Joe Chaffin: Hi, and welcome, everyone! Today, we are going to do something *different* on the Blood Bank Guy Podcast. As I mentioned earlier, I am now going to have a co-host for the episodes where I am doing “Ask the Blood Bank Guy” topics, and so I am super-proud to introduce you today to my very good friend Dr. Heidi Shafi, who has agreed to help me with hosting duties. So, Heidi, you have to tell me, how in the world did I manage to talk you into this?

Heidi Shafi: Well, Joe, you didn't have to try too hard! I think I kind of approached you and said, “Hey, wouldn't it be cool if I could just pick your brains for a few minutes, or an hour or so every once in a while?” And you thought, “Hmmm, I think that's a good idea!"

Joe: Yeah, well see, that's what happens when you volunteer! You end up with co-hosting duties on a podcast!

Heidi: Well, no good deed goes unpunished!

Joe: Clearly! Well, Heidi, we are actually going to have you on a later podcast, where you are doing the majority of the presenting, so we’ll go into your background and your bio a little more then. But just for now, can you just tell everyone real quickly who you are, what you do, etc.?

Heidi: Okay, so I am actually a clinical pathologist. I did my residency in clinical pathology and my transfusion medicine fellowship both at Cedars-Sinai, where I stayed on as faculty for a couple of years before I joined the Kaiser Permanente system as both the medical director of the blood bank and a clinical pathologist.

Joe: Very nice! Well, some of you out there may know that I worked at Cedars-Sinai for a while, so that is where Heidi and I crossed paths. She tried her best as a blood bank fellow to keep me from doing stupid things. She wasn't always successful, quite frankly, but she tried to keep me on the straight and narrow anyway! So thanks for that, Heidi!

Heidi: No problem! Any time! And I do just want to take a second to let our listeners know that Joe is a mentor of mine, and someone that not only taught me blood banking during my fellowship, but continues to be my go-to expert for all things pertaining to blood banking, so I'm quite excited about being able to do this today!

Joe: You're too kind, as usual! Well, so, hey, *you* are the host today, so all yours, Heidi! Take it over!

Heidi: Perfect. So, as I mentioned, I'm very happy to be doing this interview, and being able to pick your brains on what I think is a very interesting topic today. In the next hour or so, we are going to explore “Transfusion-associated graft-versus-host disease.” Now, for many of us, when we hear "graft-versus-host disease,” we think of the possible

negative side effects of transplantation, whether it is solid organs or stem cells. At some point during this podcast, I am going to ask you to first start by telling us,"What the heck is graft-versus-host disease?", but before that, I do want to talk about an email that you received which sparked an interest for us to do this podcast. Can you kind of go through that with us?

Joe: Yeah, you bet! Since this is an "Ask the Blood Bank Guy" episode, it is only fair to disclose that the idea to do this podcast did come from a question that a listener sent to me. Just as an aside, we are going to do this roughly every month, you guys out there listening, and I am more than happy to take on your questions. Just go to the website, BBGuy.org/ask, and you can send in your questions. I will never disclose your name or where you work or anything like that without your permission, so you don't have to worry about that!

But I got this email recently, and it really kind of opened my eyes to something. Let me just kind of take you through it; I'm not going to read all of it. The email started: "Kopolovic et al published an article in Blood last year, in 2015, which was a systemic review of reported cases of TA-GVHD, and the authors write that their findings seem to challenge the traditional thinking that risks for transfusion-associated GVHD is driven by host factors, as about 50% of the cases they found would not be considered high-risk by traditional guidelines." And the author of this email goes on to express some frustration, because he is not a blood banker, he is a hematologist/oncologist, and he feels like the blood bankers that he is associated with don't seem terribly excited about this article, and don't seem like they are kind of adapting and adjusting. Honestly, it is a wonderful, really fair email, because he wants to know *my* opinion, and whether or not I think things should change based on this article. I thought first maybe today, we would kind of go through the generalities of graft-versus-host disease and the transfusion-associated variety as well, and then at the end really kind of bring it back around to that article. Because I think you need the background to really understand how this article has the potential to really shake things up.

Heidi: I definitely agree with you, Joe. When you sent this article to me, I thought, "wow exhibition point this could really be a game changer in how we approach transfusion-associated graft-versus-host disease." So I'm looking forward to discussing a little later, but why don't we start with you telling us what graft versus host disease is?

Joe: Well, that is an appropriate first question! So let's hit that. Really, when we talk about "graft versus host disease," that's kind of a big general category, Heidi. And you mentioned earlier, that when most people think about graph versus host disease, They are thinking about the type of interaction that occurs primarily after a stem cell transplant, a bone marrow, umbilical cord, or peripheral stem cell transplant, whatever; or, the kind that comes from passenger lymphocytes carried on in solid organs. But in addition, there is a third category, and that is from cellular blood products, and we'll talk about that in just a second. But in general, graft versus host disease is simply an attack on the *recipient*, in other words, the person who is the recipient of the *graft*, whether that is an organ or a transplant or a blood transfusion, it's an attack on that recipient's human leukocyte antigens, or "HLA", by T-lymphocytes. And those T-lymphocytes come

from the *graft*, in other words, the product or organ that goes from the donor into the recipient. So, that interaction is a really interesting and quite frankly, really complicated interaction! There's a lot to it. There's a lot of details behind it, and we're not going to go into them in enormous detail. Quite frankly, I should tell everyone Heidi's done a lot of great research into T-lymphocytes and their function; she knows 50 *million* times more about it that I do, so you could probably talk about it better than I could!

Heidi: I'm not sure about that! (laughs)

Joe: We'll stay a little bit more on the surface with this, and just kind of talk in generalities. But, basically what has to happen for graft versus host disease to occur is three basic things, and we've known about this for forever. The basic requirements for graft versus host disease were described oh, right about 50 years ago, in the 1960s. Essentially, **first, there have to be HLA differences between the graft and the host**. In other words, if the graft and the host are HLA identical (and we'll talk more about that in just a few minutes), there wouldn't be any reason for one to attack the other. Second, **there have to be active, viable T-lymphocytes in the graft**, in other words, the donated product, or the product that's transfused or transplanted into the recipient. And then finally, **there has to be some sort of a problem with the host's ability to respond**; either an incompetent host or some sort of inactive cellular immunity in the host that leads there not to be sort of a response to that attack by the graft products. So that's generally what we need in order to have graft-versus-host disease, and again, that's true regardless of what type of GVHD we are talking about.

Heidi: Joe, what kind of findings do we see in GVHD, in terms of clinical signs and symptoms?

Joe: Great. That's a super question! Realistically, again, whether we're talking about transfusion-associated or any kind of graft-versus-host disease, again, we're staying in the big umbrella here, first. Basically, when we think about this being an attack on HLA, so an attack on the human leukocyte antigens, and I'm going to say, "HLA antigens," I know I will, even though it's redundant: "Human leukocyte antigens-antigens." So forgive me. But it's an attack on those HLA antigens, and in order to do that, well, those T-lymphocytes have to go to areas where there's lots of HLA antigens. And really, we think about that in three main places: The **skin, the liver, and the GI tract**. Certainly there are other places that have HLA antigens, but HLA antigens are particularly rich in the skin, the liver, and the GI tract.

So you get classically, a very characteristic rash. It's a bright red rash. It has a tendency to be a combination of both flat and raised lesions, we call that, "maculo-papular." It usually starts on the body and expands peripherally. And if you look at pictures of this rash, it's characteristically seen, in terms of the diagnostic appearance, on the palms of the hands and soles of the feet. And again, clinicians that know skin and are good with Derm (which I am not!) would tell you that it's a fairly characteristic rash. Eventually, in a few of these patients, it can actually progress all the way up to bullous formation—so actually, large, flaccid blisters, essentially! So that's the classic characteristic, and in fact, the most common finding in graft-versus-host disease. Then you have liver injury

where the liver is damaged by the attack of these T-lymphocytes, typically manifested by elevated liver function tests, bilirubin elevations eventually. And then finally, the GI tract, among the most common things where they just diffuse damage to the gastrointestinal tract. They end up having profuse watery diarrhea, can have nausea and vomiting, as well, but fairly characteristically with the lower GI type symptoms. And with ALL of this, kind of the overriding thing, well, it's not necessarily the overriding thing, but again, one of the more common things that happens is that when all these things are occurring, as you can imagine, you got a whole lot of cytokines being generated. Those cytokines include things that raise your temperature, so fever is really common in GVHD, as well.

Heidi: Okay, got it. It can be quite severe, the signs and symptoms that you talked about?

Joe: Absolutely! And you know, we're not really going to talk about GVHD with solid organ and stem cell transplants, but it's kind of broken down into acute GVHD and chronic GVHD. Mostly, we're going to stick with the acute GVHD, and absolutely, it can be very significant and very severe!

Heidi: So, that's the classic GVHD. So tell me about the transfusion-associated graft-versus-host disease. Maybe, first, about the signs and symptoms, how they're different and just overall. What the heck is it?

Joe: (laughs) Well, you bet! So, as I was saying before, when the source of those active T-lymphocytes, that are causing this attack on the host HLA antigens is a cellular blood product, really, the presentation is not enormously different initially, because just like regular GVHD, you get a **fever** typically, you get involvement of the **skin, the liver, the GI tract**, all those same kind of symptoms that you would get in an acute graft-versus-host disease, from a solid organ transplant or from a stem cell transplant, same kind of deal. But, with TA-GVHD, in particular, there's one additional finding that makes it much more significant and makes it much more dramatic. And that's that, **with transfusion associated graft-versus-host disease, another HLA rich area that those T-lymphocytes can attack is the bone marrow**. That's a *big, big problem***.**

When you think about regular GVHD in a stem cell transplant; well, if you think about that, patients that are getting stem cell transplants, they tend to get preparation before hand, usually either wiping out the bone marrow or partially wiping out their native bone marrow. Then you give them the stem cells, and even if they get GVHD, there's not a whole lot in the marrow to wipe out and there's stem cells in the product to repopulate the marrow. But if you're talking about transfusion-associated graft-versus-host disease, you can get that attack of the marrow, but "uh-oh," the product that you gave is not rich in stem cells. So there's nothing to replenish that marrow. So the bone marrow just gets wiped out and that is the biggest problem with TA-GVHD in comparison to so-called "regular GVHD."

Heidi: And this is a key point for the residents and anyone in training who's listening to this podcast. This is a very important differentiation between classic GVHD and

transfusion-associated graft-versus-host disease and something that you'll see coming up in question format and when you're on the rotations, people will ask, "What's the main difference, clinically?" And this is one of the main differences that you want to remember. Joe, is there a definition of, like so many other things in medicine, you have to have criteria to be able to be diagnosed with a certain disease. Is there such a thing for it—transfusion-associated graft-versus-host disease?

Joe: Yeah, there is. We're seeing more and more that people in the United States, and in part, because the new AABB standard that requires you to try and use standard definitions for transfusion reactions, there is definitely a definition that is being used and it comes from the CDC, the Center for Disease Control, and specifically, the National Health and Safety Network (NHSN). These definitions are published. You can do a google search for them and the downloads are, I'm 98.9% sure that they're free, you can just download the specific definitions. So, according to NHSN, again, this the definition in the U.S., I know people listen to this from other countries, so you would need to check with your own organizations, the definitions include a couple of things: first, there's a timeline between 2 days and 6 weeks, after the transfusion is completed, is the timeline for GVHD. And in order to make the diagnosis, you need 2 categories of things: the first category is **some combination of some of the things we've talked about, these are the clinical findings: rash, fever, liver dysfunction, pancytopenia, diarrhea, marrow aplasia, and hepatomegaly (a big liver).** So all those things, some combination of that, that would make you think about transfusion-associated graft-versus-host disease, **and in addition to some combination of those,** you need to have some **biopsy confirmation** of a characteristic appearance, histologically of TA-GVHD. And that characteristic appearance is seen most commonly in skin biopsies, but it's also seen in liver biopsies, as well. So the skin biopsy and well, it's been a long time since I've done anatomic—

Heidi: Derm path?

Joe: Yes, Derm path is a little bit in my rearview mirror! But there are some characteristic findings that you can go and listen to an AP podcast and find out! (laughs)

Heidi: (laughs)

Joe: Basically, there's degeneration of the epidermis, necrotic keratinocytes, and obviously, lymphocytes around the superficial capillaries. Again, NOT my world anymore! And the liver biopsies, same thing, some characteristic findings. If you've got both of those, some of those clinical findings and the biopsy confirmation that is consistent with and that makes the diagnosis of TA-GVHD.

Heidi: What about some sort of PCR testing in chimerisms? Can you tell me a little about that? It's so confusing!

Joe: Honestly, it's a fairly specialized test, this is actually also included in the NHSN definitions. It's basically how you can definitively assign this diagnoses and really, the only way to definitively say that this is TA-GVHD, even with those two criteria that I

mentioned, is if you're able to establish "white cell chimerism." And chimerism simply means there's the cells of more than one person in your body, essentially. So, you can do that with biopsies, you can do that with different kinds of samples, and basically you just run PCR and you go, "Whoops! There's more than one set of DNA here." So if you've got that, then that definitively says that this person—and again, with the other findings—has TA-GVHD. The details of that, in terms of what they are looking for on PCR, I know that there are a lot of different variants that they're looking for, but that's a little beyond where we need to go with this podcast, I think.

Heidi: I agree. Joe, I've been only practicing for three, four years, but I've never seen a case of, fortunately, I've never had to deal a case of transfusion-associated graft-versus-host disease. What about you? Have you seen any cases? And how common is it?

Joe: Well, I have been practicing for just slightly more than 3 to 4 years! (laughs)

Heidi: Just slightly! (laughs)

Joe: Just slightly! Well, in about 26 years or so, hanging around blood banks, not all practicing, but in that timeframe, I personally have never definitively seen one. I've seen suspected cases, but I have not seen a definite case of TA-GVHD. And really, I think that is true for a lot of people. When we talk about the incidence of this disease, truth is, we don't know. And there's a couple reasons for that, first is that, A) I don't believe it happens very often in terms of that classic presentation. But second, it's really easy to miss! Another words, if you've got someone that's already really, really sick, and they get a transfusion that either might, down the line lead to TA-GVHD and they expire before the symptoms occur, well obviously, you'd never know that. But further, if you've got someone who crashes ten days after a transfusion, but they're already super sick from other stuff, it can be really hard to separate that out. So it requires a lot of a very high index of suspicion to make the diagnosis. There is no question that it is under diagnosed. I mean, no question about that. What we can say is that in the United States, all transfusions related fatalities are required to be reported to FDA. I actually just went and looked at this before I jumped on the recording today, Heidi. Since 2005, there have been only three cases reported, three fatalities from transfusion-associated graft-versus-host disease reported to FDA. Between 2005 and the most recent data, which is fiscal year 2014.

Heidi: But that is <u>fatalities</u>.

Joe: That is fatalities. As we'll talk about shortly, realistically, most of the cases are fatalities, because they don't do very well with it. So not a ton of cases reported in the U.S. The study that we'll talk about later actually broke down the number of cases that they were able to find in the literature. They broke them down by particular time frames and what they show is that, in the literature since the year 2000, there's been a total of 66 cases all around the world reported in the literature. So again, not a ton of cases reported, but again, we also know that there's no question that it is under reported, significantly.

Heidi: Got it. I want to now change directions a little bit and ask you about the mechanism of transfusion-associated graft-versus-host disease. And ask you to simplify it for us so we can really understand what's going on, on the cellular level.

Joe: Okay, let me give that a shot! This is quite honestly, it's one of my favorite illustrations. I think because it displays my incredible level of immaturity! (laughs)

Heidi: (laughs) I'm not rolling my eyes or anything!

Joe: Oh no, not you. You had to listen to me for a couple of years, so I know you'd never roll your eyes! Anyway (laughs)…so, how does it happen? Let's make this as simple as possible. Normally, this is something that I show and I put up on a screen, so I'm going to have to paint word pictures here for our listening audience, so let me see what I can do. Let's just imagine, that we have two people. One is a donor and one is a recipient. Let's just assume that they are not identical twins, so there is some level of difference in their HLA types. One person has one type, the donor has one type the recipient has another type. So it's really important to understand the normal situation, in other words, what normally happens this particular patient's transfusion goes into this particular recipient. Now again, this is normal. Under normal circumstances, a transfused cellular blood product that contains viable, active T-lymphocytes, is transfused into the recipient, and the white cells that are in that product take a look around and they do exactly what you would expect a white cell to do. Another words, they look around and they analyze "what's the HLA type of all these tissues that I'm seeing in this person's body?" And they would say (as you would expect) "This is not me!" So as a result, those transfused cells would try to proliferate and would try to mount an immune response of some sort, against that host's tissues. Now again, that's normal. That's exactly what you would expect a T-lymphocyte to do. It looks around, finds something that's not **it,** it's not it's own HLA type and tries to mount a response against it. And when I show this, I illustrate that most incredibly immaturely with little Pac-men, you know those little "wocka wocka wocka" guys.

So they're trying to attack onto those host tissues, but again, under normal circumstances, the host——being a normal, immuno-competent, happy person, has a really, big, bad immune system. A great immune system that is capable of looking at those actual transfused white cells and saying, "Hey, you know what? You don't belong here. This is not your area, this is not your body—get out!" And basically mounting a counterattack, so that's the way I describe it. It's an **attack first**, by the transfused cells, **then a counterattack** by the host's immune system to get rid of those cells. Again, that's normal. We see that, we see that white cells actually hang around in someone's body after a transfusion for a few days, that's not uncommon at all and that's normal! So again, that's what we would expect to happen under normal circumstances. Now, in TA-GVHD, though, something gets thrown into the works. I tend to illustrate this, as you know, Heidi, I spent a long time in the military and it made a big impression on me, so let's talk about this in military terms, okay?

Heidi: Okay.

Joe: So under three different scenarios, we might have a problem with that normal, attack, counter attack sequence. So first, **what if the host doesn't have enough soldiers?** In other words, the troops are depleted, the patient is leukopenic. If there's not enough soldiers to fight off that initial attack, we may have a problem. That's situation one. Situation two, is **what if the soldiers are under orders not to counter attack?** In other words, the patient is immunosuppressed, either from a pharmacologic reason or from some other reason, whether that's a built-in, inherited cellular immunity or whatever, you may have plenty of soldiers, but the soldiers are not allowed to attack those invading cells. Again, that's a potential problem. The third scenario is the one that people miss, it's the one that people forget about. And that's **the enemy is camouflaged**. And we need to go into this in pretty significant detail to make sure people understand this.

When the enemy is "camouflaged," what that means, most commonly, is that the invading cells, in other words those transfused cells, are typically homozygous for a particular HLA haplotype. Now that's a lot of words. So those of you, if that's greek to you, let's talk about that for a second. I'm going to give you an example. I'm going to tell you the HLA type, the genotype, I should say, in the HLA locus, for the attacking cells and the recipient cells. And again, hang with me here, paint the word picture in your head. Okay, let's imagine that the transfused cells carry two different genes for HLA antigens, that's true for everyone. And one allele, those copies have the genotype A1B2. Now don't write me. I know, I'm making this simple. I'm just imagining: A1B2, and the other chromosome has the same allele. In other words, they're homozygous for HLA A1B2. I know that's not accurate, but we're being simple here. So he's got two copies of the same allele, if that is transfused to someone who has their HLA type being on one chromosome, A1B2, just the same as the two copies that transfused person has, but **the other chromosome** has A3B4, suddenly we may have a potential problem. What I mean by that, is that those transfused cells that are A1B2, A1B2 go into the body and they look at the body, at the recipient, they see that A3 B4 that's on the second chromosome, and they say, "Oops! Not me, I'm gonna attack." The reverse is not true, because that recipient who has A1B2 on one chromosome would recognize that homozygous person as being OK. So in other words, we'd have an attack, but we would not have a counter-attack. And that's the potential problem when the enemy is camouflaged. We call that the "one way HLA match." By the way, just so everyone knows, I'm going to put up some slides on the show page for this episode, so you can see that more graphically, and it will make more sense to you.

So again, I've talked for a long time and I'll shut up in just a second, Heidi. So the three scenarios: 1) Not enough soldiers. So not enough soldiers to counter attack 2) the soldiers are deactivated or the person is immunosuppressed 3) And then finally, the enemy is camouflaged. That one-way HLA matched, with a HLA homozygous donor and a HLA heterozygous recipient. Any of those, if you have any of those, you get an attack, but no counter attack and those transfused T- lymphocytes just start going crazy.

Heidi: So, Joe, what's the main "walk-away" take-home message from this? Homozygous donor, heterozygous recipient and the other two points you talked about:

not enough soldiers and soldiers are deactivated. And what about, is it with all products, like anything that comes out of the blood bank could cause this?

Joe: Not quite. I think that what we focused on historically and for good reason, is the so-called "cellular blood products." It's not really an accurate term to say "cellular blood products." We think of cellular blood products as whole blood, I should say, red cells, platelets and granulocytes, primarily. And we don't think of the plasma products like frozen plasma and cryoprecipitate as being "cellular products." The truth is, there are plenty of cells in there, it's just that the cells are deactivated by the freezing and thawing process in the frozen plasma and the CRYO. Generally speaking, the products associated with TA-GVHD are, as I said, whole blood (though we don't often transfuse it anymore), red cells, platelets, and granulocytes.

Heidi: Okay, just to summarize. So far we have learned that transfusion-associated graft-versus-host disease is rare, possibly under-reported, but overall, rare. When it does happen, it can be quite devastating, since it can wipe out the marrow. And as you alluded earlier, it could cause fatalities. It could be quite terrible for the patient.

Joe: Absolutely.

Heidi: So, knowing that it can be such an aggressive disease, who should we protect from it? Who's at-risk?

Joe: Yeah, we've spent a lot of time in the past working on that and trying to figure out who are the people at-risk. I think you can kind of break it down into three *main* areas, with a couple of others that are a little bit more borderline and not quite as clear. So let's just give you the main areas what I would call the "traditionally thought at-risk groups." The first one of those is **babies**. The second of those is **cancer patients**. And the third of those is **people that are getting HLA similar products**. In other words, that risk of that one-way HLA match that I talked about before. So we can go over each of those.

Heidi: Got it. Start with the babies?

Joe: Let's start with the babies. In terms of babies, really the first cases that we knew were TA-GVHD, came in babies with inherited cellular immune defects. There's a whole bunch of them and again, a lot of details behind it that I either don't know or I don't want to take the time to go into! But severe combined immunodeficiency syndrome or SCIDS, as people call it, Wiscott-Aldrich syndrome, DiGeorge Syndrome, things like that that are inherited cellular immune defects. And it's really pretty simple to understand why that would be a problem. There's no counter-attack, right? The baby can't counter-attack the viable T-lymphocytes that come in. So that's pretty clear.

Heidi: There's no immune system or it's an immature immune system.

Joe: Yep, you bet. Absolutely right. And for similar reasons, premature babies, most people think that their cellular immunity is not adequately developed for them to fight off the attack of the viable T-lymphocytes. So most people would say premature babies are

at-risk. Clearly, we know that babies who get intrauterine transfusion, that's been pretty clearly shown that those babies are at-risk for TA-GVHD. I'm not sure why the intrauterine part is such a big difference. Last week's guest, Dr. Cassandra Josephson, would be able to tell me in great detail. But the reality is we know that it's true. And the other thing we know is a really big risk factor is, well, two things that go primarily with full term babies, but really babies of any age, and that's exchange transfusion and especially, "ECMO." ECMO does seem to be a big deal. Heidi, tell everybody what ECMO is because you're closer to that than me.

Heidi: Extracorporeal membranous oxygenation.

Joe: Yay!

Heidi: So this is basically when you try to bypass the heart and lung, but still get the blood oxygenated through this "extracorporeal circuit."

Joe: See? I'm not even your teacher anymore and I still throw quiz questions at you!

Heidi: Right, I know! Wait a minute. I'm asking questions of you!

Joe: (laughs)

Heidi: I'm the interviewer here! (laughs) Exactly!

Joe: You're right! I apologize. That was out of line. (laughs) So then, the last thing for babies is the directed products. And that kind of goes with, because directed products are most commonly from family members. We'll talk about that more with the HLA similar product parts. So babies? Babies are a big deal! We spend a lot of time worrying, sometimes—maybe unnecessarily because there are some borderline indications in there. But clearly, we need to think about irradiation when it comes to pediatric transfusion.

Heidi: So, can I ask you a practical question?

Joe: Sure.

Heidi: So you're working at a hospital-based transfusion service, and you have a NICU. You have a pretty busy labor and delivery service. Would you recommend having in your policies and procedures, irradiation for all neonates?

Joe: Yeah, that's a superb question because realistically, and we'll talk about this a little later on, part of the problem with irradiated products is that when we leave the trigger for knowing when to order irradiated products completely on the clinician's plate, it can get missed sometimes. And quite honestly, I think we in blood bank sometimes, have a tendency to—I don't know if "pompous" is the right word—but we have a tendency to "sit there with our arms crossed" and say, "Well, they didn't order it, by God!" And realistically, I don't think that's the right approach. You and I both practiced in a place

that took that to quite a bit farther extreme than most places. At Cedars-Sinai they basically irradiated all cellular products for all patients and I will admit, there was a time that I thought that our mutual friend, Dr. Klapper, maybe was going too far with that. But, I understand the sentiment. For that reason, I think it's probably better, in my opinion, to over-irradiate especially in the neonatal population that it is to under irradiate. With one **very important exception**, and I think this is a real "take-home" for everybody: That babies are extraordinarily sensitive to high levels of potassium, and when we irradiate red cells and leave them sitting around, there is a substantial and significant increase in the potassium that's released into the product. And as a result of that, with that exception, if you're talking about freshly irradiated products for all babies? I can live with that, and I think that's a reasonable, practical strategy.

Heidi: So, we'll talk about irradiation a little bit later on because I do want to ask you some questions about it. But for now, let's get back to the at-risk groups.

Joe: Okay, you bet. So, the next group, after the babies is the cancer patients. When we talk about cancer patients being at-risk for TA-GVHD, you can really think of it two ways. In some cases, people are probably at risk for TA-GVHD just from their disease. Just the cancer itself can be the problem. In more cases, though, it's the treatment from the cancer that causes the problem and causes them to be at-risk for TA-GVHD. And some cases, it can be a combination of both, so when we think about cancer patients and TA-GVHD, virtually everyone thinks first about hematologic malignancies. So, blood cancers, things like Hodgkins disease, non-Hodgkins lymphoma, chronic lymphocytic leukemia, acute myelogenous leukemia, etc. All those hematologic cancers, those blood cancers that we think about. Now Hodgkins, for example, is one that's really interesting because with Hodgkins, in particular, there does seem to be some sort of an increased risk for TA-GVHD. That's just the consequence of having Hodgkins. That's kind of weird and strange and I don't really know the mechanisms behind it, but Hodgkins is really been shown or is thought to be a risk, in and of itself. With most of the other malignancies, the risk comes from the treatment. You're blasting them with chemotherapy and you're destroying their own T-lymphocytes that are the counter-attacking agents and so, they have trouble fighting off the attack of the transfused cells. So hematologic malignancies are a little bit complex. Remember the association with Hodgkins, everyone, but for most other things, it's more a consequence of the treatment. And with solid tumors, really solid tumors, when you think about things like breast cancer, lung cancer, colon cancer in adults, really probably not and of themselves any significant risk, probably not hugely with the chemotherapy as well, though again, you will sometimes see people irradiate for those patients. But when we think about it, there are definitely somewhat older reports in pediatric patients with neuroblastoma and rhabdomyosarcoma, and things like that, that may or may not have been purely related to the tumor.

Heidi: As opposed to the treatment.

Joe: Exactly. I think the people still think of those, at least to some extent, as an inherent risk just from the tumor itself. Most people will irradiate blood for pediatric

patients with neuroblastoma, glioblastoma, rhabdomyosarcoma, things like that, regardless of how much they're getting treated with chemo.

We also think about, for cancer patients, stem cell transplants. And realistically, we all know stem cell transplants don't just happen in cancer patients, there are certainly non-malignant cases, but the majority of people that get stem cell transplants are cancer patients. Well, I mean, that's just like a perfect set up for TA-GVHD, right? Because they get prepared, they get the heavy duty chemo/radiation therapy, and their bone marrows get wiped out. They're incredibly leukopenic, incredibly immunosuppressed, so yeah, clearly that's a very clear-cut indication for those patients receiving irradiated products.

And there's one other category in cancer patients, that I just wanted to mention. I talked about the chemotherapy stuff, but there's a couple of different chemotherapeutic agents, in particular that are pretty clearly associated with on their own with TA-GVHD. Most of those are related to treatment for these, well they are related to treatment for these diseases. One of those is **Fludarabine**. Fludarabine is a purine analog, basically it mimics a regular part of DNA and inhibits the DNA synthesis of the tumor primarily, it's used for CLL, chronic lymphocytic leukemia, in particular. There are other forms of purine analogs, as well, different drugs like Cladribine, pentostatin, things like that. Fludarabine is most famous. It by itself causes enough profound immunosuppression in the recipient to put the patient at serious risk of TA-GVHD. And one other one, forgive me for interrupting, Heidi, one other one that I was just made aware of recently, though it's been around for a while. I don't know why I missed it, there's a drug called **alemtuzumab**, which is basically anti-CD52. It's used in B-cell CLL as well as relapsing multiple sclerosis. And basically, it also causes substantial immunosuppression, and the package insert actually says that, "these patients should only get irradiated blood products to avoid TA-GVHD."

Heidi: I wonder if clinicians are aware this? I hope they are!

Joe: I hope they would be, too! And honestly, it's not something I have come across very often, to tell you the truth.

Heidi: Yeah, I've never heard of it until you just mentioned it right now. (laughs)

Joe: See? We both learned something today. That's awesome!

Heidi: Yes! I'm learning a lot today! So, third category.

Joe: Third category, and that's the one that we traditionally have kind of tagged onto the end and gone, "Oh yeah, there's that stuff as well." But as we will talk about later, this may be a bigger deal than we thought. And that's the patients that are immunocompetent, but getting HLA similar products and that goes back to that one-way HLA match, that I talked about before. Patients who are getting products that are close enough to them, in other words HLA homozygous donor going to a HLA heterozygous recipient, so that there is an attack, but no recognition of foreignness from the recipient, so no counter-attack. And that happens primarily in, there's a couple of places, three

main places we think about it. First is, directed donations, and again, that's primarily because most directed donations come from family members. That's just the reality. We see someone in our family that's really sick, we want to give them blood and help them out and in families, just statistically speaking, there's a much higher likelihood of there being that HLA interaction that I was mentioning. Second, is HLA-matched products and that one may seem counter intuitive to people, unless you understand that when blood centers talk about HLA matching, they really mean "let's get as close as we can get." So sometimes you'll have a product that's really close to the patient, it's not exactly the patient, and so you can have that interaction that I mentioned before.

Heidi: That homozygous donor, heterozygous recipient.

Joe: You got it, you got it! And then the last one is that same interaction in a society that happens to be HLA-limited. What I mean by that, well actually, I can just give you an example of that. In certain countries, Japan is the best example that we know of, just because of the somewhat limited HLA diversity in that population, if you get a transfusion in Japan, the risk is somewhere in the range of 1 in 1000 or so, that that one-way HLA match will occur, just with a random, off-the-shelf transfusion. That's a pretty big deal! That's a pretty high risk when you can compare that to the United States. The numbers vary in the United States, but it's generally somewhere around 1 in 20,000 to 40,000 risk in the U.S. So, substantially more likely in Japan, and quite honestly, that's one of the reasons that the number one place where TA-GVHD occurs is in Japan, historically. But they've taken steps to prevent that now that we'll talk about shortly.

Heidi: And Joe, you have mentioned that there are also a couple of other categories that there's some research or some studies shown that may benefit or I mean, be at risk.

Joe: Yeah, there are a couple of others. One of which is probably not the case in cardiac surgery patients. I think most of the thought with cardiac surgery patients is that probably the first reported cases that we really knew of, before we really knew what it was of TA-GVHD was something that was called "post-operative erythroderma." Basically, it's a milder form of TA-GVHD, and it was in Japan. It was because of that interaction, that I was just describing. Realistically now, aside from that, when we're talking about transfusions in cardiac surgery patients in the U.S. and other countries that don't have that risk, probably not a huge risk, but you'll still see that sometimes in the literature that because of that old, historical risk in cardiac surgery patients, people will talk about that. I think that's probably not a real "thing" anymore. And the last one is aplastic anemia patients. There's debate back and forth about this. A lot of times patients that have aplastic anemia are transplant candidates and so, for obvious reasons, just as a transplant candidate they would be at-risk. But more importantly, one of the treatments is anti-thymocyte globulin, which severely immunocompromises them even further, and so again, they would probably be at-risk as well.

Heidi: Okay. You've mentioned we have been talking about how this is an immune-mediated process. It's the immune system of the recipient and that is not able to do the counter-attack. So, what about AIDS patients? Are they at-risk?

Joe: You know? Up until not long ago, when I actually finally found an article, I always said there have not been a reported case of TA-GVHD in an AIDS patient, but there's actually is one now. It was in a child, a childhood AIDS patient. Realistically, the likelihood of an AIDS patient getting TA-GVHD seems to be very small. There's a lot of detail behind that. There is competing theories to why. One theory is that it appears that the CD8 T-lymphocytes are protective from TA-GVHD and obviously, in patients with AIDS, CD8 function and number is preserved much longer than CD4 function. So that may be the issue or there maybe just some other imbalance in their system because there's a lot more to TA-GVHD than those Pac-men and soldiers that I described at the beginning. Something in terms of the cytokine mix may be thrown off, but realistically, most people will tell you that AIDS patients are not at significant risk for TA-GVHD. However, I will tell you the truth, anytime somebody asks, I will give them irradiated products for an AIDS patient. I'd rather not report the next case, put it that way.

Heidi: Okay. You talked about stem cell transplant patients, what about solid organ?

Joe: Great question. With solid organs, again, there doesn't seem to be a great risk of TA-GVHD. There are some reported cases, I will freely admit to you, but the problem is how do you separate out where those T-lymphocytes came from? Did they come from the organ? Did they come from the transfusion? Most GVHD in solid organ transplant patients come from passenger lymphocytes in the organs.

Heidi: Just like the classical GVHD.

Joe: Exactly. Though again, when transplant surgeons ask for irradiated blood, I give it to them. I don't want to have that fight. I don't think it's worth it because I think that the data is still a little bit unclear on that.

Heidi: And so just again, we kind of talked about this a little earlier about how to handle the babies. So would you say if like a surgeon, or a provider asks for irradiated product, and if the facility is able to somewhat easily provide it, we should provide it?

Joe: Yeah. That's really how I feel. Again, I think that the consequences of irradiating blood or over-irradiating blood—let me be clear—irradiating blood when there may not be a solid indication to do so, I think the consequences are small, **provided you are not keeping it on the shelf for long periods of time before you transfuse it.** So, I have a very strong belief and tendency in practice to, if they ask for it I am generally going to give it to them.

Heidi: I feel the same way. Ok, we've touched on this before, but can you tell me about the prognosis of transfusion-associated graft-versus-host disease, and also, if there are any treatments for it?

Joe: That's the problem with this, Heidi, is that, unfortunately, TA-GVHD, once the diagnosis is made, it's pretty much a death sentence. You know, you'll find articles that talk about the fatality rate, and they'll pretty much all say at least 90%. When we talk about this article at the end, that's pretty much the number that they came down to, 90+%, so I think it's a reasonable number. So, in the vast majority of cases, there's really nothing you can do. You can nail them with *heavy-duty* immunosuppressives, I mean, obviously starting with steroids, people do that. That usually doesn't touch it. IV immunoglobulin, azathioprine, cyclosporin, anti-thymocyte globulin, you name it, bring out the big guns and hit them with it…It just usually doesn't work. And the problem is that marrow that's the issue. The marrow is wiped out, and not only is it wiped out, it tends to go fibrotic, and usually, there's just no coming back from that. These patients will die either a hemorrhagic death or an infectious death, typically in the span of 3-4 weeks after diagnosis. That's the fairly predictable pathway.

Heidi: Joe, so these lymphocytes that come with the donor product, they replicate inside the recipient?

Joe: Yeah, and they replicate in a *big* way! The buzz word that people use for transplant is "engraft," and that's exactly what those cells do. They engraft, they become part of that recipient, and go crazy, and just multiply and multiply and multiply, and take over the system.

Heidi: So, if someone were to transplant, what kind of HLA match do we do? I don't know the answer…

Joe: It's a great question!

Heidi: Who do we match for? Do we match for the donor lymphocytes that have engrafted, or do we match for the native marrow?

Joe: I think you would match for the native marrow, though I don't know if there's a ton of data on that, Heidi. People have done stem cell transplant, and I think early stem cell transplant may be the only thing that saves someone with TA-GVHD. In the data that's out there now, it does seem like that may be the only salvation. I have not seen in the literature who you match for, but I think that for me it would be most reasonable to match for the native HLA type.

Heidi: OK. We've thrown around the word "irradiation" quite a few times, so why are we talking about irradiation? (laughs)

Joe: (laughs) It's a good question! Well, we are talking about irradiation because realistically, irradiation is one of…I used to say it is the "only" way to prevent TA-GVHD, but now there's a little bit more information, and we'll talk about that shortly…but it is the <u>main</u> way that we use to prevent TA-GVHD. Irradiation works simply because of the fact, remember, what we're talking about is, let's go back to the military illustration, or the "Pac-man" illustration. We've got "soldiers" that are in the bag, they're active, they're T-lymphocytes that are ready to go in there and "wocka, wocka, wocka," just attack

those host foreign HLA tissues; we need something to stop them. What we have found is that irradiation, in particular doses, deactivates those T-lymphocytes, without substantially harming the rest of the product. We typically will use a dosage to the center of the bag—in the United States, the "center of the bag dosage" is 2500 centigray, or 25 gray (just a measure of irradiation), in the US, we make sure that the whole bag gets at least 1500 centigray, or 15 gray. So you have to dose the product adequately to deactivate those T-lymphocytes. It basically stops the T-lymphocytes from replicating, which is again the problem.

Heidi: There's some down sides to irradiation…

Joe: Yeah, we've kind of alluded to it. The fact that irradiation does damage the red cell membrane, there's no question about that. It's very, very clear. And as a result of that, you're going to get several things accumulating in a red cell product, like **free hemoglobin**. You're going to get leakage from the membrane. Perhaps more importantly (because free hemoglobin, OK, you'd rather not have it. Is it destructive? To most healthy people, or reasonably healthy people with adequate renal function, not a huge deal), but **potassium** is a bigger deal. Basically, when the membrane gets hit with this level of irradiation, you damage the sodium-potassium pumps, so that gradient that you normally have, keeping potassium inside the cell and pumping sodium outside the cell, kind of goes away, and suddenly you have roughly triple the quantities of extracellular potassium. And that *stays* triple for basically the life of the product. So the longer it is stored, the more potassium is going to accumulate. Really, in the short term, not a huge deal again, and especially for people with normal renal function, but for a red cell product stored for a long period of time, that can be *a lot* of potassium.

Heidi: And I know you go through this in your other lectures, but what does irradiation do to that shelf life of the blood products?

Joe: Oh, yeah, great boards questions! So, those of you studying for exams, you've got to know this. In the United States, the product has a maximum 28 day shelf life from the time that you irradiate it. 28 day shelf life from the time of irradiation. In the United States, most red cells have a shelf life of 42 days, so at the moment you irradiate that product, the expiration date becomes that day + 28, OR it would expire at the normal time, whichever comes first. So, in other words, if you irradiate at day 28, for example, so 28 days from the time that the product was collected, then you don't get an *extra* 28 days beyond the 42, it would expire at the normal day 42. But if you irradiate on day 3 of shelf life, then it's going to expire at day
3 + 28, which would be day 31. In the U.K., they use a little different number, I believe it's 14 days maximum shelf-life, and I think that's primarily for potassium issues. In the United States, though, it's 28 days.

Heidi: Joe, you mentioned that Transfusion-associated GVHD is caused by cellular products, and you kind of talked about how some of the other products, it's not that they're not cellular, it's just that the cells don't survive the production process. So, what products should we irradiate?

Joe: Well, so any of those "cellular" products, in particular for patients at risk, and again this is what we've thought traditionally, for those immunosuppressed patents, etc., the babies, all that, you would irradiate **whole blood products**, you would irradiate **red cell products**, you would irradiate **platelet products**, and then the one that everybody forgets, is the ***granulocyte concentrate***. I did a blog post on this last week, complete with some really cool pictures, by the way, so I'm not going to beat this to death, but please don't forget, everybody needs to remember this, that granulocytes, it's not just a good idea, it's essential that granulocytes are irradiated. It's key to remember that these are always going to immunocompromised recipients, *always*, by definition, and they're an incredibly fresh product, full of really active and hyper T-lymphocytes, that are more than ready to go in and do some damage. So, don't get worried about irradiation damaging the granulocyte function; that's the thing that people get hung up on. It's not enough; granulocytes are *tougher* than T-lymphocytes. In other words, the dose that deactivates the T-lymphocytes doesn't really touch the granulocytes.

Heidi: Now, lymphocytes are white cells, right?

Joe: YES! (laughs)

Heidi: They are! And lymphocytes are the enemy in graft-versus-host disease, right? So why isn't leukocyte reduction enough?

Joe: Ahh, well, yeah, some people think that it helps, actually! So, leukocyte reduction, the process of getting rid of the vast majority of the white cells in a product, generally through filtration but also through inline processes for apheresis collections, it removes a *ton* of white cells. Currently with the 4 log filters, we're talking 99.99+% of the white cells are removed. And you might think, and it might kind of make sense to you, that if you're getting rid of that many white cells, that you could get rid of the risk of TA-GVHD. But the problem is that, well, we don't know the minimum dose that it takes to create that "attack," and that proliferation. There are clearly scenarios where leukocyte reduced products have caused TA-GVHD, we know that for a fact. Now, some of it is older reports, and bedside leukocyte reduction, which we know doesn't work that well, and quite frankly, if we're being completely honest here, we would say, just by looking at the data from the United Kingdom, in their "Serious Hazards of Transfusion" or the "SHOT" data, they started leukocyte reducing everything right around the turn of the century. Right around 1999-2000, in that ballpark. And if you look at their reports of TA-GVHD, they've just dropped off the cliff. There are really hardly any cases of TA-GVHD reported in the UK. Now granted, it's rare *everywhere*, and in the United States, we've only had a few since then, as well. But, how much has leukocyte reduction contributed? It's hard to tell, but it may be that leukocyte reduction by decreasing the load of transfused white cells, it may decrease the severity, and it may make it so that if it's possible to have a less severe form of TA-GVHD, that might be the case. It's clear that of those few patients that survive, more of them received leukocyte reduced products than non-leukocyte reduced products. So there may be some truth to it. But again, I don't think that anyone really believes that it is enough by itself.

Heidi: But it can help.

Joe: It seems like it *may* help.

Heidi: It may help. What about pathogen reduction? Does that help?

Joe: Yeah, that's the wave of the future, pathogen reduction, and in the U.S., we've been behind the rest of the developed world in terms of implementing pathogen reduction. You know, I could go into this in greater detail, but we've gone for awhile so I'd just like to leave it at the fact that there are several different forms of technology. Basically, both of them involve treating a product after collection with an agent that will bind to the nucleic acid of any cell in there, and then you hit it with ultraviolet irradiation, and it crosslinks the DNA (*EDITOR'S NOTE: Actually, it crosslinks either DNA OR RNA*). So, it's obviously for organisms, but it also deactivates the white cells in that product. So either way, it deactivates those T-lymphocytes as well as the pathogens, and it seems like pathogen reduction, once it is fully implemented in the U.S., which is going to be a while, it's approved with one technology for platelets right now, but once it is eventually, I think, approved, then irradiation may become a little less important. In fact, a LOT less important, because the pathogen reduction seems to work as well as irradiation in deactivating those T-lymphocytes.

Heidi: So now, I'd like to start concluding our talk by going back to what we talked about at the very beginning, which was the e-mail you received…

Joe: It's taken me awhile to get back to that, hasn't it, Heidi?

Heidi: I know! But I'm glad! I think this has been very, very helpful and extremely educational. So, can you summarize what's the latest and the greatest in the literature for us?

Joe: You know, this article is really, you said it, it has potential to be a game-changer. The reference will be on the show page, but basically, if you are listening to this in your car, it came out in the journal, "Blood," in 2015, I think it was mid-July, July 16, I think, of 2015. It's an article from a group primarily in Canada, but also in Australia and Boston, MA. They essentially decided that they were going to analyze every single published case of TA-GVHD in the literature. This was a big job! They went through a ton of different cases, they eliminated a bunch for various reasons…again, you can read the article to see why. They ended up analyzing 384 unique cases. And there were definitely some surprises in there…you want me to talk about the surprises, Heidi?

Heidi: I do, actually! Definitely talk about the surprises!

Joe: I will talk about the surprises! You know, the article's really good; it's a good reference to keep, because it goes over the mechanisms that we have thought historically, but the first big surprise to me was that **only about half, about 48.9% (well, exactly 48.9%!) of the cases that they saw of the patients with TA-GVHD had clinical histories with classic indications for irradiation**. Think about that for a second. When we went over the classic indications, the at-rick patients, we talked about the babies, we talked about the cancer patients, things like that, only about half of them

had clinical histories like that! All the other ones were just relatively random transfusions, and that kind of makes me go, “Whoa, hang on a second! That’s a little scary!” We’ll talk more about that in just a sec.

The other thing that was surprising is that **they found no cases of reported TA-GVHD in products that were older than 14 days at the time of transfusion**. So in other words, if a product was not a fresh product any more, if it was over 14 days old, there’s no reported case in the literature that they could find, anyway, of that product causing TA-GVHD.

Heidi: Do you think this is because the lymphocytes just die out?

Joe: I think that’s exactly why, and I think everyone’s pretty aware of that. That’s been shown, is that after roughly ten-*ish* days, lymphocytes just kind of degenerate, and they’re not really very active anymore. So that’s almost certainly the reason, but I don’t think anyone had actually shown that before. We had thought before that fresh products are more likely to cause it, but it was interesting to see that of all the cases reported, no one found anything older than 14 days.

Heidi: What else?

Joe: The other thing that was interesting to me and surprising is that **there was a significant over-representation of those one way HLA match cases**. That’s really an interesting thought, that they saw a heck of a lot…well, to be fair, not every case had HLA typing, so out of those 384 cases, they don’t know the HLA types for all of them. But of the ones where the HLA types were reported, there was a really *super-high* proportion of them that were in immunocompetent recipients who got a one way HLA-matched product, either knowingly or in most cases unknowingly. That’s interesting to me, because that suggests, as I said before, that…we always have thought about this in populations like Japan, where there’s HLA limitations, and there’s a much higher risk of getting that one way HLA-match…that it may be a bigger deal than we thought. There’s definitely some over-representation in the group that they found.

The one other thing that they mentioned, I don’t know if it’s terribly surprising…in fact, I shouldn’t have called this a surprise, actually…**there was very little TA-GVHD in products that were previously irradiated**. The ones that were probably had technical issues. That, actually is not a surprise, that’s a good thing! The problem was is that the majority of the cases that they found (or at least half) was from people that you wouldn’t normally have irradiated, and then the products were non-irradiated.

Heidi: Joe, they found the products causing transfusion-associated graft-versus-host disease as the typical ones that we worry about? The cellular products? Or were there any surprises there?

Joe: Not huge. There was one of the reported cases, I recall, from Liquid Plasma, the never-frozen variety, but other than that, it’s exactly the products that you would expect. I will tell you that since the majority of the cases that they found were from the decades

prior to the year 2000…I mentioned before that they only found 66 cases since the year 2000. Between 1990 and 1999, there were almost 200 cases, so it does seem to be decreasing. That may go along with the leukocyte reduction thing. Most countries have been leukocyte reducing the majority of their products since, you know, right around that ballpark, maybe not quite as aggressively as the United Kingdom did, but certainly in the last ten years or so, the vast majority are leukocyte reduced, so that may come into play, I don't know.

Heidi: So what was the conclusion of the study?

Joe: Well, their basic thought was…they made a statement, and they made this statement, not specifically in the paper, but they made it in an AABB teleconference that they gave, and I could summarize it this way: They said that, "Donor, and not recipient factors are the primary drivers of TA-GVHD." That's a pretty strong statement! I'm not sure I can go quite that far, and believe me, these are amazingly brilliant authors that have far more credentials than I do, and I'm sure are 20 times smarter than I am, but I'm not sure that the data definitely shows that. My first thought when I read this paper, and you and I had talked about this before, and I think that we thought the same thing, was: "Well, DUH! Of COURSE they are seeing TA-GVHD in people without obvious risk, because we already irradiate for the others that are at risk! Come on! How can this be revolutionary?" OK, I'm overdramatizing a little bit, but they argue very strongly that does not explain all of the discrepancy. They feel like, and they show some population data, and some data in terms of the diagnoses of patients who were transfused, so they believe, and they make this statement, that there is still over-representation of these patients who we wouldn't think are at risk. One of the things that they bring up that I find really *very* interesting is that they reported data from the U.K., from the SHOT data, they showed over 1000 patients in the U.K., who *were* at risk for TA-GVHD, got non-irradiated products. So, "oopsies," in other words; scenarios where people that should have gotten irradiated products *didn't* get irradiated products. They looked at all 100 of those patients, and found no cases of TA-GVHD whatsoever.

Heidi: Now, was it because they were getting older products, or they didn't go into that depth?

Joe: That's a great question. To my knowledge, they don't break that down, and what we certainly can say is that the products were all leukocyte-reduced. So, who knows? Again, I'm not arguing with their conclusions, I just think that they make some pretty strong statements, and I'm not sure I can go quite as far as they do, but I think there is more to think about.

Heidi: So basically they are going with the idea of homozygous donor, heterozygous recipient…

Joe: That's that's a bigger deal than what we had thought.

Heidi: Bigger deal than irradiating for immunosuppressed patients? Do you think we need to stop irradiating for immunosuppressed patients?

Joe: I don't think anyone would go that far right now. I think that for the clear-cut indications that we've had in the past, I don't think that this data is something that would support our eliminating that right away. Then, that U.K. experience that I told you about before, though, does suggest that it may not be *quite* as important as we thought it was. But still, I don't think anyone would say, "Hey, stop irradiating for those immunosuppressed patients."

Heidi: OK, and in terms of directed donors, family members, those with similar HLA profiles, should be continue to irradiate, or should we stop irradiating?

Joe: Again, the reason why those folks *get* TA-GVHD is the reason they are pointing at as one of the biggest things, those **HLA-similar products definitely still need to be irradiated**, no question about that (or treated in whatever way, whether that's pathogen reduction or irradiation).

Heidi: As you mentioned, there are some hospitals that irradiate ALL products. There's some others that do it based on orders that come in from the clinicians. Some have policies that they do all the babies under four months of age. What about irradiating "fresh blood?"

Joe: Yeah…you know, that's a really interesting question, and I think that that question is the one that the Heme/Onc doc that wrote me that e-mail was kind of frustrated about. I think that may be where we ultimately get. You know, the data here, when they are showing that there is no TA-GVHD outside of products stored 14 days or more, the converse is that all of them DID occur in products that are less than 14 days…I suspect that as we go forward, as we study this more (which I really think that we need to do, continue to study this), we may eventually get there: That products that are "fresh products" should be irradiated as close to transfusion as possible. My guess is some of the folks involved in that paper may be looking to do that. Again, I don't want to speak for them, because I don't know that for sure, but that may be something that practice does get changed as a result of that.

But the other thing to think about is, if that's true, does that mean that, for people that we don't really *know* are at total risk for TA-GVHD, like babies that haven't had an exchange transfusion or an intrauterine transfusion, or a solid tumor patient, or a NON-Hodgkins lymphoma patient (where we don't have that inherent, built-in immune defect); if THOSE people get blood that's older than 14 days, do we NOT have to irradiate those blood products? I don't know!

Heidi: Or, do we just give *everybody* older blood? (laughs)

Joe: Yeah! In light of all the discussions going on… (laughs)

Heidi: …which goes against all the discussions about fresh blood…

Joe: Exactly! There's a lot to think about. But the good news, Heidi, is that whatever we do, we are already dealing with a rare scenario. We're not dealing with something that's occurring 14, 20, 2000 times a year, we're dealing with something that occurs very rarely. So whatever we do, to me, is just a tweak. But I think we will tweak, ultimately.

Heidi: The authors did conclude that it was the one way HLA match that was the most problematic. I don't think we're there yet, in terms of infrastructure to do it, but would you consider closer monitoring of one way HLA match. Matching patients and donors and coming up with some sort of policy for that?

Joe: That's rough. That's hard for me, I've got to tell you the truth. Clearly, the technology is not there to routinely do HLA matching on donors and recipients. We technically COULD do it, but it would be extraordinarily logistically difficult, to say nothing of the expense. You know me, I don't want to make it all about the expense, but it is an important consideration.

Heidi: No, of course! It's important!

Joe: You know, the alternative to that is to do what some facilities have gone to, as you mentioned, and just do a blanket, everything gets irradiated policy. You know, I have said before that I think that might be more aggressive than we need to be, but in light of the data that's here, that's something that a place that has the ability to do that, like a Cedars-Sinai, for example, I can understand why they would. You know, again, we're talking about small numbers, tiny amount of risk, but if it's easy enough to do, if you have the capability on-site to do it…what does it hurt? Well, probably not much, again, provided you are not keeping the product around for a long period of time after you irradiate it.

Heidi: Got it. Because again, irradiating, like you said, shortens the shelf life as well. So, you have two ways to go: Irradiating from the beginning, right when you get the product, lose two weeks of your shelf life; OR, wait until day 14 and irradiate, and then transfuse older blood routinely. But then, if you're transfusing older blood, you may not even need TO irradiate, based on what the paper said. So there's a lot to think about!

Joe: (laughs) There *is* a lot to think about. You know, the older the product gets before you irradiate it, the more of a potassium issue you have, as well. I don't think that the irradiate after 14 days thing is going to fly. My guess is that we are going to end up with some combination of irradiating stuff under 14 days and somewhat more blanket irradiation for people that might be at risk. I don't know! I think it's going to be interesting to see where all of this leads us. And really, we're speculating, so we probably should stop, but that's the reality. It's not as simple an equation as we used to think, and that's the message that I wanted to get across. I think this paper puts up a lot of questions about the way we've "always handled things," and I think it is important for every facility to think about what this means in terms of the patients that they serve.

Heidi: Well, Joe, this has been a great discussion. Thank you for allowing me to be part of your podcast, and for giving us a very in-depth look at transfusion-associated GVHD,

and including some of the latest findings in the literature, and going over this fascinating paper that I really think may be a game-changer. I appreciate it, and I want to thank our listeners for listening, and hopefully we'll reconnect later with all of our listeners!

Joe: Thanks, Heidi!