Hyperhemolysis Syndrome in the Patient with Sickle Cell Disease

Tony Casina:

Welcome to QuidelOrtho Science Bytes. We're proud to sponsor this podcast as a continuing commitment to transform the power of diagnostics into a healthier future for all. Today our topic is hyperhemolysis syndrome in the patient with sickle cell disease. I am Tony Casina, your moderator, and today we have a very special guest. I am joined by Dr. Wally Smith. Wally R. Smith, MD, is the first Florence Neal Cooper Smith Professor of Sickle Cell Disease, distinguished University Professor, Vice Chair for research of the division of General Internal Medicine at Virginia Commonwealth University, and the former Scientific Director of the Center of Health Disparities at BCU. Dr. Smith was a member of the Institute of Medicine's Committee on Standards for Trustworthy Guidelines. He has authored over 100 publications and served as an investigator on over 50 grants and contracts, including the principal investigator on 26 federal or foundation-funded grants and contracts.

Dr. Smith is an experienced implementation scientist and an expert in clinical and health services research and sickle cell disease. Dr. Smith was the principal investigator of the Pain in Sickle Cell Epidemiology Study, the largest and most detailed adult cohort, which changed our understanding of sickle cell disease pain in adults. And since 2012 has been the PI of likely the first ever randomized controlled trial of implementation sites in sickle cell disease. Start healing in patients with hydroxyurea.

Thank you very much, Dr. Smith, for being here with us today. It is truly an immense pleasure and an honor for us. Dr. Smith, thanks for joining us today.

Dr. Wally Smith:

Thank you for having me, a man of your stature.

Tony Casina:

Let's start with our first question of the podcast. Can you level set everyone by defining and categorizing what hyperhemolysis is for our audience?

Dr. Wally Smith:

Well, in order to talk about hyperhemolysis, we need to just state up front that sickle cell disease is a hemolytic anemia, and the hemolytic anemia in sickle cell disease comes as a result of defective red blood cells being cleaned out by usual garbage disposers, the spleen and macrophages, et cetera. And those defective red blood cells contain an abnormal hemoglobin, hemoglobin S, which in the deoxy form causes microfibril inside of the red blood cells misshape the red blood cell, and as a result, that red blood cell does not filter through small capillaries and venules. These defective cells are cleaned out and hemolysis occurs. And just like in all hemolysis, waste products come from the hemolysis, and they include a number of likely offenders. We know free hemoglobin, of course, is one of those offenders.

This process can accelerate causing what's called a vaso-occlusive crisis, the classic hallmark presentation for sickle cell disease. That can come from changes in temperature, changes in weather. Even in a biopsychosocial model, emotional stress can cause the release of catecholamines and can cause vasoconstriction, which can make blood flow of the red blood cells even more difficult and cause more hemolysis. So that's the sickle cell disease, normal hemolytic anemia that occurs all the time even when there is not a vaso-occlusive crisis going on.

But on top of that destruction, we have this unusual hyperhemolysis and that hyperhemolysis is due to a different process, which we're still trying to understand, but it's defined as a paradoxical drop in hemoglobin that occurs after a transfusion. It occurs usually without warning, and it happens in patients who are commonly transfused. So, it's on top of this vaso-occlusive destructive hemolytic anemia that I just described that's part of sickle cell disease. So that's hyperhemolysis.

Tony Casina:

Thank you, Dr. Smith. So how do you as a clinician recognize hyperhemolysis in your patient being transfused? And what role does the laboratory play in this identification?

Dr. Wally Smith:

Okay, so let's take that patient with sickle cell disease and the usual hemolysis going on, and let's say that they are sending you to transfusion. When you transfuse a patient like that with one unit of usually hemoglobin A containing red blood cells, you are infusing them with a foreign substance, a foreign body, but you expect a rise of about one gram per deciliter per unit transfused in the post transfusion hemoglobin. What you get instead in hyperhemolysis is a paradoxical drop. What many providers will decide is that that's just because of the sickle cell process that I explained a minute ago. It's vaso-occlusive due to sickle cell disease may be accelerated for some reason and the clinician will order another unit, a red blood cell. But suppose even after that second unit is transfused, the hemoglobin again drops maybe by a gram or more. That's how you know you have hyperhemolysis. The hallmark finding is a continued drop in hemoglobin despite your transfusing the patient.

Tony Casina:

So the individual that has one of these events of a delayed hemolytic transfusion reaction proceeding to hyperhemolysis, this is considered a provoked event.

Dr. Wally Smith:

Yes, it's provoked but not understandably provoked. Let me explain what I mean. This kind of provocation, Tony, is what we call bystander hemolysis, and it is not testable. What do I mean by that? In the usual delayed hemolytic transfusion reaction of vascular cause, you either see a small rise, no rise, or maybe a small drop in the hemoglobin when you transfuse the patient and serologically, you can test for that. You can see a positive direct antibody test and you can see evidence of new antibody reactivity. Not so with hyperhemolysis or bystander hemolysis.

Two different things. First, you don't see new antibodies. There's no apparent direct antibody test, there's no new antibody detected, and the patient's pre-transfusion testing does not show anything, or post transfusion for that matter.

Second, this bystander hemolysis is both the patient's own red blood cells and the transfuse cells that are just chewed up. And you have to assume a provocation, Tony. You have to assume that the patient's immune system is reacting to some foreign red blood cell antigen, and you just can't detect it with testing your antibodies. It's unclear still what that reaction is. You just know that both your patient's own red blood cells and the transfused red blood cells are being destroyed and that you cannot detect that it's coming from an antibody.

So, I can almost anticipate your next question. Well, what's it coming from? The last thing we can say is it might be coming from complement. And so that's where we are state-of-the-art, is to try to understand whether this is a complement-mediated reaction and whether bystander hemolysis is complement chewing up the patient's own red blood cells in addition to the provoking red blood cells that have been transfused. So that's what we understand about bystander hemolysis.

Tony Casina:

Thank you. So yes, that's always been the question as to what's driving hyperhemolysis even when there's no indication of antibodies present. I'd be very curious to see what sort of outcomes come from studies on complement and its relationship to these events.

So one of the challenges I'm sure this presents to you is how do you care for a patient that's undergoing one of these episodes and try to prevent a fatal outcome?

Dr. Wally Smith:

Yeah. Well, first of all, it's very frustrating because what you want to do is give them blood, right? And that's the absolute wrong thing to do, Tony. Stop transfusing them unless they're dying and you think you've got to give them blood and then only one unit and slowly because you want to stop the minute you think you're doing harm rather than good. I would say don't transfuse despite the number being four, five grams per deciliter. In sickle cell patients, let me just tell you, they often will have baseline hemoglobin at four or five grams per deciliter, which makes most of us faint, but which they can tolerate hemodynamically. If they can't tolerate it hemodynamically, yes, you have to try and give blood, but you've got to do so slowly, and you need to stop the moment you see that you're provoking yet another bystander hemolysis event.

The second thing you would like to try to do is to suppress this unknown immune response, and we have case reports of high dose intravenous immunoglobulin and steroids in stopping the transfusion maybe making a difference in the patient. Then last, we have new biologics, and I won't name specific drug names, but new biologics that may target their activity towards this complement mediated destruction of red blood cells. You might try those as well. But the number one thing is don't transfuse. Don't transfuse, don't transfuse. Because it will stop once all the foreign material is cleared the patient will stabilize and stop hemolyzing, but it's just doing so at a level which makes you very uncomfortable and makes you wonder if the patient can make it.

I'll say one more thing. It's kind of obvious. Don't keep drawing blood, just draw hemoglobin and hematocrit to assess the efficacy of any transfusion you have or to assess the efficacy of the situation that the patient finds themselves in. And then wait. And the waiting is the hardest part. People want to do something for these patients, but you need to just wait.

Tony Casina:

Thank you, Dr. Smith. Do lab values reveal lower levels of complements in these patients once they go through this episode or possibly higher values?

Dr. Wally Smith:

Well, you are chewing up complement in responding to this reaction. So you could see a process, right? In a patient during this phase, you could see chewed up complement, but in general, if the patient has been transfused multiple times, you might see, if you were to get them at steady state, you might see a cocked gun of complement activity. But that's where the research is right now. And Tony, people like you are doing this research. I am a sickle cell specialist and not a complement expert. So, if I said anymore, I'd probably be talking out of the top of my head.

Tony Casina:

No problem. Thank you. Well, with that, one of the things that I think us folks in the transfusion medicine world want to know is what is the role of the laboratory in the transfusion service for best practices?

Dr. Wally Smith:

Yes, yes. Well, this is the real message of this podcast. There has got to be communication. There needs to be communication for the sickle cell specialist to be on board to understand what I just got through saying and to tell the rest of the team to stop transfusing the patient because the rest of the team, not sickle cell savvy, will react to a low hemoglobin by giving blood even though that low hemoglobin is paradoxically coming from their use of blood. So, somebody who's aware of this bystander hemolysis, hyperhemolysis needs to be able to advise the team, "Hey, my patients normally get a hemoglobin of five. They're at four now even after you transfused them, and they'll probably go to a three if you do it again. Please stop."

Second, please, please, please, blood bankers, labs get involved early and do the tests that we just got through talking about, the direct antibody tests and looking for the presence of specific antibodies to rule out other causes of a delayed hemolytic transfusion reaction. And then report quickly to the team whether you see any of these antibodies. And if you don't, that's a positive test. That's a positive test suggesting that you have bystander hemolysis and that you need to stop transfusing the patient rather than trying to find compatible units. You can try to find units that have no antigens whatsoever and maybe try to use those units. But in our practice, that's a long-drawn-out procedure and really results in what I recommended at first, which is no transfusion for the moment.

Tony Casina:

Okay. Thank you. One last question more related to the patients. Are the patients informed enough to be able to communicate that when they happen to go into sickle cell crisis and appear to have low hemoglobin to share that with any treating physician at that point in time?

Dr. Wally Smith:

I seriously doubt it, Tony. I don't think that patients are that sophisticated. They understand pain. They often don't know their usual hemoglobin and they understand what transfusion is, and their logic is simple. If my hemoglobin drops and I have pain, maybe you should give me blood. But of course, blood is not a treatment for pain. Blood is a treatment for hypoxia and for anemia. So no, patients do not carry around a little guidebook to tell clinicians how to treat them. And unfortunately for that reason, patients especially in less sophisticated, not sickle cell savvy clinicians' hands will actually die from what we're talking about here because the provider will think they're doing the right thing when in fact they're doing the exact wrong thing.

Tony Casina:

Okay. Well, thank you very much, Dr. Smith, for this insightful discussion. I really want to thank you for taking the time with us today and giving us your experiences and insights on this fascinating and somewhat misunderstood topic of hyperhemolysis. Thank you so much for your time today on this podcast. It has been truly an honor to talk with you about the importance of recognizing hyperhemolysis and the challenges it brings to the patient, clinician, and the transfusion service laboratory.

Dr. Wally Smith:

Thank you very much.

Tony Casina:

I hope you all have enjoyed this broadcast episode about hyperhemolysis syndrome in the patient with sickle cell disease. Make sure to review the sections within the podcast description for any reading materials that we've suggested. Based on today's podcast, I'll leave you with our pop quiz: *What is an unprovoked hyperhemolysis event?* You can always go back and listen again. Thank you for listening and please subscribe to QuidelOrtho Science Bytes, brought to you by QuidelOrtho Corporation, where we are transforming the power of diagnostics into a healthier future for all. Take care, stay healthy and safe.