BBGuy Essentials 039: Underestimating Febrile Reactions with Christine Cserti-Gazdewich

Joe Chaffin: This is the Blood Bank Guy Essentials Podcast, episode 039.

[INTRO MUSIC]

Joe: Hi, everyone and welcome! I'm Joe Chaffin, your host. I've got to tell you the truth: I'm bouncing off the walls today! I really am. There's a couple of reasons. First, I get to share a really, really fun interview that I did with Dr. Christine Cserti-Gazdewich from the University of Toronto, and it will really help you understand the impact of febrile non-hemolytic transfusion reactions like you've never done before; I promise you that.

And if that wasn't great enough, I have some BIG NEWS! Since I started this podcast in April of 2016, I've gotten a lot of really nice emails and comments and some of them have gone kind of like this: "I really like the podcast, Joe, but what about getting continuing education credits?" Well, today is an historic episode, because this is the first of an ongoing project to offer free, that's right, I said FREE continuing education credits for listening to the podcast! One episode per month will be available for free continuing education credits. It's awesome! I've been working really hard on this. In fact I've delayed this episode in order to make this project a reality. I've been working with TransfusionNews.com and Wiley Publishing, with generous sponsorship from Bio-Rad (and they have no editorial control over this, by the way).

But here's here's how it works: Starting with this episode, AMA Category 1 continuing medical education is available for doctors. We're working toward having Self-Assessment Module, or "SAM" credits for physicians as well, some time in 2018. And laboratorians, do not think I've forgotten you because I have not! We are offering P.A.C.E. credits for laboratorians very soon; not with this episode, to be clear, but hopefully, starting with the next continuing education episode which will come out around the beginning of November 2017.

The mechanics are simple: You just listen to the episode like you usually do, whether that's on the BBGuy website, or iTunes, Apple podcasts, Google Play, whatever. On the BBGuy guy Web site (at BBGuy.org/039 for this episode), there's going to be a transcript as well as a quiz available to enhance your learning and from that page, BBGuy.org/039, you follow the link to the Transfusion News continuing education page on the Wiley Health learning site. It's all self-explanatory. You complete the steps there. You have to register (it's completely free). You do a quiz, you do an evaluation, and then you get your certificate. It's so cool!

Now, because of the fact that continuing education is, well, complicated and full of

lots of legal stuff that you have to deal with, I have to read this legalese to you, so I hope you'll bear with me through this part where I just tell you the things that we have to say:

First, a CME activity for this podcast is available through Transfusion News continuing education on Wiley Health learning. Complete the activity there to claim your CME certificate. You can access the activity page, as I said, through the Blood Bank Guy website at BBGuy.org/039. Funding for this activity was provided by Bio-Rad, who has no editorial control over the content of the episode. The two speakers: Me, Donald Joe Chaffin MD, and Christine Cserti-Gazdewich MD, disclosed no relevant financial relationships. This activity underwent peer review in line with the standards of editorial integrity and publication ethics maintained by Transfusion News the under the direction of the editor-in-chief there, Aaron Tobian MD PhD. Dr Tobian discloses honoraria from Quotient Biodiagnostics and Ortho Clinical Diagnostics for his role as a speaker and honoraria from Grifols for his role as a consultant. The peer reviewers disclosed no relevant financial relationships. Finally John Wiley & Sons, Inc. is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. John Wiley & Sons, Inc. designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

That's exhausting! So that is exciting. I'm so happy about it. And actually today's topic is exciting as well. My guest today, as I said, is Dr. Christine Cserti-Gazdewich. She is the senior author on a paper published in the July 2017 journal "Transfusion" with a great title! It's called "Feeling the burn: The significant burden of febrile non-hemolytic transfusion reactions." Christine is both a transfusion medicine specialist and a clinical hematologist, and she is an assistant professor at the University of Toronto. She's brilliant! She's so smart, and she is a lot of fun, and she has some stuff to tell us about FNHTRs that will just...burn you up. See what I did there? The legalese numbed my brain, I'm sorry (laughs). So here's my interview on febrile non-hemolytic transfusion reactions with Dr. Christine Cserti-Gazdewich.

Joe: Well hi, Christine! Welcome to the Blood Bank Guy Essentials Podcast!

Christine Cserti-Gazdewich: Thank you so much.

Joe: So I've already told the people a little bit about who you are and what you do. But I think it's it's really important for people that are learning and or are just getting started in the in transfusion medicine and clinical medicine in general to kind of hear what's gotten people to to this point in their lives, what's gotten them to to be motivated to do what they do. And for you, you have such an interesting background. So I'm just wondering if you'll quickly take us through, in particular,

what was your motivation for getting involved in transfusion medicine, of course against the context of how you trained initially?

Christine: It's a fabulous question for me at a personal level, because it takes me right back to the days when printed newspapers still existed, and when I was back in medical school. So in 1997, the "Krever Commission" or investigation into the tainted blood tragedy was published. And this saga went on for the years that I was in the beginning and of medical school, 1996-1997, and this was literally on the front page of our Toronto Star newspaper every single day. There were over a million pages of patient testimony taken from those who'd been injured by transfusions, and I found this to be so moving and devastating. And so the whole notion that something that we do, one of the most commonly performed procedures in medicine, could be this intrinsically harmful was rather amazing to me. And I felt very much, I've told others this, that I feel like a daughter of the Krever Commission because this really imprinted me. And for a bunch of reasons, I decided to migrate into hematology as a liquid system, one that wasn't confined to one body part or one ward. And then hematology allowed me to dive back into transfusion medicine, which for me was an interesting discipline, because it really has you on the pulse of what I think are the greatest dramas in the hospital, the high volume bleeders, the high transfusion-dependency individuals, and links this incredible act of civilian charity as the therapeutic (not something manufactured by a company) back to the patient's bedside and everything that we do to make that process as safe as possible got really intriguing to me. And so hemovigilance within transfusion medicine as I differentiated further, became one of my I guess hot topics as far as my wheelhouses go. So in transfusion medicine, my emphasis thus far has been on immunohematology, serology and hemovigilance. So I care a lot about adverse transfusion events and how patients today are potentially harmed by blood products, despite all the advances we've made in correcting course, making the products better and dealing with the transfusion-transmissible diseases end of things. And and as a person intrigued in immunology, it's really these noninfectious hazards and processer human safety factor hazards that are dominating, and these are certainly really interesting areas where we still have a lot of work to do.

Joe: So you are the senior author on a paper that is just fantastic. I love this paper! It was published in the July 2017 "Transfusion." The paper is called "Feeling the burn;" (Love that!) "The significant burden of febrile non-hemolytic transfusion reactions." That "feeling the burn" kind of has, from what I know of you, your sense of humor written and written all over it Christine! (laughs)

Christine: We promised to be apolitical, and that almost got written out of the paper! So I really wanted to defend the title. (laughs)

Joe: I can understand! We are going to get into the details of this paper which I think are terrific but I think, if you don't mind, I'd like to step back just a little bit. Let's

take this opportunity to help people learn a little bit about an approach to transfusion reactions in general, because I think you bring, with your clinical background, you can see both sides of this, and that's that's unique and I love that. So I want to talk about that, the approach to reactions in general, and then let's talk about the specifics of what we know about febrile non-hemolytic transfusion reactions specifically, and then we'll get into the details of your paper. You good with that? Sound fair?

Approach to Reactions in General [09:19]:

Christine: Absolutely. Great plan! I like to begin a discussion on transfusion reactions by taking a huge step back and thinking about the philosophies of why we even do this. So at three levels I like to tell students that a) Recognition matters, b) Reporting matters, and c) Collaboration matters. So the idea that recognizing a transfusion reaction, because we all lament that this is an under-recognized thing, we want our trainees to be perceptive at the bedside and in the six hours that follow any blood product administration as to any new disturbances that they otherwise wouldn't consider on their differential diagnosis. So you've got to know what you're looking for to be able to recognize it. And reporting matters because it draws the patient's injury at the bedside back to the bench and back to our connection to the provider of the blood products. So this then speaks to a public health or moral mandate on preventing what else might stem from still existing co-components that weren't quarantined, and any justification for "lookback" investigations. So this is this is the spirit of linkage; this idea that reporting matters. And that again brings us into the point of collaboration. So unless we channel everything and unless they have faith that we're going to do this, there really is no point to this. The idea of "garbage in - garbage out" means a lot in hemovigilance, because unless we've got robust data, and let's face it we're still existing and passive systems where we rely entirely on the energies of those at the bedside, we will always be struggling with underestimates and not know what the true breadth of risk is when we transfuse patients.

Joe: I think you said something...forgive me for interrupting, Christine, but I think you said something really important there that I just want to I want to clarify for our listeners. A majority of the people that listen to this podcast are in the United States, but people listen to it all around the world. So if you could tell us specifically what the hemovigilance system is in Canada, and if you're aware of how it can compare to that in the United States, can you just talk about that just a little bit?

Christine: Yeah. So Canada has a system called "TTISS" (it sounds like it should be X-rated but it's not!). So that's the "Transfusion-Transmitted Injury Surveillance System," and it came to be roughly around 1999, which was two years after the publication of the findings of the Krever Commission of Inquiry on the tainted blood tragedy. And this is a system that is federal in its primary nature. Canada's

equivalent of the FDA is Health Canada or the Public Health Agency of Canada sometimes abbreviated as "PHAC." And what this does is deputise to the provinces, the Canadian equivalent of states, provincial TTISS's, where in Ontario we have "TTISS Ontario." And so each province is responsible from the ground up for gathering hemovigilance data. And again this is completely passive, but provincial data in multi-year cycles filters up federally.

So Canada's hemovigilance system or TTISS was one of the first to join the international hemovigilance network. And there are numerous other countries that are probably even more noteworthy. You know we all lovingly reference "SHOT" or Serious Hazards of Transfusion UK. And you know in the United States, there are the CDC and AABB collaborating on trying to get at the state level, again data bubbling up so that we can nationalize our numbers. Now the FDA has fantastic reports that are uploaded annually. And you know we all open those up as soon as they come out to see what donor and recipient mortalities are as far as the blood system goes.

Joe: Yeah, but I think that the key is, throughout everything that you've said there, and certainly with what we have in the United States, and you mentioned this when you talked about your general philosophies; everything's dependent on someone recognizing, reporting, and collaborating. And without that...I mean we're all grownups here, we can be honest, right? There are steps missing in that. I think obviously up there in Canada, and certainly for us here in the United States I can speak to that.

Christine: Yeah, absolutely. Yes, so to get to material recognition of what it is we're actually looking for, I organize transfusion-associated disturbances into a triangle or a trio of things. There's the 1) "Surface skin stuff," the rashes, the allergic manifestations on one end. There's the 2) "Deep stuff," which I regard as cardiorespiratory upset, so the dyspneas and the shocks. And then 3) "Blowing your top" a kind of temperature-related event, is your febrile referrals. And those are for us are certainly the commonest reason for referral to investigate something that's gone on at that bedside. So febrile reactions are really the emphasis of the paper that we'll be going over. But each of these three things has associated with it its own differential diagnosis. Another way to look at reactions is just so that people recognize and also build into their consent discussions a description of the three most commonly encountered but minor adverse events because really reasonable people want to know. And what are the three commonest causes of transfusion related morbidity and transient related mortality and severe morbidity? So one of the things that can really kill you? So what are the top three for the minors and the top three for the things that can kill you? And we sort of go through what those are.

So you know with fevers, our first consideration is, is this a "sinister fever" or not? And by sinister fever, we're looking for these dose-dependent toxicities that could

kill a patient, that are within the product or relating to the patient's interaction with the product. And so that's namely is it a bacterial contaminated unit or is there an immune hemolytic incompatibility? And that really reflects the kinds of samples that we gather, the kind of workup that we launch to unpack that question. Of course, there's patient chart review to determine if there was an underlying mechanism for fever that was unrelated to the transfusion, where it's implicated only by the temporal correlation. And then at the end of all of that review, we try to conclude if this was a sinister fever, a fever due to the underlying condition, or as a diagnosis of exclusion, FNHTR, again the key subject of this paper. I can go on and on about what it is that we report to our hospital transmission committee, but that might be going too far at this stage.

Joe: Let's focus on a little bit on the febrile stuff because you said a couple of things in there that kind of caught my attention. I will admit that in my teaching over the years, I have I have tended to teach...not just "tended," I have flat-out taught that it is difficult at first glance to tell a, as you put it a...I forget what you said, a scary fever or non-scary fever, or high-risk fever versus a non-high risk fever or terms to that effect. I have always taught that it's difficult to tell that at first glance, and as a result, when you see something like that, when you see a temperature increase during transfusion, you should have a high degree of suspicion towards working that up and making sure that nothing significant is going on. Would you agree or disagree with that philosophy, and, either direction, can you tell me a little bit more about how you distinguish a serious or a high-risk fever versus a non-high-risk fever at least clinically?

Christine: Yeah, this is a hugely important question, and I think where we might discover a lot of heterogeneity among our colleagues in their approach to this question. I agreed with you originally, and then we've kind of gone in a direction where we stratify now our fevers for a variety of reasons. We decided, and this kind of takes on with what some other groups have said about categories of fever, insofar as low-risk versus high-risk; the AABB, Health Canada, American Red Cross, CDC, St. Jude's Children's Research Hospital; this idea that there is a low risk fever where you don't necessarily have to terminate and abort. Where you might be able to medicate your way through and finish the product, where you don't necessarily have to launch a workup, versus this high-risk fever, where there's no question you've got to cut out, stop, because there may be a dose-dependent morbidity and mortality coming. And yes, this is one worthy of gathering a lot of samples. And the reason we've gone this way is that, and this kind of speaks to the FNHTR paper itself, is that the investigation of fevers is a costly enterprise. If you're drawing transfusion serology as well as companion chemistry and hematology tests to look for hemolysis, and you're also drawing bacterial cultures, the culture bottles of which are increasingly expensive when you take the ones that bind antibiotics, you know they're resins and some of these, this adds up to a lot of sampling activity. And you know, if you have to poke the patient one more time, especially if

they don't have a Hickman or a central line that's easy to access, this is now a disincentive to say anything. And so we were worried about disincentivizing the reporting of fevers if you forced too much of a work up, and we also wanted to be cost-effective about this. So we decided to run with the lead on this idea that there's high-risk and low-risk. So what we do is if a patient has a low-risk fever, we ask that they pause, that they evaluate, they can give the patient some acetaminophen, and they can try to reinitiate the transfusion at the same inaugural standards, you know, give slowly over the first 15 minutes and check again the vitals. And if there hasn't been any change in the temperature towards the sinister category, you keep continuing until the patient proves to you that they're asymptomatic or subclinical for us what...

Joe: Christine hang on just one sec, because there's something that I think I'm missing here, and maybe you can help my really dense brain understand it. You just said that if you see one that's "low-risk"; so have you...Is there a definition of that? How have you guys made that cut off?

Christine: Important, important question. So for us...first of all so any fever is a delta 1 C temperature rise where you exceed 38 C as a result of that delta. That by itself is "fever." We dismiss referrals if the delta is less than that or if they were already close to 38 to begin with. But what for us represents a high-risk fever is if the temperature has gone to greater than 39. Anything above 39 freaks us out, and/or if the patient has physical manifestations. So if they have rigors, or if they're describing uncomfortable chills, if they've got any of those cardinal symptoms or signs of a possible hemolytic transfusion reaction: Flank pain, pain at the infusion site, nausea, vomiting, if they have vital sign disturbances, so a shock response, if their blood pressure goes down significantly, if their resp rate goes up, if they feel short of breath, if they're now hypoxic, or tachypneic. Any disturbance whatsoever be it in the symptom or sign world with a temperature that exceeds 39, that's absolutely no contest! We stop and we investigate formally in every way that we can.

Joe: OK so, I apologize for interrupting your flow. What you were saying is that if you get ones that are below that, you consider the possibility or you allow the continuation of the transfusion, is that correct?

Christine: That's correct. Now, the blood bank is notified that this has happened. And what's interesting is that some of the time, as the transfusion continues, they then become high-risk and then we stop. And so, the service is then asked to draw all the samples that they originally were discouraged from drawing. We did this, we launched this idea of stratifying high-risk versus low-risk so that we wouldn't disincentivize the reporting of what would seem like trivial fevers at the bedside at the same time as we launched electronic medical reporting of transfusion reactions. And what we had occurring after that, when we altered our policy making it easier,

i.e., patients not having to get stabbed up for workups while also going electronic to report the disturbance, we had a three-fold increase in our transfusion reaction reporting rate and that's been sustained over the last six years. So it's been a fascinating impact, because prior to that, we think that one of the disincentives to reporting was this idea of sampling-related punishment.

Joe: And we hear that a lot in the United States as well. That's one of the...perhaps the most common complaint that I get from clinicians about transfusion reaction reporting is, well first "how dare you tell me that I can't tell a benign fever from a significant fever, Dr. Chaffin, because clearly, I've practiced for 20 years and I know when it's hemolysis or not" (which I tend to argue with, but ok, never mind!). But the second thing is that "if I report this, it's going to be a delay, there's going to be a lot of stuff that ends up happening." And you're right that does have the potential to disincentivize that reporting.

Christine: Now another point on this, and this is where I feel uncomfortable with being overly liberal in forgiving people from workups is that "low-risk" fever that shows up in the first 15 minutes. If at your first checkpoint vitals, you're already mounting a fever by that extent, I'd be worried that if you're following the rate infusion rule, you know at no faster than 50 mL per hour, which would only mean you know 12.5 mL in that first quarter hour, minus the dead space like how much blood contact has really happened with the patient's bloodstream? If that small dose of transfusion is capable of eliciting a fever within such a short period of time, I don't argue any discomfort with cutting out at that stage even though by policy for us it constitutes a "low-risk" fever. So we don't want to be too discouraging of a workup. What's funny about this is now we're getting practitioners at the bedside who are asking us to work things up when the policy says they don't have to! So the tables have turned interestingly here, and sometimes we have to talk people down, we'll say, "well, you know they were 37.8 and now they're 38.3. That isn't really a significant delta. I'm telling you, don't worry about this." They may have finished their transfusion, in fact, and they only went up by 0.5. So some people are really panicky about this and others, I mean there's an incredible spectrum of practitioner response to a disturbance at the bedside. So a lot of this depends on who you're working with.

Specifics of Febrile Non-hemolytic Reactions [24:57]:

Joe: So if you don't mind let's move along and talk a little bit, let's get to febrile non-hemolytic transfusion reactions specifically, because I think we could have a lot more talk about hemovigilance and overall approach. There's a lot more that we could go into, but let's leave it there for now. So we have someone who's getting a transfusion, and they have an increase in temperature. You've kind of alluded to this already, but can you take us through just a general differential diagnosis for someone who has fever during transfusion?

Christine: Right. So I'll begin with the blood banks greatest fear or bias, which is that that there's an acute hemolytic transfusion reaction occurring and that of course informs the nature of the samples we draw. So we'll get what's called at the blood bank a "transfusion reaction specimen." But what we're doing on it is a lot of the routine blood bank-type tests, a repeat group and screen, as well as a DAT to see if there's evidence of acquired sensitization. So that address is the first thing on the differential diagnosis: Is there an immune hemolytic incompatibility? The next is, "is my product contaminated? Is this a so-called 'BaCON' or a bacterial contamination/transfusion-associated sepsis event?" The next thing is to review the patient's record to see if there's a fever due to the underlying disease, because of course we don't want to overimplicate the product. And then if all of that's ruled out then we will conclude the so-called FNHTR the febrile non-hemolytic transfusion reaction, which is supposed to be a diagnosis of exclusion. So we're not comfortable making that final conclusion until we're straight on all of the foregoing facts. The reality is that we don't always get all the rule out information. So the patient isn't always cultured, even though we ask, even though it's in our policy, the patient doesn't always have a clear chart. You know, they may not have had 5 to 10 days of vital signs surveillance already, this may have been occurring in the emergency department where there was no thermometer at home to determine if they were having fevers already. So you know there's always limitations to the data that we have. And if that's the case then we end up with these softer probability terms like "possible FNHTR," "probably underlying condition."

We'll be examining everything in the patient's record with respect to any preexisting cultures, the cultures that were done not only on the patient's blood subsequently but any other systems that got probed, because that test is a sign that someone was looking for a focus of infection. So if they'd had bronchoscopy, we'll look at sputum, BAL (bronchoalveolar lavage) findings. If they've had urinary culturing, we'll take a look at those results. We'll also review the pharmacy record to see if they've been on anti-microbials, because if somebody already started them on antibiotics the day before, we know that someone was already wondering about infection to begin with. If they were profoundly neutropenic, well, they're set up for neutropenic fever. And so these are some of the details we'll integrate and then we'll shift those probability terms. What might have been a "probable" FNHTR because it was the diagnosis of exclusion might fall down to "possible," because as we look closer at the case, the underlying disease really is a better explanation than the product.

The other bias, and this is something that came across in my training as a fellow, this idea that FNHTR shouldn't be happening with leukoreduced products, and this will take me to what is the pathophysiology of FNHTR? Because if you've got leukoreduced products, which is the case for all of Canada's components, you know we were the first country in the world to implement prestorage universal leukoreduction in August of 1999, so with that backdrop, should we even be seeing

them in Canada? When I was doing my fellowship in the United States, I was circulating through hospitals where not all of the blood came leukoreduced, and of course a nonleukoreduced unit would have that as perhaps a more eminent idea on the differential. But over here I'll tell you I still see a lot of FNHTRs in our leukoreduced blood supply and certainly more with platelets than with red cells as expected. So this takes me to speak to what are the "evil humors" that are doing this? What is the pathogenesis of FNHTR? And we boil this down into two categories. So we'll say that this is the recipient's response to any post-filtration or non-filtration residual leukocytes. So if the host is presensitized to HLA, well they've got an immune complex confrontation coming because there's white cells for them to interact with, and that will incite an immune complex or fever response. But on the other hand there is you know this idea of the "messy stew." So you've got pyrogenic mediators or cytokines, biologically active materials that accumulate in proportion to what degree of white cell contamination you have, but also the duration of storage of the product. And so we do take a critical look at was this a really old red cell? If this was a red cell fever, was it an irradiated red cell that was on the shelf and post-irradiation for maybe a little too long? And if it's a platelet, was it at the end of its life? Which is the case for most of our platelets because we want to be good stewards of a limited resource. But that does I'll say color our view of of our conclusions. So you know we really try to integrate as many variables as we can and we look at a lot of things when we go through what would for us be a case report form that we have our own institutional version of in the review of transfusion reactions. And this is a huge credit to our transfusion safety officer, who so meticulously documents all of these fields for our review when we get together in trying to decide what actually happened in retrospect.

Joe: So that is a wonderful overview, and I especially like the "evil stew" idea is that that the phrase you use?

Christine: Yeah.

Joe: That's outstanding! And I think that those two forms of pathophysiology are really important for people to understand, so let's just make sure that we're real clear on that. Now I'm going to summarize what you said and you correct me if I go wrong anywhere: You're basically saying that the two ways that these reactions happen are: 1) An interaction that occurs *after the transfusion*, when a recipient is pre-sensitized, has antibodies, and those antibodies interact with the transfused product, whether that's the white cells or whatever; or 2) It's an interaction that occurs *before the transfusion* ever happens, as the product ages, and cytokines and whatever else leads to fever is produced in the bag, and essentially at the time of transfusion, it's a transfused fever essentially. Is that a reasonable way to summarize it?

Christine: That's perfect. Yeah. And you know the other the other thing that I think

of a lot with FNHTR is that they shine heat and light on problems that the patient already has. And so, I really believe in a sort of "tipping point model" where there may be these pyrogenic mediators and residual leukocytes that have the power to directly cause them, but more often additively hasten the manifestation of the fever. So sometimes I think of these fevers as a "summit of signal." You know, the patient's already got something brewing, and that product just enables us to see it sooner. So for example, I can't tell you how many times a patient is referred with an FNHTR, and the only culture that comes out positive is the urine. So this is a person who was about to manifest their UTI, their urinary tract infection, maybe hours or days later. But there is something in the product that accelerates that manifestation, because it's cooperating with everything else that's stewing in the patient's body.

Joe: Got it. So it's acting against a backdrop of what's already happening in the patient. In a way, kind of like some of the things that we're thinking about TRALI pathophysiology nowadays, right?

Christine: Absolutely!

Joe: Something's already going on and the transfusion is just that last push over the edge.

Christine: Absolutely, I've stolen from the TRALI folks in coming up with this! It's not an original idea.

Joe: We'll call it "original" Christine, nobody will know. Nobody listens to the podcast anyway, right? (laughs)

Christine: Are you kidding? I'm a faithful listener!

Joe: That's very kind of you, very kind of you. So that kind of brings us...oh, you know, one more thing I do want to say before we leave that, because you made a point that people are asking about why these things still occur with universally leukocyte-reduced products, and I've had that question a lot here in the United States as well. And one of the things that I tell people is that it certainly has decreased the risk here in the US, but I think there's a little bit of a misconception: leukocyte "reduction" is not the same as leukocyte "elimination." There's still PLENTY of white cells in there, and they're still doing whatever they're doing. It's just that they're at a lower threshold. Do you agree with that philosophy?

Christine: What a perfect point! That also reminds us that leukoreduced blood is not a risk mitigation strategy for graft vs host disease, you know? The best we can expect, and this has been seen here in Canada as well, the FNHTR rates pre-post the implementation of leukoreduction were assessed and published in Blood. And it

really knocks it down by 50 percent, and that's an interesting number because when you look at SHOT UK, TA-GVHD did not get eliminated with leukoreduction. I mean it does go down, but when you look at the critical number of leukocytes it takes to kill people or to induce a reaction...of course, it takes a "cheering section" to pull off death. You know, you need about a million white cells to pull off GVHD in an immune-compromised host or in someone who can't deal with immune stealth (if you've got one of these homozygous haplo-identical leukocyte donors). But let's just say that you need a certain number of cells and leukoreduction is literally right at that threshold. So leukoreduction half the time will get there, and half the time won't. It literally lands on that median number. This idea of a million white cells being enough to pull off "X, Y or Zed," or in America you would say "X, Y, or Z" is really what we're facing here.

Details of Findings in July 2017 Transfusion Article [34:58]:

Joe: Thank you for clearing that up! I was like, "Zed?" No wait, I actually knew what that meant! I grew up close to Canada, so it's fine, no problem! Alright, so let us roll along, because we need to get to your paper, which is, as I said, it's one of my favorite papers of the year so far, Christine. I love what you guys did. I love the approach that you took, and I wonder if you'll just take us through it? What led you to think, "This is a paper that needs to be written? This is this is something that hasn't been done" (I'm assuming it hasn't been done). Talk through if you would what was your motivation behind doing this?

Christine: Yeah we got kind of frustrated with the fact that everything that's out there it is really on the INCIDENCE of FNHTR is and how harmless they are. How they're all grouped as minor events. And we thought, "My goodness, there's a lot of noise here!" We get 45 to 50% of our bedside disturbance referrals to investigate a transfusion reaction are febrile in nature. Now only a smaller percentage of those end up being true FNHTRs. But even if they are, you don't know that until the end of the investigation, which could be one or two weeks out. You know, you're waiting for culture results to mature, the review of all kinds of events subsequently. So, you don't have forward vision when these happen, and what you have is a fever at the bedside, and that mounts a whole cascade of health care events, and none of these are cheap. And a lot of the things that we're doing speak to two crises that are happening today. One is anti-microbial stewardship with increasing resistance, and the other is the opioid crisis. So you've got a patient who's rigoring and who has an infection, and they may or may not be neutropenic in the background. What does the ethical clinician going to do? They are going to investigate this patient thoroughly, until they know what the driver of that fever is. And so we thought, "Let's take a big step back and actually look at what these referrals for febrile reactions are doing here." We'll focus on those where we actually thought this was a possible to a definite FNHTR. So we were pretty sure, maybe not 100%, but you know we were really just selecting out the FNHTRs, and we wanted to look at what their

story was, in an aggregate statistical way. So, we really wanted to look at the consumption or resource utilization end of FNHTR, just to put a price on this, because these really weren't all that minor. And so, we decided across two hospitals which really represent more facilities than that. So, University Health Network has three transfusion locations, three separate facilities: Toronto General Hospital, Princess Margaret Cancer Center, and Toronto Western Hospital. And Sunnybrook has a number of campuses as well, but their main hospital is the Sunnybrook Health Sciences Center. So we decided because both of these hospitals are highly committed and very good at the hemovigilance that they do, we wanted to look back at our transfusion reactions databases over a three-year period from 2013 to 2015, and look at all the FNHTRs that we panned from our hundreds of reactions, and really unpack what happened with the FNHTRs. And so, these hospitals together comprised about 1500 beds, and together, the transfusion activity over this three-year period was about 180,000 components. Over 400 unique individuals suffered reactions and we counted 437 FNHTRs.

Joe: Christine, I'm sorry for interrupting. One quick question on that: It wasn't completely clear to me in your paper. Did you count all components, or just platelets and red cells or what was your...how did you figure that "n"?

Christine: Yes. So we got a little picky here, because we had virtually no reports of fevers from plasma or albumin. We cut those materials out but we included, because IVIG also had a high risk of fevers when we looked at component-specific reactions and what their nature was, we decided to focus fevers emanating off of components as defined by red cells, platelet products, or IVIG. So the cellular components and IVIG were really the denominator of exposure activity that we were emphasizing. We didn't want to dilute down the product-specific rates of FNHTR by including all the plasmas and all the albumin bottles that we dispense.

Joe: OK. OK. The only reason that I bring that up is that I think typically, and I could be wrong about this, but typically in my experience in the United States, IVIG anyway doesn't get included in the discussion in the US. Primarily I think because not every transfusion service in the United States is the place issuing IVIG. It's more commonly issued from the pharmacy, so we don't always know about it. Is that different in Canada? Do transfusion services issue IVIG?

Christine: Yes we do. It's so interesting and I want to emulate Americans so that we can offload this problem! Canadian blood banks, in fact, do bank our derivatives as religiously as we do our components. So those derivatives span everything from IVIG to albumin to the plasma-derived coagulation factors, and in fact even the recombinant factors that are meant to be the replacement for the plasma-derived clotting factors. We even at one time were banking the starches that were the substitutes for albumin.

Joe: That makes sense. When I saw that, I thought I would ask you that simply because, I mean honestly in my career in transfusion medicine in the United States, I'm certainly aware that IVIG can cause reactions, but I can't remember ever being called about it because it usually doesn't come from a place where I have responsibilities. Anyway, I apologize for that sidebar, I thought it was important to point out that difference. So I interrupted you in the middle of talking about what you guys found, so fire away! Tell us what you guys found.

Christine: All right. So we looked at three recent years up to 2015 that transfusion reactions emanating out of these high-yield products as we were saying. So the sites that we studied, there were two hospitals. But really this was four different institutions or four physical buildings comprising 1500 beds worth over those three years and we had 400 distinct individuals who manifested 437 FNHTRs on that spectrum where the conclusion was possible to definite. And these FNHTRs were a lot more eventful than we thought. So our key findings included the fact that a third of those febrile reactions were considered to be severe in their experience of them or as far as you know we saw what the health impact was. That would include fallout such as a requirement for admission, beginning new antibiotics, lots of intensive imaging, even other adverse symptoms or signs. So more than 10 percent of our febrile reaction patients also had concomitant dyspnea, for example. When we looked at the kind of fevers...

Joe: You know Christine, I'm going to be rude and interrupt you, because that really is an incredible point, that a third of these reactions that everybody thinks are just "meh, no big deal", a THIRD of them were "severe." Did that surprise you? That surprises me, I'll tell you!

Christine: Absolutely! It completely flies in the face of every systematic review or paper we read where it's stated as a given that these are, I mean it's never mentioned of course that these are fatal and we don't expect that, but that these are low morbidity reactions. And I think our findings really contest that, that thing that we take for granted. When we looked at the kinds of fevers and this was a surprise to us, two thirds of them were in that category of "high-risk" fever. We thought that the breakdown would be the complete opposite. We thought that the majority of our febrile reactions are these kind of low-grade fevers, but they really weren't. Two thirds of them merited or launched the high-risk fever protocol. 60 to 80% of the patients had blood cultures, and we know how expensive those are. One in every seven (~14%) had a disposition escalation where they required an admission if they were outpatients. A quarter of them had some kind of imaging technology applied to their chests to see if there was a pneumonia to explain what had happened. Over half of them were drugged with an antipyretic like acetaminophen. Over a third of them had antibiotics initiated. Some of them were even taking opioids like Demerol to quell seizures [NOTE: See below]. And all in all, the patients, if we take the costs for the lowest possible estimate of what the

investigation end of the pathway was averaged out to at least $160 Canadian per patient in diagnostic expenditures, and I'm excluding all the other drama that I've just mentioned as far as management tactics.

Joe: So you said Demerol for "seizures." I just want to make sure, you did you mean "rigors"?

Christine: No not seizures: Rigors! Rigors! Yeah.

Joe: That would be even worse, but I just wanted to make sure I understood. OK. Wow. So $160, you said...$160 CANADIAN; let's be specific!

Christine: $160 Canadian, yeah.

Joe: Ok. That's one of the things that really struck me with this discussion, Christine, because I'll be honest with you, if you just look at $160 Canadian, I think the cynic might say "160 bucks. Big deal! Why are we getting worried about this?" But the social aspect of it that you just said, it IS a big deal and the number of patients that were outpatients and had to get admitted with all that..we certainly know the worst place to be if you're sick is in the hospital! I'm being slightly facetious, but it's not far from that. That's a big cost, isn't it?

Christine: It's a huge cost. And now, the whole rest of the world is taking hemovigilance lead, right? We're all interested in medical error now. And you know, Canadian data recently showed that any hospitalization culminates in a 1 in 18 odds of in-patient harms. So indeed, a hospital is a dangerous place to be. And you know, despite 10 years ago now, the IOM's finding of the significance of preventable deaths in medicine from health care, you know 440,000, it didn't improve much when the BMJ published updated stats in 2016. Medical error is still the third or fourth leading cause of death in America. So, if something leads to something else, and you could argue that an overly liberal transfusion is itself a medical error, especially if it leads to patient harm that leads to hospitalization which then leads to more harm. What I'm saying is and I'm going to borrow my colleague Jakob Pendergrast's term, "cascade iatrogenesis" is what we're seeing, and that's unfair.

Joe: I agree. So, before we get to where do we take this data and where we go next, I want to hone in on a couple of things that you guys reported, because you had really, really unique...I mean, you had mentioned that you were frustrated because people were reporting incidence, and that's certainly true and you guys' focus was different. But you still had the opportunity to report some incidence stuff. So I wonder if you would just talk a little bit about what you guys saw in terms of components more likely to cause FNHTRs, maybe if you discovered an overall incidence in your setting? And the last thing and then I'll let you rock n' roll is you

mentioned that "high-risk/low-risk" thing in terms of fever and the thresholds and cutoffs that you guys use. Can you talk a little bit about what proportion did fall into that high-risk versus low-risk?

Christine: Yeah so for per-product rates, our rates were not as good as what prospective data say they should be, but overall our FNHTR per product rate was 0.24%, so about two in a thousand. And it was certainly lower for red cells, 0.17% versus 0.25% for platelets. So platelets you know almost double the odds of an FNHTR versus red cells. So that's a big underestimate. Our little graphic did show you get a kind of visual sense in terms of log scale what the relative risks are. IVIG has really wide error bars. The IVIG rate of fever was 0.19% for a patient dispensation, which would be whatever number of bottles their particular sitting encompassed. But for all products overall, it was about two in a thousand. Now that's just the FNHTR rate, that's not the overall per-product reaction rate at our hospitals, which of course would be much higher because there are all kinds of other reactions. You know 36% of our reactions are allergic, and about 20% of them are these cardiorespiratory or dyspenic referrals. So febrile reactions are really just addressing half of our referral workload.

Joe: The other question was the high-risk versus low-risk fevers in these patients that you found.

Christine: Yeah. So, we saw that more of our referrals were high-risk than low-risk. We had thought that the majority of our fever referrals are going to be low-risk fevers, but they really weren't. So, if I remember correctly, it was more than half of our referrals that actually constituted high-risk or that launched a high-risk-like investigation pathway. So even though our policy tried to dampen down the excitement of the low-risk fever, the majority of our fevers were actually constituting high-risk events.

Joe: That's really interesting. I will admit, that surprises me based on my personal practice that I would have I would have guessed that that would have been the opposite, that the majority would have been low risk. That's what you guys were thinking too from what you just said.

Christine: Exactly. So it was exactly two-thirds of our patients were actually high-risk. And that was fascinating to us, because we created an environment where there's no disincentive to reporting a low-risk fever. And still, they only encompassed a third of these referrals. So making sense of that is is difficult. So we all assume that most of the time it's a minor fever. But these FNHTRs can be pretty dramatic.

Joe: So Christine, another thing that we're seeing nowadays in I think any hemovigilance system, and as you know, you mentioned this earlier, AABB and

CDC are trying to kind of standardize these definitions, but the the concept of "imputability," the concept of "how likely is this actually to be this transfusion reaction?" It's it's something that I have often wondered about. So I'm curious: What did you guys find in terms of how many of these, or just generally, how many of these were you able to say, "This is definitely, by God, a febrile non-hemolytic transfusion reaction"? Would those numbers surprise us, I'm wondering?

Christine: Oh gosh, no! I don't think anyone would be surprised that a faint minority constituted a definite conclusion. So there were often other explanations for fever. The deeper you look, the more you find, and the more you degrade at this idea that FNHTR is the explanation. It's very tempting, and again, how do I reconcile that with this cooperative model of tipping point and adding to the patient's underlying tendency to manifest a fever if not then then sometime later? So, there's this idea that FNHTRs might just be shining a light again on on other causes. I would say that, it's actually figure 3b in the paper that shows what the bars are in their girth for possible, probable, and definite, and you'll see from the bars that we're well under 20%, probably 5 to 10% for definite. But the majority, easily half, and up to 60% depending on which site we're at, and time and so forth, because there's noise in the signal, but let's just say for all comers, half of our FNHTRs, we're only calling them "possible." We can't be sure. Again, we're sort of shooting ourselves in the foot the more we look, because we're making our stats look worse! We are signifying our uncertainty by the depth of our investigation because we often do find other things. I am skeptical when other sites say that "all of our fevers are due to FNHTRs." I know that that can't possibly be true because we know how sick patients are who get admitted and they always have other stuff going on. There's nosocomial infections, there are the community-acquired infections they've come in with. These are pronounced events in health care, and so I think transfusions just really exacerbate the ascertainment of those events.

Joe: OK, well, I would love to give you the opportunity to just kind of bring this home for us Christine. We've talked about a lot of really important and interesting stuff, and we've taken a dive into your paper and looked at your findings and the importance of your findings. So I guess my last question for you is: Where do we take this from here? If febrile non-hemolytic reactions are a problem, as you guys have clearly shown that they are, well, what do we do next? How do we how do we make the situation better?

Christine: So you know we didn't write that paper to say you shouldn't be doing all of these investigations. There's no question that if someone mounts a fever, it's a serious concern. And that is not what we aim to change. What we aim to change is every unnecessary transfusion that was the foundation of that fever that didn't have to happen, that then led to all these other process changes. So I'm really glad that you asked that question because although I guess that's a bit of a political or moral mission, but if 20% of transfusions are inappropriate and one of Jeannie Callum's

students, Jordan Spradbrow, recently published a paper re-auditing not just our hospitals but a larger number of them. If inappropriate transfusion is occurring at that pitch, and FNHTRs are this common, this cumulatively becomes important. And this is as important a message as recycling is. If you don't believe that every aluminum can counts, well then, you're not going to buy the argument. But if we believe in the cumulative strength of numbers, fevers occur commonly, transfusions occur commonly, you can cut this down, you can cut that down, the stem of all of this, or the spirit of all of this should be taking a step back from that transfusion order and saying, "OK if this is too liberal, instead of a two-unit order for a hemoglobin of 7.5, maybe the patient doesn't need a transfusion or maybe it's just one unit." You know, every product adds risk. And so, either don't transfuse or transfuse less. And that may actually be the best way of dealing with this because in our paper we didn't offer a solution to prevent FNHTRs other than to go way back to step 0 or step 1 and think again about that transfusion order. And so it's a tiny message that's embedded in the conclusion sentence. And in the discussion, but I'm hoping that our readers kind of sense that, because we can't we can't say that changing your order structures is going to deal with that problem, because scientifically that's not what we did. But it is a segue into re-evangelizing conservatism.

Joe: Boy I absolutely could not have said that better, Christine! I could not possibly agree with you more. That is an awesome, awesome conclusion and I'm right there with you. Well, Christine, this has been a really, really terrific look at this topic. I want to thank you. I've learned some stuff here today, and I am sure that our listeners have learned some stuff as well, so thank you so much for being here!

Christine: I am so grateful for the opportunity. Thank you for the interest in this paper.

Joe: OK everyone, that is it for today! Just a reminder: Go to BBGuy.org/039, and with today's episode that's even more important than usual. There's a transcript of the episode there, the link to get your continuing medical education credits if you're a physician. Again laboratorians, it's coming soon, with hopefully with the very next episode for P.A.C.E. credits, and there should be some quiz questions there as well to help solidify your learning. My humble thanks to Dr. Christine Cserti-Gazdewich for appearing on the podcast! She was awesome! I was so glad to have her. Thanks to each of you for listening, and for your feedback. Next time you're on a computer, as I always remind you, just if you can open iTunes, give this podcast a rating. It really helps us get it in front of more people. So that is all for today. Thank you again, and as we close my usual reminder: I hope that as you go through your day today that you'll smile, that you'll have fun, and above all, please, never EVER stop learning. Take care. We'll catch you next time on the podcast.