



Joe Chaffin: Welcome back to the Blood Bank Guy Essentials Podcast! This is Episode 002. My name is Joe Chaffin and I will be your host. I really appreciate you being here and thank you for checking out the podcast. Today, I am very excited to share my conversation from January 2016 with my friend Dr. Patricia Kopko from the University of California, San Diego. In this episode, you'll hear Pat and I discussing strategies for managing patients with platelet refractoriness. Pat has some unique and practical views on this subject that I really think you will find interesting; I certainly do. A little housecleaning before we start: Neither Pat nor I have any financial disclosures related to this topic. And also, the opinions that both Pat and I express in this podcast are simply our own, and they may not reflect those of the organizations for which we work.

And with that out of the way, I am proud to present to you, Episode 002, Dr. Patricia Kopko. So welcome to the podcast, Pat!

Pat Kopko: Thank you!

Joe: I want to tell people a little about you, Pat, and brag on you a little bit. You're a graduate of the Loma Linda University School of Medicine, in Loma Linda, CA, which is also *my* alma mater. Pat did a residency in AP and CP, Anatomic and Clinical Pathology, at Loma Linda and a Transfusion Medicine Fellowship at Cedars Sinai Medical Center in LA. She's worked both in blood centers and in major academic centers and she is currently a Professor of Pathology at UCSD in San Diego and she is the Director of Transfusion Medicine and the Associate Director of the Immunogenetics Transplant Lab. That's a lot of work, Pat. You sound like a busy person!

Pat: Yeah, well, what else is new?

Joe: Now I have to say (Pat knows this is coming, I'm pretty sure) that however long I end up doing this podcast, there's a very good chance that Pat will be the only guest I ever have who has not only been *struck* with a paper airplane thrown by me, but has actually *struck me back* with a paper airplane! Is that correct, Pat?

Pat: That is correct...let's just say that sitting in a medical school amphitheater for 4 hours can get boring! (laughs)

Joe: That is for sure! So before we get going today, I'm super-excited about what we're going to talk about today, because I think it's going to be really

practical for people. But I always do like to start out by asking my guests just a little bit, just a thumbnail, what got you interested in blood banking? What made you decide either during your residency (obviously during your residency) that you wanted to go into transfusion medicine as a career?

Pat: You know the funny thing is, is that I decided to do Pathology when many people decided to do Pathology. It was my second year of medical school and we had that Pathology course that ran through the whole year and I just LOVED IT! The whole mechanism of disease thing, I just loved. So I assumed that I would do Anatomic Pathology until my first Blood Bank rotation. And 2 weeks into my Blood Bank rotation I realized, “Oh this is what I want to do!” I really like the combination of the intellectual challenge of the puzzle-solving of what’s going on with this patient. Plus it’s a mix between pathology and clinical care. And it was just that right mix for me that made me decide, “let’s do Blood Banking!”

Joe: Right! Awesome! Obviously, as I’ve said, you have practiced in different environments. So clearly, you seem to enjoy both sides of things. And actually, I think it gives you a somewhat unique perspective, that you’ve been the medical director of a major blood center, as well as the Director of Transfusion Medicine in a major academic center. You think that’s helped you in your career, doing both sides of things?

Pat: I think it has because I understand the blood center so well. When I’m looking at what we can do for a patient, I know all the possibilities because I’ve been there before. And I do think it makes practicing clinical Transfusion Medicine—let’s say easier for me because I know how to interact with the blood center as well as I do.

Joe: You bet, yeah, for sure! So today, as I said, I’m really excited about our topic of discussion. We’re gonna talk quite a bit about choices and management, in patients with platelet refractoriness. I get a lot of questions about this, both from pathology residents and trainees in laboratory medicine, as well as people that work in hospital blood banks. I have to tell you (you and I have talked about this before), there’s an article published in February 2015 in *Transfusion*, that you’re the lead author on, called “Methods for the Selection of Platelet Products for Alloimmune Refractory Patients,” that for me is an absolute *must-have*. I think every resident should have a copy of this article and they should have it readily available in all Blood Banks because it’s SO PRACTICAL and so useful in so many essential strategies! So nice job on that!

Pat: Thank you! I should point out that I’m not the only author. That is a collaboration of myself, Carol Pancoska, Paul Warner, and Lesley Kresie. It was an article that came out of session that we did both at the ASH Meeting in the

AABB meeting for this topic and it was so well received, we decided to write it up for and publish it in *Transfusion*.

Joe: Well I'm very glad that you did because I think it's incredibly useful. So let's go through this a little bit, not necessarily line by line through the article, in fact, NOT line by line through the article! But I think we should start from the beginning, understanding that some of the people that listen to this podcast may have heard what you and I just said and said, "Hmm—'Alloimmune Refractory,' not really sure what we're talking about there." Let's go back to the beginning and take us through, just in general terms, what do we mean when we say that someone is "refractory to platelet transfusion?" And second, why do patients get that way? What are the general reasons?

Pat: So the simple description of what does "refractory to platelet transfusion" mean, is that you don't get the bump you expect when you transfuse a unit of platelets. So when you give a single apheresis platelet unit to a patient of average size, you expect to get a 30,000 to 60,000 bump in your platelet count. Sometimes when you give somebody platelets, their platelet count is EXACTLY the same after transfusion as it was before transfusion. And that is absolutely "platelet refractory," but then there are scales of platelet refractory. Sometimes, you have a patient who only has a 10,000 bump in their platelet count after transfusion. They may well be refractory also.

Joe: So we'll get into the specifics of how we've defined that traditionally. But just generally speaking, we're talking about someone that doesn't respond numerically anyway, the way we had hoped they would from a platelet transfusion. Is that a fair way to put it, too?

Pat: That is correct and there are a number of causes. And we lump them between "**immune**" and "**non-immune**." Non-immune can also be medical causes of platelet refractoriness: Things like fever, infection, splenomegaly. If you give patients with those conditions platelets, the patients with fever and infection are just going to use the platelets much more rapidly than someone would without those conditions. It gives somebody with a large spleen platelets, they're not going to destroy the platelets, but most of the platelets you give them are going to end up where the rest of their platelets are: In their spleen. So, those are non-immune causes. Immune causes mean antibody-related causes and the number one we think of for something that we can do something about, is patients who have HLA antibodies, also, human leukocyte antibodies is what it's called, and antibodies to human platelet antigens, which are also present on platelets.

Joe: Ok, so we will also get into the specifics of that, more in just a minute. But just in your general experience, and I think there maybe variations in people's practice, but when you see someone who's not getting the bump that you think that they might get, generally speaking, is there—how can I put this? Is there some predictability to which is more likely: immune vs. non-immune? Or is it a toss-up? What's been your experience with that, Pat?

Pat: There's a predictability. And it's also, in my experience, there's a predictability, in who is telling me the patient is refractory. I have an experienced Hematology-Oncology doctor, telling me their patient's refractory, they've got about an 80% chance of having HLA antibodies.

Joe: Nice.

Pat: If I have other physicians who are not as used to seeing this disorder, as your experienced Hematology-Oncology physicians...their positive predictive value is not as high. But what I like to do, is I like to go into the patient's chart and just look at; "When did we give the platelets? What kind of a bump are they having?"

Joe: Got it.

Pat: The other predictors are: If your patient is female and has ever been pregnant, she's got a risk having HLA antibodies. If your patient has been transfused A LOT, they have a risk of having HLA antibodies.

Joe: Got it. So, I think, is it fair to say that Heme-Onc patients and other multiply transfused patients like that, especially ladies who have been pregnant, are kind of your highest risk group for immune refractoriness?

Pat: Absolutely.

Joe: Okay. Well, I think that as we talk about this today, in my practice as well as what I'm hearing from you, I think that there are some deep misunderstandings among, not just less experienced clinicians, but also among pathologists, among pathology residents, workers in blood banks, about that kind of thing that you just described and there's definitely confusion about this. In fact I have to tell you this, that just yesterday I had a phone call from a hospital where they were looking for washed platelets and when I asked them why, they said well the clinician was demanding them because the patient is refractory to platelet transfusion. I was rather entertained, because as you and I both know, that probably is not going to help! Right? (chuckle)

Pat: No, not in any way!

Joe: Not so much. Okay, so let's move on and let's get practical here. So you're in the Blood Bank, you're either a blood bank worker or pathology resident, pathology attending, whatever, and you get a phone call from a clinician and the clinician says, "My patient is refractory. By God, I want, I demand HLA matched platelets!" We certainly know that does happen from time to time, all too often, sadly. But when you hear something like that, or even when someone starts talking about refractoriness, especially with a less experienced clinician, Pat, is there—where should we start? Is there anything simple that we can do right away to kind of get an idea if this is something real or not?

Pat: Well, the first thing you do is you look at the chart, and you decide, "Is there a reasonable possibility this patient is in fact, refractory? And if you've given them a number of platelets and their platelet count is still where it was when you started, or you've given them a number of platelets, and the best increment you've ever gotten was 5,000 or even 10,000, then there's a reasonable chance that they are refractory. Also, in some patients what you see is a pattern. You see that only 1 in 5 platelet transfusions will result in a bump or 1 in 2 result in a bump, and then you have to think, "Well, they really might have antibodies." Because maybe they have antibodies to 80% of the donor population and that's why only 1 in 5, on average, are resulting in a bump. So if I see a pattern that I think, looks like, there's a reasonable possibility that that patient is refractory, we just go ahead and order the testing. And we order HLA antibody testing, and HLA typing at the same time, and we also order a screen for Antibodies to Human Neutrophil Antigens (*editorial note: Dr. Kopko intended "Human Platelet Antigens" here; see page 7*).

Joe: So you're doing that based on what you are seeing after a solid evaluation of the chart. Before we get to the testing, let's talk about the chart evaluation and what you're looking for there. I mean obviously, there are clinical features and I'm totally with you on patterns and the like. I think, one of the things I've seen and I'm guessing you've probably seen as well, is scenarios where someone says "well, this patient's refractory," and I look at the timing of their platelet counts and there's one morning at 6 am and there's another the next morning at 6 am, etc. Can you talk a little about how platelet counts are, timing-wise? How platelets should be measured to get an idea of whether patients are getting a bump?

Pat: So ideally, you would like to see a platelet count within 10 min to one hour post-transfusion and that is the gold standard. However, if you've got a platelet count 2 hours later and you've got absolutely no bump, you do have to suspect your patient may be refractory. And so for me, I think that, whereas I like to see

the platelet counts between 10 mins and an hour, I don't absolutely demand it. If I look at the whole case and it looks to me like, ok, so it wasn't in an hour but 3 hours later and they've got absolutely no increase in their platelet counts, and they're female and we've given them a hundred transfusions in the past, then I won't make the patient wait, until I order the testing. I know that there are people who disagree with me about this, and a number of people say, "well, you give them an ABO-compatible platelet first and see if they get a response. And then, if that doesn't work, you do a corrected count increment and if they don't have a response on two, then you order the testing." I have a lower threshold for ordering that testing, and it may be because I am an HLA Director! I understand the testing so well, and recognize that it is an inexpensive, easy test to do that gives you all sorts of information. And with that information, you can find the best transfusion choice for your patient and if I order it today when I have a high index of suspicion, I can have platelets that are the best platelets for my patient by tomorrow, instead of dragging it out over several days.

Joe: Gotcha. Basically you get to the answer more rapidly and you shortcut some of the hoops that we have traditionally made people jump through.

Pat: Yes, and if the answer is no, for a very reasonable price, I am able to tell the clinicians, "No, your patient does not have HLA antibodies. We will continue to issue random platelets."

Joe: Got it. Okay, so I'm going to push the pause button for just one second because you mentioned the use of ABO-identical platelets or ABO-compatible platelets. And again, considering our audience, that may not necessarily be obvious to people why that traditionally has been thought to help. So forgive me, if you can back up for just a sec. I mean you know, *it's a platelet*, right? It's not a red cell, why would we care about the ABO compatibility of a platelet?

Pat: The reason we care about the ABO compatibility of the platelet, is not so much the platelet itself but the antibodies that the patient could have. So if your patient is Group O and they have a high titer anti-A platelets and you give....if your patient is Group O and they have high titer anti-A, if you give them a platelet that is Group A and there are lots of Group A platelets sitting on everyone's shelf.

Joe: Yes, there are.

Pat: They could destroy that, not from HLA antibodies, but from anti-A antibodies because platelets express A and B antigens.

Joe: Yep. Got it. So platelets do have A and B antigens on their surface and so theoretically they could be cleared faster. I'm sure there is some data, but I'm not sure there is a ton of data that makes a massive difference, is there Pat? Or am I wrong about that?

Pat: It can make some difference in up to a third of patients, but if you've got somebody who you give a platelet to and they get no response, it is not likely to be from an ABO incompatibility, in my experience.

Joe: Got it. Ok, so now that we've gone back for just a second to cover that, I'm going to let you get to what you are wanting to get to which is—let's through again, just real briefly, from your perspective so let's set up where we are. We've got someone who we've been told is refractory to platelet transfusion. We've evaluated their chart, we've looked at all the data that we have available, and it does appear that there is an issue there, and we decide, okay, we're gonna order a "workup." From your perspective, what's...tell me one more time, you mentioned it before but let's go over it again. What are the things that people should be ordering in terms of that work up, in that scenario?

Pat: If you have a high index of suspicion that your patient may have HLA antibodies or be refractory due to antibodies, the simplest thing to **order is a test for HLA antibodies and HLA Type**. You don't have to order them together, because if the testing for HLA antibodies is negative, well then you did an HLA Type for A and B, and it's only the A and B loci that you need to type for; you do not need a full typing like would for a bone marrow transplant. So if your patient doesn't have antibodies, they didn't need that test; however, since I work in a hospital with a large cancer center, they often end up needing special platelets, so we order them together, in fact, what we order is: A screen for HLA antibodies, a screen for Human Platelet antibodies, and the HLA Type for A and B, all at the same time.

Joe: The screen for Human Platelet antibodies, you obviously have, it sounds like you have ready access to that. I'm not sure that's as readily accessible outside of a major institution. Is that correct, Pat, or am I wrong in that statement?

Pat: Most hospitals won't have it. Most places will need to get it, either through a reference lab or through a blood center. A number of blood center labs will have the test because it can be done in an ELISA test now. So it's not that difficult to find it if you really need it, but you don't have to order it to start. You can start just by getting the HLA testing because it is much more likely that your patient, if they are truly refractory for immune reasons, it is much more likely that they have HLA antibodies instead of antibodies to human platelet antigens. We just order it all at the same time because we have ready access to it.

Joe: Right. Understand, understand, but certainly the most basic test, and the most essential test in someone that you have high index of suspicion is the HLA antibody screen, right?

Pat: Yes.

Joe: So let's talk about that a little bit. I know that HLA antibody testing has really changed and I would say has improved a lot over the last 10-15 years or so, and I'd love it, with your expertise as an HLA Director, you're the perfect person to tell us how about how that process has changed? How we're better now? How things are more useful now in terms of HLA antibody testing?

Pat: So I'm gonna date myself here because I started in HLA when we were still using serology to identify antibodies. And it is a long, complicated, expensive process that does not give you the best results because you have to take a panel of 50 cells and incubate each of the 50 cells with the patient's serum and then look for cytotoxicity, and then based upon that, a human being needs to do an analysis to figure out what the antibodies are and it is much more difficult to do than an antibody panel—a red cell antibody panel. But about 15 years ago, new testing became available that is flow cytometry-based, most of it's done on what is called a "Luminex," which is a small flow cytometer that is multiplexed. And these multiplexed platforms, you can run a hundred, and now even more than a hundred beads in one sample. So the screening assay will have multiple beads with multiple different HLA antigens on them and you run the screening assay and you can tell if your patient has antibody—yes or no.

If the answer is yes, there's a single antigen test with, you've got a hundred beads—in each of the beads, has a different HLA antigen attached to it. So you can screen for one hundred different HLA antigens in one test. And the limitations of this test compared to the old cytotoxicity test are exceedingly small. You know it used to be hard to say, "okay do they have B44 and a B45 or am I gonna just call it a B12?" Here you can tell somebody has a B44 antibody and does not have a B45 antibody. You can tell that they only have antibody to 2 members of a CREG Group instead of the entire CREG Group or "Cross Reactive Antigen Group."

Joe: We're gonna come back to Cross Reactive Groups in just a second, but I think that what your telling us in terms of that testing is that it's obviously, it's more rapid, it's more sensitive, right? Considerably more sensitive, is that a fair statement?

Pat: Considerably more sensitive.

Joe: Is it too sensitive sometimes?

Pat: There are some indications, depending on the purpose, it can be too sensitive, and that is why you need to establish a cutoff in the HLA lab for where you're gonna call an antibody and where you're not gonna call an antibody.

Joe: ...and that's probably deeper than we need to go in this podcast! (laughs)

Pat: You can tell the hesitation in my voice!

Joe: I did—and I think what you were thinking is “is Joe really gonna understand what I'm about to say?”, which is probably wise on your part!

Pat: (laughs)

Joe: So let's move on! I want to make sure that we spend a little time here in our last 10-15 min together, to talk specifically about the choices. So you've gone through that process—let's just stick with HLA antibodies and come back to antibodies against Human Platelet Antigens later on. But let's say that screen comes back positive, and you know that you have a patient who has HLA antibodies. Traditionally, I think that clinicians have thought that there really is only one option in that scenario, there obviously has been only one option a long time, but they've said “**HLA-matched platelets**” for forever in that scenario. Your article outlined 3 fairly common and different in concept options for patients with HLA antibodies, so could you take us just briefly through the 3 main options for someone with HLA immunization?

Pat: Okay, but before I do that, just a little comment. It doesn't matter so much what the clinician orders. So—

Joe: (laughs) Wait, wait, wait! Say that again!

Pat: It doesn't matter so much what they order, and this is something I try to—I spend a lot of time trying to explain to my residents. The clinician can order HLA-matched platelets. They order HLA-matched platelets because that's the one piece of information they know. But think about this like the pharmacy: Do the clinicians always get exactly what they ordered?

Joe: Clearly not.

Pat: If they ordered the brand name do they get the generic? Yes! All the time. If they order one drug, and the pharmacy formulary is, “no we use *this* drug instead,” they get that drug instead. This is the exact same thing. HLA-matched

platelets take forever to find because you have to find a donor, you have to run a HLA-matched list, you then have to—a true match for your patient is not going to be sitting on your blood center shelf. The blood center then has to run that list, has to start calling donors, has to get ahold of the donor, has to get a donor to come in and donate, which usually doesn't happen the same day. The donor has to successfully donate, the donor then has to have that donation tested. We're talking about a 72 hour process at a minimum. On the other hand, there are other types of platelets that can be available much more quickly for patients with HLA antibodies. One of them is "**cross-matched platelets.**" So cross-matched platelets come about when your blood center takes a sample of your patient's serum and literally does a cross-match with the platelets they have available in their inventory or platelets that are about to be in inventory and determines if the platelets are compatible. Those platelets can be available in less than a day. In fact for large hospitals, if they do the platelet cross-matching in-house, with platelets they have in inventory, those platelets can be available within hours. So when does your doctor, who ordered HLA matched platelets really want them?

Joe: (chuckles)

Pat: Do they want them as soon as they can get them? Or do they want them 3 days from now, maybe? They really want them as soon as they can get them. So what they're really saying when they want—when they order HLA matched platelets is, "I want platelets compatible with my patient."

Joe: Right.

Pat: And so, if you can get cross-matched platelets available quickly, why wouldn't you use cross-matched platelets? Then the other option is something called "**antigen-negative platelets.**" Blood centers that HLA type their platelet donors, they typically will type almost all of them. If you successfully make a donation, the second time you donate again, the blood center will ask if they can HLA type you. So blood centers that can HLA type donors can literally have thousands of donors typed. Because of that, they can take the antibodies that your patient makes and exclude them from the search. So let's make this simple and just say, your patient has an antibody to A2. That means 42% of the platelets on your shelf are incompatible. But if the blood center has a program, and they can run that program and say "show me all platelets in inventory, that just lack the A2 antigen," they get that list, they can go over what's in inventory, and they can ship it to your hospital. Sometimes, they can call you up and say you've got a platelet in inventory that will match your patient. And you can have platelets within hours if you choose antigen-negative platelets. One of the

things I think you're probably going to ask me, "well, which is better? Cross-matched or Antigen Negative?"

Joe: You read my mind.

Pat: So the answer is, "What do you have available?"

Joe: (laughs) Is that really an answer? Come on!

Pat: That is the answer! If your blood center has cross-matched platelets available, they are perfectly acceptable. If your blood center has both HLA antigen-negative platelets and cross-matched platelets available, those are perfectly acceptable, too. I tend to like antigen-negative better.

Joe: Why is that, Pat?

Pat: I think it's just because I'm a HLA Director (laughs). There is no scientific evidence to this! I can't pull out something and show you that one is better than the other because in general, they really aren't....I think, Larry Petz has a paper that does show the antigen-negative are a little better for the corrected count increments you get. But cross-matched platelets are perfectly good platelets.

Joe: Right. I have to tell you, what you are describing is the way I practice as well. And I really have seen both on the clinical side and from the blood center side, very little difference in terms of response. And I think, as you said, there is data to support that, and I am with you. I think whatever you can get the most rapidly is the product of choice, in those scenarios. The antigen-negatives work well, but I did want to ask you one thing, and I think that you might know this is coming as well, because we've had a discussion about this not long ago. So, to a resident, the antigen-negative concept is generally pretty simple to understand because they think of it, kinda sorta like what we think about with red cells. Someone has an anti-K, we give them K-negative red cells. It's kind of, it's obviously a little more complicated than that but it's a similar concept. But occasionally, I've had clinicians and pathologists say, "Well, wait a minute, what about cross-reactive HLA antibodies? Do you worry about those? Do you need to make sure that this particular antibody against this particular antigen, do I have to choose things that are negative for everything in that cross-reactive group?" How do you respond to that?

Pat: My response would be, "15 years ago yes. Today, no." Because our ability to determine exactly what antibodies the patient is making is so good that we can now not worry about cross-reactive antigens anymore. If we didn't find the antibody when we did the testing, you do not need to worry about it.

Joe: Yep. Got it. Okay, so just a really actually fairly simple process and as you said, it has the potential to get us a compatible product very rapidly for the patient. And as you said, that's what we're looking for, right?

Pat: Yes, because it doesn't do your patient any good if you get them a HLA matched platelet 72 hrs. from now, and they've bled into their head 24 hrs. from now.

Joe: Yes, that is certainly true.

Pat: So the reality is, we almost never order HLA-matched platelets. Almost never. And it is because we are able to get antigen-negative platelets and cross-matched platelets so readily. The only time that we order HLA-matched platelets is when we have a patient who has made so many antibodies, that they make antibodies to usually its more than 95% of the population. Then it can become hard to find antigen-negative platelets and in that case the blood center will have to recruit specific donors instead of using what is available in inventory.

Joe: Got it. One other objection that I occasionally hear about using either the cross-matched or the antigen negative strategy, and I'll throw you a little bit of a curve with this question (hopefully not too big of a curve because I know you have an answer). One of the things I have heard people object to is, "Well what about if you do this and you're not matching them, aren't they going to form a whole bunch of new HLA antibodies?" How do you respond to that one?

Pat: The interesting thing that is, that's in that paper that you cited. There is a study that showed supporting patients with cross-matched platelets from the time they began to the time they ended, the percent of incompatible donors, which is also expressed as something as a calculated PRA, did not increase.

Joe: Nice. That was a pretty big study as I recall, was it not?

Pat: It was fairly a large study and they did not see an increase in the calculated PRA while they were supporting them. And again, it is so difficult to obtain HLA-matched platelets. Why would you make your patient wait for 72 hours when you could get them something now? It's the whole concept of, "well, I'm going to make them wait because they might make antibodies." Well, if they do make antibodies, what are we going to have to do? We're going to have to use HLA-matched platelets! It's a bit of a circular argument, in my opinion.

Joe: I agree with you. Well, we could take a moment to talk about HLA match grade, but I think we kind of covered the HLA-matched issue enough, Pat.

You've clearly shown to me that antigen-negative and cross-matched are reasonable alternatives. Everybody gets confused about the HLA match grade stuff anyway, certainly trainees do and just for reference purposes so everyone listening will know, I'm going to put the HLA match grades, the traditional categorization on the website. But just one quick question about that, does using antigen-negative or cross-matched platelets, Pat, make the whole match grade argument, you know, an "A" vs a "B1U," is that completely obsolete?

Pat: It really is because it doesn't matter if they have a cross reactive antigen. Because what you really want to know is do they have an antibody to that antigen. So it is something that, I think really is somewhat obsolete. I had one thing that I would like to add.

Joe: Please.

Pat: So, say you're at a hospital that is supported by a blood center that has cross-matched platelets, but does not have HLA-matched platelets. What do you do?

And the answer is: Your blood center undoubtedly works with another blood center who can find you HLA-matched platelets or antigen-negative platelets. So part of the problem can be with really highly immunized patients. If they are making antibody to that more than 95% of the population, you're not going to be able to support them with cross-matched platelets.

Joe: Sure.

Pat: And so you will have to switch to either to antigen-negative or HLA-matched platelets. And in that case, you need to ask your blood center how can they get you HLA-matched platelets or antigen negative matched platelets and they will have a way.

Joe: Got it. So we've gone through the scenario where someone who has HLA antibodies, that there are **3 main options: HLA-matched, cross-matched, antigen-negative**, and functionally, probably the best choices in terms of having rapidly available platelet products, unless the patient is highly alloimmunized, are probably cross-matched or antigen-negative. What we haven't talked yet about or other than just briefly was antibodies against platelet specific antigens or "HPAs." I think there's some concern out there about that, so why don't you talk to us about that. Are those a big deal? Do we actually see antibodies on a regular basis against HPAs?

Pat: You see them but you do not see them nearly as often as you see HLA antibodies. So if you're only going to start with one test, that's why you should start with the antibodies to HLA antigens. A way you can pick up HPA antibody is occasionally if you don't have HLA antibodies but you ordered cross-matched platelets at the same time you ordered the test, and you have incompatible platelets, you really need to do that HPA antibody test.

Joe: Okay, hang on, let's emphasize that again for just a second. So say that one more time, you've got someone who has, you've done an HLA antibody screen and yet the cross-match is incompatible. Was that the scenario?

Pat: Yes. If that happens, you're probably looking at HPA antibodies.

Joe: Got it.

Pat: Also, if somebody is refractory, they're not getting good 10 minute to 1 hour post-counts, you're not finding HLA antibodies, you really do need to test for HPA antibodies.

Joe: Okay.

Pat: But the thing is, most blood centers don't test their platelet donors for any HPA antigens and if they do, it's only HPA-1A. So some blood centers will have platelet donors who are HPA-1A negative. But beyond that, your only option is cross-matched platelets.

Joe: Thank you for bringing that up because that was going to be my next question. Okay, so you found a HPA, what does that mean? Because I certainly can tell you my blood center, other than as you said, a few HPA-1A's, we don't have rolls of platelet antigen tested donors.

Pat: No, because the need for them is not great and the testing is expensive.

Joe: Yep. Okay. Well, here is what I would like to do, Pat, if you're amenable to it. I want to take us through just a couple of scenarios, that talk about some of the things we've discussed. Near the end of your article, there's a really cool flow chart that just gives kind of a general approach to these things and it doesn't get into the specifics of some of which we talked about timing or anything like that. It's just a general approach, so I want to get your take on a few scenarios, so that we can re-emphasize what we talked about to our listeners. So, let's just say we have a patient who has had several platelet transfusions and we've looked at the chart, and clearly the patient is not responding either on a 10 to 60 minute count, or as you said a couple of hours

later or whatever. The patient needs a transfusion and they've sent the antibody testing, but it's not back yet. We don't have that information. What would be the best choice in a scenario like that, from your perspective?

Pat: Well, first of all you can always use randoms, but try cross-matched platelets. If you do a cross-match, the cross-match and the HLA antibody testing, not always, but often correlate. So if you have a calculated PRA of 50%, if you cross-match 8 units, you can expect about 4 of them to be compatible. So you can get compatible platelets even before you have your antibody testing back.

Joe: Right. Okay, so cross-match in that scenario. And is it safe to assume then that, if say that you test 8 random donors from your shelves and all of them are compatible, obviously it's not predictive that the antibody test will be stone-cold negative, but it's probably going to be, if there are antibodies there, probably not many. Is that a fair statement?

Pat: That is a fair statement.

Joe: Alright, so let's take that same patient, who's not responding, and we have the screen back. The HLA antibody screen is positive, but they have not completed the identification of those antibodies. So you're in slightly a more advanced situation, you know there are antibodies there but you don't know what they are. What would you choose in that scenario?

Pat: I choose cross-matched platelets until the testing is complete. There is no reason to wait to get platelets until that testing is complete. You can get cross-matched platelets based upon just sending a sample for cross-matching.

Joe: Right. That's a great point. A lot of times, I think we in hospital blood banks, we have a tendency to think of it sequentially, well I can't do this until I do that, but realistically you can do a lot of these things simultaneously and save yourself a lot of time.

Pat: Yes, and I think that in the past there's been a philosophy that you must do all of this sequentially because if they don't need HLA-matched platelets, they're really expensive and hard to get and so we shouldn't jump through that hoop unless we have to. Cross-matched platelets are not that expensive and they are not hard to get. So you can always start there while you're doing your work up and hopefully get a better platelet product for your patient while you're completing the work up.

Joe: Okay, so let's do one or two more. Let's take that same patient. We've got the antibody screen back, we've got the antibodies identified, so we have a

group of HLA antibodies and let's just say we know the patient's HLA type. So theoretically, in that scenario, I would assume all 3 choices that we talked about would be possible: HLA-matched, cross-matched, antigen-negative. I think I know what you're gonna say, but what would you choose in that scenario?

Pat: We typically will then use antigen-negative platelets. For one of the reasons, is that you don't have to keep sending sample to the blood center. They know the patient's antibodies and they will just send you platelets that do not have those antibodies. So it makes it easier for both the transfusion service, and the blood center that, okay, we want 2 platelets every other day and we do a standing order. It just makes things much easier on both sides instead of trying to finesse things, well this is how many we could find. They know this is what we want through this course of chemotherapy.

Joe: That's a really good point. I think people—it's easy to forget that repeated cross-matches require a sample every time. That adds a layer of complexity and logistical difficulty to it, when you're just looking for antigen-negative, that's a simpler process for a blood center.

Pat: And for us, on the hospital side because we don't have to keep sending sample.

Joe: Yes. Got it. Okay, so one more thing, and I love this in the article because you snuck this right at the end of the article and it's beautiful and it's something that I freely admit, I was not aware of. Tell us about your neat little “anti-B44, -B45 trick?”

Pat: So, we call that the “when all else fails.” So if nothing is working and you're having a really hard time, but your patient has antibody to so much of the population, you can ignore B44 and B45, and that will often open up a larger supply of donors. And the reason that you can ignore B44 and B45 is they tend not to be well-expressed on platelets. And so there are times when you're really struggling to find any platelets, that ignoring B44 and B45 can make a difference.

Joe: Got it. That is a great trick that I have actually used since I saw your article and it absolutely can really help. It really can, so thanks for that!

Pat: It's funny, every once in a while, I get an email from somebody I don't know saying, “I just want you to know—it works!”

Joe: (laughs) Very nice! That's a great call. Well, so I think we've beaten this to death in a good way. We've talked through the different options, including the

approach, the testing that's needed, the main 3 options for patients with HLA antibodies with immune types of refractoriness. So, Pat as we close our time together, you and I are going to figure perhaps a couple of images to put on the website to kind of illustrate these points. Maybe something around that flow chart in that article, but we'll have some hopefully helpful images on the Blood Bank Guy website to help people understand some of the points we've made here. But just as we close, what would you like to tell people, again, considering residents, blood bank techs, and the like, that are just looking for a summary of how to approach these patients?

Pat: So, I think the most valuable things to know are just because a physician ordered HLA matched platelets, that's not what they mean. They mean "get me a compatible platelet as soon as you can." Don't get hung up on the words, "HLA-matched." That's the first thing. The second thing is, find the platelets as quickly as you can, and if that means just getting cross-matched platelets without getting any of the work up done, do that first and then switch to what you consider better platelets if you consider them better platelets as your testing comes in. I think the final thing that's most important: **Work with your blood center.** Call them. Talk to them. They are always willing to help you and if you're thinking they're not, assume you have a miscommunication! Because in my experience, if you think the blood center is being difficult it is because they don't understand what you're asking.

Joe: And speaking as a current blood center director who has also worked on the hospital side, I think that is a very fair statement. I know you know that from both sides as well, Pat. We—I say we as blood center directors, take it very personally to get appropriate products to patients as quickly and appropriate manner as possible.

Pat: One of the things I like to tell my residents—when a physician orders HLA-matched platelets and they carry that order through as an HLA-matched platelet, and the patient has a calculated PRA of 20%, next thing that's gonna happen, is either, their lab is going to call me and say, "Are you nuts?!?" or one of their Medical Directors is going to call me and say, "Are you nuts?!?" (laughs) So, if you're the resident out there, remember, just because it's what they're asking for, doesn't mean that's what you have to give them.

Joe: Awesome! Well Pat, this has been great! Some wonderful, really, really practical tips—I can't tell you how much I appreciate you taking time out of your day to talk to me. So thank you so much for being on the podcast.

Pat: You're welcome!