

**BBGuy Essentials 065:
Transfusion and Jehovah's Witnesses with Jed Gorlin
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Jed: This is Jed Gorlin, Medical Director of Innovative Blood Resources in Minnesota, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, everybody! I'm really happy to welcome you back to Blood Bank Guy Essentials, the podcast where I am laser-focused on helping each of you learn the essentials of Transfusion Medicine. This is Episode 065, and my name is Joe Chaffin.

Today, I'm really excited to be interviewing one of the most unique and charismatic gentlemen that I know. His name is Dr. Jed Gorlin, and we're going to be talking about a topic that, frankly, we all wish we really would never have to deal with. That topic is what to do when someone shows up at your hospital [and] says, "I'm a Jehovah's Witness, and I do not want any transfusion whatsoever." Jed's going to walk us through exactly how he's handled these challenging situations and give us some great advice on things that we can and we can't do.

But before we get there, you should know this is NOT a continuing education episode. You can find other episodes where physicians and laboratorians can get those wonderful continuing education credits for no charge whatsoever. You can find that at BBGuy.org/podcast. You just look for episodes that end with the letters "CE" (Shocking! It's a brilliant code, but I think you can break it!). Anyway, you can also visit wileyhealthlearning.com/transfusionnews. At that site, you'll be able to find, again, all of the continuing education episodes. The continuing education episodes there at that site are brought to you by TransfusionNews.com and Transfusion News is brought to you by Bio-Rad, who has no editorial input into this podcast.

Now, I want to be really, really clear on our topic for today. The point of today's interview is NOT to either make fun of or make light of the beliefs that those who are Jehovah's Witnesses have about blood transfusion. They're not the only people who refuse transfusion, for sure, but Witnesses are really kind of out on the front lines of those who do say "No" to transfusion. They've made their position abundantly clear in many, many publications that are freely available, so again, we're not going to be talking about anything that's not readily available and published already in many cases by Jehovah's Witnesses. The point is, it is what it is, and what I hope we all learn from this interview with Jed is exactly what to do when you're faced with a patient who just will not accept blood as a result of a very closely-held religious belief. Jed has great insights. He's faced this on numerous occasions, and he's kind of become a little bit of a "go-to" person on this, just because he's faced it so much in blood bank world.

Speaking of Jed, Dr. Jed Gorlin is Medical Director and Vice President of Quality Affairs at Innovative Blood Resources. His duties include Memorial Blood Centers in Minnesota, Nebraska Community Blood Bank, and the Community Blood Center of Greater Kansas City. Jed's background is in Pediatrics and Pediatric Hematology/Oncology, but he's also board-certified in Blood Banking/Transfusion Medicine. Jed has been around for a while, and he's served in numerous leadership capacities in AABB throughout the years, including Chair of the Standards Committee, actually, for the 20th and 21st editions of the *AABB Standards*, and he's also been an AABB board member. Jed is a chapter contributor to 21 published books and anthologies, and author or co-author of over 120 published papers and abstracts. Jed's a great guy, you'll see right away. If you haven't heard Jed before (he's been on this podcast before but if you haven't heard him), Jed is unique and hilarious. The guy cracks me up, and I can't wait for you to hear this interview with Jed about "Transfusion and Jehovah's Witnesses."

Joe: Jed, my man! Welcome back to the Blood Bank Guy Essentials Podcast!

Jed: It is an honor to be here.

Joe: Well, it's MY honor, sir. I have said before in many forums how much respect I hold you in, and even though I know that's going to go straight to your head and you'll be unbearable for the rest of this interview, it's really great to have you back. You and I talked, I think it was a couple years ago now about iron in blood donors, but today we're going to go a completely different direction and we're going to talk about patients and what to do when transfusion is not an option. Something that you have become a bit of an expert in, and kind of a "go-to" guy with this, Jed. How did that happen? How did ... in organizations like America's Blood Centers, you have kinda become, by default, expert almost in discussions about patients with ... Jehovah's Witnesses patients, and patients that won't accept transfusion. How'd that happen?

Jed: First of all, in all humility, there certainly are many other medical directors that have been faced with this same conundrum. I happen to have the dubious distinction, however, of being both medical director at the blood center in the Twin Cities, but also the largest of the three level one trauma centers. And for reasons that are probably historic, it happens to be the hospital of choice for the Jehovah's Witness community locally. The combination of Jehovah's Witness and level one trauma is not an ideal combination, but we try to serve where we can.

Joe: Gotcha. Well, some of the materials that you have put out, lectures that you've given, have been really useful to me in my practice, and clinicians in the areas where I serve, so thank you for that. I've told you that before, but I want to officially thank you for the work that you've done.

I'm wondering if, just as a way for us to get started with this, Jed...I have seen some of the things you have published about patients who will not accept transfusion, such as Jehovah's Witnesses, and I saw one in particular where you described a very acute and kind of scary case that you guys had at your facility. I wonder if you'd just take us through the early part of that, and give us the background on how these things can present.

Jed: This was actually a referral case, and the referral sort of biased significant portion of the therapy, not necessarily to the positive, may I add. Not only are we the largest of the level one trauma centers, but we are the only hyperbaric oxygen chamber in the region. So, a previously healthy 31-year-old was transferred to us because of the referral for hyperbaric oxygen. She happened to be a Jehovah's Witness who was delivering, I believe, not her first child, and it was complicated by prolonged labor, chorioamnionitis, difficult extraction requiring vacuum assistance which resulted in a perineal tear and subsequent significant blood loss.

48 hours after delivery, her hemoglobin was down to 4.4 [g/dL], and that's when they decided to transfer her. That was down from 11 [g/dL], so more than half her blood volume was on the floor somewhere. They obviously replaced her with fluids, but at that point, she was essentially refusing all transfusion of cellular products: Red cells, platelets, plasma.

When she got to us, she was awake, alert, normal mental status, was fully aware. Had the discussion of what she would and would not accept. We actually have a "Bloodless Medicine" self-designation, and so there is a "bloodless medicine order set." Gives the residents a whole list of things, which we can talk about in a bit, things to discuss. But basically, we immediately ascertained what she wouldn't take. Interestingly, there were surgical interventions that were done. It was retained placenta, so she went ... Well, they went to first the IR suite, where she underwent bilateral uterine artery embolization. One thing is stopping ongoing bleeding, but that was recognized that she also still had retained placenta that was continuing to ooze, so she went to the OR for removal of that.

She received tranexamic acid which probably everyone with significant postpartum hemorrhage should get, then she also got empiric antibiotics for endometritis because of the concern with the retained placenta that there may have been some infection setting up. That was now day three post-delivery.

Joe: Okay. So just to be clear, Jed, she was sitting at 4.4 [g/dL] hemoglobin, but clinically, she was relatively stable at that point?

Jed: Awake, talking. Because of the very low hemoglobin that we didn't have the option of transfusing, she was sent to the intensive care unit. As you could imagine, given that she was still having ongoing bleeding that didn't really cease until the multiple procedures in the operating room, and she re-

equilibrated the following morning, her hemoglobin was down to 3.1 [g/dL]. And she was starting to get agitated, confused, EKG was showing mild changes, diffuse ST segment depression, and that's when I got the call.

Joe: Wow. Okay. Well, everyone, I'm going to hold Jed right there, and we're going to come back around to this case at the end, and find out all the things that happened. And it's really a great story, but I want to back away for just a second, Jed, and let's talk a little bit about patients in general who refuse transfusion, or patients in whom transfusion is not an option.

I wonder if you have some perspective on this, Jed, and just in your program or anything that you might know nationally. Has the group of people that are saying, "Hey, transfusion is not an option for me," has that changed over the years? If you looked at people that were interested in "bloodless medicine" today as compared to, say, in the 90s or even early 2000's, is there any difference? Or is it still just all patients that are Jehovah's Witnesses?

Jed: Refusing blood is not isolated to the Jehovah's Witness community. I would say it is most common. Clearly, Christian Scientists may choose to refuse all medical care; that's obviously a whole different conundrum. I would say in my experience, it has been largely, personal experience has been largely limited to the Jehovah's Witness community.

I need to interject here that my origin is as a pediatric hematologist and then Director of the Blood Bank at Boston Children's. In kids, this is very simple. The Supreme Court Justice Oliver Wendell Holmes, in the definitive case, said, "You can make a martyr of yourself, ma'am, but not of your children." We literally, within five minutes, could get the lawyers on the phone and a patient transfused. And I had a mom look me in the face and say, "I cannot personally give you permission to transfuse my child," who was in quite extremis, "But if you want to call the judge, that's okay." There clearly are parents who don't want the responsibility on them, but understand that ... well, understand the Supreme Court directive.

That said. The Supreme Court has also ruled that adults have autonomy and can make decisions that may not be in their medical best interest. You can be sued for assault and battery if you transfuse a Jehovah's Witness who has clearly refused, even if you think you're saving their life. You may be saving their life, but that may not be what the patient wanted.

Joe: Okay. We'll get to some of those details in just a few minutes when we talk about discussions that we have with Jehovah's Witnesses prior to, hopefully, prior to them needing blood, but let's just talk a little bit about Jehovah's Witnesses in general, Jed, and their rationale for why they decline blood. Is this a religious issue or is this a medical issue for them?

Jed: I really make no pretense that I am or should be the spokesman for the Jehovah's Witness community. I certainly have tremendous respect for

people to have whatever religious beliefs they so choose, and it is our role and responsibility as clinicians to, as much as we can, and that's a point for discussion, accommodate their needs and wishes.

There are several places in the Old Testament that refer to not taking of blood. It is not lost upon you that, at the time The Bible was written, nobody was being transfused. Among other things, they didn't have needles and tubing and syringes and bags and anticoagulants that made it possible. It's not reasonable, even in retrospect, to assume that that reference was DIRECTLY discussing transfusion, and how it gets extrapolated to transfusion is, in fact, a theologic conundrum beyond my expertise.

Joe: Understand. Understand. And that is completely fair. And everyone, I share what Jed just said. It's not in any way my goal, or, I know, Jed's goal to denigrate anyone's religious beliefs or interpretations of The Bible that may differ from other folks. This is simply a way to try and understand what we're facing as Transfusion Medicine professionals, and figuring out ways to try and take care of people as best we can.

With that being said, Jed, my next question for you regarding Jehovah's Witnesses is, it's just a myth or fact question, and it's simply this. Is this a myth or a fact? All Jehovah's Witnesses approach that restriction the same way.

Jed: Since you set it up that way, I'm going to fall on the side of "myth." The Watchtower, which is the publication of the Jehovah's Witness Society is fairly definitive in proscribing, i.e. not allowing, red cells, platelet and plasma transfusion. It's completely up to the elders and individuals what derivatives, plasma fractions, coagulation factors, et cetera, they choose to take. And it can be quite variable, even within a local community, what patients will accept beyond the standard products.

Joe: Okay. For things ... you mentioned clotting factors and derivatives. Can you give me some examples of some of those things that might be optional or individual choice? Or local choice?

Jed: We have, unfortunately, had the experience of a patient accepting first, Factor VIIa, which is, of course, a recombinant product; and then tranexamic acid, which is, of course, not a blood product; and then prothrombin complex concentrate. And unfortunately, that's a very thrombotic complication. Had multi-organ failure, probably from thrombosis. The family refused an autopsy. But certainly lost pulses in distal parts, and had a fatal outcome. So, I have concluded from that experience that combining Factor VIIa with prothrombotic treatments is probably not ... and stuff that prevents you from breaking down clots, is probably contraindicated.

- Joe:** Yeah. I share that belief, by the way. I've seen a patient with similar complications, just as an aside. I mean, things like albumin, is that a local decision, as well? I know it's technically a blood product, but-
- Jed:** Again, that would fall under the derivative category, and we've certainly had patients, often after consulting of the elder, be fine with that.
- Joe:** Okay. How about donating their own blood, either prior to surgery or having their blood collected during the surgery?
- Jed:** That's somewhat variable. As a general rule, preoperative autologous donation is not generally accepted, but intraoperative blood salvage often is, with the logic that it's never really separated, it's a continuous circuit connected to the patient. Again, I'm not sure that intraoperative blood salvage was addressed in any theologic documents, but it's a "derivative thought."
- Joe:** I understand. Okay, okay, fair enough. That was well put, my friend. You've already mentioned, Jed, that there is some variability that, generally speaking, red cells, platelets, plasma by themselves are no-go's, but there is some variation. I wonder if...and again, I don't want to put you in the position of speaking for Jehovah's Witnesses in general, but in your experience, have you seen scenarios or are you aware of scenarios where individual Jehovah's Witnesses have made choices that perhaps the church did not agree with, and are you aware of what kind of either social or religious consequences there are in those settings?
- Jed:** I can only speak from a very limited personal experience. I have known people that in the ... I guess when push came to shove, did in fact subsequently accept blood products. I think they survived, and I think at least, an anecdotal thing, were personally troubled but certainly were not excommunicated or excluded from their church. But then again, this is Minnesota and we have "Minnesota Nice."
- Joe:** [Laughs] That is a very, very good point. Very good point. Okay. Well, Jed, I want to make this, for people that are listening, as practical as possible. And you mentioned, with your kind of unique status as medical director of a blood supplier as well as medical director of a clinical facility, you get involved in this in a big way.
- I would love for you to kind of take us through how to approach a patient. And as I said, we'll come back to your patient that was more of an urgent situation, but let's just imagine we have a patient who is Jehovah's Witness, is refusing blood products, and needs an elective surgery, say, in a month or two. And the surgeon calls you and says, "Okay, where do we start? What do we do to try and make sure this happens?" What about pre-op preparation? What kind of things need to happen, from your perspective, for this patient prior to them even getting to the hospital for surgery?

Jed: One would like to think, in the ideal world, that we'd hear about this well beforehand. And let me share a recent example. As I mentioned to you in an email, about two weeks ago, I got a call from the obstetrician. A woman has come in who's had multiple C-sections before, and is about to deliver. And the nurse midwife knew that she was a Jehovah's Witness, but didn't particularly communicate this to the OB staff beforehand. And she came in with a hemoglobin approaching 10 [g/dL]. Had they known about this a month before, they could have done stuff maybe as simple as just giving iron and folate, perhaps more complex to give erythropoietin and iron, which they usually do almost universally accept. In fact, The Watchtower has sort of officially declared that that's acceptable, because getting the hemoglobin up higher to start with means that even if you have a bleed, you're less likely to fall as far.

Knowing well [in] advance, and optimizing the hematologic parameters certainly doesn't hurt, and may well help. I would argue that this is actually true well beyond the Jehovah's Witness community. Unfortunately, we see a large number of women come in with little prenatal care, and it certainly does not enhance outcome. I would encourage all to optimize prenatal care, because it certainly makes things easier down the line.

We discussed the fact that we have this bloodless medicine order set, which was good because our obstetricians had forgotten completely about it, that not only gives the checklist of things to discuss but we happen to have the Epic electronic medical record. It puts a hard stop. You can't order blood, or you can't order blood without an override.

But what we didn't do is derivatives. We had a patient who was a Jehovah's Witness, and I don't remember whether it was ITP or something else, got IVIG and only after the fact was it discussed with, "Oh, by the way, it was a derivative." In fact, this person, this case, the person was completely fine with having a derivative, but we learned the hard way that our hard stop wasn't directed at all the possible derivatives. And since our order set talks about Profilnine and not Kcentra, because we wrote it so long ago, there clearly is some updating needed to do as derivatives come and go.

Joe: Jed, when you talked about that, the form that you use, does it spell out ... I mean, are we talking about a list, a whole, giant list of different components and derivatives and fractionated stuff, et cetera, and specifically requiring a Yes or No/accept or decline for each one of those?

Jed: It's more of a menu and serving suggestion, divided up into different categories of things you may wish to discuss with the patient. There's certainly ... the hard stop is a one click. The minute you order the bloodless medicine order set, the hard stop is immediately put in place for the primary blood products. The stuff that the transfusion service is dispensing, as opposed to pharmacy.

Each of those individual things on the list is more of a discussion tool as opposed to individual boxes to check off. Among other things, our clinicians have significant "EMR fatigue" and if we made them check a box for every possible thing, they would never use the order set.

Joe: That makes total sense. The reason I asked that, Jed, is that I have been asked by hospitals that I serve, in my role as a blood center medical director, that are trying to develop their own program just as a "just in case." They've said, "What if somebody comes in that's a Jehovah's Witness? How do we figure this out?"

I found ... I'm guessing you're probably aware of this, but I found something on the American Society of Anesthesiologists website. They have a committee on patient blood management, and they made ... I'll put a link to this on the show page for this site, but they made a two-page, fairly extensive consent for blood products form as a tool for people to use to go over with patients. And I'm not sure how that differs from yours, but it is very much menu-driven and lots of different options. Everyone, again, we're trying to be as practical as we can with this. If that's something you're looking for, I'll have a link for it on the show page [BBGuy.org/065].

But Jed, you've talked about seeing these patients as early as possible, kind of figuring out what they will and won't accept when you've got time to work through that. And treating pre-op anemia, for example, with erythropoietin and iron. Is there anything else that we would need to think about in these routine patients? Medications they might be on, things like that.

Jed: Certainly, people could be on blood thinners just like any other patient, especially if they're older and they have other comorbidities. Trying to reduce anything that would increase the chance of bleeding and trying to ... or even Aspirin for underlying heart condition, you probably want to stop that well in advance. So, review of things that inhibit coagulation.

And then there may be, if they have a mechanical heart valve, you may not be able to take them off blood thinners entirely, but you may want to get them at the lower end of the anticoagulation range. Or those are at least discussions worthy of having.

And then, probably having lower trigger for using antifibrinolytics like tranexamic acid. Or surgical procedures where delayed bleeding is certainly a possibility. And then finally, where interventional radiology might be appropriate, you might want to have the discussion beforehand as opposed to having to call them emergently after the fact.

Joe: That makes total sense . So, we've talked about the routine patient, and there's something that I've seen that you've done, and that you've implemented in your facility, that's kind of an algorithm for scenarios that are, when you don't necessarily have that much time. And you've alluded to this

already in terms of talking about adults being able to make their own decisions and children not necessarily being covered by their parents' decisions. I wonder if you would mind just, again, kind of talking us through that real quick? Someone comes in, they're an adult, in those situations, how do you kind of go through the algorithm either in your brain or on paper, for the choices that you're going to make for those patients for transfusion, for surgery?

Jed: We encourage the primary clinician dealing with the patient to go over what options and interventions they will accept or won't accept, and the additional surgical options. There are other surgical techniques for decreasing postpartum hemorrhage, various trussing of the uterus, or even hysterectomy, in the case of postpartum hemorrhage. That is generally a discussion that the obstetrician, for example in that case, might be having. I tend to get called 24/7 by folks in the ER or OR to come talk to the patient, which I always find ironic, that the blood transfusion doctor is the one talking about NOT transfusing. And we're certainly willing to do it, but we are generally more in the background of supporting those procedures.

Joe: What about the scenario, Jed, where... gain, you've said, adults have the right to make their choices. Kids, the courts have shown that they should be given therapy according to standard medical care. What about the scenario where you have an adult who isn't capable of saying whether or not they want blood, but you have a family saying, "This guy always said he didn't want blood. He is a Jehovah's Witness." How do you handle scenarios like that, where you can't talk to the patient specifically?

Jed: Oh. That's a hard one, and I'm sure we would get hospital lawyers involved. If there is any written documentation that this is the patient's idea, then we are certainly obligated to follow that. The tougher situation is where you'll have a spouse, or even more problematic, more distant relative or friend, making that claim but there's no independent way to verify it. And that's a bit of a judgment call.

There certainly have been suits saying, "They didn't follow my advice," but I could also see honestly defending that saying, "I have no evidence that that is actually what the patient wants in this scenario." I defer to my legal and ethical colleagues there.

I will say, as a digression, where in my role as pediatric oncologist at Boston Children's, I did get a kid through brain tumor therapy with no transfusions. Now, it was certainly significantly less aggressive than something like leukemia therapy. It was more radiation and only modest chemo. We just sort of adjusted doses to not to get to the hemoglobin or the platelets quite as low and, to the best of my knowledge, the kid is fine today.

Joe: Jed, I have had Steve Frank on this podcast last year, where he talked a decent amount about the Bloodless Medicine program at Hopkins, and he

went over, in more detail than I want to go over with you today, some of the intraoperative, post-operative management stuff. Talked about surgical technique and optimizing temperature, and local hemostatic agents, cell recovery, things like that. I don't want to spend a lot of time going over those with you again (by the way, everyone, that's BBGuy.org/048, for that interview with Dr. Frank).

There are two things that you had mentioned earlier that I wanted to make sure that we talked about a little bit, and the first is the use of antifibrinolytics such as tranexamic acid. And you mentioned a study that's made quite a number of waves in the transfusion medicine community, and I'm assuming in the obstetrical community, as well, and that's the "WOMAN trial." Would you mind just kind of talking us through some of that data and that information that came from that, and address, perhaps, people's reluctance to use tranexamic acid.

Jed: Yeah. Why don't we just jump to the "CRASH-2 trial," because it's probably a little more generalizable. This was bleeding in trauma, and I would point out that it was done in a very international scope including many places where the availability of blood for transfusion was not at all guaranteed, so it's not necessarily completely extrapolatable to major trauma centers in the United States where lots of additional resources are available. But simply and unequivocally, there was a significantly better outcome, less mortality and morbidity, if people got tranexamic acid within three hours of the event, and actually, no benefit thereafter. The reduction was modest. It was 10, 15% less morbidity, but when you have 20,000 numbers, it's pretty easy to choose statistical significance.

Similarly, the "WOMAN trial" was all women presenting with postpartum hemorrhage, it wasn't giving tranexamic acid to everybody, because some of those trials have been less successful. And again, there was a reduction in mortality, but that was modest. It was 2.2% down to 1.8%. It was statistically highly significant, because of the humongous numbers, over 20,000 participants enrolled. The absolute reduction was modest, I would ... The ACOG (American College of Obstetrics and Gynecology) is recommending it, but it's a bit of a "soft recommendation" given the modest reduction. Clearly proven, but the magnitude of the benefit is modest.

Joe: But do you think in this group of patients, in this group of patients where transfusing red cells is not an option, do you think that maybe the trigger should be a little quicker to go to something like TXA?

Jed: Absolutely. Would I automatically give it to every woman having a normal, vaginal birth? Probably not. But if you had ... ACOG and AWHONN [Association of Women's Health, Obstetric and Neonatal Nurses] have all these wonderful risk factors for postpartum hemorrhage scaled criterion, and if you are at elevated risk for hemorrhage or significant blood loss, then, yes, I would absolutely consider it.

- Joe:** Okay. The other thing I wanted to circle back around to, Jed, because you had used a phrase regarding how we will try and accommodate people's wishes, and I wrote this down because it struck me. And I'm quoting you, "As much as we can." What did you mean by that? "As much as we can," we will try to accommodate their wishes.
- Jed:** We did have a patient that wanted to burn incense while on oxygen. There are things that are contraindicated not only the patient's safety but the safety of the staff. We also have a unique patient population from Southeast Asia here in Minnesota that likes to sacrifice pigs, which we can't allow on Children's Hospital property. Yeah, there are certain things that you can't accommodate, Joe, even if it might be visually quite unique.
- Joe:** Ah. You know, they say ... in interview school, they say, "Never ask a question for which you don't know the answer." And lesson learned, because you just caught me by surprise with that one. Nice job! That's fantastic.
- Jed:** One of the genesis of this call, of course, is the fact that we have had significant experience with using the polymerized cow hemoglobin. We can talk about that now or later as you see fit.
- Joe:** Absolutely. Well, I absolutely want to get to that, but maybe right before we get to that, Jed, we've talked about some of the basic stuff that's done intra-op and post-op for patients in whom transfusion is not an option. What I wanted to get to, before we talk about some of those hemoglobin-based oxygen carriers, are there other interventions that can be done, say, when the hemoglobin is dropping despite all those routine things that you're doing. Some of the things that you might describe as more aggressive, maybe "desperate," I don't know. And you had mentioned the hyperbaric oxygen as one possibility. Other things that might be done, really aggressive things that might be done for a patient where you're really trying to minimize their oxygen use. Could you summarize those real quick before we talk about the oxygen carriers?
- Jed:** A tool that we actually use a lot on many patients is a tissue oxygen saturation monitor, and one of the things we've learned from that is how low a hemoglobin people can actually tolerate and still be perfusing tissues quite well. And I'll talk about that in a case that did get cow hemoglobin later.
- We certainly are blessed with a interventional radiology suite that can embolize off just about anything, and has 24/7 availability. That's obviously not available everywhere, and there's also a program "Stop the Bleed," trying to train community citizens on putting pressure on bleeding sources in the field, can actually be an amazing help and not to be underestimated.
- Joe:** Jed, one of the things that I know you have some expertise in and you have talked about in several different meetings that I've heard you speak, is the use of artificial oxygen carriers. And that's something that we have ... You

and I have been around blood banking for awhile. I remember when I was a resident and I decided that I was going to go into blood banking, I had one of my pathology attendings told me, "Oh, you're going to be out of a job in five years because artificial blood is coming." And that was well over 20 years ago. Clearly, we're not quite there yet with routine use, not even close to there yet with routine use, but I wonder if you'd just talk us through the role, if any, of artificial oxygen carriers such as hemoglobin-based oxygen carriers in these patients who are significantly anemic and you don't have the option of giving them blood.

Jed:

Sure. Before we get to the hemoglobin-based oxygen carriers, I certainly am old enough, and perhaps you may be old enough, to remember that amazing picture of the mouse on the front cover of *Science*, suspended in the middle of a bunch of clear liquid. And that was perfluorocarbons, and apparently if you're the size of a mouse, you can get enough oxygen out of oxygenated perfluorocarbons. But if you're a person, apparently the amount of oxygen that can go in there versus the side effect toxicities, especially pulmonary, is such that it just didn't work very well. And it was never a licensed product, but even in the clinical trials, was just not found to be efficacious. And that's not, to the best of my knowledge, not even available on any compassionate release protocol.

From a hemoglobin-based oxygen carrier...and I'll just digress for a second, hemoglobin or an equivalent is found in basically every large creature because you can't dissolve enough oxygen in fluid to meet the metabolic needs of larger organisms. And you can pump as much oxygen as you want, you can have hyperbaric oxygen, and yes, you will increase with hyperbaric oxygen the amount of oxygen dissolved, but it is a pittance compared to the amount of oxygen that could be carried by an oxygen carrier.

And so, without being overly theologic about it, the reason why we have blood cells is because they carry oxygen so well, and allows us to grow to large size and do things that consume a lot of oxygen. But the marvelous thing about those oxygen carriers is they collect the oxygen in a high oxygen environment, and then magically know to let go of it in a somewhat less oxygen tension environment. In the typical day-to-day setting, where you're sitting at your desk, you're only releasing about 25% of the oxygen that's carried. If you're doing extensive exercise, and drop the pH and oxygen tension of those tissues, then you can release a significant ... more about, probably not even 100%.

We are designed to capture as much oxygen as possible, but only release it if and where it's actually needed. The concept of oxygen-based carriers is if you can have the good part about carrying oxygen in a way that can not only grab on but also let go, that is a good thing.

Now, as surgeons learned from acute hemolytic transfusion reactions, if you release all that hemoglobin into the bloodstream, it being a relatively small

molecule, it leaks out the filters called kidneys, clogs them, and wreaks terrible havoc. It causes hypotension and renal failure, and that's not a good thing. I would point out that within one year of Landsteiner's discovery of blood groups, it was being used in paternity, in courts for paternity cases in Austria, but it took over 20 years for American surgeons to routinely adopt it, proving how hard it can be to change surgical practice.

That said, the initial attempts at hemoglobin-based oxygen carriers was essentially cross-linking hemoglobins together to achieve some minimum size that it wouldn't then be filtered out, and there's been some additional modifications, as well. But suffice it to say, there had been multiple clinical trials and multiple companies trying to obtain licensing for this product, and there is no such thing as a free lunch, and several of the companies have gone under trying to license this for trauma indications. And I think much more clear is things like Jehovah's Witness, where there really is not an option. There, I think the comparison becomes much clearer.

Now, Jeff Carson has wonderful articles on, essentially, what we've learned from Jehovah's Witnesses and the mortality above a hemoglobin of 5 [g/dL] is approaching 0%. At a post-operative hemoglobin below 3, it's about 50%. And a post-operative hemoglobin below 2 is approaching 100%. Just because someone has a hemoglobin of 5.5 or 6, that might normally concern us, it might normally trigger us to transfuse, but unless the person has underlying angina or some other compromise of normal tissue oxygenation, they're unlikely to have mortality from a hemoglobin above 5.

That's sort of the first lesson. And in fact, because these are not licensed products, you can't just get them when you think you might need them. There's an entire process you need to go through to obtain release, and one of those criterion is essentially, in addition to no alternative, i.e. Jehovah's Witness, or severe hemolytic anemia where transfusing is impossible, doesn't have to be a Jehovah's Witness, but also typically hemoglobin's well below 5.

Joe: Jed, we've talked about hemoglobin-based oxygen carriers in general. I know that there have been in recent years, and things perhaps are changing right here in early 2019, but there have been a couple of different products that were under study that you have described ways to use them before. I wonder if you'd just thumbnail what at least have been a couple of options in those scenarios. Without endorsing anything, just, what are the tools that we've had in our toolbox for those types of oxygen carriers?

Jed: If your dog develops severe autoimmune hemolytic anemia, you can go to the University of Minnesota Veterinary Hospital and get "Oxyglobin," [NOTE: Dr. Gorlin inadvertently said "Oxypure"] which is a licensed product, and it is in fact the exact same stuff as HemoPure, which is intended for people but which is only released by emergency IND, and I'll talk more about that in a second.

What it is, is a polymerized hemoglobin that's been around now for, I guess, two decades, and is largely the same product, to the best of my knowledge. And although it's polymerized so it shouldn't leak out of your kidneys, it doesn't last terribly long in the circulation. And the stated half life is about 19 hours. Typically, it's something that is a bridge tool, that only lasts sort of a day at a time for infusion. Then there's another company called "Sanguinate" that, in addition to polymerizing it, added something on it that makes it stay in the circulation longer. I have no personal experience with that because when we were about to sign up for their clinical trial, they actually closed it while they're going from a phase I to a phase II clinical trial. So, to the best of my knowledge, that is not currently available even under emergency IND, though I could be simply unaware if it's been made available again.

The source is the most pristine group of cows one can imagine. You could imagine that with concerns about, "Have you ever even eaten a beef sausage in England?" that the FDA is not going to be excited about allowing direct infusion into the blood of a lot of stuff from cows. These are truly pedigreed herds that have been kept isolated from the rest of the world, and are periodically documented to be prion-free, according to the manufacturer. And so, at least the theoretical risk of prion-related disease, if not eliminated, is at least practically minimized. That alone, I think, has not been a contraindication. One would like to think that we are different enough from cows that we would make an immediate immune response, at least in patients who have had repeated or multiple doses. That has not been observed. Either we are closer cousins to cows than we thought, or there's something about this polymerized hemoglobin that just doesn't seem to be particularly immunogenic.

Joe: Jed, I know that you have been in, obviously, involved in the administration of one of those particular products, and in fact, I believe you're working on publishing something regarding a group of patients that have received that. Could you preview that for us, and tell us a little bit about ... I guess the basic question is, does it help?

Jed: The honest answer is, we don't know. And let me get back to the first case.

The lady got hyperbaric oxygen because that's why she was transferred, and the accepting clinician who was in charge of the hyperbaric chamber and this person's care, quickly jumped into two-a-day sessions. The fact that that didn't actually add a whole lot of oxygen, especially between sessions, was not lost upon the clinicians. The patient certainly wasn't waking up, and they contacted us.

I made a misnomer. There is no such thing as "compassionate release." Let me repeat: there is no such thing as compassionate release. That implies all sorts of things, like "if you have compassion, give us this!" Where the honest answer is, for products we don't know if they work, that's why they're not licensed yet. The FDA has what's called an "Emergency IND process," and

24/7, they are available. And my guess is, even during government shutdown, they are probably available. They're just not paid. Poor guys.

And they are incredibly good! I want to give a major shout-out to colleagues at the FDA who have been incredibly collaborative and responsive in the four or five times I've contacted them for this. And they get back to you right away. They facilitate communications with the manufacturer. Basically, you need to have a clinical case where there's very high likelihood of mortality without the use of these products. You need to have approval of the manufacturer. There still is about a 24-hour delay in getting the product to you. They literally FedEx it overnight.

We are interested in multi-use IND, and so there are a number of academic centers, including University of Michigan, that are planning to apply for a multi-use IND, and only probably way after that's approved can additional sites tag on. But that would allow us to have the product on-site, which if you're a trauma center, is handy.

But getting back to that first case, it is a "bridge therapy," so when you have a massive hemorrhage, you make more blood, but it takes about a week to 10 days to have a significant increase in your hemoglobin. And for a product that only lasts a day, that requires quite a number of doses. We gave enough doses to get the hemoglobin from under 2 (I think the person got down to the low 2's, anyway), up to a hemoglobin of 4.

Here comes the next question. We're a lab, and when you send labs where the plasma is the "color of Merlot," or if you're particularly sophisticated, Cabernet Sauvignon, the lab says, "Sorry, this is a hemolyzed specimen, we can't give you a result." You really want to have good communication with your lab. And here's where it's really helpful to have an automated cell counter, because the hemoglobin will be the sum of the patient's own hemoglobin and the infused product. The hematocrit is generally a measure of the patient's own cells alone. And at least talking to the Sysmex manufacturer, what it literally does is it counts up the MCV's and adds up all the little cells together and does a calculation of what the calculated hematocrit ought to be by looking at the size of the cells. You can imagine, free-floating hemoglobin doesn't trigger an MCV detector. It is a quite accurate way to be tracking where you are, and so, I had to essentially bribe my own laboratory staff to give me the result that they refused to put into the electronic medical record. And at least we could track ...

And to make a long story short, functionally two units a day would maintain the hemoglobin. We kept the hemoglobin essentially at 4, and by a week to 10 days later, she's "retic'ing in" on her own, wakes up out of her coma, and says, "See? God takes care of us!" And, you know, I have no objective evidence to say that she isn't right.

Joe: Good for her. Wow, that's awesome. Wow! Everyone, I will have a link to the paper that Jed was involved in, in writing, in the annals of the American Society of Thoracic Surgery ... I'm sorry. Annals of the American Thoracic Society, is that correct? Yes, that's it. That link will be on the show page for this particular episode [BBGuy.org/065].

So, she walked out of the hospital?

Jed: She walked out of the hospital fine, and in fact, the community talks to each other significantly enough that when we had a patient that had a motorcycle accident, her family actually had talked to the postpartum hemorrhage lady, and one of the reasons why they asked to come to Hennepin is they knew that we could do this.

Joe: That's amazing. I mean, obviously, there were a lot of steps that had to be taken, and as you said, perhaps in the future, the mechanism for getting that particular product might be different. But the principle of, in this particular case and in some other cases that I know you're working on reporting, Jed, that there seems to be some value. Let me ask you this question, before I let you go. In the cases that you've studied and in the literature that's been published about some of these hemoglobin-based oxygen carriers, the bovine hemoglobins, is there anything that we can glean about if you're going to do this, whether you need to really give substantial amounts of it? Is it something to kind of dribble in, or is it something you really got to hit people hard with? Or do we know?

Jed: I'm sure I don't know. We are in the process of trying to submit a case series of at least 10 patients that, each of them got 10 units or more, with the concept that if you lived long enough to get 10 units or more, you must have been at risk of having a hemoglobin that was essentially approaching 0. On the flip side, the fact that you lived long enough to receive all 10 units suggests that you probably were stable enough that maybe you weren't at risk of dying immediately, anyway.

I can see how reviewers can twist it one way or the other, but at the very least, I think it would create a basis for saying, "Yes, we really should be doing a prospective clinical trial in this community, because then we can know, have a better answer, is it truly life-saving or are we just treating ourselves until the patients that survive retic in?"

Joe: Jed, before I let you go ... and this has been great, thank you so much for doing it, but before I let you go, I wonder if I can circle back around to what I told you before, which is that I get phone calls from hospitals that I work with, that are concerned about, what do I do if someone presents and says they're a Jehovah's Witness, or for whatever other reason, they say, "I don't want to receive blood. Blood is not an option for me." How would you counsel people at hospitals that are concerned about that?

I mean, just as practical as we can: Where should they start? What are the keys to getting going for having ... to get something in place, to be prepared for that eventuality, when someone comes in and says they won't take blood?

Jed: I think it's worth having internal policies and procedures on what you would do, so that person doesn't have to reinvent the wheel at the time of an emergency. That doesn't mean that every hospital has to offer the myriad array of alternative procedures or treatments, but you may want to be aware of what hospitals in your community might be offering, some novel interventions.

I would somewhat caution about the role of hyperbaric oxygen. The limiting factor for this patient getting out of the hospital was really rather severe ARDS, and it isn't at all clear to me that it wasn't related to eight days of hyperbaric oxygen therapy, which is known to be pulmonary toxic.

Joe: Well, Jed, that's great advice. I think people that are listening, this is, as Jed said, you don't necessarily have to have the same type of program that would be found in highly advanced and super-specialized medical centers, but it is not a bad idea to be prepared in some way with at least the basics of what you're going to do. Jed, anything else you'd like to discuss before I let you go?

Jed: I think it's also, at least, instructional if nothing else to have communication with the Jehovah's Witness community. Almost every community has a hospital liaison, and you'd rather be on good speaking terms with them beforehand. Because they can come in somewhat oppositional, and it's just nice to clear the deck and say, "We're not here to be oppositional. We're here to work with you to the extent that we can," and you've already heard those caveats.

Joe: Okay, Jed. This has been great. Thank you so much for taking the time to do this with me, my friend. I really appreciate your insights, and I think you've really helped us learn some great steps to take when transfusion is not an option. Thank you, my friend.

Jed: Thank you!

Joe: Hey, it's Joe with just a couple of closing thoughts. You know, dealing with situations where someone is refusing transfusion based on religious beliefs doesn't tend to be real satisfying for those of us in the scientific fields. But I think it's really very important for us to understand that these beliefs are very real, and these beliefs are very, very important to practicing Jehovah's Witnesses. Working through these situations, yes, it's challenging. Yes, it's difficult. But it's very worthwhile.



The truth is, we've actually learned a lot from Jehovah's Witnesses, many, many lessons that have helped us in the patient blood management movement with helping to understand how people can go without transfusions, that we used to think needed to be transfused.

My thanks again to Jed for sharing his thoughts with us.

Remember, you can find a detailed glossary, quizzes, videos, and a ton of other free resources at BBGuy.org. In addition, you can find references and other useful information on the show page for this episode, at BBGuy.org/065.

You can also listen to previous and future episodes directly on the website, on Apple Podcasts, Google Play, Stitcher, Spotify, etc. I would really love it if you would [give this podcast a rating on Apple Podcasts](#) and subscribe! That will help get the podcast in front of more and more people, and I really would very much appreciate that.

Got a lot of fun episodes coming! The next episode will be an interview with Dr. Jerry Sandler on IgA deficiency and anaphylaxis. Lots of great stuff coming in the coming months, and I can't wait to share all that with you.

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