BBGuy Essentials 060CE:
Transforming Inventory Management with Nancy Dunbar
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Joe Chaffin: Hey, everyone. I am so happy to welcome you once again to Blood Bank Guy Essentials, the podcast designed to help you learn the essentials of Transfusion Medicine. This is episode 060CE, and my name is Joe Chaffin. Today on the podcast, I have a wonderful interview with my friend Dr. Nancy Dunbar from Dartmouth. Nancy is going to help us work through some really potentially challenging situations regarding how we use special blood products that we tend to get short on. More on that in just a second.

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This episode is one that I have been wanting to do really for quite a while. I run across situations like this commonly in my blood center practice and in my previous practice in hospitals. I've certainly seen this way, way too often, where we have shortages of particular types of products, things like O-negative red cells, and AB plasma, and apheresis platelets. In many cases, those are shortages that could potentially be avoided if we as a group, as an industry, as a blood bank collective would make wiser choices with how to use these products to begin with. My guest today is someone who has published on this very widely, and she is someone who you will know if you have listened to this podcast previously. Her name is Dr. Nancy Dunbar. She is an Associate Professor of Pathology and Laboratory Medicine at Dartmouth, where she is the Medical Director of the Transfusion Service at the Dartmouth-Hitchcock Medical Center.

Nancy is brilliant, she is widely published, well over 40 papers in peer-reviewed journals, she's got book chapters, she's got editorial boards, she's done all kinds of stuff. What I love most about Nancy's research is that so much of it is focused on the *practical* stuff, and that's partly informed by the fact that where she is at Dartmouth there are a lot of inventory challenges for them just based on their geography. They're very far away from their blood supplier, so they have had to learn to make really smart choices with some of those special products that I talked

about before. She's published on this, and I really can't wait for you to hear her talk about it, because she's going to say some things, I promise you, that are going to challenge you a little bit, but they are going to make sense.

They are things that if we think about it, and if we consider, we can really help make a dent in the ongoing shortages and crises that we have with O-negative red cells. "We're short on O-negs," "we're short on platelets," "we're short on AB plasma." All those are things that we end up having to say way too often, but if we just take some proactive choices that Nancy will talk to us about, and in fact take some choices when things get “hairy,” we can really put ourselves in a better situation, and further, we can put our patients in a better situation. That's really what it's all about. I won't make you wait anymore. Here's my interview with Dr. Nancy Dunbar on how to transform your blood inventory.

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Joe: Well hey, Nancy! Welcome back to the Blood Bank Guy Essentials Podcast!

Nancy: Hi, Joe. Thank you. Glad to be here.

Joe: It's really cool of you to join me again. You know, most people, after they talk to me are like, "Wow, never again." Just the fact that you're doing this shows, I think, great mercy on your part [laughs].

Nancy: [Laughs] It's my pleasure, thank you.

Joe: Well, so Nancy, I'm really excited to talk to you today about something that I think is really very much in your wheelhouse. You have published a lot of stuff on different aspects of inventory management. I'm excited to get your perspective today on the challenges that hospital blood banks face in terms of inventory management, specifically with plasma, and platelets, and especially with red cells (we'll spend most of our time on red cells today).

I just have a question just to kind of set the stage for this because, come on Nancy, let's be real with this for a second. I think everybody is aware that every time we publish the usage data for blood, certainly in the United States and maybe to somewhat lesser extent around the world, but definitely in the United States, it's like every time we get a new publication there's another 10% to 15% drop in the amount of blood that's being used. Come on, *everybody* knows that red cell use is way down, other products to an extent are down. Aren't blood centers just "swimming" in inventory, Nancy? Why do we even have to worry about inventory management, for goodness' sake?

Nancy: Well, I wish that was the case. I wish that our suppliers were swimming in inventory, but the reality is as our utilization of blood has decreased, the collections have decreased in parallel. It's not in the interest of blood suppliers to collect more than can be used. So, they're always navigating that fine line between having “just enough” without too much waste. The reality is, we do continue to struggle with shortages nationally. I know that one of the large suppliers sent a letter to us and other customers this summer just notifying us that our standing orders were going to be reduced by 75%, and that's reflecting the reliance our blood supply has on high school donations. When kids are out of school in the summer, we don't collect as much blood. It does impact us, I think our rural location here in New Hampshire gives us some unique challenges, but I don't think that we're alone in facing sort of routine challenges in maintaining an adequate inventory, in spite of the fact that we've reduced our utilization in this country.

Joe: I find your situation very interesting. I think many academic medical centers tend to be in very urban locations, and as a result, have potentially different access to blood suppliers and different resources. You guys, I think calling you "urban" would be pretty much incorrect [laughs]. You guys are really a "rural" academic center. I'm wondering if you can just kind of talk us through a little bit, what are the challenges that you face not being in the midst of some big major transportation hub?

Nancy: Yeah, I think our situation is unique, and I think it's really driven a lot of my research, just the practical challenges we face on a daily basis. We are rural, some people have referred to us as a "micropolitan" area, because our hospital really has four towns nearby, each about 10,000 people. In our immediate vicinity, there aren't that many people, but we serve a very large geographic area, and we serve about a million patients between Vermont, New Hampshire, Western Maine, Northern Massachusetts. That's our catchment area. We are about three hours from Boston, on a good day, you know, door-to-door. That's where our closest supplier is, and so whenever we have shortages, we are really looking at a minimum of three to four hours to get resupplied.

We're a tertiary medical center, we have a level one trauma center, we have Heme-Onc transplantation program that does both auto- and allogeneic transplantation. We do have a lot of potential to use a lot of blood products. We're a surgical referral center, we do a lot of complex cardiac surgery. We have potential for a lot of utilization and it can be quite unpredictable, and yet we don't have a ready access to a supply of blood. That is, I think, what makes us somewhat unique.

General Challenges with RBCs, Plasma, and Platelets:

Joe: As someone who works in a blood center now, I do work with a lot of more rural facilities, none with nearly the complexity of what you guys are doing.

One of the things that I have found in dealing with more rural facilities, is that I have seen in recent years a trend towards saying, "Well, we're out here, we're so far away, so we really just want to load up on the group O's," for example, "in red cells, in particular the O-negatives. We really want to keep a really large inventory out here, use O more than anything else because hey, we're not going to be able to get replenished very quickly." It seems like the complexity of your population, you would have to keep a mixture of ABO groups. That's a long way of introducing the question, which is, how do you manage that ABO mix in terms of **red cells** in your inventory?

Nancy: Yeah, so like I said, we're about a 400-bed hospital. We keep about 350 red cells at any given time. Really, only about 100 to 120 of those are group O. We're really designed to provide type-specific blood. Even for our trauma patients, we try to switch as early as possible. I think the path of least resistance in a perfect world of unlimited resources, yeah I mean, if everyone would just use O, it would be so much easier. The reality is, not only can we not do that because that's not being a good steward of the blood supply, but even if we wanted to, our suppliers just can't. They can't support us in that. We have standing orders for things like group O red cells, and particularly group O-neg red cells, we have a minimum inventory of 20 units. Most of the time, we are not at that minimum inventory. Our standing orders, because the suppliers just simply don't have the units to send us, they are routinely cut. Just because there are too many people who need that product and they can't send us what we expect. We kind of live in a perpetual shortage and we just adapted, I think, our practice to be able to sustain ourselves even with those challenges.

Joe: Wow. I just did a little "back of the envelope" math, which is always dangerous when I do this, Nancy, but if your target is to keep in the range of 20 O negs, amidst a 350 unit inventory, that's like 5% or so.

Nancy: Right.

Joe: 5% or 6%?

Nancy: Right.

Joe: Yikes, right?

Nancy: Yeah, it's really low. You know, I mean I think overall, the percentage of patients who need O negs about 8%, and most places utilize more than that.

Joe: Yeah, interesting challenge. Wow, I just threw that out. "Interesting challenge," that's the understatement of the year, right? I'm sure that is something that you deal with on a near-daily basis. Again, keeping with your... (and I don't want to make you give away all your secrets), but I'm

curious, how about **plasma**? Is it a similar discussion with plasma in terms of the "tug of war" back and forth with AB in particular and the other blood groups?

Nancy: Yeah, absolutely. We try to keep about 270 units of plasma on our shelf, and only 20 of those units are group AB.

Joe: Wow.

Nancy: You know, that's not very many. One group AB TTP patient can just deplete everything in a day.

Joe: Right.

Nancy: That's another area where we've had to really get outside the box and think about solutions to sustain ourselves with that limited supply.

Joe: Okay. I can't let this go without asking about, we're in the midst of the end of summer and I can speak for myself and my blood center when I say that platelets have been a struggle in recent months. I guess, let me ask you about that. What kind of targets do you have for apheresis **platelets** and is that a struggle for you as well?

Nancy: Yeah, you know, platelets are interesting because we do collect platelets in our own local donor center, and that is our priority, to have platelet donors. But, it's a challenge because the donors can't predict when we need platelets, and there is a delay in the availability of donated platelets as the infectious disease testing is performed. We can't really pivot in real time, but we try on any given day to have about 12 to 15 platelets on hand at the beginning of the day. On a typical weekday, that's kind of our projected utilization. You know, it's a very unpredictable number. On Tuesday last week, we had a surgical bleeding emergency and a patient used six platelets in four hours. That kind of wipes us out, and we can't call on our local hospitals nearby because none of them keep platelets on the shelf. That's definitely something that has to come from one of our blood suppliers and they don't always have platelets to spare. Of the things we manage routinely, platelets is our biggest challenge that we struggle with on a daily basis.

Use of Group A Plasma in Trauma (STAT Study):

Joe: You have published extensively, really kind of across the three main areas of struggle that you just outlined, in terms of the red cells, in terms of the plasma, and in terms of the platelets. We're not necessarily going to go in that order, but I'd really like to hear a little bit about some of the work that not only you've published but perhaps you've implemented there at your hospital as well. I'd like to **start with plasma**. Now, Nancy and Tait Stevens from Loma Linda were on this podcast on episode 36, it was in 2017, actually. You can go to BBGuy.org/036 and listen to both Nancy and

Tait talk more extensively in particular about the use of group A plasma in trauma settings.

Nancy, given that you've already discussed this with me on a previous episode, I know not everybody's going to run and listen to that right away, so can we just thumbnail a couple of articles that you did and kind of what those articles mean? The first one was published in Transfusion in 2016, and it was a survey article that you and Mark Yazer did on behalf of the BEST Collaborative, and it was called, "A possible new paradigm: A survey-based assessment of the use of thawed group A plasma for trauma resuscitation in the United States" [NOTE: See link at BBGuy.org/060]. We just talked about AB plasma and what the challenges are with AB plasma, so I wonder if you could, just kind of a high-level overview, what you found on that survey, and kind of what the interpretation of that might be?

Nancy: Yeah. We sent this survey out in 2015, really to find out what other centers were doing, because about 2012 here at Dartmouth we started using thawed group A plasma for trauma patients. That was because prior to that, we had been thawing group AB plasma on demand. The reality was, in a trauma patient we were finding there was a delay in the availability of the plasma, because you need to have that 30 minutes thawing time. So, patients were getting an early deficit of plasma while that plasma was thawing. The easy solution would've been, "well, let's just keep some AB thawed all the time," but practically, that was impossible for us. We couldn't go to our suppliers and ask for a 25% increase in the amount of group AB plasma, which is what we would've needed to have it on the shelf at all times thawed and ready to go.

We knew, or I knew, that other places that were similar to us, places like the Mayo Clinic and Penn State Hershey, both rural trauma centers, were using group A plasma thawed for patients of unknown blood group. We had changed our practice and the whole point of the survey was to identify, "Who else is doing this and how recently have you implemented it?" We were pretty surprised, actually, that we got about 61 responses from trauma centers, and most of them had thawed plasma available, quite a large number of them kept group A plasma, and 69% were using it for all comers. It was definitely, appeared to us, at least, that practice was changing, that as more people were sharing their experience and centers perhaps were struggling with finding enough AB plasma, that people were starting to change their practice and adopt the use of thawed A plasma.

Joe: Wow. One question before we leave that study, because the question I get most often about the group A plasma thing is, “Well, if I'm going to do that and if I know that 10% to 15% or so are going to be incompatible, shouldn't I be doing titers to make sure that anti-B in that group A plasma is not sky-high?” What did you guys find in terms of the proportion of people that were doing titers?

Nancy: Yeah. I think certainly here at Dartmouth we titer. When we went to our transfusion committee and said, "We think we want to start using group A plasma. There are risks, the risk of hemolysis and of your AB patient due to the anti-B, we think we should be titering it." That's what we do, but we were surprised to learn that of most of the centers that were using group A plasma, almost 80% were not performing anti-B titers. A large proportion were not limiting the amount of volume that a person could receive. It made me feel like we're a little bit extra cautious here, I think there's definitely rationale for that caution, but I think there's also data. If you've been titering these, it's not frequent that you encounter a high-titer unit, and a high-titer unit isn't necessarily predictive of complications. I think there's a lot that we don't know, and this field does seem to be changing quite rapidly.

Joe: That led you, all of that data I think, led you to ask the next very obvious question, which is, "If this many people are doing it, what is the *safety profile* of this?" That led to a paper that again you and Mark Yazer and the BEST collaborative published again in Transfusion, this time in 2017. This is what we spent a lot of time discussing on episode 36, "The Safety of the use of Group A Plasma in Trauma." That was called the "STAT study." Nancy, give us again, the thumbnail of what you guys found in the STAT study.

Nancy: Yeah, I think that we always knew we wanted to do a large study to see whether there was any detectable signal of harm associated with the use of group A plasma. I think you need to convince people about those risks and the relative safety to justify your own practice, right? The survey, one of the intentions of the survey, was to identify centers who were using thawed A plasma for patients of unknown ABO types so that we could then approach them to see whether they might be willing to collaborate and contribute patient-specific data to do a retrospective study to look specifically at the group B and AB patients who received group A plasma in the setting of the trauma resuscitation. To see if there was any detectable signal, and looking at a very crude measure, just mortality compared to expected mortality based on their severity of injury, and to compare them to the group A patients who were getting type-specific plasma, essentially, the group A thawed plasma, to see if there was a difference. If there was a difference, that might question the practice, and if there was no difference that could potentially make those of us who are doing it feel a bit more secure in the practice, knowing that the risks were non-zero but low of harm.

Joe: And was there? What did you guys find?

Nancy: There wasn't, and we were actually very pleased to see that. So the big challenge of a study like this is the power, right? You need enough patients to detect a meaningful signal and we were able to get almost, well we got over 800 identical patients and about 350 patients for whom the

plasma was incompatible, and what we were pleased to see is there was no difference in overall in-hospital mortalities. The two groups had essentially no difference in that. There was no difference in the early mortality, the first 24 hour survival, and there was no difference in the hospital length of stay for these patients. So those are really very crude measures of potential harm from receipt of an incompatible plasma unit. We don't exclude the possibility that there was a low level of hemolysis that did not contribute to those very crude measures, but the reassuring thing is we didn't appear to be harming people at any higher rate than we predicted based on their injury.

It would be foolish to say that this study proves that it's safe. **It doesn't. It supports the idea that we're not harming people in a way that's readily detectable**. It doesn't exclude the possibility of low-level of harm, and the fact is that these patients are extremely complex. They're severely injured, many of them. So it's hard. It's hard to study that population.

I think the reality is that a prospective study that very carefully measures markers of hemolysis in these patients is very difficult if not impossible to do. It would be incredibly expensive and is probably unlikely to happen. So I think the reality is that this may be as much information as we are going to be able to have about this question, and I do think that each hospital has to look at their own situation, their own trauma population, their own resources, and make the best decision for them. I certainly believe that getting plasma to a patient who's traumatically injured early is going to help their outcome. I think waiting to thaw type-specific plasma in a patient who's actively exsanguinating is potentially harmful in and of itself.

Platelets and ABO/Rh Choices:

Joe: Okay Nancy, let's move on from plasma and talk a little bit about platelets. I'd really like to start with discussing how we issue platelets in terms of ABO and Rh. What are the generally accepted rules? In particular, let's start with ABO and platelet transfusion.

Nancy: Yeah, so that's tricky. It's a little bit different than the classic kind of paradigm we're taught in medical school, where we try to avoid incompatible red cell transfusions and we try to avoid incompatible plasma transfusion, because platelets are the one thing in our inventory we generally keep a very limited supply of, and that's mainly due to the short shelf life of that product. So, for example, in my hospital, we may have on any given day, 10 platelets. So, when you think about platelet compatibility, you have to think about the compatibility of the PLASMA that the platelets are floating in, as well as the actual compatibility of the PLATELETS themselves.

So, platelets do express ABO, and some patients don't get as good of a response to the platelet if you give them an ABO-incompatible platelet (if they're like an O and they get an A, for example). But the reality is that we have to sometimes cross both of those barriers, just because of our very limited inventory. And if you look at work (it's been done quite a while now) surveying people about their practice, people are kind of all over the place on what they do. Some people say, "Well, it's not very much plasma and that potentially incompatible plasma, if you give it to like an O platelet to an A patient, you know the A antigen is not just on their red cells, it's on their endothelium, and then it gets adsorbed and so there isn't as big of a risk of hemolysis." So, some people just don't really think about ABO and just give platelets as platelets are requested. Other places, and we are one of the more conservative places, we actually TITER the anti-A and anti-B levels in our group O platelets, and we make sure that they're "low-titer" if we're going to give them to a non-O patient.

Joe: So, Nancy, let me interrupt you there for a second. Why specifically do you titer group O's as opposed to titering groups A's and group B's?

Nancy: Yeah. So the reality is, we don't often have group B platelets, so that's an easy question [laughs]. And we know that group O people in general tend to make higher titer anti-A and anti-B than an A person would make anti-B, or a B person would make anti-A. And I'm not exactly sure why that is, but that's been demonstrated. So typically, we, if we're going to give an incompatible platelet (because we tend to get a lot of O platelets for some reason...it's a common blood type), we do titer that. That's our policy, and if we have to give, for example an A patient a B platelet or vice versa, we CAN titer that. We don't routinely titer that (it's not a situation we encounter as frequently), but it is something we *can* do. But routinely, when we bring O platelets into inventory, as a standard practice, we'll titer all of them. And then if it's a "high-titer" unit we'll set it aside so that only a group O patient would receive that.

Joe: I almost hesitate to ask this question, because I know that things are all over the board, but when you say "high-titer," what do you mean? And I say that acknowledging that people do this differently. So what do YOU mean when you say that?

Nancy: So we do an immediate spin, single dilution, 1:50 in saline, and if that is negative, it is considered "low-titer."

Joe: Gotcha. Okay, so forgive me, I interrupted you. So, when you have these platelets that are group O and low-titer, do you use them across the board as kind of... in other words, you would feel comfortable giving those to a group A or a group B, or an AB patient?

Nancy: Yes and no. Of course, it's a little more nuanced than that. So for the first platelet in the 24-hour period, that is acceptable to give a low-titer without

any consultation with the Transfusion Medicine physician. But if a patient's requiring more than one out of group platelet in a 24-hour period, then we do let the Transfusion Medicine physician know, so they can potentially monitor that patient more closely for signs or symptoms of any kind of hemolysis, or make sure that the platelet transfusion is really indicated. But that again is our local practice, and I think we are on the more conservative side of the spectrum, regarding ABO incompatibility in platelets.

Joe: Well what about, you mentioned that some people kind of don't even consider it. Some people do a strategy more like yours. Are there people on the other side of that?

Nancy: People even more conservative than us?

Joe: YES! [laughs]

Nancy: Yeah, yeah, so you can do all sorts of things. You can, I mean, if you really, if you are "rich in platelets," I guess you could only give ABO-identical platelets; that would be, I think, ideal. I don't think anyone would argue with that. You could certainly wash the platelets if you are worried about either incompatible plasma or soluble antigen that can potentially complex with antibody in the recipient. That's something that there is some concern about in some areas. So those are things you can do. I mean everything has a risk and a benefit. You know, washing the platelets removes things that might potentially be harmful, at the cost of reducing the count of the product that you're transfusing, and at the cost of more processing time and handling, and tech time. So, everything has to be weighed against the risks and the benefits.

Joe: You bet. I think maybe we could summarize it by saying, in a perfect world, everyone would agree, I think, that ABO identical is best, but based on logistical and supply concerns, the *prevailing practice* is to cross ABO boundaries in one way or another with platelet transfusion. Is that a fair way to put it, Nancy?

Nancy: Yeah. That's a fair way to put it, and I think as far as meeting regulatory requirements, you just have to define what your procedure is. So, you have to describe if you're going to give ABO-incompatible products, what that process is, and as long as you have a well-defined process, that is acceptable.

Joe: Okay. Well, and I think both you and I are aware that there are some people that would very strongly disagree with that, and I'll just say it: Dr. Blumberg at University of Rochester would have fairly strong disagreements with that practice. He's published on that, in fact, I think I will link to one of his articles that he has published with his arguments and

his editorials regarding why he doesn't think that is the safest practice in the world [NOTE: See links at BBGuy.org/060].

But Nancy, we need to move on and talk about Rh. So, can you give us a little thumbnail about how we consider the Rh boundaries, in particular Rh-positive platelets going to a Rh-negative recipient?

Nancy: Yeah, so the good thing in this scenario is that the platelets do not express Rh. So what you're actually worried about are the small number of red cells that might be in that platelet product, that could alloimmunize an Rh-negative recipient. And we know that that happens. It seems to happen more frequently in whole blood-produced platelets. They have a higher degree of red cell contamination. And it's not clear to me if it happens with any regularity in apheresis platelets. I suspect it's quite a rare complication of apheresis transfusion. But the data I think was mixed because they didn't really specify whether people got whole blood platelets or a combination of whole blood platelets and apheresis platelets. So, the jury's still out on that.

So, again, I think some places just transfuse platelets without regard or concern for Rh. We tend again to be more conservative. So, if we give an out of Rh group platelet to a woman of childbearing potential, we do offer RhoGAM, to cover not just that platelet but a certain volume of platelets within a certain time period. So, that is something we occasionally do. Interestingly, we stopped offering RhoGAM to NICU babies because we don't think they can make antibodies when they're premature and in the neonatal ICU, so we do give out of group platelets to that population and we don't give RhoGAM. But most others do at least have the opportunity to receive RhoGAM.

Joe: Okay. Again, let me try and summarize what I think I heard you saying and what my experience has been as well, is that in general, giving that Rh positive (apheresis) platelet anyway to an Rh negative recipient, generally is considered fairly low risk though the data as you said, is a little challenging. And in terms of what we need to do in those scenarios, generally a single dose of Rh immune globulin is protective for those patients.

Nancy: Yeah, well that is what our approach is, so we are hopeful that, that's the case [laughs].

Joe: [Laughs] Fair enough, I understand. Well, you know again, those are questions that I get quite often from facilities that are concerned about crossing those boundaries, both with ABO and with Rh, so I really appreciate you going through that.

Before we leave platelets, I'd like to just mention a couple of other strategies that you've described, and the first is the extension of platelets

from five to seven days, and we don't have time to go into great detail on this, Nancy, but what can you tell us about that?

Nancy: Yeah, so that was something that kind of came onto the scene with the draft guidance that the FDA published, to both reduce risk of bacterial contamination and increase the availability of platelets. And so, there's a pretty well-defined process that's described in the guidance that does allow for extension to seven days. So, we've been doing that since about 2015. It does involve additional testing and additional tech time. But it's really been very impactful for us as a rural transfusion service, quite distant from our suppliers, because it does give us an extra two days of platelet shelf life, which can really make the difference between having a shortage if we get unanticipated demand.

Joe: You have described that in the past elsewhere, so we won't go into any more detail on that. And everyone, I should make really clear, just to put everything on the table, my friend Nancy has already disclosed that the company that manufactures the test that allows you to go from five to seven days, that she's been compensated for her role on the medical advisory board with that company. Take that for what it's worth. Again, we're not saying anything more about it, but it's important I think for us to get that out on the table [NOTE: Please see disclosures at www.wileyhealthlearning.com/transfusionnews].

Nancy, one more thing you have mentioned in the past, the use of "splitting platelets," or using low-dose platelets, and I'm curious about that. What do you mean by that?

Nancy: Yeah, that's another strategy we find to be quite useful in our rural location, distant from our suppliers. So, many of our suppliers, the majority at least, do put the count of the unit on the bag when we receive it into inventory, or communicate that to us on the packing slip or something. So we know how many platelets are in the bag. And a standard requirement for a platelet, an apheresis platelet, is 3×10^{11}, but we know that some platelets are very big. We call them "juicy platelets," and some platelets are closer to that 3. And it all just depends on how close they were to making a "double" or a "triple" out of the donation, based on their own splitting rules at the manufacturer.

But sometimes we have in our inventory a platelet unit that's 6.0×10^{11}. Just was so close to being a double and just didn't quite make the cut, and so we unexpectedly kind of get what we consider "two platelets for the price of one." If we have shortages, we'll split that into two bags. We routinely split units that are higher than 5.0×10^{11} and give them to non-bleeding patients, just as an inventory-sparing strategy, and during severe shortages, we can go even lower. That gets to involve the Transfusion Medicine physician when we're making those decisions, but that can help us sometimes to not have nothing on the shelf.

Joe: Right, and to be clear, for the smaller facilities out there that are listening: This isn't something where you can just "pour the platelets out of the bag" [laughs]. It requires a sterile docker and proper technique, right?

Nancy: Right, and you have to be able to label platelets, because we relabel them as divided units, and so I believe that would require at least FDA registration, because you are at that point in time, "manufacturing." So, yeah, that's not an option for everyone but it is quite helpful for us in our setting.

O-negative Red Blood Cell Choices and Strategies (OPTIMUS Study):

Joe: Well that's great Nancy, thank you again for that. I want to move on to talk about red blood cells, in particular O-negative red blood cells. You have been involved, in fact, you were the lead author on a really, really cool and somewhat groundbreaking article that really has helped people to understand how O-negative red cells are being used in current blood banking. That study was published in Transfusion earlier this year, in 2018. It was called "O-Negative Product Transfusion, Inventory Management, and Utilization during Shortage" and creatively entitled the "OPTIMUS Study" (as "Transformers" are running through my head, Nancy!) I'm sure that was completely unintentional right, there was no intent there? [laughs]

Nancy: No, no. That was definitely by design. That was definitely a nod to "Optimus Prime." [laughs]

Joe: That's fantastic [laughs]. So before we get specifically to what you guys found, I wonder if we could set the background a little bit. We talked earlier about the fact that blood usage in general is down pretty substantially in over the last 10 years or so. Do we have any date to suggest whether or not O-negative red cell use is changing over that time frame?

Nancy: Yeah, we do. There are utilization surveys that happen and they provide datable from the collections and the transfusions, so we see both sides. I think the most recent data, or at least the data we quoted in the OPTIMUS Study, showed us that even though overall utilization was down, the use of O-neg as a proportion of the utilization was actually increasing. People are using less blood, but they tend to be using more O-negative, and there are lots of reasons for that. It is concerning, because there's a mismatch between the current utilization and the available donor pool. Which means that there is predicted that there will be shortages, and there already are.

Joe: Yes, you and I have both experienced that first-hand. Me from my current role in a blood supplier, and you in your role in a hospital transfusion service. There's no question that O-negative shortages are not getting better, and in fact, I fear that they're somewhat getting worse. Let's talk about general principles about O-negative use. Nancy, people listening to

this podcast are going to be at varying levels in their career, but just from the big picture perspective, generally speaking, **who should and should not get O-negative red cells**?

Nancy: So there was a great study done by Michelle Zeller, with the BEST Collaborative, and we here at Dartmouth participated in that study, the "GROUP study" [NOTE: See reference at BBGuy.org/060], and that really tried to answer those questions: Who's getting O-negative blood? We know that obviously O-negative patients are getting O-negative blood, but we also know that a lot of other patients are getting O-negative blood. It's the population that you can predict, it's the trauma patients of unknown ABO type, the Emergency Department bleeding emergencies who roll in the door, you don't know what their blood type is, you give them O-neg because that's the universal donor. It's the neonates in the ICU, who, it's just easier if you're keeping small aliquots of fresh blood, it's easier to keep O-negative for those patients, because then it doesn't matter who's using it, and it's compatible with everyone. It's your bone marrow transplant patients whose blood types are changing, and O-neg might be the type that's compatible with both the donor and the recipient. It's your highly alloimmunized patients who need antigen-negative blood and group O blood and O-negative blood is often the type of blood that's been antigen typed, so if we need to grab units that are antigen negative, it may be more likely that it's O-negative.

The types of patients who use O-negative blood beyond those who are O-negative are a wide variety of patients. I think that's why we see that mismatch in donor and supply, because it's not just going to people that are O-negative, it's going to a wide variety of patients for a lot of different reasons. Not to mention the fact that nobody wants to waste O-negative blood, so when it's getting "old," if you happen to have the luxury of some getting expired on your shelf, you're going to give it to someone that's not O-negative because you don't want to throw it in the garbage [laughs].

Joe: Right. Yeah. For sure.

Nancy: So that's another not unexpected finding. So the GROUP study really clarified, "Where is all the O-negative going?" That really inspired me to ask a very different question on the OPTIMUS Study.

Joe: Okay, I promise you we will get to that in just a second, but there's one more background question I'd like to ask you before we get there which is this. You talked about the patients that are getting in the GROUP study, that you mentioned those populations were outlined that are getting O-negative blood, so let's switch the focus for just a second. Let's imagine that a patient is Rh-negative, whether that's O-negative or another blood group, what would be the consequences for those patients if they did NOT get Rh-negative blood? So what? Why do we care about that? What's the big deal?

Nancy: Yeah, I mean it's funny. We're kind of ingrained to think about the Rh barrier the same way we think about the ABO barrier, but they're really two very different problems, right? You give out of group ABO blood you might have intravascular hemolysis, and a transfusion reaction, you could potentially die from that. When you give Rh incompatible blood, as best we can tell, there's generally no immediate risk. A very, very, very small portion of the population may have preexisting anti-D antibodies, but it doesn't seem to cause immediate intravascular hemolysis, if the stars align in such a way that a previously alloimmunized patient gets Rh-positive blood. So really, the way I think about it, all you're really doing for most patients is potentially "burning a bridge."

So, we know that people who are Rh-negative who get exposed to the D antigen can make an antibody against the D, an anti-D antibody. So if they make an antibody, then for subsequent transfusions, then you need to support them with antigen negative blood as you would for any other antibody. D is unique because it's the only non-ABO antigen that comes labeled on the bag [laughs]. We don't know without testing it what is Kell negative or Jk^a negative, and we give people incompatible units all the time, which is why people make antibodies. It's hard for people to kind of wrap their head around.

Joe: [laughs] Nancy, do we have data on how often that happens, those Rh-negative people that get Rh-positive blood, and how often they make those antibodies?

Nancy: Yeah. As most things, what we thought we know, we didn't really know. So the very early studies were done in prisoners actually, where they took healthy people and they gave them an exposure to the D antigen, and then they followed up to see who made antibodies, and about 80% of them did. Which tells us that the D antigen is very immunogenic. Interestingly, when we repeated those studies in *actual patients*, sick patients, not healthy people, we found a much lower rate of alloimmunization, so it depends on which population you're studying. Trauma patients appear to be in the ballpark of 20% of those who are exposed to D antigen will make an anti-D antibody. Other populations may be lower, like critically ill patients. We've not studied all populations, but we have a sense that the D antigen is immunogenic, people will make antibodies, but not 100%, and it may be lower than we previously thought.

Joe: Okay Nancy, I can't quite leave this yet, there's one more thing I want to ask you because I hear this kind of thing a lot. Blood bank technologists say things to me like "Well, we were going to switch but we couldn't get a hold of the pathologist to get permission" or "we couldn't get a hold of the clinician to make sure that they were okay with our switching." How do you feel about things like that, should those be barriers to switching?

Nancy: No, I mean I think those kind of issues reinforce the fact that this should be protocolized, it should be something that you're not trying to get agreement or consent from the various stakeholders at the moment when the patient is requiring transfusion. That's why you should have policies and procedures in place that allow for switching that don't require permission. So, for example, we have a policy and procedure in place that if we get blood on the helicopter, it's always O-pos. I think that's not the time to be wasting time trying to get permission from the pathologist and/or the clinician who's caring for the patient, because that's only delaying care. And the bottom line is, if you run out of Rh-negative blood, they have to be switched simply because you don't really have any more Rh-negative blood, then it's no longer really a choice.

So, I think that **I tell clinicians, "You're going to get group O uncrossmatched blood when you have a patient who's exsanguinating, and it might be Rh-negative and it might be Rh-positive. That's really my call, and so just trust me to do my job."** We know we have these switching rules in place and they've already been agreed upon by the stakeholders so there isn't this "panic at the moment" thing, and "we've got to let people know." It should just be sort of “protocol-described,” and people have faith in us to do our jobs and take care of patients, and at the same time, take care of the blood supply.

Joe: Yes. Okay, well with that context and that background, Nancy, I know you're chomping at the bit to get to OPTIMUS. I'm anxious to hear about it. Let's talk through OPTIMUS. In particular, you had mentioned that the findings in the GROUP study led you to want to ask a different question. What was that question, and how did you structure going about finding the answer?

Nancy: It was hard to pitch this study. It really took a while for me to explain, "This is what I want to know," because it's such an unusual question. GROUP told us, "Who are the people who are not O-neg that are using O-negative blood?", because that's the low-hanging fruit to target, reducing utilization, right? A very concrete example is, we give O-negative to every person who rolls in the emergency room who is bleeding, before we know their blood type. Maybe we don't want to do that. Maybe we can conserve blood by giving select patients O pos.

The OPTIMUS study was, "Okay, let's imagine a really worst-case scenario. Let's think about, 'What if I really didn't have enough O-negative blood to support my O-negative patients?'" I'm not talking about switching someone who's blood type I don't know. I'm talking about, "I know what your blood type is. You're O-negative and I don't have enough to give it to you," How do I decide? As a transfusion service medical director, how do I decide? Who's going to get the O-neg? Who am I going to say, "You know what? Today you're going to have to get O-pos, because I just don't have enough for you." That to me, seems like kind of a really shocking question.

It really takes everything we've been taught about giving people the right blood type and saying, "Well, sometimes I'm just not going to be able to do that."

How do I prioritize who gets the O-neg and who gets the O-pos in that situation? That's how OPTIMUS was born. We really wanted to look at, "Who are our O-negative patients who are using O-negative blood?" so that you could identify populations where you could actually make an impact on utilization if you did have a shortage and have some medical rationale for who you might switch to O-pos.

Joe: Wow. Yeah. There are a lot of people out there right now that are shivering with goosebumps, saying, "Wait. What? You know somebody's O-neg, and you're not giving them O-neg?!" That's a little bit terrifying. But, at the same time, as you said, these are really, really important questions that we have to ask. Nancy, tell us, how did you gather data for this? Where did you search, and how did you do so?

Nancy: We approached many of the same people that had participated in the GROUP study, because they had already selected transfusion data. What we wanted to ask for wasn't that much additional data than what GROUP had asked. We needed to know about all the transfusions that a center gave in any given year to all patients, and what blood type of the units were, and what the blood type of the patients were, because that can help you figure out what's the utilization of O-neg and what percentage of that is O-negative patients actually getting O-neg, versus non-O-neg patients getting O-neg?

Then we also wanted to know about the age and the location and the gender of the patients, because we thought those factors might help us create “switching rules.” Who are we going to switch? Are we going to do it based on age, gender, location, some combination? Where do you get the biggest bang for your buck? Where do you have some medical justification for that decision-making? We collected those data, and then we were able to retrospectively analyze it in terms of the impact, if you had decided to give certain populations O-pos instead of O-neg.

We were able to get 31 sites participating from around the world; mostly in Europe, North America, and Oceania--Australia, New Zealand--almost a half a million transfusions internationally, to help us understand how we use O-negative blood for O-negative patients.

Joe: Let's just ask the most basic questions. You can take us through this however you want. The first and most obvious question is: What did you find, in terms of the total percentage of O-negative utilization?

Nancy: It's about what you would expect. I think the 2015 blood utilization survey in the US, had the demand at about 10.8%. Our study, all-comers, came in

at a little less than that, 8.7%. But there was a range. In Israel, we had a number of sites from Israel. They were low, or on the lower end, less than 5%, and some sites were over 10%. As I thought about why are we lower than the blood utilization survey, I think it reflects more of an academic medical center population that may already have some O-negative conservation measures in place; things like using O-pos for trauma, switching people who are using a lot of O-negative blood, if they are having a large demand for blood.

Our findings weren't that different than what you would expect, and there was some variation both geographically and from center to center, right in line with what we'd already known from previously published studies.

Joe: Just for reference's sake, Nancy, this is just for, again, for those that aren't necessarily familiar with O-negative, do we have any idea what proportion of our blood donors are O-negative?

Nancy: Yeah, I think that same U.S. 2015 survey said that about 8.2% of the donors are O-neg. There is a mismatch of supply and demand, which is why we see the shortages that we see.

Joe: Again, I don't want to tie your hands in terms of how you want to go through this, but I guess, for me, the next most obvious question would be: Did you get an idea of how many of those O-negative units went to specifically O-negative patients?

Nancy: Yeah, that was the first question that we wanted to ask, to see how we would compare with GROUP. We saw, not surprisingly, that only about 56% of the utilization was specifically for O-negative patients. The remaining was for non-O-negative patients, for all the reasons that the GROUP study identified. We know that the O-negative population using O-negative blood is only about half of the actual O-negative utilization. There is a lot of low-hanging fruit in the non-O-negative population to address before you necessarily have to start switching your O-negative patients.

Joe: I would love for you to take us through specifically the things that you guys talked about towards the end of the paper, in terms of your thoughts and potential recommendations, regarding age of the O-negative recipients and location in the hospital of those O-negative recipients. I'll leave it to you to exactly how you want to do that.

Nancy: The first thing we wanted to look at was: How does the use of O-neg shake down by age? Not surprisingly, quite a large percentage of the O-negative utilization is in older patients. Those are the patients that are more likely to get transfusions. That shouldn't be a big surprise, but it's interesting because we worry a lot about exposing someone to the D-antigen and alloimmunizing them, because we worry about the impact on future pregnancies. The nice thing is that if most of our users are patients

over age 50, then the impact in potentially switching women in that population is low, because that population is very unlikely to have a subsequent pregnancy that's compromised by D-alloimmunization.

I wasn't surprised to see that, like blood utilization in general, most of the O-negative people getting O-negative transfusions are elderly patients. That's not surprising, and I think it was a very large proportion of our study. I think it was **45% of the O-negative patients who received O-negative transfusions were more than 50 years old**. That's already a target population, if you just wanted to do an "age-based switching rule," you could pick any age group. "Today I only had five O-negative units so any patient over age 50 is going to get O-pos today." That's one really easy way to do that. That has the ability to cut your O-neg utilization by half, essentially.

That was the first easy group to analyze. I think in Transfusion Medicine, we try to be really thoughtful about risks and benefits. We wanted to take a much deeper dive and not just say, "Okay, as of today, we're just going to use age as the cutoff," because not all 50-year-olds are the same, right? Or 60-year-olds or 70-year olds.

Then we looked at location. Who uses a lot of blood? The location of the O-negative utilization ... you know, most of the largest utilizers were the hospital ward. That might include Heme-Onc patients. But the second largest was the intensive care unit. That jumped out at us as a potential area where you could switch patients, because patients in the intensive care unit are critically ill by definition, and those patients are less likely than other transfusion recipients to actually survive a year beyond their transfusion episode. If you are an ICU patient requiring transfusion, the odds of you surviving compared to another patient in the hospital, who's also receiving transfusion, they're lower by virtue of your location.

We thought, "Well, gosh, if intensive care unit patients are using a lot of our O-negative inventory--that's about 20% of the O-neg used by O-neg patients--could that be a population where you could selectively apply switching rules?", which potentially could be less impactful than switching, for example, a Heme-Onc patient who has maybe potentially many, many more transfusions that they may be receiving on a chronic basis. Alloimmunizing them and then burning that bridge where they're now going to need O-negative support, because they've made an anti-D is less helpful, right?

Intensive care patients either are going to survive their illness and potentially not require a transfusion, or they're going to not survive, and you won't have to deal with the consequence of their alloimmunization. Then we looked at the intensive care unit, and then we broke it down by age. Essentially, we were targeting for about a 10% reduction in overall O-negative utilization. **The population we identified that almost reached**

that target 8.8%, was to switch ICU patients over age 50 to O-positive units during shortage would reduce your overall O-negative utilization by about 10%.

You can slice it a bunch of different ways, but I think having a metric to say, "Okay. I have a shortage. How can I cut use by about 10%?" That's one way to do it, and thinking about risk versus benefit in that population.

Joe: Nancy, to be clear, I just want to make sure that I'm understanding. Is it your thought in the conclusion of this paper that switching those O-negative ICU patients over 50 to O-positive, is that something you're recommending or considering at all times or just at times when you have shortages?

Nancy: No, I think just at times of shortage because, like I said, you're burning a bridge and you do have potential downstream consequences that you may have to address if you do that, so I think that would be sort of a "tool in your toolbox." I would hope that hospitals are already addressing the other ways to reduce utilization. Like I said, here at Dartmouth, we only have O-positive on our helicopter. We do keep some O-negative emergency release units that we give to women child-bearing potential, if they come in through the ED, but essentially, once we switch you, you're switched until the bleeding stops.

We also switch even women of childbearing potential who start out on O-neg: Once they've used 6 units, if the bleeding continues, we switch them. We switch surgical patients who are using a lot of O-negative blood very, very quickly if it's anticipated that they're going to deplete our blood supply.

Those are things we already do. That's where, I think, centers should start. Really reserving this switching for routine transfusion as kind of a last resort for really the situation when you are told by your supplier, "We have to cut your standing order," and you're down to 5 units on the shelf, and you have to make some tough decisions about who you're going to protect from alloimmunization today, and who you're going to take the chance they're going to become alloimmunized.

In my practice, I don't see this as a permanent solution. I see it as a very fluid, looking at your inventory on a daily basis and making those tough choices. This just gives you some justification, some data to say, "Well, how about this population? I have to switch somebody. There's some rationale for why this population may be a potential target to actually yield some actual savings."

Joe: I think really for me, Nancy, that is the biggest value ... I think this is an incredibly valuable paper in general, but what you just said, I think, is the biggest value. From my perspective of this paper is that we all know that in Transfusion Medicine, you're going to come to places where you're going

to have to make difficult choices. Having to make difficult choices without any frame of reference, makes those choices doubly difficult, I think. What you guys have given us, is somewhat of a framework and somewhat of a, not necessarily a "guideline," but a general idea, I think, of where to look for possibilities and where data exists. I think that's really, really crucial. I salute you guys for that. I also salute you for the cool name of the article, by the way [laughs].

Nancy: Yeah, well, thank you! I just want to say, because this is so interesting to me: When we started this project, I thought that the real interesting question might be trying to get some clarity about where to switch women of childbearing potential, because in the article, we talk about different approaches. Some people use 50 as the cutoff. Some people use 45. Some people use 55. When do you say a woman is “past childbearing potential” as a blanket statement? I thought that the interesting finding would be that. Where should you make that cutoff?

The reality is that population uses so little O-neg that it doesn't really matter where you put your cutoff. 45, 40, 50, 55; it doesn't matter. You're not gaining much by moving that dial slightly. It's not that population that's using the supply. Agonizing about whether you switch people at 45 or 50 or 55 is just that: You're agonizing, but you're not really accomplishing anything, because those aren't the people who are using most of your O-negative blood.

Joe: But we're blood bankers! We like to agonize about little stuff! [laughs]

Nancy: I know. We do! I think it's so funny that until you actually see the data, you probably don't realize that it doesn't matter. Just pick a number! Just pick a number and be okay with it! Then figure out what you're going to do when you really don't have blood, and you really have to make those tough decisions.

Joe: That's fantastic. Well, everyone, again, the article was published in Transfusion in, I want to say, June of 2018, Nancy--I believe that's correct--in June of 2018, called "O-negative product transfusion, inventory management, and utilization during shortages: The OPTIMUS study." We've spent the most of the time on it today because I intended for that to be the main focus. Nancy Dunbar, thank you so much for being with us. Thank you so much for explaining your thoughts behind this article, and for giving us really so many practical tips and things that we can hang our hat on.

Nancy: It's my pleasure! Thanks so much!

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Joe: Hey, it's Joe with just a couple of quick closing thoughts. My thanks once again to Dr. Nancy Dunbar for joining me today. I think that was a really

interesting discussion. I hope it was useful to you. There's a lot of really practical stuff in there that you could put into place very quickly that could really make a difference, not just for your hospital, but for the entire blood inventory in your area. It can really make a big, big difference.

Remember, you can go to www.wileyhealthlearning.com/transfusionnews and get your hour of totally free continuing education credit for both doctors and laboratorians. Also, you can go to the show page for this episode, which is BBGuy.org/060 and you can find references, links to the OPTIMUS study that we described, as well as multiple different other studies that Nancy talked about.

If you have the opportunity, I would love it you could go to Apple Podcasts and search for Blood Bank Guy Essentials. Give this podcast a rating, a review, a subscription; all those things help new people find the podcast. Really, that's what I'm trying to do is get the podcast in front of as many people as possible.

I have a lot more episodes of Blood Bank Guy Essentials coming soon, lots of great guests, lots of interesting topics, and I can't wait for you to hear all the things that are coming up. Until that time comes, my friends, as always, I hope that you smile, and have fun, and above all, please, never, EVER stop learning! Thank you so much for being here. I'll catch you next time on the Blood Bank Guy Essentials Podcast.