# Previously Untreated Patients with Hemophilia Matter

As regional hemophilia treatment center, Children's Mercy follows more than 900 patients with bleeding disorders. Listen as Shannon Carpenter, MD, pediatric hematologist/oncologist and director of the Hemophilia Treatment Center at Children's Mercy Kansas City, discusses hemophilia A and B in children, current treatments and promising new research studies and options on the horizon, such as the PUPS Matter cohort study.

Featured Speaker:

## Shannon Carpenter, MD, MS

Shannon Carpenter, MD,MS, is the Associate Division Director, Section of Hematology at Children's Mercy Kansas City and Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine. Dr. Carpenter received her medical degree from the Virginia Commonwealth University, Richmond, Virginia. She completed a residency in pediatrics at Children's Hospital Medical Center in Cincinnati, Ohio and a fellowship in pediatric hematology/oncology at Duke University, Durham, North Carolina. She is board certified in pediatrics and pediatric hematology/oncology.

Transcription:

Michael Smith, MD (Host): So, out topic today is hemophilia, the new treatments and an interesting new study conducted out of Children's Mercy Hospital. So, my guest is Dr. Shannon Carpenter. She is the Section Chief of Hemophilia and the Director of the Kansas City Hemophilia Treatment Center. Dr. Carpenter, welcome to the show.

Shannon Carpenter, MD (Guest): Thank you. Thank you for having me.

Dr. Smith: You know I think what would be nice, Dr. Carpenter, if we start it with a nice overview, a review for a lot of the practitioners that listen to this show about hemophilia; the different types, how it's been treated in the past. Just kind of give us a nice refresher.

Dr. Carpenter: Sure, I'd be happy to. Hemophilia is a bleeding disorder and it is due to the lack of clotting factor within the blood. The most common type of hemophilia is hemophilia A, which is due to a lack of clotting factor VIII. But there is hemophilia B which is due to a lack of clotting factor VIIII and there are rare bleeding disorders that aren't called hemophilia but fall under the hemophilia treatment center that are missing other factors within their blood. We take care of all bleeding disorders without hemophilia treatment center and we cover not just Kansas City; we also cover all of the state of Kansas and we cover down all the way to Arkansas, half of Missouri and up to Nebraska and Iowa. We have about 900 patients with bleeding disorders that we take care of and we actually do outreach clinics to a number of different places around the area. But our goal is to have patients be – have healthy lives. The patients with hemophilia have an increased risk of bleeding. I'm going to specifically focus on hemophilia A for a moment and hemophilia B.

There is stratification of severity with hemophilia A and B where patients who have less than one percent of the clotting factor in their blood have severe disease and those patients are apt to have

spontaneous bleeding into their joints or muscles that can be very crippling. And so, our treatment for those patients is to give them the factor back and to do it ideally prophylactically to prevent bleeding. Which means infusing factor into the vein as often as every three days or even every other day or every day for some patients. Which is obviously, a very labor-intensive thing for a family with a small child. So, out job as a comprehensive hemophilia treatment center is to ease the burden of that treatment and to make sure that patients have access to comprehensive care that allows them to have the best life and the best outcomes because those joint bleeding episodes can lead to joint contractures and actually cripple patients. And that is what used to happen before we learned that it's better to be prophylactic in terms of our treatment.

Dr. Smith: So, one quick question. When you talk about the injection of the missing factor; is there issues with the immune response to that? How well does that actually work?

Dr. Carpenter: Well it works great but unfortunately, about 20-30% of patients with severe hemophilia A will develop what we call an inhibitor and that inhibitor is an antibody because their body doesn't have factor VIII and so they see that as a foreign agent and so that antibody cases the factor that we infuse to not work as well. For those patients; we do have some bypassing medications that can help them keep from bleeding. We have had some major advances on that in the recent past, but we have – but for many cases they don't work as well, or they may have more bleeding, or they have to be given more frequently. So, best to not have an inhibitor and then if you do get one the treatment would be to try to eradicate that inhibitor with large doses of factor regularly to drive that inhibitor down and cause what we call tolerance. But of course, it's a big deal to get an inhibitor and it usually happens in the first 50 exposure days or the first 50 times they have gotten that medication. And so, it tends to happen in young children. And so, you have a small child who gets now an inhibitor and needs a much more intensive treatment in order to get that to go away.

Dr. Smith: Yeah, so, this idea of tolerance and trying to break that immune response, bring down that antibody; how well does that actually work and are we looking – are there some new treatments on the horizon so that we can even avoid all this all together?

Dr. Carpenter: Yeah, so it usually works. We tend to quote about 60% of the time, probably – that's probably about right in doing that what we call immune tolerance therapy. We do have a new medication that was recently approved for children and adults with hemophilia A and inhibitors that is called HEMLIBRA and that medication is a very interesting scientifically medication because it is not a factor, but it takes the place of factor VIII in clotting. So, it's kind of a – what we think of as a factor 8 in the medic. So, it is an antibody that is – doesn't attack anything within the person's body, so you think about a monoclonal antibody; a lot of times you think it's going to go after something in the recipient's body but that's not the case here. In this case, what it's doing is it actually takes the place of factor VIII in coagulation and acts like it and what we found is that medicine has been very successful for the treatment of bleeding and stops bleeding in many of our patients with hemophilia inhibitors. So, hemophilia A. we can't use it for hemophilia B. it doesn't work because factor VIIII is what's missing there, and this takes the place of factor VIII. But there are many patients who we have on this new medication that were struggling with their inhibitors or they were in that group that where the immune tolerance therapy didn't work who now are doing very well with much less bleeding on this new medication.

Dr. Smith: Yeah, that's amazing that you are mimicking one of the factors in this very complicated cascade of forming a clot. I mean that's pretty awesome sounding and pretty amazing actually.

Dr. Carpenter: It is, what I like to say – I like when I try to teach some of the fellows and such about it, I say it's really sci-fi cool. I mean it really is. It's – when this was first announced at one of the meetings when it was first brought out is this is something that people were working on, it created quite a buzz as you can imagine, and we are thankful that it's turned out to be a relatively safe product. And but it certainly got our attention really quickly just from the fact that it's such a novel and creative way to attack this problem.

Dr. Smith: Yeah. What boggles my mind with it you know the whole clotting cascade is enzymatically driven, it's a biochemical reaction and there's lots of things that are going on there, so this antibody that you're using has to match perfectly, right, in its chemical composition, in its function I mean that's pretty amazing science and that is really cool.

Dr. Carpenter: It is and what's really cool about it is it doesn't actually look like factor VIII at all. It actually looks like an antibody. Right, it just has the appropriate binding sites to do that. There is even more interesting things coming down the pipe where instead of trying to turn on the on switch for clotting, which is what we have been doing by given factor; there is an effort to then turn off the off switch for clotting and so to go after some of the natural anticoagulants like antithrombin and try to reduce them to allow patients to restore that clotting balance for patients who right now have in contrast, too much of them.

Dr. Smith: Yeah, but that's interesting too, right because you have to have a control mechanism as well, right, so if you are starting to turn off the anti-clot compounds, how do you control – like how then do you start to break down the clot. I mean how do you control that then? I mean that seems to be a problem with those.

Dr. Carpenter: So, that's a concern and they are still in clinical trials, but it is finding I think that sweet spot where coagulation balance is restored. So, right now if you think of clotting as a balance scale with bleeding on one side of the scales and clotting on the other side of the scales; right now, hemophilia patients they are far weighted to the bleeding side. So, to restore that balance, to take away some of those inhibitors, you have to get it so that those are now equally balanced without tipping it too far toward the clotting side. And of course, people aren't static systems, right. We get sick, we have surgery, trauma and so those things change that balance sometimes unpredictably. So, those clinical trials are really important, and we are anxiously awaiting to see what comes of those. But we are very hopeful that they will be positive outcomes because we do think that this allows us more options for treating patients that we haven't had in the past.

Dr. Smith: Well and these kind of clinical trials, because hemophilia when you look at the total population is not affecting too many people, but like how do you build confidence in these clinical trials when maybe the number of subjects is a little lower than what you would want?

Dr. Carpenter: So, that's an area that is something that we are actually working on with the NIH right now to try to think about how we are creative in designing trials for hemophilia. Because it is a rare patient population. In some cases, we have to power trials a little differently to ensure that we are

getting the appropriate information but there are some more creative trial designs that we can use and actually next week, I'm going to a state of the science at the NIH that is for hemophilia and inhibitors which is gathered not only many of the leaders in hemophilia treatment, but also has tapped into bioinformatics and people who understand large data sets and research design experts who can help us think about ways to study this rare outcome in a rare disease in order to better understand it and in order to get the most information with a limited patient population.

Dr. Smith: Yeah, yeah. Very again, what another interesting aspect of all of this. Let's get into the last part here. So, you are involved with a new study, correct? Tell me a little bit about that.

Dr. Carpenter: So, in order to – as a part of this effort is to follow patients who have not been treated with factor to understand why certain patients get inhibitors so that we can perhaps intervene even before patients ever see factor in order to prevent them from getting inhibitors instead of just waiting for the inhibitor to occur in those 20-30% and then trying to get it to go away. So, we have developed with the American Thrombosis and Hemostasis Network and I'm one of the national PI's along with Dr. Courtney Thornburg at Rady in San Diego, the idea of a cohort study where we have multiple sites around the United States where we will enroll children with hemophilia at the time of diagnosis before they receive any treatment and collect data on events that they have, genetic data, treatment data so that we can hopefully identify some risk factors pretreatment that we can modify to prevent inhibitor development and then we will utilize that same platform to hopefully develop some interventional trials to prevent inhibitors in the next phase of this.

Dr. Smith: That's amazing. Do you have any thoughts, any theories on why some people develop these inhibitors?

Dr. Carpenter: So, there are some known risk factors. We know that if you have severe hemophilia, if you have less than one percent of factor in your blood, and if you have certain genetic mutations then you are at higher risk of developing an inhibitor. So, people who have very large deletions of the gene have nothing within their body that looks anything like factor VIII and so that puts them at higher risk of developing inhibitor. And that kind of makes sense.

We know that certain ethnicities are at higher risk. So, African derivation or Hispanic derivation people who have a 50% chance just about of developing an inhibitor if they have severe hemophilia. We don't know why. We don't know what the why that would be a difference within ethnicities. The rate of hemophilia around the world is about the same with the exception of a few small pockets where it is higher because of people who intermarry. But we don't understand why – what influences or what immune influences maybe causing those patient populations to develop inhibitors more.

There is some evidence that suggests that certain immune genes may play a role in someone who is more apt to develop an inhibitor. And there's some really interesting studies looking at the antibodies that develop before the actual inhibitor develops that where certain antibody switching may predate the nullifying inhibitor, so those studies are pretty fascinating as well. And whether we could intervene when we found that first antibody that wasn't a neutralizing antibody to try to prevent that clinically significant antibody from forming. But then there are other things like certain treatments, such as high doses of factor at the time of when they first see factor, what we call a danger signal that may rev up the immune system. There may be – there was a recent study that said that patients who received

plasma derived factor which is obviously made from donor plasma, may have less of a risk of inhibitor development versus those who receive a recombinant factor product. So, those – it's multifactorial and there is some thought that it may even be – there may even be influences of in utero exposures that could predispose a child to develop inhibitors later on.

Dr. Smith: Wow.

Dr. Carpenter: So, lots to look at.

Dr. Smith: Fascinating work. Listen Dr. Carpenter, it's amazing and I want to thank you for the work that you are doing and it's just fascinating and good luck with all the research and thank you for coming on the show today. You're listening to Pediatrics in Practice with Children's Mercy Kansas City. For more information, you can go to **www.childrensmercy.org (http://www.childrensmercy.org)** that's **www.childrensmercy.org (http://www.childrensmercy.org)**. I'm Dr. Mike Smith. Thanks for listening.