BBGuy Essentials 089CE:
"The Transfused and the Breathless" with Christine Cserti-Gazdewich
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Christine: Hello! I'm Dr. Christine Cserti-Gazdewich from the University of Toronto, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi everyone, and welcome to Blood Bank Guy Essentials, the podcast with just one goal: Helping you learn the essentials of Transfusion Medicine. This is episode 089CE, and it is March 24, 2021. My name is Joe Chaffin, and I am your host. Today, I'm going to discuss in some pretty significant depth transfusion reactions that involve the respiratory system, especially Transfusion-associated Circulatory Overload, and that discussion will be with the wonderful Dr. Christine Cserti-Gazdewich from the University of Toronto.

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So, I believe that recognizing and treating and of course, preventing transfusion reactions is pretty close to the most important job that a Transfusion Medicine physician like me can do. Right now, the things that cause more deaths related to transfusion are, in fact, things like Transfusion-associated Circulatory Overload, or "TACO," and Transfusion-related Acute Lung Injury, or "TRALI." Does that surprise you? They cause far more deaths than anything like HIV or hepatitis or acute hemolytic transfusion reactions, in fact. TACO in particular has been diagnosed so much more in recent years, and it is in fact, today, the number ONE cause of death after transfusion! That is scary…

Today, my friend Dr. Christine Cserti-Gazdewich is with me to talk about TACO and TRALI (but especially focusing on TACO). You can find previous episodes of the podcast covering TRALI in greater detail, but I wanted to make sure you are solid on the details with TACO by the end of today's episode.

Let me tell you a little bit about Christine. She has been on the podcast in the past. She is actually a transfusion medicine specialist and consultant hematologist She was originally trained in internal medicine and clinical hematology in Toronto, and she had her fellowship training in transfusion medicine at Harvard. She has been at the University Health Network for 14 years, where she co-directs a large blood transfusion service through several teaching hospitals of the University of Toronto. She also has oversight responsibilities for a number of community and rural client sites across Ontario. Her chief interests in practice, leadership, and research are in immunohematology, hemovigilance, and complex andconstrained hemotherapy scenarios.

I'm very excited for you to hear Dr. Cserti-Gazdewich, so here we go with a discussion Christine likes to call, "The Transfused and the Breathless!"

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Joe: Hey Christine, welcome back to the Blood Bank Guy Essentials Podcast!

Christine: Thank you so much for inviting me back, Joe.

Joe: When you were here, I can't even remember how long ago it's been, but you talked about febrile reactions, and you gave us a really great look at some hidden features and things that weren't widely appreciated necessarily. I wanted to build on that with you, Christine, because you gave this amazing talk at a conference in Australia that we were both at virtually, not physically there, unfortunately, specifically on cardio-respiratory reactions. And I loved your title. Tell me again, what was the title of the talk, Christine?

Christine: Yes. It was "The Transfused and The Breathless; Sketching the Taint That Remains."

Joe: That is a magical title and it makes me so happy. I just wanted to hear you say it again. Oh my goodness...

Christine: I sometimes meditate on, you know, good titles for talks, you know, as an act of procrastination. And then, you know, if I get something that pumps me up, I think I might do a better job, so…

Joe: That is fantastic. I love it. Well, you nailed that one. It sounds sufficiently "daytime drama- like," and it definitely captures attention. So, we are going talk specifically about cardiopulmonary reactions and focus most of our time on Transfusion-associated Circulatory Overload and Transfusion-related Acute Lung Injury.

But I'd hoped for just a few minutes before we get there, if you could just talk us through a little bit about just general approach to transfusion reactions and how you guys look at it up there in Canada, which I'm sure is fairly similar to the way we do it in the United States, but I think you

guys have some unique twists. Just kind of talk us through, if you wouldn't mind, your general approach, Christine.

Christine: My approach has been changing over time because I feel like the messaging around reactions has to kind of get a little philosophical and a big step back on really why we care. So, people might say, "Oh, you know, there's been a disturbance and I'm not going to bother connecting to anyone about it."

And so one of my first points is, why connectivity, why sharing, why complaining is key? And so this is so that people get the sensibility that, for all the good that comes out of blood, there might be some bad and that, to get into co-component quarantine or "lookback" and reporting and, amassing signals so that we can have a dynamically informed consent of the true risk of transfusion, we need good connectivity. And so I really want to push this message that connecting to me, connecting to the blood bank on what you've seen is so important and I will value your input. And so, you know, it's really just encouraging communication before all of those recognition principles kick in. And that's so key in our learning, but I want that philosophy to be instinct.

I then want to prepare my listener to, to know that this is going to be common. You know, if transfusion is the most commonly performed procedure in healthcare, in at least 10% of registrations or stays, and a transfusion reaction is going to occur 1 to 10% of the time, we're going to see a lot of material if we are reporting on truth. And so I want to get people cued into expected occurrence rates.

And so that sort of just sets the tone, and then I unpack what you might see. And so, when it comes to the acute reactions, I like to split everything into threes. And so, you know, I talk about the "three acute disturbance archetypes," you know, “blowing your top” with a fever. So the "fire and ice" or febrile transfusion reaction archetype. Then the kind of superficial or mucocutaneous allergic stuff and then going deep into the cardiorespiratory or visceral. And that's the stuff that really hits your patient hard, that may be more distressing, that may in fact be life-threatening.

This also follows the order of frequency. So, febrile reactions account for about half of our referral load, and then allergics follow secondly. And although cardiorespiratory would seem to fall in that third place, it's definitely one of these "last but not least" situations because there are just so many things dogging this particular category.

And when I talked about the "taint that remains" in my title, what I was really getting at was that, this is still kind of nebulous, unconquered territory. Transfusion has this really triumphant history of defeating, bringing down to, you know, lightning strike risk rates of transfusion-transmitted viral infections. This has been an incredible triumph after the tainted global blood tragedy. But what remains are all of these risks that

we don't entirely have a handle on. Yeah, we've risk mitigated against TRALI in many ways, but there are a lot of other respiratory events that continue to dog us. And so, I'm really enthralled and hounded by this category of patient disturbance experiences, and see that we have still a lot to do.

And so, you know, these respiratory reactions, I find no matter how "expert" I feel I'm getting at this, that I'm still really in the dark, that these are really hard to conclude no matter how aggressive I am in real time gathering the data that I need to evaluate against diagnostic criteria.

Joe: Before we get into the specifics of these cardio-respiratory reactions, Christine, I want to go back to something that you said earlier, and you said something about, in the range of 1 to 10% of transfusions will lead to a reaction of some sort. And I'm sure that there are people that are sitting there that have been in their hospital transfusion committees, for example, and have looked at the proportion of "reported," and I use that word deliberately, transfusion reactions, and have seen numbers that are more like 0.1% if they're lucky. So what's the discrepancy? You're telling me it happens 1 to 10% of the time and people, in blood banks, we hear about them WAY less than that! What's the deal?

Christine: Yeah. So the deal is all about the prospective versus the retrospective lens of data. In retrospective data dredging, or the data that depend on people being active reporters, which ironically is called, "passive surveillance," you know, you have to put a lot of energy in it to yield what you've witnessed. And so that's really going to be the tip of the iceberg. So when you look at these hemovigilance systems where they depend on that "reporter will," you do have rates that are generally much smaller, you know, like, 1 in 1000 being a typical rate. So 0.1, 0.3, 0.4%, those are really typical numbers in national hemovigilance schemes for the commonest reaction types.

But then when you look at some really interesting papers that have algorithms that link the ascertainment of the release of a blood product with marks of hypoxia on arterial blood gases going down in relation to transfusion events, papers like this or prospective studies that have looked at transfusion reactions, that the rates appear to be much higher. So orders of magnitude more, one to two log scale more frequent.

So Rick Kaufman, in a substudy of the "PLADO trial," saw that platelet transfusion reactions occurred quite often in that prospective platelet dose study. Jeannie Hendrickson, in a “Transfusion” paper in 2016 showed a high rate of transfusion reactions, higher than what we normally see in other reporting schemes.

So, I would say, these glimmers of different information maybe better approach the truth, and should be front of mind when we think about what we're seeing, because, you know, if we indoctrinate ourselves on this idea

that reactions can only happen 1 in 1000 times, I think we might be more prone to the cognitive error of dismissing what we're seeing.

Joe: That's a hugely important point. I'm certainly not convinced, and I don't believe that a lot of clinicians are "ignoring" transfusion reactions or possible transfusion complications. But I do tell them that, in the situation where something comes up and they don't take the time to investigate it, most of the time they're going to be right, and the patient's going to be fine, but when they're wrong, the results can be catastrophic and that's when they're going to regret it.

That's a rabbit hole we could go down for a while, I think, Christine, I'm sorry for that, but let's get back to where we were heading, and that's specifically looking at cardiorespiratory reactions. You were senior author on a paper that was published in Vox Sanguinis in 2019 that I found really fascinating. It gave a really granular look over a four-year period of the referrals that, in your practice, you and your incredibly esteemed colleagues up there in Canada, took a look at what proportions of things you were seeing.

Let's establish a couple of things before we move into some of the details of these specific cardio-respiratory reactions, and again, especially Circulatory Overload and Transfusion-related Acute Lung Injury. Just from a practical perspective, from a learner's perspective, when you have a reaction, a suspected reaction reported to you, what are the things that kind of tickle your brain and kind of move you in the direction of the "cardio-respiratory bucket," if you will, for this particular type of reaction?

Christine: That's a great question. You know, everyone's going to define this a little differently. So, for symptoms, what is the patient experience? Are they short of breath? Are they having, you know, a sense of doom? The patient experience is one facet of this and every hospital has their own kind of worksheets or check boxes in terms of salient symptoms.

But then you get into the objective signs, which is where, you know, you can be unambiguous. And so, changes in your heart rate, blood pressure, respiratory rate, and your peripheral blood oximetry, usually that's just your non-invasive finger probe. So if there are any deflections there, the question is, you know, how does a group define a significant deflection?

So, you know, obviously getting from normal to abnormal range in any of those vital signs would be a consideration. Different groups define that a little differently. So, the AABB might say that an an important increase in heart rate is "delta 40," or getting up to above 100 per minute, and being more than 15% off of your baseline. And then for blood pressure, we tend to hone in on the systolic. And so if you drop by "delta 30" to get to less than 90, or if your deflection downwards is by more than 15% from your baseline.

So everyone's going to have a different kind of numerical guide and people want numbers or guidance so that they know if this is a worthy disturbance to call in. But I like to say that if you have any questions, call us. So, you know, our blood bank is always open to receiving calls, and we have some clinician decision support built in with our technologists trained on what some of the important numerical deflections are, and we've got this spelled out in the clinical policies as well.

So I think everyone's going define tachycardia or bradycardia, hypertension or hypotension in their own specific way. But I think, in general, significant deflections, so more than 10 to 15%. And in absolute numbers, you know, units of more than 30 or 40 for whatever you're talking about.

Now, resp rate is a little interesting, because I'm always a little cynical about the resp rates that people report. That's not as clear, I don't see as much consensus on what constitutes a major resp rate change, but certainly if the patient is visibly using their accessory muscles or their diaphragm looks like it's moving differently and they're clutching their bedrails, their neck looks like they're using their accessory muscles, their intercostals are in drawing. You know, resp rate is going to be not always that clear cut. So, you know, if 12 goes to 24, you're going to call that significant.

And for hypoxia, our alarm bells ring if someone's desaturating to less than 90, or if they maintain their oxygen saturation by contrivance, which is to say somebody turned up their nasal prong oxygen rate to keep them at 95%.

Joe: It's cheating. That's what it is. Cheating. Okay. So I think among all those wonderful tidbits, one of the things that you said that I hope that the clinicians listening to this really take home: I think it's really important for clinicians and nurses to understand that the blood bank is anxious to help them with these discussions and transfusion services everywhere have medical directors and have resources and people that will help you these evaluations.

Those are great tips, Christine. I wonder if you would take us through again, just from a high level, what's your differential diagnosis? When you see somebody that is having some of these changes that you think, "Ooh, this really kind of looks like it's a cardio-respiratory type of reaction," what are the major players? What are the major entities that you think of in terms of that differential diagnosis?

Christine: Yeah. you know, I would start off with, the first two way split, which is whether or not edema is present. And if edema is present, then dividing between cardiogenic versus non-cardiogenic. So, I mean, really the most important thing is, is it cardiogenic or not? Because cardiogenic, i.e., TACO, Transfusion-associated Circulatory Overload, is going to be the

likeliest diagnosis. And then after that, you know, there's going to be a host of non-cardiogenic possibilities, as well as the underlying disease process. And then the "dustbin category" known as “TAD,” Transfusion-associated Dyspnea.

So if you suspect that the patient has pulmonary edema when they are having their distress response, usually that would be tied to some clinico-radiologic examination to establish that point. Are there crackles? Is there fluid being coughed up? So you know, on a chest x-ray, does it look like there's edema? If there is edema, if there's clinico-radiologic evidence of edema, is it cardiogenic or not?

And so, the bedside correlates, I think what we struggle for the most and what's most valuable in real time and what doesn't get trapped in a lab result on a screen for someone to look at 10 hours or 10 days later is how suffused they looked. So, was their jugular venous pulse distended, elevated? Did they have peripheral edema? Volume status in the patient may not be as rigorously documented depending on where they're located in that healthcare system. They may be on a low-intensity ward where daily weights or precise "ins and outs" aren't being done. And so we're really relying on real time information.

And so, you know, if we're fortunate enough to get a page reflecting a concern this way, this is our golden opportunity to get as many factors as we can to distinguish between cardiogenic versus non-cardiogenic. Do you have a cardiac chamber stretch biomarker test at your institution? Do you have NT-proBNP or proBNP available? This hasn't embedded itself in all policies everywhere. I've been chatting with colleagues about whether or not BNP is part of their own internal transfusion reaction investigation pathway. I hear a bit of a mix. I think we just really need to get to brass tacks and make sure we get the best bedside details we can, the vital signs and the physical examination parameters.

Joe: I want to give you the opportunity to spend a decent amount of time diving into the details of both transfusion-associated circulatory overload and transfusion-related acute lung injury, and you've just kind of defined some of those distinctions. I wonder if before we get into the specific details, could you give us just a very high level overview of what's different and what's similar, and you've already mentioned cardiac, non-cardiogenic, but can we maybe just a little bit more between those two entities? Between TACO on the one hand, TRALI on the other hand, how in theory anyway, from the big picture perspective, do we separate them?

Christine: So the non-cardiogenics, your big player would be TRALI, or allergic bronchospasm, or the off-target features of dyspnea from reactions that tend not to make you think of dyspneic transfusion reactions, the classic manifestation. So incompatibility reactions and bacterial contamination can also manifest in dyspnea, so they remain on the differential diagnosis. So I would cluster all of those guys together in the non-cardiogenic realm.

And this is why, you know, the blood bank still has that spirit of wanting to look for whether or not the product was contaminated and for whether or not we dispensed something incompatible. So the classic tests that happen in the febrile range are still going to apply to your dyspneic transfusion reaction patient, because there may be off target features.

If there aren't allergic stigmata, so usually the patient's got some giveaways, like wheezing or stridor or angioedema, urticaria, et cetera. So you've got some things in that bin to help you classify.

If you're not observing these features and the patient has edema... And so if we lift back up to that edema category, cardiogenic versus non-cardiogenic, and they don't look like they're cardiogenic, well then, we're now worried about an immunopathogenesis, that's very interesting: The story of TRALI, transfusion-related acute lung injury. This is whole different ball game from cardiogenic. This is not the fault of anyone's circulatory system or the volume at hand. And this is where we get into the distinguishing realm of a "dangerous doctor" event versus a "dangerous donor" event.

And so, this is underpinned by leukoagglutinins usually, or other mediators in a product that, kind of hyper activate the white cells that happen to be resting on the pulmonary capillaries surrounding the alveolus. Those white cells, you know, if they're more numerous or particularly primed, and sick patients have a lot to degranulate, and if something lands on them to stimulate them to do so, like a cognate leukoagglutinating antibody that microbicidal arsenal explodes en masse, and every lobe will light up like ARDS or a "flooding" of the alveolus. So this is not a transudative water flood through an intact basement membrane, but an "immune burn" where a proteinaceous material is flooding the alveolus. So a permeability leak event, if you will, that's got an immune basis to it.

That's not something we've got a drug to throw at. This is a situation where the patient needs to be stabilized by good respiratory TLC. It may be a code blue call. It may be a need for intubation, mechanical ventilation, or positive pressure. The patient may not respond to diuretic, because again, this wasn't about the capillary getting juiced out and transudating water across an intact basement membrane. This is really about a proteinaceous oozing flood.

The good news in this situation is that whatever the mediator was that caused this was present in a finite quantity, it's not a reduplicating or active immune response. You know, this is a finite amount of antibody or a finite amount of "evil humor."

And so the damage will have been done in the acute range. And this is about stabilizing the patient, allowing them to heal through that. And so, you know, if the patient wasn't already sick with something that's got an

intrinsically high case fatality rate to it, they may be able to get through this reaction with some supportive care.

Joe: Hey, my friend, let's get into the weeds. What do you think let's do a little TACO versus TRALI stuff. Let's do a little taco, discussion. Are you ready?

Christine: Yep!

Joe: There's been a lot of work done on TACO, and you and your group up in Canada have been responsible for a decent amount of it over the last few years. I know that TACO has recently been looked at, and that we have a relatively new definition of what TACO is and how to define it. Actually, let's just start here. What are the consequences? Is transfusion-associated circulatory overload a serious reaction?

Christine: Absolutely. And this is such a central question, you know, in a session on cardio-respiratory reactions, this is number one. This occurs commonly, 1 to 10% of encounters may have a TACO within them. We assume it's a reversible entity, if we throw diuretics at it; we don't know 100%.

I think the most important point here is that it's risen in rank as the commonest reaction entity among transfusion-related deaths. So although transfusion-related deaths are not common, thank goodness, if you look at the deaths that do occur all over the world; Canada's hemovigilance scheme is called "TTISS," the Transfusion Transmitted Injury Surveillance System, in the UK, we have "SHOT," in the US you have the FDA. If you look at the attributable proportion of transfusion-related deaths due to TACO, it's more than a third now. It's now twice as accountable among transfusion-related deaths as TRALI was. Just 5-10 years ago, we were all expounding TRALI as the number one cause of transfusion-related death. It's probably still in many textbooks. But this has certainly supervened, this is in position number one.

So this really is part of that "taint that remains," and this may be because we're recognizing it better at an individual level. So if we get away from the aerial view and the deaths attributability, because someone might say, "Oh, well deaths are rare, so I don't, care about the proportion in a rare entity." But if you look at TACO at an individual level, one in five of our TACOs has ended up in the ICU. And the case fatality rate for TACO can be as high as 1 to 10%. So that 1 to 10% number I keep quoting repetitively is not because I'm forgetting, it's because a lot of things kind of jump into that particular log scale, and it is an easy thing to remember and to teach people with. So, I think at an individual, and if you interview anyone, the distress level is high.

Joe: What I found interesting, and this is just an aside, Christine. I wonder if with your clinician background, I wonder if you can give me your perspective on this. I have found personally when I've suggested that TACO is going on that clinicians often have a resistance to it. And I think

part of it maybe comes from the little play on words that you mentioned earlier, the "dangerous doctor" thing, that clinicians take TACO as a personal insult.

I wonder if you've experienced that with your clinician colleagues, and whether there is some resistance to A, reporting, or B, even recognizing it, because it feels like this is someone's fault as opposed to TRALI which is more, "that's that bad blood product." Have you seen that dichotomy?

Christine: Couldn't agree more. I want to be sensitive about this. I do feel bad about, you know, the zinger of "dangerous doctor" versus "dangerous donor." You know, it's really meant to make it more memorable, but I do have to be sensitive to the idea that this, obviously, can come across as a criticism.

It's delicate ground. I do believe that these events may be under-reported because of a self-consciousness to have, you know, maybe a lost opportunity recognized. That maybe, making space for that blood unit with preemptive diuresis for example, not that we've got RCTs yet to establish that as proven beneficial, but just as a common sense idea, you know, a two unit transfusion that could've just been a single unit that might not have tipped them over. So I think people are afraid of being opened up to some root cause review.

There's no question that this is delicate territory. It's also an opportunity though, every time it gets identified, to educate somebody, and maybe things will change after each person gets contacted. So I do think that that personal one-on-one outreach is important, and that we do have to speak some truth to what's happening. That's going to be an art in negotiation and delicacy and fairness.

Joe: Indeed. Appreciate that perspective. Let's move on and let's talk about this new, or this updated definition of TACO that came out in 2018 from the ISBT working party. Can you walk us through the current main criteria for diagnosing TACO?

Christine: Yeah. I want to just commend the group for how rigorously they came up with the required elements and the additional elements and the numbers of elements that I sometimes call these "cassettes" in my talk, because I put nice little boxes around each idea or point or criterion in the definition.

So, you know, this was very well-examined, and the winning definition was a requirement of one of the first two features, which is **respiratory distress or pulmonary edema with one or more of three other features for a minimum of three criteria**. So in that first band where you have to have one of two or both of these required elements, the respiratory distress is tachypnea, dyspnea, cyanosis, hypoxia without other causes, bronchospasm, wheezing. It's an important definition because you can have a patient who is anesthetized. So how do you qualify respiratory distress in that event? It's going to be hypoxia.

And then for the pulmonary edema, it's either physical findings or the radiography, so left heart strain. So, crackles, orthopnia, cough, audible S3, frothing pink sputum, and on radiography, effusions, a widened vascular pedicle, vessel enlargement, peribronchial cuffing, Kerlee lines, alveolar edema, cardiac silhouette enlargement.

So, what I like about this definition is that radiography is included but not required. This is a point of some potential criticism of the TRALI diagnosis, which still requires radiography. What do you do if you're at a center that doesn't have radiograph machines? So, TACO does not require a chest x-ray, but if it is done, it's an asset.

And then, for the three other options, the one or more of, if you've got one of the above, one or two of the above to get to that total of three, you've got **cardiovascular system changes, fluid overload, or natriuretic peptide**.

So for cardiovascular system changes, it's getting stuffed up. So, tachycardia, a blood pressure that jumps. Now, if you go into cardiogenic shock, the blood pressure could go down, but you've got to have someone savvy and the recognition of that, JVP distention, or central venous pressures, if you've got a transducer actually measuring that, and peripheral edema. So cardiovascular system changes.

Now, fluid overload: That's someone who numerically is getting positive fluid balance or weight gain, or if you give them diuretic, or if you ultra filter off and dialysis that excess volume, you've got a response. So those would be elements of fluid overload. So either metrically stuffed up or visibly improved when volume is removed.

And then for natriuretic peptide, it's whatever you've got. So that may be your NT-proBNP or your BNP. Now what's problematic here, so you've got to be greater than, the upper limit of normal and one and a half times your pre-transfusion value. But what do you do if you don't have a pre-transfusion value, and, are you going to use a non comparable sample that's been stored longer than that biomarker is necessarily stable for, therefore you might underestimate your pre-transfusion BNP, and overestimate that shift? Consequently, you may not have anything to retrieve, in terms of a comparative pre-transfusion specimen. So I think, you know, that final cassette often isn't there. Which means you're working with fewer qualifying criteria.

And so I think one of the major points I tried to make in the Australia lecture was that, whereas TRALI historically had a definite and a possible definition, the TACO definition is you have it, or you don't. And there isn't the nuance of "possible TACO." So we have not broken into that frontier of softer criteria or a recognition opportunity for something that almost meets the definition. And, you could argue that maybe there's value to that so

that you can be inclusive on what might be a truer number due to an under-estimate from criteria that are too stringent.

So, you know, how many times do I see a patient who's got the distress, and who has a pulmonary edema and who has cardiovascular system changes, so that's now three criteria, but they had some underlying reasons to have had their pulmonary edema the way the TRALI patient might've been at risk with risk factors, or their cardiovascular system changes could be due to like, they might be tachycardic because now they're panicking from the distress that they're having. So how do I distinguish that from a panic attack, for example, or if a patient has a febrile TACO, you know, you can get tachycardic when you're febrile. And so you might be over calling some of these features or under calling them.

So it just goes to show that each of these cassettes are different in the eye of the beholder, especially if these are not mathematically defined with precision.

Joe: So Christine, as I listened to you describing the definition of TACO, one of the things that I notice in there when we're talking about vital signs, for example, that there is nothing in there about fever. And I have to tell you, I've taught pathology residents blood banking for, you know, 25 plus years, and I always used to say, until the last few years, I always used to say that one of the ways to distinguish circulatory overload from transfusion related acute lung injury was the lack of a fever, a lack of a temperature increase in TACO, but sadly, it appears that I was wrong about that. You and your group have contributed to that knowledge, as well as additional studies that have been done. So can you talk to us a little bit about fever and TACO?

Christine: I'd love to. So this is a bit of a blind blindsiding thing in the recent literature, is febrile TACO a thing, or "Hot TACO," as some smarter people than me have, have coined this entity? So, Chet Andrzejewski a few years ago, published a fascinating paper where, you know, a third of his TACOs were found to have inflammatory features. And so we decided to look at our own data set. This was just at UHN, three-year period. 10% of our reactions were TACO. And what we found was that a third of them had developed a fever even after subtracting those who had had a fever at baseline. And so we thought, "Boy, that's really weird," because if this is just a "matter of plumbing," if this is just a congestive event, that's all about water and nothing more, why would you have a fever? This is not an immune complex event, like a leukoagglutinin in TRALI, this is not an immune complex event, like an allergic transfusion reaction.

And so what we decided to do is we thought, "Okay, well maybe everyone's febrile in the hospital. You know, they're sick people in the hospital." So we decided to take a look at our allergic reactors, as there were many of them, and we all know that allergy is an immune complex event. You've got an allergen with an IgE that docks into a mast cell. So

yeah, so, if anything's going to have a fever, it's going to be an immune complex event rather than a fluid event. And what we were shocked to find in terms of our odds ratios, was that the odds of developing a fever in TACO versus allergic reactions was five-fold.

Then the other interesting rabbit hole that we found in this cut was that the odds of a pre-transfusion fever if you had TACO versus an allergic reaction was 15-fold, as if to say that fever was actually making you more vulnerable to volume. Digging around for some relevant literature in our discussion, we found a paper on the injection of BNP in dog models being an inducer of fever.

So, it makes you wonder whether or not there's something that entwines inflammation with the cardiovascular system. And, you know, CRP is an important biomarker for cardiac risk. Chet Andrzejewski advanced this cool phrase of "fluidic angioplasty" as a hypothesis where maybe if you overdistend the vascular space with volume, you may have atheromas that crack under that strain, and that might release some pro-inflammatory mediators into the bloodstream. We looked at interest with that idea and went to see if, in our data set, there was an association of Hot versus non-Hot TACO with older blood units or older patients. And we didn't see an association, but our numbers may just have been too small.

So, you know, there's gotta be something inflammatory happening here, but then, red cells are more "TACO-genic" than platelets are, and platelets tend to be more pro-inflammatory products than red cells are. So we're not yet able to make sense of what the exact pathogenesis is here…

Joe: I saw someone describing, I forget what article it was in. I think it was in a transfusion med review article, it was, by Bosboom, from 2019 and a phrase in there really struck me. They said "Starling's original model describing the distribution of fluids over the body fluid compartments is insufficient." As you said, there's more to this than just some more volume, a little extra volume. There's more going on. And, and I think we're still trying to figure some of that out, wouldn't you say?

Christine: Absolutely. What a beautiful quote!

Joe: We know what TACO, at least in terms of the definition, is supposed to look like, and we've talked about some of the variants and the "Hot TACO" thing, let's talk a little bit about how we identify people that might be at risk for TACO, because obviously it's important to diagnose it, but I think it's at least as important, if not more, to prevent it. So mitigation for TACO; what are the things in terms of how we prevent this? And who's at risk?

Christine: Yeah, the AABB is in your spirit on this one. So, you know, accreditation standards really do expect lab to bedside prevention efforts, and that's a twofold move. That's identifying who's at risk and modifying the order. So the AABB Standard 5.19.7 in the 30th edition of the manual spoke to

having a policy for responding to requests for products for patients identified by the ordering physician as being at increased risk of TACO.

And my handy acronym for this is "**CRAP**," where the "C" is cardio-respiratory dysfunction, the "R" is renal dysfunction, the "A" is age or advances in age, and the "P" is positive fluid balance. So it's all sort of obvious, but the cardio-respiratory dysfunction will encompass people who've had MI, CHF, who are diuretic users, have had abnormal cardiac studies, and folks who have the cardinal vital sign abnormalities suggesting those impairments. And then renal dysfunction, you know, that'll be obvious, a person who can't clear their solutes and fluids might be accumulating. And young and old extremes of age are going to increase your risk. So it's almost like a parabolic function. So, you know, pediatric neonatologists are worried about this, and geriatricians are worried about this, and anyone who cares for patients greater than the age of 60 or 70 is going to hopefully have keener eyes. And positive fluid balance, again, if the chart isn't documenting all of this, we may be missing a signal, but someone who's gaining weight, their ins and outs are showing a positive fluid balance, physical signs, the edema.

Now, some nuances here. If you have a very small body and a standard-sized order, they may not be able to tolerate that. The person who is adapting to their anemia, we have to be conscious of staying away from the temptation of giving four units of red cells to someone who comes in with a hemoglobin of 3 or 4 grams per deciliter. You want to fix them fast, but you know, they may have been hyperdynamically compensating for some time. And so, those transfusions ought to be given slowly, because they probably didn't get there fast if they didn't have an associated hemorrhage being observed with their anemia presentation.

So there's quality of care things here. So the unwritten verbal order might've been given too quickly, the patient who wasn't getting looked at, really big-sized orders.

One term that we coined in a TMR paper in 2013 was "STACO." So, saline preempting your TACO. So preceding crystalloids. So sometimes patients, you know, have more than just a "TKVO," or saline running to keep vein open. They may have been getting 100 cc per hour. It may have been a sickle patient who was getting aggressively hydrated for their vaso-occlusive pain crisis. And they got hemodiluted down. And so the irony here is that the very thing that sets you up for TACO is the thing that may have artifactually hemodiluted you to what looks like a level of anemia that then calls for a red cell transfusion. So you get built up for that red cell transfusion by virtue of a risk factor for the TACO that you're about to get, which is really just too bad.

Joe: So practically speaking, Christine, once you identify folks that are potentially at risk utilizing some of those things that you've told us, what are some practical tips to mitigate that actual risk? What are the things

that a clinician can actually do in terms of how they are ordering things, and what a blood bank can do to try and make this better, or to prevent it?

Christine: Having detection be a little more automated or ambient or. Not require so much thought and review would be ideal. So anything that can build our digital systems better to kind of flag at-risk patients. So for example, you could build an algorithm that recognizes "CRAP." Now, if you have a person or a system that identifies the at-risk person, then you need some options. And that could be kind of reminder alerts as well. So this is kind of tying into the potential safety digitization here.

Or, you know, you've got to give some kind of tools or at least clinical policy constructs. And so, what we would advise is, maybe trigger a little more conservatively. Cancel your order. Consider alternatives. If you have an iron deficiency anemia, and the patient is not in a rush to correct their hemoglobin to maybe give their bone marrow is shot at self recovery if the only problem is a missing hematinic. Reduce your order size. So instead of that two unit red cell order, a one unit order. Some people split products. Not all hospitals will have labs that can do product splitting. So that all depends on the internal capacity. Using concentrates instead of components. And so, this might be some off-label use, but PCCs or fibrinogen concentrates instead of plasma and cryoprecipitate, respectively. Giving a slower infusion rate. So allowing yourself that full four hour post spike time to give the product, instead of zapping it in, in one or two hours.

And then, you know, this might be a little controversial, but making space for the unit that's coming in. You know, we've got rampant "pre-medication culture" across many hospitals and especially in Heme-Onc divisions. Nobody criticizes giving diphenhydramine or acetaminophen before transfusion. And yet if we put the same cap on, you know, pre-medication wise, you could argue that furosemide kind of falls into that category. So, should we make some space? A little bit of furosemide in someone who's got good kidneys, whose electrolyte levels you're not worried about may be able to accommodate the incoming red cell volume if they've had some space made first. So, 40 milligrams of furosemide could give you up to a liter of urine output. So you may not have to give so much, but, it's on the table as one of many options to make that transfusion safer.

Joe: So Christine, before we leave TACO, I think one of the things that I've heard you talk about before, and I heard you talk about in the Australia lecture, which I think is so important include a couple of final aspects about this.

And one is how comparatively easy, it seems, to trigger transfusion-associated circulatory overload. And the second is products and the ease of triggering TACO. Could you talk about those two things?

Christine: Yeah. So what's really fascinating is how disproportionately red cells are represented in TACO. And this has even when you correct for the denominators of your inventories dispensed. The median invoked volume is often less than 500 cc. We found 500 cc, but there are papers out there of 250 mL or 300 mL.

So it's a surprisingly small volume that can tip someone over, but very red cell-centric. And so the connection here may be simply the fact that red cells compared to other things like platelets, which are mostly plasma by volume or a bag of saline, which is all non-cellular extravasating material, is that the red cell is highly intravascularly confined. You know, the unit crit is 65 to 85%. So you don't have as much extravascular distribution. That stuff stays in the circulatory system, these erythrocytes. And so this may simply be mechanical, kind of mass strain in that space. Whether or not, you know, there are other factors peculiar to red cells that give you a link between the small volume required and the feature of febrile TACO is still an unanswered question. But I think there's more to explore here.

Joe: I think that that 250 mL or 500 mL volume is one of the things that makes clinicians say "That's just not fair!" Right? I mean, especially with given what we talked about before that there is some kind of a personal feeling of "I've done something wrong," maybe in this setting with that small amount of volume, again, that just doesn't seem right that would cause a problem. And, and it's part of what makes TACOs so challenging, I think.

And I do think that we need to move on and just talk quickly about TRALI. Everyone, I have done previous podcast episodes on transfusion-related acute lung injury. So Christine and I are not going to take the time to go into every little nuance and detail about TRALI or “TRAH-LI” as it's called elsewhere. Christine, have you noticed this? I think people in the US tend to say "TRA-LI" and people elsewhere say “TRAH-LI”? What’s up with that?

Christine: Yeah. You're right. And, it's so funny that you say that because I had someone who was very astute who wrote the word TRALI, ”T-R-O-L-L-E-Y" in the chart. They knew it was a thing and they knew what it was about, but they didn't know what it stood for and what the exact spelling was.

So TRALI, transfusion-related acute lung injury, 2019 was the bumper crop year for important cardio-respiratory reaction revisions. So, Alexander Vlaar and others in Transfusion 2019 published the new TRALI definition, which was an important upgrade on the previous definition.

Which had not been, done or redone, since the 15 years of its Canadian Consensus Society definition. The Berlin ARDS criteria changed in May of 2012. And then, you know, there was a desire to escape this absurdity of "possible possible TRALI." So, let's just change how we categorize "definite" versus the not so certain.

And let's kind of go over what the main "cassettes" are for criteria. So you need three criteria. In the first set, you've got to have an **acute onset with hypoxemia**. So that PaO2 over FIO2 or "PF ratio" less than 300, or room air hypoxia at less than 90% or other clinical evidence of hypoxia. With the radiography, so you've got the **bilateral infiltrates** that can be chest x-ray, CT ultrasound, with the **absence of left atrial hypertension**, or if present, it's not thought to be the contributor to the hypoxemia. And so that could be other metrics, on tap. So echo, pulmonary capillary wedge pressure, the physical observation.

So again, it's gotta be an **onset within six hours** of the transfusion, which is very interesting because the TACO definition allows you to get up to 12 hours. But the TRALI definition is a 6 hour cutoff. Now pulmonary edema or left atrial hypertension studies have to have been captured within 24 hours of the event, although the acute presentation has to be experientially within the 6 hour time window of the transfusion. And to be a "definite TRALI," there can't have been alternative ARDS risk factors or features of direct or indirect lung injury. And so, that would be things like aspiration or pneumonia, contusion, vasculitis, toxic inhalants, indirect lung injuries, so sepsis, multiple trauma, burns, pancreatitis, cardiopulmonary bypass.

What's interesting in the definition is that leukoagglutinating antibodies are not a required feature. Even though, you know, antibodies are pathognomonic or defining signatures of other immune complex diseases, you know, TTP, for example, HIT. And so I'm aware of some colleagues who kind of take issue with the lost opportunity to allow this to at least be an optional cassette. It won't make or break the definition, or I should say “not required.” So confirmation of cognate relationships are not required. Although I can't imagine anyone, if they saw proof of cognate antibody, recipient-specific antibodies, arguing against the case. It would certainly be in support of it.

Joe: Right. And I also can’t, forgive me for interrupting Christine, but I also can't imagine a blood center, when TRALI is reported to that blood center, who wouldn't evaluate the donors for those antibodies, right? I mean, we're still going to do that work.

Christine: If you have the power to do so. Absolutely. So I think in systems where... you know, in Canada, we, at the hospital transfusion service level, are not the blood producer. And so, we have a relationship with the national options, which are Canadian Blood Services, or if you're located in Quebec, HemaQuebec. So, whether the donor gets investigated is going to depend on that producers' TRALI review group decision on donor testing. So we don't always end up necessarily learning or, having input on, this donor definitely got tested and did or did not have the antibody. I think we would get information back if there was a pertinent positive, but we don't always know how the sausage got made.

So, for TRALI, the definite TRALI, this is now "TRALI type I." So that's where it's unequivocal and you've met those diagnostic criteria that I mentioned, but the previous definition of "Possible TRALI," is now winnowed down into something known as "TRALI type II." And that's not just any kind of PF ratio change despite an underlying risk factor. This really pulls the wheat from the chaff. So, "TARDS" or "Transfused ARDS," is different from type II TRALI. TARDS, if someone gets ARDS or acute lung injury within six hours of their transfusion, if they were already worsening in the last 12 hours before the transfusion disturbance, they are not a type II TRALI because they were already on a trajectory of getting sick.

However, they may have had risk factors or respiratory features before the transfusion. If they were stable in the last 12 hours, and then they had the transfusion with the disturbance within the six hour window thereafter, THAT is the person of interest for TRALI type II.

So, possible TRALI used to be used to include TARDS and basically anybody who had any kind of a trajectory before their transfusion. This is now a purified trajectory. So, type II allows for someone who has background risk factors, but those risk factors had to have been stable in the 12 hour period before the transfusion. I find this part of the definition of the most exciting, and helpful. And I feel like this is a really important advance because it does help us to cut out the TARDS, that may simply have just been worsening in temporal association, but who were already kind of getting sick already. I think the hope here is that historic possible TRALI cleans up a little bit.

Joe: So Christine, in the interest of time, I would like to just kind of have you walk us through a little bit, how you look at these, kind of big picture perspective. We've spent a lot of time on TACO reviewed a little bit and talked about some of the new things on TRALI.

So I wonder if you would just kind of big picture for us, and I hope to include one of your slides that you have in this presentation on the show page for everyone, how to look at these diagnoses and how to kind of separate them. Some practical high-level tips for, for what kind of points you in, what direction to make a distinction between the different types of TRALI and ARDS and TACO.

Christine: Perfect time to ask this with these publications, because they are important tools now and they, kind of help orient us to a better way of looking at things. Hypoxemia, I think, is point number one. Now it's going to be shared between your TRALI type I, type II, ARDS, or the TRALI-TACO overlap / "can't tell them apart" scenario. Hypoxemia is not required, you know, you can have a TACO patient who radiologically looks edematous and whose cardiovascular parameters have changed, but, you know, you don't necessarily have to have hypoxemia for TACO.

The radiologic edema is a feature for that TRALI spectrum, you know, type I, type II, ARDS, or the TRALI-TACO overlap. So radiological edema is really part of the definition. If you don't have a chest x-ray, you may infer that it's a possibility, but a reviewer of that may take issue

Timing then: So 6 hours is your window. And it makes sense for an immune-mediated event where you're infusing a live passive mediator, that's going to land on a target. So it makes sense that the window there should be observed a little more narrowly, i.e., within six hours. TACO, if you take TACO's definition of itself, rather than the TACO definition in the TRALI paper, gives you an allowance of 12 hours. I like that because, you know, you might get transfused in the evening and not realize you've got orthopnea until you're struggling for breath in the morning from having been lying down. So there's a bit of a time window difference.

The risk factors or the background features are really what help you make some sense, or to sub-categorize more cleanly. So if there was really nothing else on the table, then it may be a type I, if you lack any features of overload and didn't have anything else going on. If you had something going on, but you were stable in the last 12 hours, TRALI type II. ARDS, if you were already worsening in the last 12 hours.

And if you have congestive features, then you have to look to see whether or not you think they accountably dominate for what you saw, or can't rule out or may have been a subfeature. So if you cannot rule out or if it may have been a non-dominant subfeature, it could be this overlap situation, TRALI / TACO. But if you really think that congestion dominated as the mechanism of harm, then you've got your TACO.

So again, we look back to those cassettes that are required, in the diagnosis. So, just to reiterate, in **TACO: Respiratory distress, or edema, one of those two features or both, with cardiovascular system changes, fluid overload, or natriuretic peptide abnormality**. In **TRALI: That six hours non-cardiogenic, flash radiologic pulmonary edema with significant hypoxia, in that 6 hour window without the risk factors or underlying features**. And if it's not the underlying disease, and if it's not an off-target manifestation of immune hemolytic incompatibility or contamination of the product, if it's not the underlying illness or anything else, then you're entitled to that dustbin of "TAD," transfusion-associated dyspnea.

Joe: Well, Christine, you've given us a really great look at this. And we've spent a lot of time, obviously, especially on transfusion-associated circulatory overload. And I really appreciate your perspective, both as a blood banker and as a clinician. I think it’s going to be really, super helpful for people. So thank you so very much for being with me. I really appreciate it.

Christine: Thank you so much. I really enjoyed chatting with you and I'm so glad that you've chosen to emphasize this really important taint that remains.

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Joe: Just a couple of quick closing thoughts: Don't forget to check the show page for this episode at BBGuy.org/089 for direct links to the articles that Christine and I talked about in this episode. Also, if you have a question that came up as you were listening today, you can submit a comment there at BBGuy.org/089, and I'll be sure that Christine gets a look at it. Also, if you are a physician or a laboratorian, be sure to go to wileyhealthlearning.com/transfusionnews to get your hour of totally free continuing education credit. My thanks for the continuing education sponsorship to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as of course to Wiley Health Learning.

Also, if you have a chance, I'd really appreciate you giving the podcast a rating and review at Apple Podcasts, so that other learners can hear about Blood Bank Guy Essentials. I do still read every review there, and I really do appreciate your feedback very, very much.

I'll be back soon with more fun and interesting episodes, including an update on Rh genotyping with my friend Sue Johnson, transfusion in several clinical settings like ITP and thalassemia, and I'm even going to interview one of the creators of a very special immunohematology test, the monocyte monolayer assay (the Mighty MMA!). All of that and more is coming in 2021.

But until then my friends, I hope that you smile, and have fun, tell the ones that you love that you do, 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.