BBGuy Essentials 094CE:
Thalassemia Essentials with Sujit Sheth
Released March 2, 2022

Sujit: Hi, this is Sujit Sheth from Weill Cornell New York Presbyterian Hospital in New York, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, everybody! Welcome back to Blood Bank Guy Essentials, the podcast designed to help everyone learn the essentials of Transfusion Medicine. My name is Joe Chaffin, and I am your host. In today's episode, I had the opportunity to interview Dr. Sujit Sheth, who is a pediatric hematologist and director of the New York Comprehensive Thalassemia Center. I really enjoyed talking to Dr. Sheth , and I can't wait to share the interview with you.

But first, this IS a continuing education episode. The free continuing education credit is provided by TransfusionNews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into the podcast. This podcast offers a continuing education activity where you can earn two different types of credit: One *AMA PRA Category 1 Credit™*, or one contact hour of ASCLS P.A.C.E.® program credit. This activity also may be used to fulfill Lifelong Learning Continuing Certification requirements for the American Board of Pathology. To receive credit for this activity, to review the accreditation information and related disclosures, you just need to visit www.wileyhealthlearning.com/transfusionnews. One important note: The continuing education credit is no longer available two years after the date this episode was released; in other words, credit for this episode will expire in March of 2024.

I think that here in the United States, when we think about transfusing patients who have hemoglobinopathies, we tend to think first about patients with sickle cell disease. That's not surprising, because sickle cell disease is obviously such a very big deal for us here (and I have previous episodes where I've discussed sickle cell disease and transfusion in detail). But worldwide, thalassemia is *also* a very big deal, and there are really some significant differences in the treatment of patients with thalassemia when compared to those with sickle cell disease, and some of them might surprise you.

I am very grateful that the amazing Dr. Melissa Cushing at Cornell connected me with Dr. Sujit Sheth in order to discuss Sujit's expert perspective on some things that we don't talk about often enough in the US, from my perspective. To save time, if you'd like to read Dr. Sheth's full biography, just go to the show page for this episode at BBGuy.org/094. In short, he's one of the world's leading experts on care of patients with thalassemia, and he directs one of the largest United States centers for care of these patients, which is called the New York Comprehensive Thalassemia Center. I recorded this interview with Dr. Sheth in 2021, and I'm really happy to share it with you now.

So let's go! Here is my interview with Dr. Sujit Sheth discussing the essentials of thalassemia.

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Joe: Hi, Sujit. Welcome to The Blood Bank Guy Essentials Podcast.

Sujit: Thank you. It's great to be here.

Joe: It's such an honor to have you. The more I've looked at this topic, what we're going to talk about today with the thalassemias, is the more I think that it is under-appreciated in blood bank world, especially in the United States. I think worldwide, it's obviously a bigger issue, but I think in the United States, we have a tendency to not give thalassemia the respect that it deserves. Let's just put it that way. But before we get to all the fun stuff that we have to talk about with thalassemias, I wonder if you'd just tell us a little bit about your practice and how you got interested in doing this kind of thing.

Sujit: Sure. So first of all, it is a privilege to be on because I think you have such a wide audience that this is really a good forum for me to be able to talk about this disease that I feel so passionate about. So my practice is really focused on disorders of red cells and disorders of iron metabolism. So I run the thalassemia program here at Weill Cornell New York Presbyterian. We have about 170 or 180 thalassemia patients between the α ["alpha"] and β ["beta"] and major and intermedia of which about 115 or so are on regular blood transfusions. And then the rest of my practice is sickle cell disease, spherocytosis, pyruvate kinase deficiency, enzymopathies, other membranopathies, and then disorders of iron metabolism as well.

Joe: What is it that got you fascinated in that? You said you're passionate about it and that's awesome, what drove that passion for you, Sujit?

Sujit: I grew up in India, I went to medical school in India, I did a residency in India before moving here and saw so much of thalassemia there because it is very, very prevalent there. There, they didn't really have the resources to take care of these patients optimally, certainly not to provide them with iron chelation therapy, and they all died in the first or early second decade of life. And I just felt like this is really something that is treatable, is preventable, and so that brought me to wanting to train further in hematology, which is why I came here to do a fellowship and then just felt like the research part of it, as well as the clinical care part of it was something that I wanted to continue to do here.

Joe: What is the New York Comprehensive Thalassemia Center? I saw that as part of your bio and that's something that you're currently in charge of, Sujit?

Sujit: Yes. So I moved to Cornell from Columbia about 10 years ago and took over the New York thalassemia program and sort of expanded it to include more sort of outreach into the region, so now we have collaborators all the

way from Boston, through Philadelphia, all the way to Atlanta, Georgia, in fact, and the center takes care of all of the patients here. We participate in a bunch of clinical trials, we have a whole lot of research ongoing as well, and so the center sort of tries to bring together clinical care, pushing the envelope with clinical trials, as well as research and education. I think the education bit is also very important because we do want to provide educational materials, both for patients as well as for providers.

Joe: Sounds like you're doing great work. And as I said, it's fascinating to me that a disease like thalassemia, that is so big worldwide, and we're going to talk about that in just in moment, you're running a very large center in the biggest city in the United States and still the number of thalassemia patients that you have is, it's a big number, but it's not in the thousands or tens of thousands, right? It's still, here compared to other places not as numerically as big an issue, right?

Sujit: Absolutely. Absolutely. And we are probably the largest single center where we actually take care of all these patients on site in the United States. And considering that they're probably about 2000 to 3000 patients with thalassemia in the entire United States. We have about 10% of that population here in New York, and that's just traditional from all of the immigration patterns way back when patients or individuals from the Mediterranean came to New York first.

Joe: That makes total sense. And we will get into all of that in great detail in just a little bit. But I think before we talk about the abnormal parts of hemoglobin, and obviously thalassemia, like sickle cell disease, they're hereditary hemoglobinopathies, and so we have to start, I think, from the normal. So I wonder Sujit, if you would take us through, for our audience, just to make sure that they're clear on how this should work, how hemoglobin development and structure should normally work.

Sujit: Sure. I'll try to be quick. So the hemoglobin molecule is a heterodimer, two globin chains that are made as the result of expression of genes from the α-globin cluster, two β-globin chains that are made as a result of expression of genes from the β-globin gene cluster. And there's an evolution, there's embryonic hemoglobins, and there's fetal hemoglobin, which is two α and two γ ["gamma"]. And then there's adult hemoglobin or hemoglobin A, which is two α and two β. If you have an imbalance where you don't make enough α, you don't make enough β, then you have a thalassemia syndrome. α-thalassemia, if you don't make enough α, β-thalassemia if you don't make enough β.

And so essentially what happens is that in the marrow, erythropoiesis is really a two-phase process. You have the proliferative phase, and then you have the maturation and differentiation phase. The proliferation phase is driven by erythropoietin, and it just goes from stem cell through BFUE, CFUE, to the proerythroblast. And then there the maturation phase begins, and that's when hemoglobin starts to be made within these red cell

precursors, which go through a number of different stages, eventually leading to the extrusion of the nucleus and the formation of a reticulocyte that then matures to red blood cell, comes out of the bone marrow into the circulation. So when you have thalassemia, essentially what's happening is there's a problem here with, because you can't make this hemoglobin normally.

Joe: Okay, here in the United States, we see a whole lot more patients with sickle cell disease as opposed to thalassemia. So could you just contrast the two quickly in terms of, and we'll get into the details of course on the specific types of thalassemia, but just from the big picture perspective, how does a thalassemia issue compare to a sickle cell issue?

Sujit: Sure. So sickle cell is as a result of a point mutation in the β-globin gene that leads to a single amino acid substitution in the β-globin chain, that then leads to this abnormal hemoglobin, abnormal in terms of its solubility. But erythropoiesis in that situation is effective. So you do have two α-globin chains that bind two β-globin chains. The two β-globin chains just happen to be sickle β-globin, but they are β-globin chains. And so you have effective erythropoiesis, and so red cells are coming out of the bone marrow as a result of this effective process.

In thalassemia, since you don't make α or β, whatever is deficient, there is precipitation of tetramers in the maturing red blood cells, and as a result of that, you have the formation of "hemichromes," which bind iron into these aggregates, and that results in intramedullary apoptosis of those precursors and essentially ineffective erythropoiesis. So the hallmark of thalassemias is ineffective erythropoiesis. The hallmark of sickle cell disease is effective erythropoiesis, except that the hemoglobin that you're making is an abnormal hemoglobin, abnormal in terms of its solubility.

Joe: I'm a blood banker and I like to simplify things when I can, is it fair to call sickle cell disease a "qualitative" issue and thalassemia a "quantitative" issue? Is that too simple?

Sujit: Absolutely. You hit it right on the head.

Joe: So with these thalassemias, and as I said, we're going to talk about them, you mentioned with sickle cell, that it's a specific point mutation. Let's just get to the nitty gritty of thalassemia. And again, I know that there are different types, but just from the broad perspective, are we talking about one specific mutation or one specific genetic issue, or is it bigger than that?

Sujit: It's much bigger than that. For instance, in the β-thalassemias you have over 200 mutations have been described.

Joe: Wow.

Sujit: These are mutations in the gene itself, in the β-globin gene itself, or in its promoter, and then to complicate matters further, you have something called a “β^{+}" [NOTE: Pronounced “beta plus”] mutation where you have some expression, but it's not normal. And then you have a "β^{0}" [NOTE: Pronounced “beta zero”] mutation where you have no expression of the β-globin gene at all, and depending on what part of the world you're from, the mutations are actually different. So you can say that in individuals from Asia, you're likely to have these mutations, and individuals from Italy or Greece, you're like to have these mutations, and so on.

Joe: You mentioned before, and we've talked from the beginning, the few minutes that we've been talking already, that in the United States, this is not as numerically large an issue as it is in other parts of the world. Let's be a little bit more specific about that. First let's say, and I keep comparing it to sickle cell disease, and I hope you'll forgive me for that, but I just think that so many of my audience have a reference point with sickle cell disease, because it is a larger deal in the United States, but globally, which of the two is more common? Thalassemia syndromes versus sickle cell, which is more common globally?

Sujit: So approximately 1.5% of the Earth's population of humans carries a thalassemia mutation. At least one.

Joe: Wow.

Sujit: So that's about 80 to 90 million people.

Joe: Holy cow!

Sujit: And it's estimated that in the United States, as I said, it's estimated about 2000 individuals, in Italy, for instance, there's estimated to be about 6000 individuals, but the numbers are really enormous in Asia. And as a result of immigration from Asia, the numbers are increasing in the United States amongst Asian patients. And that is the Indian subcontinent all the way through Burma and Thailand and Vietnam and Laos and Cambodia, and then all the way up through into China where you have a different set of mutations, but you have a lot of thalassemia there as well.

Joe: That's enormous. I mean, 1.5% of the world is, I can't even wrap my brain around that. That's a huge, huge impact. And so, as you mentioned, Sujit, and I've heard people talk about, and I hate to use a pithy phrase, but I've heard people talk about the "thalassemia belt." What does that mean? Is the distribution in some geographic recognizable pattern?

Sujit: Yes. In fact, the Mediterranean is where it's supposedly originated to sort of protect you from malaria. And then it sort of went through the Middle East and Asia Minor to the Western part of India, and that has been traced by anthropologists to be related to the invasions of Alexander the Great. And then it's sort of, those mutations kind of stopped there in the Western part of India because Alexander had to turn back because he fell ill. And

then these mutations that arose in the rest of Asia, Southeast Asia, are kind of different. So they're not the same as the Greek mutations. But then the belt extends from the Mediterranean, through the Middle East, India, Southeast Asia, all the way up through China.

Joe: Let's dive into the thalassemias a little bit, and just generally speaking, Sujit, how would you categorize the main types of thalassemia? Is there a breakdown that we can do just to give us big broad categories?

Sujit: Sure. So it's really quite a spectrum, and you have thalassemia minor, which is basically individuals with the trait who have a mild microcytic anemia and no symptomatology other than that, and do just fine. And the only implication for them is for the next generation when they're ready to have kids of their own. And then the most severe form of it, which is on the other end of the spectrum is what we used to call "thalassemia major," we still call thalassemia major, but now we call it "transfusion-dependent thalassemia," and these are individuals with the more severe mutations who manifest early on in life, usually in infancy and require regular transfusions starting early and then all through their lives.

And then somewhere in between is that intermediate spectrum. And these are individuals who may be diagnosed a little bit later, maybe in the five, six, seven, eight, sometimes early second decade of life, even mid to late second decade of life, and these individuals who don't require regular transfusions in moderate anemia, but may occasionally require transfusions, but do have a whole lot of other complications that are related to the ineffective erythropoiesis, bone disease, vascular disease, and they do develop iron overload as well.

Joe: Okay. So Sujit, this is probably an exceptionally dumb question, but I think people do get confused sometimes with terminology, and when you said thalassemia minor, thalassemia intermediate, thalassemia major, are you speaking specifically of issues with the β-globin, or is that terminology true for both the α and the β types?

Sujit: No, that's true for both types. So if you have the trait, you have thal minor and you can include the α as well as β-thalassemias in that situation. The majors are either both β-globins are mutated or all four α-globins are mutated or deleted. And again, you're transfusion dependent there as well.

And then in intermediate category, you have the β^{+} individuals, but you also have in individuals with hemoglobin H disease, hemoglobin H Constant Spring, which are α-thalassemias.

Joe: Okay. So it does get a little complex there, but I hear what you're saying. The terminology does overlap. So let's talk a little further about the β versions versus the α versions. I feel like in our conversations, when we talk about these clinically, and when we hear about these patients, we talk

a whole lot more about the β-thalassemias than the α-thalassemias. Why is that, Sujit?

Sujit: That is because β-thalassemias are much more common clinically in the severe category. So we have a lot more transfusion-dependent β-thalassemias, because when you have four α genes deleted or mutated, usually it results in hydrops fetalis and intrauterine fetal death. Okay. And so we don't have that many individuals with α-thalassemia major that are born every year, because they don't make it through the entire pregnancy. You have a lot of α-thalassemia, but it usually falls in the intermediate category, and that's the hemoglobin H and the hemoglobin H Constant Spring. So there's a lot of that, but the majority of the transfusion dependent patients and the majority of the patients who have complications related to their thalassemia are β-thalassemia individuals.

Joe: Okay. So I think most of the rest of our time, we're going to talk most mostly in terms of the β-thalassemias. But before we leave the little bit that we've talked about with α, I just want to make sure for my audience, you just used a term that I know people have heard, but I want to make sure they're clear on what it is, and that's "hemoglobin H." That's not, again, we hear that in blood banking and it kind of goes in one ear and out the other a little bit. I don't want to leave that, because I know there are some important ramifications of people that have a lot of hemoglobin H I believe things can precipitate more or you can have hemolysis more, but can you just talk to us real quickly before we leave α-thals about hemoglobin H?

Sujit: Sure. So hemoglobin H is essentially tetramers of β, and the result when you have so much excess of β compared to α, and that is when you have three α-globin genes deleted out of the four. All four would result in hydrops fetalis, because you can't make fetal hemoglobin either. Three deleted, you would have hemoglobin H disease, and then if you have two deletions and one Constant Spring mutation, then you have Hemoglobin H Constant Spring because now three are not working again, but two are deleted and one is abnormal, as opposed to the deletional form where all three are deleted. The non-deletional tends to be more severe because the hemoglobin H and constant spring will come out and they have a much more of a hemolytic phenotype as well. And essentially constant spring, just to go back, constant spring is a mutation that results in an extension of the β-globin chain by 31 amino acids, but it also makes it very, very unstable.

Hemoglobin H, on the other hand, you can have a significant proportion of hemoglobin H in the circulation. You know, you can go up to 5, 6, 8, 10%. Usually the more you have, the less functional hemoglobin you have as a sum total, because hemoglobin H does not really transport oxygen very well. So individuals with hemoglobin H generally, if they have a low proportion of hemoglobin H, they generally have no symptoms at all and do fine. When they have higher proportions of hemoglobin H then you

might start to see some symptoms mostly related to decreased oxygen delivery to tissues.

Joe: Thank you for helping me out with that. I think for the rest of our time, as we talk about not only what the normal clinical course of people with different types of β-thalassemia might be, or different levels of severity of β-thalassemia, and then get into how transfusion fits into all of this, if you wouldn't mind, take us through, perhaps, in a little bit more detail, you talked about the ineffective erythropoiesis, not being able to efficiently make hemoglobin in people with thalassemias in general, and obviously even more so in β-thalassemias. So if you could, Sujit, just talk us through a little bit about how that works a little more, and you've given us an overview of that, but what is it specifically that causes the harm? You mentioned the imbalance, you mentioned excess of α-globin chains, again, just walk us through, what is it that keeps red cells and hemoglobin from being efficiently formed in β-thalassemia.

Sujit: Sure. So as I mentioned, two phases, right? You have the proliferative phase, and then you have the maturation/differentiation phase. The proliferation phase happens perfectly normally because you have normal stem cells, they have the mutation, but the stem cells themselves, otherwise are fine. Erythropoietin stimulates the stem cell towards erythroid differentiation. You have the burst-forming unit erythroid, or the BFUE, then the CFUE, all of that happens perfectly normally. Once you get to the proerythroblast, that's when the sort of differentiation and maturation process starts, and that's when these cells start to make hemoglobin, and that's when the α and β-globin genes start to be expressed.

And so then the proerythroblast goes through various stages, the basophilic erythroblast, the polychromatic erythroblast, the orthochromatic erythroblast, and then it forms a reticulocyte. That's under normal circumstances. From the proerythroblast stage to the basophilic erythroblast stage, that's when you start to make hemoglobin. That's when the α-globin expresses, the β-globin expresses, or γ-globin depending on if it's intrauterine and you're making fetal hemoglobin.

Now, when you have these mutations, now we'll focus on the β-globin mutations. You have β-globin mutations, there's an excess of α. There's nothing for the α to bind to, because you don't have enough γ expression. And those α four tetramers will precipitate.

Joe: Sujit, forgive me for interrupting, because I think that's a hugely important point. Am I understanding this correctly that there's like no feedback loop, in other words, the α is just, α's normal, so it's just cruising along going, "Hey, I can make things normally," but since there's not enough to bind to, because the β isn't being made efficiently, you just end up with like "soup" of α-globin. I'm obviously simplifying.

Sujit: Exactly right. No, no. I think that's a perfect explanation. That's exactly right. That's exactly what happens, because the α-globin gene cluster, which is on chromosome 16, is independent. It's controlled by its own promoters and it's independent of the β-globin gene cluster, which is on chromosome 11.

And so, you have your normal complement α, that just keeps churning out α-globin, and you don't have anything to bind to and that's when you have the problem.

Joe: What are the end features of ineffective erythropoiesis? What do you end up with on the far end of that when you're not able to make your α and β chains in their normal balances?

Sujit: These α-four tetramers will precipitate, iron will bind into that complex to form "hemichromes." These hemichromes are toxic to the developing precursors, and the precursors then undergo apoptosis. And then because you have apoptosis, you're not making enough red blood cells, and so you're anemic. And so the feedback loop then is that because of the anemia, you increase your production of erythropoietin, and that drives proliferation. So now you have this process where there's increased proliferation, driving proliferation more and more and more because you have anemia on the one side. But there's a block in the differentiation/ maturation process. And so what happens is that the bone marrow then expands tremendously.

So the medullary cavity expands, the medullary space expands, it eats into the cortices, and so the bones get thinned out. Also because EPO is produced in such high amounts, it's driving extramedullary hematopoiesis. So whatever rests of cells you had sitting in your liver and spleen will get stimulated as well. And so your liver enlarges, your spleen enlarges, and then you form these erythropoietic, these nubbins of tissue that are all erythropoietic tissue as a result of EPO stimulation, that forms in the spine and the vertebral bodies, can extrude out of the vertebral bodies and form these masses that can then even impinge in your spinal cord.

And then you have a lot of bone disease elsewhere. So because you have so much EPO, areas of the bone marrow which would normally go from being red marrow to being yellow marrow remain red marrow. And so your skull bones expand abnormally. The bones of your face, your maxilla, your sinuses don't form normally, and that leads to a lot of disfigurement of those bones and so an abnormal bone structure that leads to the sort of typical facies that we call these individuals as having.

Joe: Frankly, that's sounds awful, Sujit. I mean, in different parts of the world where perhaps someone might not get care, and you mentioned this from where you grew up, are we talking very early, very young fatality for untreated patients?

Sujit: Yes. So if you have the most severe form of β-thalassemia is β^0/β^0 [NOTE: See images at BBGuy.org/094 for more on possible genotypes in thalassemia). So you have no expression of β at all, and these individuals become severely anemic in early infancy. So usually you reach a physiologic nadir at about two months of age, and then your hemoglobin stabilizes, goes back up because you start making EPO. Here, you're making more and more and more EPO, but nothing is coming out of the bone marrow. So you're becoming progressively more and more anemic. And these individuals with β^0/β^0, if they're not treated, if they're not transfused, will usually die by the age of two years of heart failure, just from the severe anemia and lack of any oxygen delivery to tissues. If you have an intermediate phenotype, you could keep going and you could become more and more anemic, but you don't really require regular blood transfusions to survive, but you will have all these other complications, because of the bone disease, the vascular disease, the iron overload that develops, all of that will happen as well.

Joe: Okay. So talk to us a little bit about the iron overload, Sujit. You've talked about the extramedullary hematopoiesis, and obviously the consequences of severe anemia and forgive me, I may have interrupted you there when you were going to talk about thal minor and what happens with those patients. We'll get back to that in a second. But you mentioned iron overload. Are you talking about iron overload even in the absence of transfusion?

Sujit: Yes. So when you have ineffective erythropoiesis, there's a sort of feedback loop and ineffective erythropoiesis suppresses hepcidin levels. Hepcidin is the master regulator of iron metabolism in the body and lower levels of hepcidin means you tend to absorb increased amounts of iron from your intestinal tract. So individuals with ineffective erythropoiesis, and the more ineffective erythropoiesis you have, the lower your hepcidin levels are, the more iron you absorb, and you can become iron overloaded, just like somebody with say hereditary hemochromatosis, it would increase their iron absorption, become iron overloaded, except these individuals absorb far more than that because their hepcidin levels are so low and they become significantly more iron overloaded at significantly earlier ages. And so they do develop iron overload despite not getting regular transfusion. And then most of them an occasional transfusion here or there, which also contributes.

Joe: I see. So your body's basically saying "I'm anemic, I need more iron," even though the problem is not iron. So you end up overloading.

Sujit: Exactly.

Joe: Ugh. You were talking about the natural course of disease without intervention, and you mentioned with thal major, very early death, thalassemia intermedia, generally significantly longer life, but what about thalassemia minor?

Sujit: Thalassemia minor has a normal life expectancy. So these individuals who just have a mild microcytic anemia lifelong, and they don't develop iron overload. They don't have significant ineffective erythropoiesis. Their bone marrows are functioning quite well. You have one normal functioning β-globin gene, if you have the trait, right? So one is functioning normally. That is able to compensate and balance since the degree of ineffective erythropoiesis is very minor, if any. So they do fine.

Joe: With that as a background, since this is a transfusion-related podcast, I think we should get to the transfusion part of this, and let's talk a little bit, Sujit, about how we use red cell transfusion specifically in the care of patients with the different forms of thalassemia, and I think what you've already established, and I appreciate you mentioning the fact that, and let me make sure to confirm what I thought I heard, that rather than calling thalassemia major that, the term tends to be "transfusion-dependent thalassemia" now, is that more of an official term than thalassemia major?

Sujit: Yes. We have moved away from the sort of major and intermedia to, because major intermedia came about and had some genetic implications as well, in terms of what type of mutations you have. And it's not really consistent, right? So individuals who are transfusion-dependent used to be called thalassemia major. Individuals who are not transfusion dependent used to be called thalassemia intermedia for the most part.

And you had individuals who had β^{+}/β^{+} mutations who could be transfusion dependent, and therefore could be called thalassemia major. But in everybody else's mind, you could say that this was more of a genetic differentiation. So if you had intermedia, then you didn't have β^{0}/β^{0}, and you could have β^{+}/β^{+}. But then you had intermedias who were becoming transfusion-dependent. Intermedia by genotype were becoming transfusion dependent. And this was their phenotype was more of thal major. So to do away with that confusion, we just have moved away from that for the most part. And we say you're transfusion-dependent, irrespective of what genotype you have, it doesn't implicate your genotype or you're not transfusion-dependent.

And for transfusion dependent, we've generally accepted a sort of cut off of getting eight or more transfusions in a year.

Joe: Oh, okay. Eight or more in a year. Got it. I don't know that I had seen that definition. So eight or more Def red cell transfusion episodes in a year, or eight or more units?

Sujit: No, episodes.

Joe: Okay. Let's talk specifically about it. So in those transfusion-dependent thalassemia patients, I'm assuming that those transfusions have to start early in life and continue throughout. So how do you make those decisions

and how does that evolve over time in terms of what your transfusions that you're giving to these patients?

Sujit: That's a great question. So this is where there's a lot of sort of individual leeway in terms of how you approach the scenario. So if you have, the most severe form is β^0/β^0, typically, as I mentioned, your physiologic nadir is reached at two months and you continue to become more anemic. So somewhere between four and seven months, you have severe anemia. So your hemoglobin is now down to 5 or 6, or even as low as 4. And you start to need to be transfused in order to prevent you from, in order to allow you to grow, develop, and not be cranky and irritable all the time, not have a heart rate of 200 all of the time, and so you need to intervene at that point and start regular transfusions. So the goal of our regular transfusions is really twofold. One, we want to allow normal growth and development, provide a normal quality of life, but two, we also need to suppress this ineffective erythropoiesis, because if we don't suppress the ineffective erythropoiesis, then they will continue to have all those other changes. The bone changes, the hepatosplenomegaly, the vascular disease, all of those things could continue to happen if you don't suppress them adequately.

Joe: I hope that everyone that's listening, I hope you don't miss that point. That's that is a revelatory point that you should really, really, really clearly understand, because some of the stuff that we're going to talk about, Sujit, in just a few minutes, and especially in terms of what your target thresholds might be, and we'll get into that in a second, to blood bankers, sometimes we hear about the thresholds that you want in thalassemia and we're like, "My goodness, that seems really high!" But I think what you just said is a great explanation for that. You're not wanting these patients to hang around anemic because we've already talked about what the consequences are, right? As opposed to someone with sickle cell that you can tolerate a little more anemia, is that accurate, that there's significant difference there?

Sujit: Absolutely, absolutely true. We don't want these individuals to make their own red cells because their own red cells are abnormal, and these abnormal red cells that are coming out of the bone marrow, they're fragmented, they're deformed, they cause a lot of vascular disease. They will go stick to the vascular endothelium and cause problems. And so you want them to be suppressed as much as possible. Not only to keep the bone marrow a normal size in terms of not having a hypertrophied bone marrow and therefore the bone disease, but also to prevent all these vascular changes from occurring. And this is progressive if you don't keep those cells away.

Joe: So Sujit, in a typical patient, once you start them on transfusions, what's the frequency that they typically get red cell transfusions, or does it vary widely between patients?

Sujit: It does vary. So when we start, usually in infancy, we're transfusing once every four or five weeks. And we do this, one, to minimize the number of visits that they have to make. But also because at that time, their needs are kind of less than what they would be if you were a child or an adult. These are infants, so they're mostly sleeping and they're not walking, they're not running, they don't need a whole lot of oxygen delivered, they don't need a whole lot of energy. All they need that energy for is to grow. And so we are able to transfuse them a little bit less frequently. We do still have that transfusion goal that we want keep them at, and that goal is somewhere, a pre-transfusion trough level, somewhere between 9.5 and 10.5 grams of hemoglobin [NOTE: 9.5 to 10.5 g/dL].

Joe: So that's pre-transfusion *trough* level, everyone. Again, I want to make sure that you're clear on this. Forgive me, Sujit, I keep talking to the audience because I think that's important to understand. You're not talking about transfusing just to kind of get them to a peak of above that. That's as LOW as you want them to be, right?

Sujit: Exactly. And the rationale for that is pretty straightforward, right? So we know that your "EPO thermostat," if you want to call it or whatever, the level at which you start to make increased amounts of erythropoietin, is when you get to below 9 and 9.5 [g/dL]. That's the threshold at which your EPO secretion goes up. And we want to prevent that EPO secretion from going up, because that's going to drive the ineffective erythropoiesis, it'll drive the proliferative phase, which will then not mature. So you want to suppress, you want to keep EPO to a suppressed level as possible and prevent this effect on the bone marrow. And that's how you come up with this threshold of 9.5 to 10.5 grams. They did studies a long time ago to look and see, could you have adequate growth and development at different levels, and you could probably have adequate growth and development at lower levels, but you won't suppress the ineffective erythropoiesis enough.

Joe: And just so we're clear, Sujit, I want to get into if the blood bank weeds here in just a second in terms of what those red cell transfusions should be, how we should match them, et cetera. But just so we're clear, in your practice and in most practices, are these just simple transfusions? We're accustomed to hearing about exchange transfusions in sickle cell disease. Are these just simple red cell transfusions generally?

Sujit: They are generally, yes, simple red cell transfusions. The only exception might be if you had somebody with α-thalassemia major and who was making a lot of hemoglobin H, you might consider exchange transfusions for those individuals.

Joe: Okay. When we talk about these red cell transfusions, when you know you have a patient who's going to be coming in who needs a red cell transfusion, and you're talking to your blood bank there at Cornell, are there special features of the red cell transfusions that you ask for

typically? What are the thoughts generally speaking on what you need from the blood bank in those settings?

Sujit: So we typically will send, when we are deciding, okay, this is a patient who's going to start on regular blood transfusions, we send off a couple of samples to the blood bank to do a little bit of extended phenotyping. So we like to get the CDE, Kell, and oftentimes the Duffy as well, just so that we have a little bit more of an extended phenotype and minimize the risk of alloimmunization moving forward.

Joe: Can we contrast that for a moment, Sujit? I know you're very well aware, obviously you're very well aware as a pediatric hematologist that sickle cell disease has a very, very large alloimmunization risk. How does that alloimmunization risk in thalassemia compare?

Sujit: So I think the alloimmunization risk in sickle cell is much higher. And I think that's understandable because your donor population is mostly Caucasian. Your recipient population is mostly African American. Here we had the recipient population also being mostly Caucasian for the longest time. Now it has kind of shifted, and now we are seeing a lot more Asian individuals with the thalassemias that we're following and treating. So that has changed a little bit, but in the past, the rates of alloimmunization, were somewhere around 5 to 15%, depending on what center you looked at data from. Now we are down to less than 5% as a whole, and that's really because of this strategy of doing some extended phenotyping.

Joe: And when you talk about extended phenotyping, you're not generally talking about full matching, but typically Rh and Kell, is that what you are thinking?

Sujit: Yes.

Joe: Okay. So Sujit, I know one of the things that's been talked about from time to time in patients like this is whether or not there is benefit to using "fresher" red cells. What's your philosophy, and what does the literature say about that?

Sujit: I wish that we could actually do a trial where we could test this in thalassemia patients specifically. The literature has a lot of information about people who get sporadic and random transfusions, not about people who get regular blood transfusions for whom iron overload is a significant problem. So the literature is mixed and there have been studies in neonates which have shown that there's no difference. You have other studies that show that there is a difference in terms of the survival of those red blood cells and therefore sort of how well you can keep them transfused. But none of those really address the issue of somebody who gets chronic transfusions.

So if you had fresher cells, and if you could demonstrate that they survived longer, and therefore somebody who was getting fresh cells as a

routine could get transfused less than somebody who was getting random cells, which were an average of three weeks old or four weeks old, then you could show that this actually makes a difference in this particular population. But the fresher the better, I think, if it's true that these cells survive longer because we do want to minimize the amount of red cells that they get, and so the longer red cells survive, the less transfusions we'd have to give and the less iron overloaded they'd become.

Joe: And that seems logical. I understand that the studies haven't been done, but it does seem logical that the longer you're able to go between transfusions, potentially the less iron overload risk you have. That makes total sense to me.

Sujit: Yes, no, it's intuitive, we just have to prove it.

Joe: I gotcha. I understand. Any other special modifications to red cells? Of course, everything in the United States now is leukoreduced. So I don't even think that's a question. Anything like irradiation washing, things like that, that you do?

Sujit: No. We don't like to routinely irradiate. Some centers just give irradiated blood as a standard, which is fine. There's no contraindication to irradiating, but radiating does reduce the shelf life of the product. It does cause some potassium leaking and all of that stuff, which all of you guys know much better than I do. And so we'd rather not, we don't require irradiation, let's put it that way.

Okay. As far as washing, again, we don't do washing because now the leukoreduced cells take care of a lot of the reactions that these individuals were having. Yes, you don't wash out all of the protein, which could cause the allergic types of reactions, but we do tend to pre medicate individuals who've had reactions in the past. And so the risk of that is quite low. And so it's now not standard of practice anymore to wash cells at all. Very few centers do it. And the only time we will request washed cells is if somebody has a long of severe reactions each time, then we'll wash it. But otherwise, no.

Joe: Okay. That makes sense. I guess one other last question before we talk about what the future is and what the treatment options are, in sickle cell disease, we are always concerned about the risk of delayed hemolysis and even in those rare cases, hyperhemolysis, which is potentially cataclysmic. My assumption is with thalassemia, since you're not seeing as much alloimmunization, that wouldn't be as big an issue, but I wanted to confirm that.

Sujit: We definitely see less of it. And I think also, the point you made is absolutely true in terms of the alloimmunization part of it. But sickle cell is also, it's an inflammatory condition, even at baseline. Thalassemia is not so much, unless you're severely iron overloaded and you have a lot of

problems related to that. So yes, we don't see the delayed hemolytic transfusion reactions as much at all in thalassemia as in sickle cell disease.

Joe: So, Sujit, we've talked about the general aspects of these diseases and even gotten into some specifics and what causes the problems. And we've talked about in those transfusion-dependent thalassemias, how we treat them with red cell transfusions. So I think one of the things that we need to make sure we cover, it doesn't necessarily apply to the blood bank, but I want to give you a chance to talk about it, it does apply in a way, so when we're giving people transfusions chronically in addition to the underlying issue with iron, I know that one significant part of your practice is worrying about whether or not these patients are getting iron overload and potentially treating that. So can you give us just an overview of how you manage thalassemia patients in terms of either treating or preventing iron overload?

Sujit: Sure. So we'll talk about "minimizing" iron overload, you can't prevent it at all. If you're getting regular transfusions, you can't prevent it. Even if you're not getting regular transfusions, you can't prevent it because that increased absorption in the intermedia patients is going to happen. You can minimize it. And in the transfusion dependent patients, we minimize it by preventing them from developing these allo- or autoantibodies, which would just reduce the lifespan of the red cells that they would get and therefore increase their transfusion requirement. We try to keep them suppressed enough so that they don't develop hypersplenism as much as possible. That's the other cause of reduced survival of the transfused red blood cells is if you develop hypersplenism and then your transfusion requirement goes up and up and up.

So as a whole, the field is moved away from splenectomy in these individuals. But sometimes we get to the point where the spleen has enlarged to a point where you worry about spontaneous or traumatic rupture, as well as it's causing so much hypersplenism and it reducing the lifespan of those circulating red cells so much that the transfusion requirement has gone up tremendously and we might have to actually consider doing a splenectomy. So that might reduce the transfusion requirement that way as well.

In terms of treating the iron overload, chelation therapy is a mainstay of that. Obviously you can't phlebotomize somebody you're transfusing on the other side, so it has to be chelation therapy. And so there's three different chelators that we use, and we can use them as a single agent or in combination. Again, there, compliance, compliance, compliance. That's the most important thing for these individuals to prevent them from having complications and to maximize their life expectancy and reduce their morbidity as well as mortality. So chelation therapy is challenging from the compliance standpoint, but we are able to get by pretty well. We have good chelators available now to be able to manage them well.

Joe: When I was in training, and it's been a long time ago, Sujit, I remember hearing that iron chelation therapy is fairly, well, miserable for the patient. Is that still true?

Sujit: It used to be miserable because it involved getting a subcutaneous infusion over 8 to 10 hours every night, or at least five nights a week. We now have two oral chelators that are approved for use worldwide now pretty much, and that, one is once a day, one is twice a day, or three times a day, and compliance with that has gone up tremendously compared with the subcutaneous infusions. The morbidity has gone down tremendously. In fact, I can confidently say that my pediatric patients who were born in the era of oral chelators only, none of them have significant iron overload-related complications. They're doing well and expect them to have near normal life expectancies as a result of that.

Joe: That's fantastic. Oh man. That's awesome news. I think as we close, Sujit, again, I want to ask you to break out your crystal ball for a second. I know that there are some forms that are available now and some that we're talking about in the future of potentially curative things that we can do. So can you tell us a little bit about what we can do now and what you see on the horizon in the future?

Sujit: So right now we have one approved agent that promotes differentiation, it's called “Luspatercept,” and it allows differentiation to progress more normally with the background of ineffective erythropoiesis. So when you have ineffective erythropoiesis, you have accumulation of these TGF-β ligands, and what this drug does is it traps those ligands, removes them from the equation, and therefore allows differentiation to proceed more normally. They did a clinical trial, it was called the "BELIEVE" trial, and they showed that you could reduce transfusion requirements by 32% to 50%, and it was approved by the FDA in 2019. And so that is another way of minimizing the amount of transfusion you get and reducing your iron overload, but it is not curative.

There are other drugs in clinical trial. There are pyruvate kinase activators, there are phosphodiesterase 9 inhibitors. There are hepcidin mimetics that are in clinical trials, but they're very early on so we don't really have that much local data on them, but they have shown proof of principle and they're promising.

On the curative side, or the curative intent side, you have gene therapy. We are now fairly advanced with the gene therapy trials, the longest patient is almost six years out from their initial gene therapy. And this is essentially an autologous transplant where you harvest stem cells, you send them to a laboratory, the cells are either inserted with a gene of interest through a vector, a lentiviral vector, or they're edited by either zinc finger nucleases or by CRISPR/CAS. And then those modified stem cells are reinfused into the patient after myeloablative conditioning therapy has been given. And then those cells will go and graft, and now you can

become transfusion-independent because you're making enough β-globin to not have the ineffective erythropoiesis and to not be anemic as a result of that.

So the gene addition trials are fairly well advanced, and those have shown very promising results. The gene editing trials are still a little bit premature. We have data now on I think at last count, eight thalassemia patients, seven or eight thalassemia patients that was presented at ASH last year, and very promising results from that standpoint as well. So, looking to my crystal ball, I say, I want to retire in eight years from now, and I hope that we'll have curative therapies and all of my patients will be cured and I'll retire with the clear conscience that I did my bit.

Joe: That's fantastic. I love that. Okay. Well, let's make that the plan then, Sujit. Let's do that.

Sujit: I would love to.

Joe: Sujit, I can't thank you enough for this really, really enlightening tour through what you deal with both clinically and from the transfusion perspective and how we can help you in blood bank world. I think this has been a great look at thalassemias and I really appreciate you doing this. Thank you so much.

Sujit: Thank you, Joe. It was my privilege, and as I said at the beginning, I feel passionate about this disease and so being able to reach a wider audience makes me feel very happy. So thank you.

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Joe: Hey everybody, it's Joe. As I mentioned, you can go to BBGuy.org/094 for images that will illustrate some of the things that Dr. Sheth and I mentioned in this interview. I'm really grateful to him for allowing me to share those slides with you.

Remember, if you are a physician or a laboratorian, be sure to go to wileyhealthlearning.com/transfusionnews to get your hour of totally free continuing education credit. As always, thanks for the continuing education sponsorship to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as, of course, to Wiley Health Learning.

As always, I hope you will consider going to Apple Podcasts to give this podcast a rating and subscribe. Since the last episode, a pathologist who is not primarily a blood banker named "Paul" did so, and he said, "Over the last 10 months…I have listened to most of these podcasts and…it has been a great learning experience for what is new in transfusion medicine." Thanks, Paul, I really appreciate that kind review. You should know that I make this podcast, in part, for people just like you. I'm here to cover the essentials, just like the podcast name says, so please keep listening! Reviews really help others discover the podcast, so I'd appreciate

so much any of you going to Apple Podcasts and giving a rating and a review, and you could hear your review read on the next episode!

Next up on the podcast is an interview I did with a good friend of mine, Dr. Chris Gresens from Vitalant, on the little known and understood blood product called “Liquid Plasma.” You will hear all about how this tidy little plasma product might be exactly what you need in your transfusion service! I also have an interview with AABB Chief Medical Officer Dr. Claudia Cohn coming soon, with a discussion of the ins and outs of blood shortages (I hear we might be having one of those right about now!).

But until that time, my friends, I hope that you smile, and have fun, tell the ones that you love just how much you do, and above all, never, EVER stop learning. Thanks so much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.