# BBGuy Essentials 066:
# IgA Deficiency and Anaphylactic Reactions with Jerry Sandler
***Released April 10, 2019***

**Jerry:** This is Dr. Jerry Sandler, and this is the Blood Bank Guy Essentials Podcast.

**Joe**: Hi, everyone! Welcome to Blood Bank Guy Essentials! This podcast, as I hope you know by now, exists for just one reason, and that's to help you learn the essentials of Transfusion Medicine. This is episode 066. My name is Joe Chaffin, and I'm super-glad to be your host. I have a really interesting interview today with Dr. Gerald Sandler from Georgetown, and this interview might shake some what you think you know about the dreaded, the awful, the TERRIBLE anaphylactic transfusion reaction!

But before we get there, you should know this is NOT a continuing education episode. You can find other episodes where physicians and laboratorians can get continuing education credits for free at BBGuy.org/podcast. Just look for episodes that end with the letters "CE." You can also find those continuing education episodes at wileyhealthlearning.com/transfusionnews. The continuing education episodes at that Wiley Health Learning site are brought to you by TransfusionNews.com and Transfusion News is brought to you by Bio-Rad, who has no editorial input into this podcast.

For today's interview, I wanted to invite someone whom I have known… sorta…for a really very long time. Dr. Jerry Sandler is a professor of pathology at Georgetown, and almost needs no introduction, and I'll tell you how we met in just a minute.

First, though, let me give you some thumbnail thoughts on our topic, because I think it's important for you to have a background on this. Going all the way back to the first report, which was in 1968, Transfusion Medicine practitioners and clinicians have really been aware of an important association between IgA deficiency and anaphylactic transfusion reactions. Now, IgA deficiency is really common, it's like the most common primary immunodeficiency, and we think there are probably lots of people walking around with IgA deficiency that don't even know they have it (because they don't have any symptoms). But IgA deficiency can be different in different people. Some just have low levels of the antibody and no symptoms, while some completely lack IgA and may have significant symptoms. Some of those who totally lack IgA can make *antibodies* against IgA (we call that, shockingly, "anti-IgA"). In theory, when a person like that is exposed to IgA, like when they have a transfusion, they can have near-immediate shutdown of their airways, collapse of their respiratory system and their blood pressure. That cataclysmic event is commonly called an "anaphylactic transfusion reaction." Now, to be more formal and to be more precise, the standardized name for that reaction is actually a "severe allergic reaction," but everybody knows what you mean when you say, "anaphylactic reaction."

To be clear, for you learners listening to this podcast, what I just described is exactly what you should regurgitate on an exam if someone asks you about severe allergic/anaphylactic reactions. However, as Jerry is going to tell us, the reality is that it is REALLY uncommon to find a patient who truly has anaphylaxis after transfusion, and then, when you do, the vast majority of THOSE do not have IgA deficiency with anti-IgA. Further, having IgA deficiency with anti-IgA does NOT mean a patient is definitely going to have a severe allergic reaction when they are transfused! It's really important, because blood banks spend lots of time either washing cellular blood products to remove IgA, or trying to get plasma from IgA-deficient donors (remember, you can't wash plasma!) for patients with a history of either IgA deficiency or of anaphylactic reactions.

Jerry has had a front row seat to this discussion in his previous role, during his time at the American Red Cross, as he will tell you about, and he has some very strong opinions that I can't wait for you to hear.

So one last thing before we start: I first met Dr. Sandler well over 30 years ago, when I was a very young and incredibly dumb pathology resident at Walter Reed Army Medical Center in Washington, DC. I was fortunate enough to do an elective rotation at Georgetown, and I met Dr. Sandler and saw him in action first hand then. Seeing Jerry's brilliance is one of the biggest reasons I fell in love with Transfusion Medicine. Here's the amazing thing about that: Jerry actually *remembers* me! I'm pretty sure that means I was probably super-annoying, but it's pretty astonishing that he remembers me!

Anyway, I'm enormously happy to bring you an interview with someone who made a huge impact on me when I was a young physician. Here's my discussion with Dr. Jerry Sandler on IgA deficiency and anaphylactic transfusion reactions.

**********

**Joe**: Jerry, welcome to the podcast! How are you?

**Jerry**: I'm well today! Thank you.

**Joe**: It's so great to talk to you! I do want to tell you, and I've said this to you before, that your impact on me when I was a young pathology resident is greater than I think you'll ever know. And I think everyone listening to this podcast should know that one of the reasons that I do what I do is because of the impact that you had on me when I was just learning how to be a pathologist and had no idea that blood banking was what I wanted to do. So thank you for that, sir.

**Jerry**: Well, thank you for kind words. You should feel very proud about the way your career evolved.

**Joe**: That's very nice of you to say. I'm so excited to talk to you today, Jerry, not only because of our shared from long ago history, but this is a topic that I think is really, really fascinating. As a blood center medical director, I get calls fairly often about people wondering about anaphylactic transfusion reactions and the association with IgA deficiency. And I think it's probably fair to say, you can correct me if I'm wrong on this, but I think it's probably fair to say that you have written more about this entity and this association than perhaps anyone on the planet. So I'm so excited to hear your thoughts on this… Do you think that's right, Jerry, you've probably written more about this than anybody else? Don't you think?

**Jerry**: I don't know for sure, but I can say I've written a fair amount, in two phases, and I'm sure you'll want to get into that. Phase one, when I was at the blood supplier level and was supplying IgA-deficient plasma and dealing on that side. And then phase two, when I moved to a university hospital and was actually seeing patients and making decisions about anaphylactic transfusion reactions.

**Joe**: Why don't we start, Jerry, if you don't mind, with just the definition of an anaphylactic transfusion reaction, just to make sure that everyone is with us and on the same page? So when we use that phrase, "anaphylactic transfusion reaction," what are we talking about, regardless of the cause? How do we define that?

**Jerry**: Well, today, 2019, it should be defined clinically as a catastrophic reaction that has been precipitated by a transfusion of red blood cells, plasma, platelets, or Cryo, possibly an injection of IVIG, or even an injection of just gamma globulin. That is the setting, and it's primarily a pulmonary reaction of bronchospasm, laryngospasm, shortness of breath, collapse. It's a catastrophic diagnosis that's made clinically. The issue I think got confused, because in 1968, the definition of an anaphylactic reaction in the original report that made the association with IgA deficiency and anti-IgA was if, I think it was six or eight myeloma-coated red blood cells in a hemagglutination assay were agglutinated by plasma...these were IgA myeloma proteins taken from patients. And that was the definition. It was a *serologic* definition and we'll be getting into it. I think that's clouded the subject.

**Joe**: Let's stay on that for a second, the clinical presentation of a patient. Is this something you expect in terms of a classic definition anyway, early in the, in the reaction, is this something that happens, you know, a couple of hours after or is this something that's an acute dramatic presentation?

**Jerry**: Well, it is so rare that I have probably in the course since 1968 when I finished my training and went in, and that's more than 50 years ago, I have seen less than five true anaphylactic reactions. I have seen well more than a hundred people get some really severe adverse reactions at the time they're receiving a blood transfusion. I am sure in retrospect that some of

those early reactions were TRALI. I think some that I've seen recently where the white count has gone down very dramatically were TRALI. I think some of the others were totally unrelated to the transfusion, and were related to catastrophic bleeding and other events. But in terms of the timing, it's like penicillin. It's like a bee bite, it's not something that's going to happen two hours later. If it's truly anaphylactic, it's going to happen within a matter of minutes after the allergen has been presented to the circulation.

**Joe**: I'm anxious to get to the history and the part that you've played in the overall discussion about the association with IgA deficiency and anaphylactic reactions, Jerry, but one thing I want to make sure that we hit before we go there: Is there a difference between the anaphylactic reaction when someone takes penicillin or gets a bee sting and the anaphylactic reaction from blood transfusion, for example, there's a very clear IgE association with the bee sting/penicillin stuff. Do we have that or do we have, do we know whether IgA...IgE, excuse me, is the villain in anaphylactic transfusion reaction?

**Jerry**: You put your finger right on the key point. That's the key point. The penicillin/bee bite reaction is an immediate degranulation of mast cells precipitated by an IgE antibody. Very, very well described by standardized laboratory testing, and that fits into the constellation of immunologic observations in allergy. Allergy anaphylaxis is an IgE-related event. **The association of IgA and IgA deficiency / anti-IgA has been defined from the original observations by a "hemagglutinating" antibody that has not been studied by class**, but IgE doesn't do that, and there's only one or two papers, 30 or 40 years old, of a single case report or maybe two, where someone did some IgA testing, and didn't have the typical IgE findings that you find in penicillin allergy. So we're dealing, when you say, “Is this IgE?”, the answer is “No!” The test that's done by laboratories is a hemagglutinating antibody. That must be an IgM, but it even has not been studied to see what it is. So not IgE.

**Joe**: Jerry, I think we should take a little trip back in time and let's hear about how this has come through in your particular career. Everyone, just so you'll know, Jerry has already alluded to this, but I think it's fair to say that over the course of time, Jerry has come to a somewhat different position perhaps then he used to have though, from from reading your, some of your previous things, Jerry, I think that a little bit of doubt crept through even back in your older stuff, but I don't want to spoil it for everyone and I want to let you tell the story. So let's hear how your involvement came into play, I think it was when you started at the Red Cross, is that correct?

**Jerry**: Yes, in 1978, I relocated from a previous 10-year career as a clinical hematologist and came to the American Red Cross as the medical director of the National Reference Laboratory, which included a laboratory that was already doing anti-IgA and IgA testing using the, at that time, 10-year-

old method, for measuring using passive hemagglutination and passive hemagglutination inhibition assays. So I come into the job at Red Cross headquarters and there are requests coming in relatively frequently: "We need IgA-deficient plasma," or "We need blood samples on this patient to be tested for IgA deficiency and anti-IgA," which was an ongoing service at that time by the National Reference Lab of the American Red Cross.

So I got up to speed as I did with a lot of things, by writing some reviews. I went back to the original report by Girish Vyas and Herb Perkins and Hugh Fudenberg. That was a 1968 paper [NOTE: Vyas GN, Perkins HA, Fudenburg HH. Anaphylactoid transfusion reactions associated with anti-IgA. Lancet 1968;ii:312-5]. That was the first observation making this association. I picked up, as a clinical hematologist, my Mollison; I had the ninth edition at that time and there was basically a 10 year review of cases of anaphylaxis associated with hemagglutinating anti-IgA in Mollison's reports. So I just followed what was going on. Wrote a review, and said, "Here is the background. Here is the assay, and there are a few cases of this. And we at the National Red Cross have the capability of testing donors, identifying donors who are deficient in IgA and whose plasma agglutinates in a way that has been the standard for anti-IgA definition."

So I continued to do that. Physicians in American Red Cross blood services and in hospitals would send samples to our laboratory at the National Red Cross, and we would do two things: We would test for IgA deficiency, anti IgA with hemagglutination-type tests standard at that time. And then we would supply plasma from donors who had been identified by testing to be deficient in IgA. And then came about 1990, and I said to the team I was working with in that lab, "You know, we've done a lot of testing and what have you, let's summarize it and do a definitive article on this." And at that time, we had about 32,000 donors who had been tested. And I'm looking now at the article that we published in journal "Blood" in 1994 [NOTE: Sandler SG et al. Hemagglutination Assays for the Diagnosis and Prevention of IgA Anaphylactic Transfusion Reactions. Blood 1994;84(6): 2031-2035]. And we found that about 17% of the plasma samples that were sent from physicians in Red Cross blood centers with a suspected diagnosis of IgA-related anaphylaxis did have IgA deficiency and anti-IgA, which meant that about 83% of the time, those physicians missed the diagnosis, that it had nothing to do!

So we started with that observation: 83% of the time someone in a hospital says, "You know, we just had an anaphylactic transfusion reaction and we'd like to send the plasma," and then the job at the blood center for the medical director was to say, "Well, tell me more about it, because I don't send things up to the reference lab unless I think they're valid." And then that screening was done, and the samples came pedigreed to us, but **only 17% of the time did they make the criteria of IgA deficiency with anti-IgA**. Okay. So that was one data set.

Then we had another data set. We had a data set of 32,000 healthy blood donors whose plasma sample had been tested by the very same assays: Passive hemagglutination and passive hemagglutination inhibition that we used to make the diagnosis. And we found that **1 in 1,200 healthy blood donors had IgA deficiency with anti-IgA** by this method. Wow!

**Joe**: Wow!

**Jerry**: We took the number of transfusions that were being done in the United States at that time and divided by that number came up with a number that if these tests that we were doing and our laboratory and using them to diagnose a relationship, if they were accurate, then when we should be seeing 60 cases of transfusion-related IgA-associated anaphylaxis every day! In other words, the assays were terribly inaccurate and made an extraordinary over-diagnosis.

And then the third observation, of course, was the reason this was happening was the event anaphylaxis and the suspicion that it was associated with the blood that was going in at the time and so forth was so rare that no one institution, even a very large hospital, just didn't have enough to do any kind of clinical trial or have a series. That all of the cases that were published were individual case reports. Virtually none of them described how they did the testing. And many of them didn't in fact have a method that we would have considered equivalent to the one we were using. So we became exceedingly skeptical of the relationship of IgA and anti-IgA with anaphylaxis.

**Joe**: Wow. Your 1994 article that you referred to (and everyone, I will have a link to that article on the show page for this episode) is very, very sobering, especially with what you were just saying about how 83% of patients that were thought to have IgA related anaphylaxis didn’t, and that 1 in 1200 healthy donors should have been set up for IgA-related anaphylaxis.

So Jerry, just before we go from where you went from there and and take a quick discussion of the limitations of the passive hemagglutination tests that you are describing, I just want to make sure everyone is right there with us. So at at the time when you wrote that article in 1994, the thought process was that a person who was at risk for IgA deficiency-related anaphylaxis was not just someone who had IgA deficiency as defined by having fairly low levels, but someone who had severe IgA deficiency, almost undetectable, and the presence of a detectable hemagglutinating anti-IgA, which as you described is not necessarily IgE, in fact, probably isn’t. So is that a fair way to describe where we were at that point, that in order to be at risk for IgA deficiency-related anaphylaxis, you had to have severe deficiency and anti-IgA?

**Jerry**: Yes. With regard to deficiency of IgA, at that time there were basically two definitions, particularly in pediatric practice. There were children with

recurrent infections and were tested in immunologic labs, and if they had 5 mg/dL IgA in their plasma, that was considered to be sufficiently low, to start them on some sort of immunoglobulin replacement therapy. So if you went to a clinical lab at that time and talked about IgA deficiency, you might be talking about something at the level of 5 mg/dL. The definition of IgA deficiency that we were using at the National Reference Lab and other labs that were doing this for transfusion-related anaphylaxis, were using assays that probably were accurate at the level of 0.05 mg/dL, which is essentially none! In other words, just using basic immunology, if you are making an alloantibody that is anti-IgA, you probably do not have IgA yourself, and 0.05 mg/dL, which was the lower limit of the assay, was probably absent. You just [DON'T] have it. And the surprising thing of course is that's a lot of people who are absolutely deficient using that hemagglutination assay, which was probably incongruent, that is to say, if children were highly symptomatic with 5 mg/dL, it's hard to believe that there is a very large population out there, at least 1 in 1,200, that has ABSENT IgA. One would think that those people would be symptomatic if the assay was an accurate assay.

**Joe**: You have written since then, and you've expressed to me directly your concerns about that particular assay, the passive hemagglutination assay and the passive hemagglutination inhibition assay. Would you care to just kind of give some thoughts on that, on the limitations of that particular test, which I know you were involved in using for a very long time. What are your feelings about that particular test in this context?

**Jerry**: In 1991, with a little overlap, I transitioned to Georgetown University Hospital and I was medical director of the transfusion service. So I was now in a different situation, being called occasionally for an allergic reaction or a pulmonary reaction, other things. And so I kind of kept my eye open to see anaphylactic reactions. And since then, from 1991 until now, I might've seen two, three, four, five, not very many that I would put in the category of a penicillin or a "bee sting" anaphylaxis, using current clinical diagnosis. So I became skeptical, increasingly skeptical about those assays that we had at the National Reference Lab, which were the identical assays that we used to define the relationship. In other words, it was fairly well accepted in the medical community from 1968 going forward that there was a valid relationship between IgA deficiency and anti-IgA, and transfusion-related anaphylaxis. So to change the assay didn't seem very logical. It seemed if you wanted to be credible, someone says, "I think I got what's in the literature, here's a plasma sample." If I am going to say, "No, you don't," and I'm using a different assay, then people would say, "Gee, I wish you would be using the assay that defines this relationship, because I really think this meets the criteria." So we kept the assay because people wanted it.

I would say my hesitation to accept this increased as I left the laboratory environment and went into the clinical environment and saw the absence,

and then started asking my colleagues, Mindy Goldman, Jeff Winters, others who had laboratories, and they said, "Well, yeah! We're kind of seeing that too." Which leads up to where we were when I published the more direct, complete position in January of 2015.

**Joe**: You did have some things that were published in the interim, Jerry, including you and Dr. Vassallo, Ralph Vassallo did a tag team in "Immunohematology" in 2004, I believe, as well as a kind of a, for me, a landmark, "How do I manage patients suspected of having had IgA anaphylactic transfusion reaction?" paper. That was in January 2006. So what I'm curious about is, between 1994 and then when you published those papers in 2004, 2006, and then the 2015 paper where you, I mean the title is, "The entity of IgA-related anaphylactic transfusion reactions is not evidenced based," was your timeframe or was your development of your thoughts gradual over that time or did you feel mostly the same way as you did in 2015, and just took a while to get to the point where you were ready to come out and make that strong statement?

**Jerry**: Let me just look at some of the papers I've got in front of me here. I'm looking at one that came out, the one in 1994 says, "PHA for anti-IgA lacks specificity for identifying persons who are truly at risk for anaphylactic reactions. The consequence is an over-diagnosis of IgA anaphylactic transfusion reactions." So that's in the 1994 paper. And then, from there I go to 2004, and I have a paper then in "Immunohematology": "IgA anaphylactic transfusion reactions are uncommon, and the majority of clinical diagnoses are not confirmed by the detection of anti-IgA in the patient's plasma." And then I did an editorial, so that's 2004. The world is still kind of skeptical, so I did an editorial in 2011 and that was in journal "Transfusion," which says, "If these laboratory test results were specific and truly predictive of an anti-IgA related transfusion reaction, we would observe more than 60 anti-IgA related transfusion reactions every day in the United States."

Well, at that point, I called the persons responsible for the American Red Cross National Reference Laboratory, which was the one that was doing the testing. And I've now left, I'm over at the university hospital and I say, "You know, guys, I see you're still offering in ads in journal Immunohematology that people can send the plasma sample to you and they can get a hemagglutination IgA level, and an anti-IgA. You know, aren't you persuaded that you should just say there's no need to do this anymore?" And if my memory is accurate, that conversation was something like, "Well yeah, you're probably right. But the people out there, all of them just aren't persuaded, and a lot of them still want this test for one reason or another. So thank you. Thank you for your submission and we'll consider it." But so far as I know, as late as today, one can get those assays performed.

So at that point I contacted my colleagues, Anne Eder, who was the senior VP at the Red Cross over the laboratory, if I'm not mistaken; Mindy Goldman, who was at the Canadian Blood Services in Ottawa, Ontario, Canada (and they were doing the test in Canada); and Jeffrey Winters who was at the Mayo Clinic, and his lab was doing a lot of IgA testing. and said, "What's your experience?" And they said, "Well, you know, I think you've got it on the right track. We're not finding this." And they gave me their data and we agreed that we would publish the paper in 2015 and just step up the language. The academic words that we had been using previously weren't apparently as persuasive.

So, I guess I'll tell you that I'm the one who said, “I tell you what, let's begin this by going to Hans Christian Anderson and tell the story of the emperor who marched with his new suit that really wasn't a new suit. It was nothing. And everyone just kind of went along with that until an innocent kid said, ‘You know what? He's not wearing anything!’” And that's so the readers understood that we were saying, "You know, why do you people follow this? There is no ‘new suit’ out there. There is no connection." So we began the article with that anecdote as a way of trying to put into colloquial language the fact that we just don't think that link is evidence-based.

**Joe**: Well and I would HIGHLY recommend to everyone listening to this podcast to read that commentary. As Jerry said, it is in the January, 2015 edition of the journal "Transfusion." There will be a link to this, as I said, on the show page for this episode. You've been banging this drum for a while and it perhaps took the "emperor's new suit" analogy to get people to pay attention a little bit. I have to ask, what has been the feedback for you since you put that article out, since the four of you put that article out?

**Jerry**: I have had no personal contact with anyone who has the resources to resolve this. That's really what the problem has been. You know, I would like to be able to say that someone's called me and said, "You know, I've got plasma from 10 patients with this, and we're going to test it with a variety of methods and what have you." No one seems to have multiple assays or one good assay, and if they're testing using hemagglutination, no one seems to have an IgE or a [inaudible] or anything in that category to apply.

There's still the problem. Someone has a patient, let's say, and then just to give you an example, here at Georgetown, a physician has a patient heading for surgery and the physician witnessed what he considered to be an anaphylactic reaction to a previous transfusion. And he really wants to know if the patient can be transfused. The only way that I think you could dissuade that person is to do the assay and show that the person has normal IgA or doesn't have anti-IgA.

Now what do we do if someone needs plasma? And I'll tell you our experience. I have to mention a brand name because there's only one brand name that has this product available in the United States. And that is that Octapharma makes a product known as Octaplas. This is pooled plasma, solvent-detergent treated, at 200 mL volume. Now this is the equivalent of fresh frozen plasma, pathogen-inactivated. But the real advantage of this, not only that it's pooled, so there's anything aberrant in one bag of plasma, it's been diluted out. But most importantly, it's filtered so that it's clear, like saline, it's yellow-colored plasma, but it's crystal clear. No red cell fragments in there, no leukocyte fragments, no stray platelet fragments. This goes in just like saline. And when we have used this in patients who have this history of anaphylaxis, we have never had a reaction. And I can say I've done this more than a half a dozen times. Because there is an issue here. If someone has a true anaphylactic transfusion reaction, there's a concern. That person probably does have an immune reaction to something in the bag. It may not be IgA.

So my quarrel is not that the entity of [transfusion]-related anaphylaxis doesn't exist. It exists. It's a scary reaction. It's been observed by decades of physicians. We know that's an entity. My quarrel, of course is that I don't believe it is associated with IgA or anti-IgA. And most importantly, I don't believe that doing those tests identifies a person who has a risk of anaphylaxis. *[NOTE: The edit in the first sentence of this paragraph is at Dr. Sandler's request based on his intent. He said, "…IgA-related anaphylaxis" but as is clear from the rest of this interview, he intended to say, "…transfusion-related anaphylaxis"]*

I also think that the Red Cross experience (which is someone has had that reaction and they need plasma, so you go to the Red Cross and you get a bag of IgA-deficient plasma), that plasma has come from someone who's had a half a dozen bags of their plasma transfused to six people or more without any adverse reaction. So the experience of, "Well, I had a terrible reaction when I gave standard plasma to my patient. I got this IgA-deficient plasma from the Red Cross years ago and it just went in just fine," that does not satisfy the fact that because it was IgA deficient, it establishes the relationship with IgA! All it says is, if you take plasma from someone who's given multiple units without a reaction, it works.

**Joe**: Before we get into some specific scenarios, I wonder if you would talk a little bit about something that we've danced around a little, which is that, and you said very clearly you do believe that anaphylactic transfusion reaction is an entity, but you question the IgA deficiency association. I get that. But if it's not IgA, has there been any discussion or thought about what it could be? What's the differential diagnosis when someone does have an anaphylactic transfusion reaction?

**Jerry**: I have gone over the history of 40 case reports that are in the literature, there's a paper that we published. Let me see when that was…that was in

2003. We looked at 40 cases that were in the literature at that time. Well, that's what we really want to start. To answer your question. For example, for example, there was a paper that's published, a fatal reaction in someone who is IgA deficient, and the autopsy on that person did not show any signs of anaphylaxis, that is laryngospasm, bronchospasm, or any of those signs. In fact, the person had a myocardial infarction. God knows how that got in the literature, but it's published. It's referenced in many of my papers, because that is the quality of the diagnosis of anaphylaxis in many of these case reports. So to start to answer your question about anaphylactic transfusion reactions. I want to point out that many of the case reports, if you look them up in the literature and read them, they don't meet criteria for what I call bee sting/penicillin type of anaphylaxis. So that's the beginning.

As I indicated a little bit earlier, I may have seen or came after the event of a half dozen since 1991 when I came back to the university here. And, I would say that since 1991, probably half, that would be three, are probably true TRALI. I would say that I was called and someone had a really severe reaction, shortness of breath and the whole thing, we didn't in those days get x-rays. So we didn't see the "whiteout," and we didn't measure the white blood count, which typically will drop in a case of true TRALI. So I would say that of half the cases I've seen here, I probably was looking at TRALI before TRALI was known as a clinical entity. I saw probably one in those decades of a latex reaction. I think there was one that we found out later by taking a piece of the glove of the attending nurse, I guess it was, and sticking it on the back of the person and got a really bad reaction, and then send the patient to a dermatologist who did a proper test and that person was allergic to latex and that would be 20 years ago.

So, I think that there have been entities since, let's say, the 1990s, TRALI, latex allergy, and other things that have come in. But I would say that most of the reactions that I've been involved in and that I've reviewed in the literature do not meet current criteria for a true anaphylactic bee sting/ penicillin type allergic reaction.

**Joe**: As I look back at some of the articles that you've written, as I mentioned before, you did an a wonderful article in January 2006 "Transfusion" where you describe "How I manage patients suspected of having had an IgA anaphylactic transfusion reaction" [NOTE: Transfusion 2006;46:10-13]. And I wonder, you gave three specific scenarios in that paper and they're excellent. But I wonder if you are looking at this now and you were writing this paper now, I don't know if you would split this out into multiple different scenarios, but I just wonder how you would approach people in these cases. For example, people that have a history of anaphylactic or anaphylactoid reaction and you need to transfuse them now or you have a little time to work them up. What are the options and what are kind of the ways that you would approach patients in that scenario?

**Jerry**: The first consideration here is that the only place that we transfuse is in a medical environment. So, I would say, "You're going to do this in the outpatient, or is it going to be an inpatient transfusion?" And in either case, it's really easy to say that because this person has a history of anaphylaxis, no matter what we're doing, we're going to have to address the anaphylactic aspect that this person has. So if it's going to be red cells, it's easy to wash the red cells and that would be safe in terms of anaphylaxis. Red cell transfusions don't cause anaphylaxis unless you're missing the ABO blood type. So, no, we were not going to be doing red cells. This is a person that just needs plasma.

And at that point I would say there are some options. Is there time to get the test? Can we do an IgA and anti-IgA test? "Sure. Plenty of time." Well, there's no harm in doing that because if we get negative results, that should make it easy for the clinical team to just give conventional product, because the information is not accurate. So we could just do the test, but let's say that the question came up because it WAS done and they have a clinical laboratory IgA deficiency of 5 mg/dL. I would say, "Well, send it to a national lab where you can get the type of test that's been associated with it." And if that comes back negative, we're off with that.

But if it's plasma, let's say, well what we're dealing with here is a factor XI deficiency person, and that person is going to need plasma in order to have a procedure done. I would then as I indicated, say, "The easiest thing to do here is just get some Octaplas." It is the safest plasma to be using in this case, not because of the IgA issue, but because it is just a very carefully filtered, pooled product that will go in. We don't know what the allergen is that's causing this, but a very clear filtered product would be the safest. And then I would always add, "Look, you want to get all the team comfortable, just have them take a vial of epinephrine, 1:1000, don't unwrap it, don't open it. Have a syringe there for the doctors." It won't hurt because this person has a history of anaphylaxis. So think you're trying to control the anaphylaxis; forget the IgA aspect.

**Joe**: So Jerry, I think that that what you just described is a great description of the patients with histories of reaction and and trying to figure out how to manage all that. I have no heartache with that. The one scenario that does come up for me fairly often though is the patient who walks into the hospital and says, "Hey everybody, I've been told I have IgA deficiency and I could die if I get a transfusion!" I get those calls actually fairly often in my blood center. I wonder how you respond to that. The patient who knows or has been told that they have IgA deficiency but maybe has never even been transfused and almost certainly has had no workup for anti-IgA. How do you respond to those scenarios?

**Jerry**: I would divide that into two scenarios. One, the person is in the emergency department and they're getting ready to give a transfusion and the person gives that history. And the other scenario, which I'll get to in a minute,

would be the person's been told, "You're going to have to have your hip replaced and I'll schedule you for two months when I have time on my schedule." So I'll get back to the hip replacement.

Let's take the person in the emergency department who has bled down and is about to get a blood transfusion. And I would, in that situation, try and determine whether there was a true anaphylactic reaction. "What happened? What were you told?" "Oh, I got hives all over the place. I just had terrible hives and they gave me Benadryl and it was just an anaphylactic hive reaction." So if, you know If you don't have a real valid history and the person's never been transfused, I would just say, "Look doc, your patient here has got a problem. You've got to give something, but the most I would do is just make sure you know where the epinephrine is and the syringes and go with what you have and do it." Now in my particular hospital here, we have the Octaplas pools, crystal clear plasma. And I would say, "You know, the smoothest transfusion of plasma is this filtered product. So, it's so easy to give it, and it would define whether he has IgA deficiency or he's allergic to something else." So that would be in the emergency department. [Just go] with standard products, no washing, no nothing, but just know where the syringe is, because anaphylaxis or severe allergy doesn't necessarily have anything to do with the IgA.

Now you've got someone who's going to have a hip replacement in two months. You've got plenty of time to get an IgA level in the right laboratory and an anti-IgA, and that should just clear it up. If it doesn't clear it up, and there is a deficiency of IgA and anti-IgA, then the scenario would be very similar except the timing allows to get IgA-deficient plasma if that's what the person needs. In other words, I am willing to recognize that despite the fact that I have written some pretty clear statements in the literature, I don't think that the standard of practice in the United States has come to the point of ignoring patients who come in and say, "I have had anaphylaxis." So although I am preaching, "Ignore the association with IgA deficiency," I don't think that it's a standard practice in the United States, and until it does become so, so I'm willing to compromise the simple thing. Call the Red Cross and get a couple bags of IgA-deficient plasma and don't treat someone's child, spouse, or what have you in a way that they think is callous.

**Joe**: I mean I don't think this is just academic. This happens in real life in terms of these discussions, and I think it's super-important for everyone to know what to do. So Jerry, I honestly, I can't thank you enough for spending the time with me and discussing this. Before I let you go, is there anything else that you'd like to leave us with?

**Jerry**: No, I would just emphasize the last point, and that is that as physicians, I think we have to recognize that people could have some very strong opinions about how they want the children, their spouses treated. And if all it involves here is calling the blood center to get a different blood product,

and you are not going in the face of someone who was not only dealing with a bleeding spouse or child or surgery or what have you, you have to have a certain amount of mercy. And I would say that you want to read my articles and you want to follow the science wherever there are people who accept that, but until it becomes the standard of practice nationwide, approach the situation with a certain amount of mercy, understanding that people's feelings can run pretty high here.

**Joe**: I think that's a great way to look at it. So Jerry as, as I said before, I'm so honored that you joined me. I'm so appreciative of your thoughts and your expertise and for your impact on my career. Thank you so much, sir!

**Jerry**: Have a nice day. Bye bye.

**********

**Joe**: Hi, it's Joe, with just a couple of things before I let you go.

I mentioned at the top that if you are a learner and someone asks you about mechanisms for anaphylactic/severe allergic reactions, you should go straight for that IgA deficiency and anti-IgA deal! That's where you should go, that's how you should answer those questions, because that's pretty much what they want. BUT, if you are in the real world, you should be aware of just how uncommon it really is to see severe allergic reactions be associated with IgA deficient patients. We still look for it, and we should look for it, I believe; I agree with Jerry said, but we usually don't find it. As Jerry said, many of those reported in the old literature were probably something else.

Remember, you can find the references Jerry discussed and other useful information on the show page for this episodeThat will be at BBGuy.org/066. There's lots of other stuff at BBGuy.org, including a detailed glossary, quizzes, videos, and tons of other free resources.

You can also listen to previous and future episodes of this podcast directly on the website, or Apple Podcasts, or Google Play, or Stitcher Radio, or Spotify. This is cool, actually: You can even "Ask Alexa" to play the Blood Bank Guy Essentials Podcast on your Amazon device (I just did this the other day; it's so cool!). If you get the chance, please go to Apple Podcasts give this podcast a rating and subscribe!

So, the next episode will be a continuing education-eligible interview with my friend Dr. Carolyn Burns on how to make wise choices in patient blood management. I can't wait to share it with you.

But until that day comes, my friends, as always, I hope that you smile, and have fun, and above all, never, EVER stop learning. Thank you so much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.