray sources. It's an x-ray tube, and they don't decay over time.

So you know, let's say an x-ray instrument has a lifespan of 10 years where it's going to be delivering that dose, your exposure times aren't going to be increasing over that period of time. Whereas it takes two minutes in 2020 to irradiate, it's going to take you two minutes in 2025 to irradiate. So there's going to be no decay of the source. So lots of folks are, and my facilities included, are taking a very serious look at x-ray sources.

There's also, and I think it's worthwhile to point out for maybe people who are administrative folks who are on this podcast: The U.S. government has a strong interest in trying to eliminate or decrease the number of cesium irradiators for all the reasons we just talked about. And if you Google irradiation guidelines or AABB irradiation, AABB has a wonderful website, wonderful resource for this that actually takes you to a document that there's a program basically from the Office of Radiation Safety in the U.S. that is now currently looking to reimburse hospitals for the cost of removal of cesium sources. Because you can imagine, you cannot just put these in a dumpster behind the hospital! You know, there's significant costs, SIGNIFICANT costs, on the order of like $100,000 to $200,000 for just *removing* the cesium sources. So the U.S. government has taken a real interest in the safe removal and replacement of these.

So, if you go online and Google this, there's money available for removing cesium sources. There's even money available for reimbursing partial costs of then bringing an x-ray irradiator in house. So for all those logistic purposes, if at the end of the day you're getting the same delivery of radiation via an x-ray source with none of the logistical hurdles, and frankly, just a safer product, I think that a lot of people in the community, including myself, are really looking to change to x-ray going forward for all the reasons we just...And I don't get any money from the x-ray irradiator consortium people! I just think that, you know, the U.S. government has seen this as well as something that is probably for the long-term safety. It probably makes more sense for us to try and rely more on x ray sources and try and get away from the cesium or cobalt sources over time.

Joe: 100% agree with you that is the direction that people seem to be going. I would be being less than fair, however, if I didn't point out that some have expressed reliability concerns about some of those x-ray irradiators, fair or unfair. I'm not judging either way, but people have thought of those old cesium ones as "workhorses" that last forever with the caveats that you said. But the x-ray ones have had a reputation as needing more maintenance.

Chris: Joe, I totally agree. So, I've had a number…and I think these are worthwhile conversations again for folks who maybe are a little higher on the chain where you're maybe making administrative decisions for your hospital, or those of you who are training now who are going to be directors out there yourself, your radiation safety officers are really excellent resources for this. So I've actually met with our radiation safety officer at the facilities I cover, and we went through all the highs and the lows, and she's wonderful and she had experience with x-ray irradiators, and she definitely has that experience too, that while they have the safety benefits, they actually do have some reliability...say "potential" reliability concerns, and frankly, the lifespan on them is shorter than a cesium irradiator.

So, with all, like you said, with all the caveats that their cesium source will decay, again, I think speaking in ballpark generalities, most people peg the lifespan of an x-ray irradiator at about 8 to 10 years. So while the upfront costs may be cheaper for an x-ray irradiator in the short term, in the long-term, you can probably hold a cesium source as I just expressed to you at least 15 to 20 years at the two facilities I have, that's probably the youngest of the x-ray radiators, excuse me, the gamma radiators. The x-rays probably really do need to be replaced on a 10-year basis. So, you're paying less upfront, but you may have to more frequently replace them just because of the fact that these things do, you know, break down or are sometimes less reliable over time.

Joe: So, let's talk a little bit about, and you've already mentioned this, I don't want to spend a whole lot of time on this, the complications, the things that happen in the bag that we could be concerned about. And you mentioned potassium. Would you like to just briefly touch on that? Concerns about increased potassium in the bag following irradiation?

Chris: Yeah, sure, Joe. So it's probably the most commonly known complication of irradiation. So, and really when we talk about potassium leak, we're really exclusively talking about red cells. So at least at my hospitals, the two products we are most frequently irradiating are red cells and platelet products. And we talked about granulocytes, we don't give many granulocytes at our hospital, so I don't have as much experience with irradiating those. But the concern always is primarily with red cells, that when you irradiate a red cell unit, you are going to do some damage to the red cell membrane itself. The osmotic fragility, frankly just the strength of the red cell membrane is probably a little bit reduced.

So, you are getting a little bit of lysis of red cells in those bags. And thinking back to just basic medicine, when you lyse cells in a contained space, one of the things that leaks are intracellular contents like potassium or lactate dehydrogenase, LDH. So there are sometimes concerns that if you're going to be giving a product like a red cell that's been irradiated to someone who can't tolerate a potassium load or to maybe a very, very small person like a neonate, that you want to be wary of the potential increases in potassium in those units that accumulate in the supernatant, and then actually get higher. So if you'd irradiated a unit on day 1, if you look at that unit by day 5 or day 10, potassium will slowly but steadily increase there. That's probably the biggest concern with, with product irradiation.

Joe: To go along with what Chris just said, in a previous conversation that I had on this podcast with Dr. Cassandra Josephson about neonatal red cell transfusion, that's one of the things that she pointed out, is that especially with the babies, you really want to irradiate the product as close as possible to the transfusion, because it's kind of time-dependent, right Chris?

Chris: One hundred percent, Joe. So I had referred to some of the British guidelines. I think in the British guidelines...in the US guidelines, they don't get as specific, but often what they're saying is that you don't want to give anything to a neonate or a small child that's been more than five days since it's irradiation source. It's just kind of a very conservative approach to minimizing hyperkalemia or high potassium loads in these very small recipients.

Joe: So, we won't take the time to go into some of the other concerns that people have raised, for example, about reactive oxygen species, but that information is available in your article. Chris, I want to make sure that we give good consideration to the indications, to the WHY we do this? I recognize that there are some differences both internationally and even in the United States, but what do you think we can agree on? What are the things that are "consensus" indications for irradiation?

Chris: Yeah. I had anticipated this question coming, Joe. And I think the way you phrased it is the perfect way to phrase it, because I think there's a certain ground that we all agree on that I think no one would argue that you should irradiate. And then there are lots of other indications out there that, you know, even at my facility, we've changed practice in the last 10 years, where we used to irradiate, we don't anymore.

So if I had to sort of give the rundown of saying, okay, these are the disorders or conditions where I think everyone agrees that you should be doing it. And you know, I don't think there's a lot of pushback, certainly we have really got into this in gory detail, but **any directed donations from a first or second degree relative** for the HLA risk that that carries, I think no one would quibble that that requires irradiation. **Anything that's an "HLA-selected product."** So, at my facility we give, and I'm sure yours as well, we give lots and lots of HLA-matched platelet transfusions. We give sometimes crossmatch-compatible platelet transfusions where again, the reason why they're crossmatch-compatible likely is because there's a shared HLA type between the donor and the recipient. Anything where there's either HLA selection or HLA match or crossmatch, really trying to evade HLA antibodies, strongly recommended that all those products be irradiated. That's kind of the two big ones that you know, you don't even necessarily have to be immunosuppressed, but you may be at risk for having GVHD, even in an immunocompetent individual.

Then we kind of get into the disorders where I think no one would disagree that there's an immunodeficiency or potential immune suppression that puts the patient at high risk for GVHD. So, we had spent quite a bit of time talking about earlier about **immunodeficiency disorders, congenital cellular immunodeficiency disorders**. So again, some of the more common ones being DiGeorge syndrome or “SCID,” again where the patients just are not going to be able to mount a T-cell response to that transfusion. I don't think anybody would quibble that if you have a congenital cellular deficiency, like one of those, that really should be irradiated.

We talked, you mentioned Dr. Josephson, and certainly I think most individuals feel that for **intrauterine transfusions** and **for most neonatal transfusions up to four months of age**, just the children do not have really developed or mature immune systems, and as a result of that, it's likely the safest approach to give those folks irradiated products. There's actually some data that suggests that if you received intrauterine transfusions as a neonate and now you're born, you’re probably at higher risk for GVHD for any subsequent transfusion you get until your immune system matures. So there's fairly strong data and fairly strong recommendations that if you're a neonate who received intrauterine transfusions, you should continue to get irradiated products until about four or five months of age.

Joe: I am right there with you, and on the neonatal transfusions, what I've seen most commonly is people saying that if a baby is **preterm**, that they’re at greater risk for TA-GVHD. But to be honest, for me in my practice, if people ask for it, even in a full-term, I usually say, “Okay, fine.” But I think we should probably at least acknowledge that the risk is significantly greater for preterms, right?

Chris: Yeah, I totally agree Joe. And I think that's my philosophy as well, is that, I think what we're looking here is, you know, we're trying to mitigate a really, as we discussed earlier, almost uniformly fatal reaction against not a ton of risk. You know, certainly potassium issues are there, but those can be controlled with a fresh product. So I agree. I think the highest risk is mainly for your preterm,

particularly your preterm who's been intrauterine transfused. If you look at those British guidelines that I keep referring to, they actually say that if you have a full-term infant who is less than four months of age, there's no strong evidence to suggest that they're at high risk for GVHD. But if someone asks for it at my facility until about four months of age, would not going to give a lot of pushback. And so I think it's a really important point and certainly there are international guideline documents that reflect exactly your point, which is that if you're, you know, a normal, healthy, no suspicion for a congenital immune deficiency disorder, but maybe just anemic term infant, there may not be a strong indication to radiate there and there may not be a high risk for GVHD.

And then beyond that, there's fairly strong feeling, I think in the international community, that **Hodgkin Lymphoma** does require irradiation as well. It's a pervasive disorder. It's treated with strong, immunosuppressive chemotherapy. So Hodgkin lymphoma, every guideline I've looked at nationally as well as internationally lists Hodgkin Lymphoma. And then finally there are a number of classes of **drugs** if patients are on, it's recommended that because of the immunosuppression associated with those that those patients receive irradiated products. Those include things like **purine analogs, purine antagonists, alemtuzumab** (again, we're throwing a lot of heavy duty drug names out there). Alemtuzumab targets something called CD52, which is a marker on essentially all lymphocytes. So when patients are on that drug, whether they're receiving it for conditioning before transplant or they're actually being used to treat lymphoma, they have severe lymphopenia. So those patients for instance can be, you know, a really strong risk for GVHD. So drug associated immunosuppression is important.

And then last, but by no means least, I don't think there's any quibbling that **patients in the peri-transplant for stem cell, whether it's an autologous or allogeneic transplant**, those individuals should receive irradiated products. Having said that, lots of opinion out there as to when you should start irradiating, when you should stop irradiating. And I don't think there's any clear guidelines for that. We can get into the weeds if you'd like on that, as well…

Joe: I can't help but point out, because I've seen this so often on standardized exams for pathologists, everyone that's listening, if you're a learner, please remember if they try to trick you by saying that you irradiate the actual stem cell product, that's not what you want to do.

Chris: A big no-no on that one!

Joe: Yes, big no-no on that one. But in terms of cellular blood products, agreed. Why don't you just address real quickly the little bit of controversy that there may be on when to start and stop with that?

Chris: Yeah, sure. And you know, Joe, it's a very common question we get on my consult service. So, for example, I think it's not often in doubt if you have someone who's got say, very common at my facilities, someone will have a history of Hodgkin Lymphoma and be recurrent Hodgkin Lymphoma. They're a young person, and

they're going for stem cell transplant. So, we're irradiating for that person probably for life anyway. So, it doesn't really raise a huge issue to just continue to irradiate during and after their stem cell transplant.

The question really becomes is, let's say you have someone who's maybe not immunosuppressed at baseline, sickle cell disease being an example, where we're doing more transplant at my facility. When do you start irradiating for that person? And we will sometimes get calls from clinician saying, "Well, my patient's *potentially* a stem cell transplant candidate for their sickle cell disease." So, should we start irradiating then? And I would personally say no. And I think I keep coming back to this British guideline. The bottom line is, and sort of the mentality I like to go by is, you really should probably start when the conditioning chemotherapy or conditioning radiations for the transplant has begun, because that's when the patients at highest risk for the TA-GVHD. Frankly speaking, lymphocytes are not going to be forever in circulation of individuals. Like other products, they're going to be cleared from circulation, they're not going to be "infinite" in their circulation. So, someone getting a transfusion 8, 10, 15 months before transplant, who's not immunosuppressed, it's probably very little risk for that person getting GVHD once they get their transplant. So, we tend to abide by the rule, at my facilities, when the person's getting their actual, again, conditioning chemotherapy, their conditioning radiation, that's the time you start.

We continue it for stem cell transplant folks during the transplant. And I have to say, Joe, at our facility, that's a *lifelong* indication. And I can tell you our rationale for it, I'm not saying it's the *right* rationale, but at least what we do. The way I've always thought about this is that these patients can always have relapse of their initial disease, which may have, you know, again, put them in an immunosuppressed state, they could lose grafts. So, we tend to irradiate "for life." Some individuals, and some guidelines say, you can stop irradiating in the stem cell transplant period once you have adequate evidence of engraftment, and once you have adequate evidence that the immune system has been reconstituted. The problem is that there's not great tests to show when… we have pretty good tests for engraftment, we don't have great functional tests for showing someone who's truly immune competent. So, some guidelines would say, well, once the patient's off their immunosuppressive therapies, once they've got cellular engraftment, you can stop irradiating. We don't do that at my facilities, to be totally frank. We just continue to irradiate for life. And I'm curious to hear your thoughts on this, to be honest.

Joe: I've practiced in places that do it both ways, Chris. My "go-to comment" on irradiation, quite frankly, is that I would rather irradiate unnecessarily than ever diagnose TA-GVHD. So that's my bias, and I'm fully cognizant of the guidelines that suggest that once engraftment and the lymphocytes are back, you probably don't need to in these patients. But again, my perspective is, I would rather do it than ever have to make a diagnosis of TA-GVHD.

Chris: Joe, I can't agree with you more. I think that's always my feeling as well, is that the course of these patients post-transplant are so unpredictable and the

consequences of TA-GVHD are so severe that to me it's worth the additional time and the minimal risks that come with this. But again, if you're more conservative… or maybe that IS the more conservative route… If you're a little bit maybe more *progressive*, you could try these other routes. I just don't, to me, I just don't think there's enough data to suggest that there's clearly an evidence-based path for either approach.

Joe: Well I'm going to hit you with some rapid fire stuff, Chris, on some controversies, that we have kind of alluded to a little bit, and some of them you've already kind of touched on, the preterm versus non-preterm in the neonates, for example. But one big one that I get asked still fairly often, surprisingly enough, is what about frozen plasma and thawed deglycerolized red blood cells?

Chris: Yeah, we get that question all the time too, Joe. Sometimes from very angry senior hematologists who say, "Well, I did this at so-and-so facility where I came from, why aren't we doing it here?" for the frozen products, the frozen deglyced [NOTE: "deglyced" = "deglycerolized"] and the frozen thawed. And, the bottom line is that no guideline I've ever found recommends irradiation for frozen deglyced or frozen thawed plasma products, cryo.

And the bottom line is, and I think we have a table of this in our review article, the number of cells that actually survive the freeze-thaw process are so minimal that they're really not capable of mediating transfusion associated graft-versus-host disease. And to back that point up, we could not find a single report of TA-GVHD associated with frozen plasma products, associated with Cryo, or associated with frozen deglyced red cells. So, I think the literature experience combined with the national guidance would suggest you're wasting your time, frankly, for irradiating those kinds of products. So, I would say a pretty firm "no," to those that our facility.

Joe: And of course, there's always an exception to everything, Chris.

Chris: Right!

Joe: …and my facility actually not too long ago, started providing a product which is a *never-frozen* plasma product for trauma situations that is called "Liquid Plasma." Any thoughts on that?

Chris: Yes. So this, as you said, Joe, this is the exception, and I would strongly recommend… you know, obviously you don't have to irradiate ALL Liquid Plasma, but if a patient meets one of the criteria that we discussed earlier, is on an immunosuppressive medication, has a history of an immunodeficiency, if you're doing this to someone who's at risk because of a medication they're receiving, then absolutely Liquid Plasma, never frozen does contain a large number of viable lymphocytes and that would be totally appropriate to irradiate.

Joe: Okay. What about patients who receive solid organ transplantation? We've talked about hematopoietic stem cell...

Chris: Ah, very hot button issue at my facility Joe!

Joe: Let's hear it!

Chris: So, until about five years ago, at Yale and VA Connecticut, we irradiated for patients who had solid organ transplant, despite a dearth of data. And as part of the process of reviewing the data and reviewing our practices, we don't recommend that anymore. And I think U.S. guidance, international guidance would suggest that the risks are extremely low and if there is GVHD seen post-transplant, it's often from lymphocytes that are present in the organ graft themselves, not from any transfusions the patients might have received in the peri-transplant period.

Joe: Okay. One more. And that is the thought that, "Well, gee, Chris, we're leukocyte reducing everything, why do we have to irradiate too?" Can you talk about that one?

Chris: I definitely can, Joe. So, it's really interesting. So, if we kind of loop back to a conversation we had had earlier, come back to one of those British studies we mentioned earlier, in the SHOT database, which is the UK's hemovigilance database, there were in excess of about 400 cases over I think about a five year period of time where irradiation should have been done and wasn't. And to the best of their ability, no GVHD was observed in those cases after transfusion. And actually, the authors of that guideline, one of their arguments was that, perhaps this was because all those patients received leukoreduced blood. I think it's a dangerous pathway to go down, because I think the consensus argument is that **leukoreduction may be *helpful* in reducing GVHD, but it is *not sufficient***. We generally are looking for a "five log" reduction in either just total removal of white cells or for inhibition of lymphocytes. We don't achieve that, typically, with leukoreduction.

So certainly leukoreduction, it's probably not hurting, you know, by just bulk removal of white cells. I think it makes sense to say that maybe we may be helping to *minimize* GVHD, but it's not a definitive treatment. So, if someone has any of the conditions we talked about earlier, if there is a high risk for GVHD, even using a leukoreduced blood supply, irradiation at this point in time is still deemed to be an essential step.

Joe: One last thing, and this is not really controversial, Chris, but because I forgot to ask you about it a few moments ago, let me ask you about this now. And you mentioned, you talked about granulocytes earlier. I still get the question sometimes, "Well, why would you irradiate granulocytes? Wouldn't that inactivate the neutrophils in the granulocyte concentrate?"

Chris: Yeah, and it actually does not. So, granulocytes, we definitely do recommend. It does cause some damage, Joe, I think, at least from some of the guidelines that I have seen… again, I don't have a ton of experience with those… from some of the guidelines I've seen, it may actually alter the function on the neutrophil slightly. So, the recommendations are that you might want to give those granulocytes as soon as possible after the irradiation, but there is still the fundamental phagocytic

function of those granulocytes is there. We're not really looking for the granulocytes to proliferate in an individual who is receiving those, we're looking at them to give basic phagocytic function for fungi, bacteria, et cetera. Those functions are maybe mildly perturbed, but, it's still safe and effective and *important* to irradiate those products without the concern that you're going to blunt their efficacy or impact.

Joe: As we close our time out together, there's a couple of things that I want to make sure that we hit. And first, there's something that is commonly misunderstood among those that are learning are our specialty. And that's the rule, at least in the United States, the so called “28-day rule” that is somewhat different in other countries, I'm aware. So, I wonder if you just take that on and describe what we're talking about when we talk about the 28-day rule in response to irradiation.

Chris: Obviously for a product that's going to outdate in less than that period of time, i.e., platelets or granulocytes, there's no changing of the label for those products. So, if you irradiate a platelet on day three, maybe you get it from your blood donor center or have it irradiated at day three, you irradiate it at day three and most facilities are throwing platelets at day five, that's not going to change.

It's really for red cells that this is a problem. And really, in many respects it comes back to that potassium leak in that you don't want these products sitting on your shelf for prolonged periods of time, basically where potassium is accumulating in the supernatant and then potentially causing problems for your recipient. So, the ruling essentially is, is that from the date of irradiation, those products have a 28-day shelf-life, or you expire them on their original shelf life, whichever comes first. So, if you have a truly fresh unit that expires, say 41 days from the time of receipt, if you irradiate that today, you have to expire it 28 days from the time of radiation. But let's say you're irradiating a unit that's already maybe three or four weeks old. If you irradiate that unit and then it was going to expire on Tuesday or Wednesday of next week anyway, you're still going to honor the original expiration date.

Joe: So, you don't get extra time for irradiating, in other words… [laughs]

Chris: Unfortunately, you do not, Joe! I wish there was some sort of, you know, *rejuvenation* and that came with irradiation…

Joe: Yes! That would be beautiful…

Chris: …but no. Maybe that will be a subject of future studies.

Joe: There you go.

Chris: Yeah, it's 28 days or the original expiration date, whatever comes first.

Joe: The other thing that we need to talk about, Chris, is the potential future that we might have in terms of other mechanisms aside from irradiation to kind of deactivate those lymphocytes. What can you tell us about what the future may hold for us?

Chris: Yeah, Joe and I would actually say the future is now, so very excitingly, I want to say it was about two or three years ago…yeah, that's about right…the FDA approved in the U.S. what people call either "pathogen reduction" or "pathogen inactivation" technology. And really briefly, the way this works, at least for the one that's FDA-approved in the U.S., is that there's a compound called a "psoralen," which is added to the product. That psoralen binds to nucleic acids, whether it's in white cells or whether it's in bacteria or viruses. And then it gets exposed to UV light, and essentially it breaks the cross-linking of those nucleic acids such that whatever's in that bag that has DNA, be it up a bad thing like a parasite or white cell, which is not necessarily a bad thing, they're not going to be able to proliferate downstream from that.

And with the approval of this, it was recognized that, well, you know, this pathogen reduction technology works just as well in giving you that five log reduction in lymphocyte proliferation as irradiation does. So I can tell you, Joe, we actually at the two facilities I cover, Yale and VA Connecticut, we're moving toward a high percentage of our platelets now being pathogen-reduced, you know, at any given day, maybe 80% or more of our platelet inventory are pathogen-reduced. We do not irradiate those products anymore because the FDA, and I think our experience has told us that, we are basically giving them an equivalent treatment, which is this pathogen reduction technology. So it's pretty exciting. It's certainly, logistically speaking, it minimizes the time of one less processing step with lots and lots of our patients who receive platelets require irradiated products.

And right now, in trials, there are pathogen reduction technologies that are being tested for red cell products as well. And it will be interesting to see if those A, work and B, if those do work, those might give you an alternative that if you have a pathogen treated or pathogen-reduced treated red cell product, you may not necessarily need to irradiate that product going forward.

Joe: So Chris, a couple of things before, just a couple of last things before we go. You had talked about, now I could be wrong, but I've heard there's some sort of a "British guideline." Is that true? [Laughs]

Chris: I've alluded to it once or twice…

Joe: Once or twice, once or twice.

Chris: It is my go-to document a when I'm teaching my residents and fellows when we have a question, "Should we irradiate? Should we not?" It's one of the few, I think truly vetted guidelines that actually, not unlike the ASFA scoring systems and the ones that I think we use in the blood banks community quite frequently, actually grades evidence and looks at the available data. And, I really, really love this document, and I think the last iteration of this was 2012, so there may be a new one coming soon. But until that time, I think it's probably the best international document that's out there or at least the best I found that's out there providing guidance for irradiation.

Joe: So everyone, if you will go to the show page for this episode, which is BBGuy.org/074, I will have a link for you to download that UK document that will give you some great information as, as Chris said, I have, I have used it extensively as well.

The last thing, Chris, that I want to mention is the article that I've alluded to, the giant review article from 2015 by the Canadian group that looked at and identified almost 350 cases in the literature of TA-GVHD. And we really don't have a ton of time to talk about that a whole lot. But, everyone, I do want to mention, I have talked about this on the podcast before in episode 13. So, if you go to BBGuy.org/013 and listen to the last 10-15 minutes or so, I have more discussion on this, but Chris, is there anything from that article that really jumps out at you as either concerning or eye-opening?

Chris: Yeah, Joe. I think the shocking part of that to me was that there were a fair number, a fairly high number of individuals who suffered from GVHD in that series that would not have qualified as necessarily something I would have called an "immunosuppressed" individual. And it does raise some questions, and I think even in the article, if I'm not mistaken, Joe, they also ruled out, we spent a lot of time talking about homogeneous populations with regard to HLA; Canada is not a particularly homogeneous HLA population. So the authors, I think really in their conclusions and discussion excluded. Certainly some of the cases may have been due to HLA homogeneity, but given the heterogeneity of HLA in their country, they excluded, you know, that that's not probably not the driver for most of what the GVHD that they were seeing. So I think it's eye-opening in that, certainly as we alluded to earlier, the diagnosis may be missed. It may be underdiagnosed, but it may be coming more frequently in patient populations that we wouldn't suspect it in. And, I think that's an important consideration for the transfusion community, that we might want to be a little bit more perhaps, you know, liberal in our use of radiation.

As long as we think it's not causing significant risks to the recipient, or if we're using routine products like pathogen-reduced products, we may get the added benefit of having a reduction of GVHD that might be of general benefit for even non-immunocompromised individuals.

Joe: Chris, this has been really just an amazing experience for me as, as always, I love talking to you. I love your approach to things. I love the way that you bring out the information in such an easy to understand way. Thank you so much for being here and for doing this with me.

Chris: Joe, as always, really been a pleasure and I'm look forward to doing this again with you sometime again on another interesting topic.

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Joe: I'm truly grateful to my friend Chris Tormey for joining me. One thing I wanted to add that I should have mentioned at the time: When we talked about the required minimum doses of irradiation, Chris mentioned that the target to the

center of the product is 25 Gy or 2500 cGy. Occasionally, you will hear and see people (especially on exams) use the term “rad” to define the minimum dose. They don’t mean, “dude, that’s RAD!” (OMG, I have lived in California for too long!). “Rad” is an older term that is essentially equal to cGy, so that minimum dose is 2500 “rad” just like it’s 2500 “cGy.” Don’t get fooled.

As always, you can hear past and future episodes of this podcast directly on the website at BBGuy.org, or you can go to Apple Podcasts or Google Play or Stitcher Radio, or Spotify, or really anywhere you find your podcasts. Thanks for the reviews and kind words, especially the ones on Apple Podcasts, where I recommend you make your reviews and comments.

If you are a physician or laboratorian, don’t forget to visit www.wileyhealthlearning.com/transfusionnews and get your hour of totally free continuing education credit from listening to this podcast. My thanks for that as always to Transfusion News, to Bio-Rad, who brings you Transfusion News, and to Wiley Health Learning.

Finally, my thanks to Transfusion News Assistant Editor Dr. Daniela Hermelin from St. Louis University. Daniela wrote the continuing education materials for this episode, and is a brilliant physician and friend.

The next episode, which is coming in a couple of weeks, is another continuing education-eligible interview with a true rising star in our community. Her name is Melissa Cushing from Weill Cornell in New York. She is going to tell us all about how much we’ve ignored a super-important coagulation factor, and the interview is called “What About Fibrinogen?” Melissa is terrific, so I can’t wait for you to hear it!

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.