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Advances in Hemophilia: From Joint Health to FVIII Guidelines and the Clinical Integration of Rebalancing Agents

Announcer:
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Dr. Young:
Hello. My name is Guy Young. I'm a Professor of Pediatrics at the University of Southern California Keck School of Medicine and the Director of the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles, and welcome to this activity. It's called *Advances in Hemophilia: From Joint Health to Factor VIII Guidelines and the Clinical Integration of Rebalancing Agents.*

We'll be covering three topics with three outstanding—I guess I'll call them discussants since we're in the podcast world, or I could just say three experts. And the topics are going to be optimizing joint health, which will be with Dr. Annette Von Drygalski, guidelines for factor VIII levels with Dr. Steve Pipe, and finally, rebalancing agents, current evidence and clinical integration with Dr. Robert Sidonio.

CHAPTER 1

Welcome to the first part of our discussion on advances in hemophilia care. In this segment, we're going to focus on optimizing joint health, which, as we all know, remains one of the most important long-term challenges in managing hemophilia. We'll take a closer look at what optimal joint protection really means today, how we think about subclinical bleeding, how we monitor joint health over time, and how we translate consistent hemostatic control into meaningful outcomes for patients at every stage of life.

And with that, I'm going to introduce the person that I'm going to have this discussion or conversation with. Her name is Annette Von Drygalski. She is a Professor of Clinical Medicine. She's the Director of the Center for Bleeding and Clotting Disorders, the Associate Director for the Center of Excellence for Hereditary Hemorrhagic Telangiectasia, Program Director for the Coagulation Medicine Fellowship, and Associate Program Director for the Hematology Fellowship, and all of this is at the University of California San Diego in San Diego, California.

Our learning objective for this segment is to formulate strategies to address the joint health-related unmet needs of patients with hemophilia in clinical practice. And with that, I welcome Dr. Von Drygalski to discuss the first topic, and it's really to set the stage about when you think about joint bleeding and arthropathy across the lifespan, what has the most over the last 20+ years, what are the problems that persist even in the prophylaxis era?

Dr. Von Drygalski:
Thank you, Dr. Young, for this kind introduction. And yes, as someone who only sees adult patients with hemophilia, there is a significant proportion of patients who have suffered from joint bleeding in childhood, and I think we get to that and how that will influence their trajectory of joint health throughout the different stages in life.

So those patients often have severe arthropathy, arthritis. I don't think we quite understand the pathobiology of hemarthrosis and how it all ends up mostly arthritis, but it's not rheumatoid arthritis, it's not all osteoarthritis. So there's something in the middle we don't understand, but it is a very debilitating condition, and it's sort of a self-fulfilling prophecy. Once there is joint damage, it will just continue. So that's the current adult population, I'd say midlife and beyond, often in their 30s and beyond.

And what has changed over the past 20 years to maybe when we all started to now is that the young generation of hemophilia patients—and Dr. Young can relate to that very well because he sees a good proportion of children—those who now graduate into the adult world have hardly any joint damage anymore because they had no bleedings or very little bleedings. Some don't even recall ever having had a bleed. And that obviously changes the aspects of joint health quite a bit going forward. And that is caused, in a good way, by the availability of factorless treatments that provide a general hemostasis level that can be maintained continually throughout their lifespan, or new factor VIII or factor IX products that are long lasting, or half-life or ultra half-life extended, that can just be infused at a very low frequency, maybe once weekly. So all of that has contributed to this accelerated, thank God, joint health in youth.

Dr. Young:
Well, thank you, Dr. Von Drygalski, for that answer. So yes, we are in pediatrics doing the best we can to minimize bleeds in patients, but mostly it's about minimizing overt bleeds, the bleeds we can see.

And we know from the Joint Outcome Continuation Study that, you know, joint damage can accumulate over time. Granted, that was with drugs that were only available back in the 2000s, the standard half-life drugs, and clearly things have changed today.

But I think we still have some issues with what we consider to be something we call subclinical bleeding, which is a tricky thing to think about. So I want to spend the next segment discussing that. So if you can help us to sort of define, understand, you know, what is subclinical bleeding, how should clinicians think about its relevance for long-term joint outcomes, and just to give us a sense of where we are with this tricky topic of subclinical bleeding?

Dr. Von Drygalski:
Well, in my definition, subclinical bleeding is bleeding into the joint space that goes unnoticed and therefore is not reported. And there are no good numbers to suggest how much subclinical bleeding is going on. And then blood in the joint is not ideal, because I think we can all agree on iron being the incendiary agent to cause joint damage. Iron is toxic. It can accumulate not only in synovium but also in cartilage and other structures, and it's been well shown that the accumulation of iron in those structures is directly proportional to outcome scores—the clinical outcome scores such as hemophilia joint health score or MRI joint scoring with validated MRI scores. So blood in the joint is never a good thing, overt or un-overt.

And there are some data in adults, though, with arthropathy, so granted they already have some preexisting unfortunate joint status that might make them more prone to bleeding, and often it's really hard for these patients to sort out if the pain is arthritic or plus/minus blood. So about 30% of all arthropathic joints that, at any given time, if you perform an ultrasound exam—and ultrasound is very sensitive to blood on the order of actually a few milliliters—you will find blood in those joints. So how that, though, in the adult world, where patients already have a lot of arthropathy and pain, will continue to influence their joint deterioration is less well known.

In pediatrics, and I think this is where Dr. Young is going to reference the Joint Outcome Study—it's a landmark study now, was published 2007, I believe, in the *New England Journal of Medicine* by Dr. Manco-Johnson—just having toddlers being put or randomized onto prophylaxis with an available factor products versus episodic treatment. And she could show for the first time that there was a good number of little patients who had hemosiderin accumulation in their joints, although they have never indicated that there was bleeding. And so maybe they didn't say they had pain, maybe the parents didn't report it, maybe the children didn't feel it, a little unclear, but it does happen. And to my understanding, that really translates into joint health later, because those children with subclinical bleeds, be they episodically noticed or if they had them subclinically, turn out, once they were, you know, reevaluated 20 years later, had worse joint health status, and that is an important finding.

Dr. Young:
Okay, thank you for that. So when we're thinking about protecting joints long term, we know obviously preventing overt bleeds is a key aspect of that, but how do we connect the outcomes of wanting to protect the long-term joint damage, so kind of the day-to-day decisions about patients' activities, functioning, quality of life? What are some of the things that go into the way you approach trying to protect or at least preserve joint health, even in those that have had it damaged, in your kind of day-to-day clinical care of these patients?

Dr. Von Drygalski:
Well, one large part is providing protection with hemostatic agent, be it their preferred factor regimen or non-factor regimen, to ensure they will not have any overt joint bleed.

So personally, for me, even one bleed on any kind of regimen is one bleed too many, because blood in the joint, as we said, has downstream effects, propelling downstream effects that we just can't foresee and might be negative.

So if someone reports—and that's not a subclinical bleed—a clinical bleed, we will bring them in immediately into clinic to scan their joint with ultrasound to ensure there is really blood in the joint, because that has a treatment decision tree in terms of optimizing their factor prophylaxis, ensuring adherence, or non-factor prophylaxis, ensuring adherence.

And also making sure that there is nothing else in the adult world that can precipitate that. For instance, in the adult world, we have gout, we have pseudogout, we have rheumatoid arthritis appearing very often in midlife. So these are things that can set a joint up for bleeding, and it doesn't always have to be a sporting event or was spontaneous. This has to be considered. So we do an aspiration if there's fluid in there, just for good internal medicine practice, and send that off for analysis, because let's say if there's gout, there's treatment for that.

Dr. Young:
Alright, thank you for that. So as you mentioned, you take care of adults, and a lot of adults did not have the benefits of the many drugs that we have now or even being on prophylaxis. So you have lots of adults who already have significant arthropathy. And while obviously trying to prevent further bleeding is a key part of what you do, can you discuss a little bit about how a multidisciplinary approach looks like for the patients who already have established joint disease and what you can do for them going forward?

Dr. Von Drygalski:
Yeah, thank you for that question. That's very important. So as we said, first, it would be very advantageous to understand better the pathobiology of hemophilic arthropathy to have more targeted treatments. However, our understanding is rudimentary, and I want to start with that as to leading into this sort of comprehensive care approach and what to do about.

There are maybe two things that are specific to hemophilic arthropathy. Obviously, iron is the inciting point that's not true in osteoarthritis, not in rheumatoid arthritis, and for whatever reason, that iron causes a lot of synovial hypertrophy with what we call vascular remodeling, also easily visible on the ultrasound with the Power Doppler function showing quite some neovascularization, vascular pulsing, like in pulsating blood in that thickened synovium. And if patients bleed, that is—I call that vascular bleeding. It has almost nothing to do with clotting factor or any other non-factor prophylactic protection, because these vessels are fragile. And it matters also in terms of rehabilitation and what to do with these joints if there is a lot of that hypertrophic synovium with that vascular remodeling going on. So that is one point I want to say is specific to hemophilic arthropathy and might be important for physical therapists who are part of a comprehensive team to know.

The other interesting aspect is that there seems to be a deficiency of the ability to clear iron stored as hemosiderin in various joint compartments, being the synovium or the cartilage. That iron is literally trapped. So once—and that maybe comes back to the point—well, even one joint bleed, even in childhood, is one too many, because that iron has really a hard time coming out of the joint. It sits there and causes more damage.

So think about an athlete who has maybe a joint injury and a bleed. That athlete can clear the hemosiderin and the blood and the iron, probably not a ton of downstream effect, but a hemophilia patient cannot. We see that in the mouse model, and we see that in adults who haven't bled in years, and we have published about that, yet the previous iron sits in the joint.

So these are two specific points to make regarding the pathobiology. And the next question is how do we address it. The multidisciplinary team definitely has a physical therapist on board to look at those components and provide conservative measures that are beneficial, on the individual clinical assessment and maybe imaging assessment with ultrasound.

Then we have the orthopedic surgeons at our institutions. We have two we work very closely with. One is a joint surgeon only for the ankle, the other one for the knee—these are the most affected—to figure out what is possible before joint replacement, from ankle fusion to ankle maybe partial arthroplasty or any kind of cleanouts, quote unquote. So and that is a constant back and forth. And of course, us as physicians to ensure that they have the adequate clotting factor or non-factor protection.

Many want a little more than just physical therapy, so we would work with nutrition, maybe for weight loss. That's an issue, right? Or other supportive professionals to figure out what could be good programs for moving again, tailored to the patient.

Dr. Young:
Great. Thank you very much for that really great answer. We're going to close with monitoring. And when I say monitoring here, what I mean is diagnostic imaging monitoring. And we really have, I think, the best person for sure in North America to discuss this, probably the whole world, which is Dr. Von Drygalski, who pioneered the use of musculoskeletal ultrasound into our real practice. So we're very honored and lucky to have you answer this final question.

And really it revolves around the different imaging techniques, and it's essentially how do you choose between MRI, x-ray, and musculoskeletal ultrasound—maybe we just say MSK-US. It's basically, I'd like you to discuss what the strengths and weaknesses or benefits or limitations of each of these modalities as we close this discussion on joint disease.

Dr. Von Drygalski:
Well, thank you very much. Very honored. Thank you, Dr. Young, for that nice comment.

Well, so we have x-rays, and those were discovered and with scores attached to them more than 40 years ago by Dr. Pettersson. So we call them Pettersson scores. But as you can imagine, they are very non-sensitive to progressive joint damage since they mostly show cartilage and bony changes, at which point it's a late stage. It would be too late. Even a Pettersson score of 1 out of 13 would mean a lot has gone on before that that we could have captured, and so they are just no longer practical for the modern world of medicine.

The next thing, therefore, to find more early and soft tissue changes were MRI scores developed by various groups over the last 15 years, I would say. One of them, the International Prophylaxis Study Group, we both are members of that, and they are validated. And of that, we can see soft tissue changes, hemosiderin, semi-quantitative accumulation and all of that. But it is very difficult to put someone through an MRI scanner for all six joints every year, every half year. It's just difficult, not feasible in essence.

And then over the past several years, we came out with musculoskeletal ultrasound as a way in sentinel positions—it's not perfect. It can't look deep into the joint. That is a limitation—in sentinel positions to look at synovial hyperproliferation, cartilage damage, osteochondral problems. And here at the University of California San Diego, we have developed a protocol. It's called the JADE protocol, where we can measure those structures very precisely.

But there are other scoring protocols also proposed, like the HEAD-US in Italy.

The problem is with all of these—and I include even the Hemophilia Joint Health Score which is a clinical exam—we never have shown that serial evaluation with these imaging studies and based on progression, based on these imaging studies, making changes—being hemostatic clotting factor changes, making different physical therapy plans or any kind of intervention—that that would change the outcome. And I am not sure that we will ever be able to show that, because it's a rare disease. It's difficult to do these exams.

So it's great to have that technology available. MSK-US, we mostly in clinic use it for bleed yes/no, and for synovial hypertrophy with vascular remodeling as a point-of-care bedside answer to these questions.

Dr. Young:
And that's fantastic. So Dr. Von Drygalski, thank you very much. It's really an insightful discussion.

It's clear that we made significant strides in reducing joint bleeding, optimizing joint health, but we're still working towards essentially perfect joint health. I mean, we haven't gotten there yet. And so I think a main takeaway for clinicians is understanding that protecting joints isn't just about counting bleeds. There's the subclinical bleeding that we talked about. There's the prevention and management of long-term joint damage and preserving joint function and, of course, supporting quality of life through the multidisciplinary team, as you discussed. Because many patients will at some point need help with physical therapy, certainly diagnostic imaging and the ultrasounds, and hopefully we can avoid surgeries, but we know that that may be inevitable as well.

So thanks again for helping us lay the foundation for the rest of this conversation that we're going to have today.

Dr. Von Drygalski:
Thank you.

CHAPTER 2

Dr. Young:
Welcome to this segment on guidelines for factor VIII levels and how they inform treatment decisions in hemophilia management. For decades, factor VIII levels have been central to how clinicians assess bleeding risk, design prophylaxis strategies, and evaluate treatment effectiveness. In this discussion, we're going to take a closer look at how factor VIII targets have historically been used in clinical practice, what the current guidelines recommend, and how new data are shaping expectations around higher trough levels, sustained bleed protection, and what that might mean for long-term joint outcomes.

So for this segment, I'm going to introduce Dr. Steven Pipe. Dr. Pipe is a Professor of Pediatrics and Pathology, and he's the Lawrence A. Boxer Research Professor of Pediatrics at the University of Michigan in Ann Arbor, Michigan.

Before we get going, I'm just going to state the learning objective for this segment. It is to assess the impact of factor-based replacement therapies on factor VIII levels according to various guidelines.

So the first question for you, Dr. Pipe, is factor VIII levels have long been central or key to how we think about hemophilia management. Can you briefly walk us through how clinicians have historically used factor VIII levels to guide treatment decisions?

Dr. Pipe:
Yeah, thanks, Guy. Well, certainly factor levels have been central to clinical diagnosis going back decades. It's how we diagnose hemophilia, often with a prolonged clotting-based tests like aPTT and then eventually a specific factor assay, factor VIII or factor IX. But it's also how we assign severity. And so still going back over many decades, we define the expectations about clinical outcomes for patients based on their residual factor level. So severe is factor VIII or factor IX level of less than 1%, moderate is between 1 to 5%, and then over 5% is mild disease.

We also rely on factor levels to screen patients for inhibitor complications, and it's often the first way that inhibitors are picked up after a clinical presentation. With regards to how we use factor levels in other aspects of clinical management of hemophilia, we use factor assays to do dose adjustments when patients are on routine factor replacement. We rely on factor levels during acute bleed management and, of course, during surgical interventions. And then, for a long time, we have been using pharmacokinetic-guided prophylaxis in order to optimize factor dosing. So really, for several decades, factor levels have been central to everything that we do in hemophilia management.

Dr. Young:
Great. Thank you very much for that. So building on that, and I promise I'm not going to date us, but we are roughly the same vintage and started out around the same time, and I remember back then that we had targeted factor VIII trough levels with prophylactic therapy of around 1%. We felt okay if we're above 1% or 1% or higher, then we're happy with that. But the goalposts have shifted, and most recently the WFH guidelines have started to shift these goalposts. So can you talk about why we're increasingly considering higher trough levels of factor to prevent bleeding?

Dr. Pipe:
Well, as you said, you know, we have to go back to the early days of initiation of prophylaxis, and beginning with the Swedes and then in the Netherlands. It was the observation that patients with non-severe forms of hemophilia had less joint disease, and even having a few percent of residual factor VIII or factor IX was enough to significantly reduce joint disease and the risk of joint bleeding. And so natural history studies done over many years have really confirmed that.

And if you look at that traditional prophylaxis trough target that you were mentioning of, say, 1 to 3%, in some ways that was a practical application of monitoring trough levels, because at the time all we had were the plasma-derived factor products as well as what are now considered the standard half-life recombinants. And to have a reasonable prophylactic regimen of, say, three times per week or every other day, that was the targets that you could reasonably end up with in the 1 to 3% range.

But if we look at some of the large studies that have been done—and of course the key one would be the U.S. Joint Outcome Study—and that directly compared standard half-life applied prophylaxis to on-demand treatment of toddlers and then looked at joint outcomes. And of course that was a dramatic outcome in that study. It was a relative risk ratio of about sixfold for osteochondral damage in the on-demand group versus those who were on prophylaxis.

But when those toddlers were first evaluated at age 6, about 93% of the participants had zero osteochondral damage when they were initiated on prophylaxis compared to less than 60% if they were on demand. But those patients, both the early prophylaxis and then what would be called the late prophylaxis group, the entire cohort were invited to continue prophylaxis all the way up through age 18.

And disappointingly in that long-term continuation study, now only 2/3 of the patients who were in the early prophylaxis group are free of osteochondral damage, and there was further deterioration in the late prophylaxis group, where less than 1/4 of the patients had no evidence of osteochondral damage.

And worse, if you dig down into the MRI results from this study group, what became apparent is that the evidence of joint deterioration in joints that the patients or the parents swore had never had any overt bleeding in that joint. And so this raises this prospect of subclinical bleeding, and that's been reinforced now in multiple studies.

The Canadian Dose Escalation Prophylaxis Study looked at osteochondral outcomes in patients on that prophylaxis study, and they also found anywhere from 1/4 to 1/3 of so-called bleed-free joints had evidence of osteochondral damage. And then subsequent large prospective studies have highlighted that subclinical bleeding is a real phenomenon.

So I believe that that was a significant influence on the WFH recommendations to move toward higher trough levels, trying to get above 3 to 5%. And the natural history studies would support that if you could get patients closer and closer to the mild range, you could dramatically alter the risk for adverse joint outcomes.

The trouble then was to do that with standard half-life agents was really challenging. These were really aggressive protocols to get patients in those trough levels. So thankfully all of the extended half-life innovations that came in the early 2000s were allowing us to use fairly reasonable prophylaxis regimens, again, maybe two to three times per week, but in some cases still every other day, in order to drive up those trough levels. And that has resulted in improved joint outcomes for a number of patients.

Dr. Young:
Great. Thank you for that. And that's a great segue into this next question or topic, which is about the ability to reach and sustain these higher targets. Now we're talking here about 3 to 5% from the WFH, but you alluded to even higher targets in the mild range where we can probably abrogate even more joint disease. So maybe you can just briefly go through the different iterations of factor VIII concentrates that we currently have and what they can achieve for patients.

Dr. Pipe:
Sure. The extended half-life group of factor products are either agents that have conjugates added to them, like pegylation or fusions to proteins like albumin or the Fc portion of IgG, as well as some additional newer innovations which are driving even further sustained levels of factor in the plasma.

And when these became available initially in the clinical trials, if you look at the outcomes, they were a little bit better than standard half-life agents, but at the time when they did those trials, they were really aiming to reduce the burden of prophylaxis. And so you look at the regimens, they were typically twice-a-week infusions for factor VIII, maybe once a week for factor IX with the EHL agents. And in some cases they tried to extend that to 10 days or even 2 weeks with the EHL factor IXs.

But it became apparent that if we're really going to improve outcomes, we really need to raise those trough levels higher. And I think there's a very good study that you're familiar with, the PROPEL study. And what they did is they used a pegylated form of factor VIII which had enhanced pharmacokinetic properties, and they analyzed the pharmacokinetic performance of that agent and compared it to targeting two different factor VIII trough levels, either a traditional 1 to 3%, which would be called the reference arm, or a higher trough level. In this case, they aimed for between 8 to 12% in what we'll consider the elevated arm.

And the outcome from that study really supports that if you move those trough levels higher, you will get better outcomes. And if we look at one of the parameters

they used, it was the proportion of patients who had zero bleeds while they were on the prophylactic regimen. And whereas those with the traditional targets had zero total bleeds in around the 40% range, those who were targeted to the higher trough levels in that 8 to 12% range, that proportion actually increased to about 60%.

And then if you look at the spontaneous joint bleeds, this is where it was really remarkable, where the proportion of patients who had zero spontaneous joint bleeds—sort of the hallmark of hemophilia—was 85% bleed-free in the group that were targeting the higher levels. Now, does everybody need a target of 8 to 12%? That's not clear. We do think higher is better.

Dr. Young:
Thanks for that. And so moving on, there is a relatively newer product that is essentially targeting these higher troughs. Can you talk about the novel mechanism of action or essentially the way that our newest factor VIII product, efanesoctocog alfa, basically builds into this sort of profile?

Dr. Pipe:
So what's really driving this particular innovation is the issue that factor VIII products, whether they're standard half-life or all of the EHL innovations, the pegylated products, the Fc fusions, they're all subject to a von Willebrand factor–imposed half-life ceiling. And what's happening there is these proteins are still primarily stabilized in the plasma by binding to von Willebrand factor, just like natural factor VIII is. And so the half-life can really never be any better than a traditional factor VIII–VWF conjugate. And if we look at the half-lives of any of the innovations that have led to an EHL form of factor VIII, their half-life is improved only about 1.3 to maybe 1.5 times the standard half-life equivalent.

So what the aim was with efanesoctocog was could we decouple factor VIII from von Willebrand factor and then through other innovations drive even longer half-life. And the way they did that is they started with the base Fc fusion molecule, and then they added a covalent linkage to a recombinant portion of VWF called the D′D3 domain. This is the domain of von Willebrand factor that really stabilizes factor VIII and protects it in plasma. And they linked that conjugate through Fc fusion technology. And then in addition they added a series of repeating hydrophilic sequences. These are natural amino acids that provide sort of a watery shield around the molecule. These are called XTEN polypeptides. And in that combination, what they were able to achieve is now a factor VIII product which has pretty much three- to fivefold half-life extension compared to standard half-life, and again a marked improvement over other

EHL factor VIIIs.

And what's also unique about this product is it has sort of an altered pharmacokinetic profile, where instead of a rapid drop right after reaching peak infusion in the plasma, there is a more gradual decline over time. And in the adults who were in this study getting prophylaxis with just a once-a-week infusion of efanesoctocog, they still were able to maintain factor VIII levels that were in the non-hemophilia range, so above 40%, for around 3 to 5 days, depending on the individual. So this concept of a high sustained factor level and what this could potentially do for joint outcomes is really interesting.

Now in the clinical trial, the results were pretty substantial. So they had patients who were on their traditional standard-of-care factor VIII prophylaxis on a lead-in study, and then they were switched to efanesoctocog. And what they saw on the prestudy of factor prophylaxis is a mean annualized bleed rate of about 2 to 3, which has been pretty typical for decades of follow-up in patients on factor VIII prophy. But with efanesoctocog, that dropped to 0.69, so showing that this altered pharmacokinetic profile and this decoupling from von Willebrand factor had a significant improvement in joint protection.

Dr. Young:
Thank you for that comprehensive answer.

So finally, on our last question is really about translating all this into practice with respect to, you know, pharmacokinetic optimization and then real-world considerations like the patient's lifestyle, adherence, treatment burden. So yeah, maybe if you can sort of summarize what we have available and how should clinicians individualize prophylaxis based on things like activity level, bleeding history, adherence, etc.?

Dr. Pipe:
Yeah. Well, I think we've always had a holistic view of our approach to comprehensive care for our patients. So we're concerned about physical health, about bleeding, about joint outcomes, but we're also concerned about their psychosocial well-being and about their quality of life. So when we're choosing the ideal regimen for them, we want to take into account all of those parameters.

Now, there are clearly objective variables that guide treatment decisions—what's the bleeding phenotype of the patient, what's their joint status, what's their treatment adherence, how good is their venous access—but also what's their lifestyle, what do they want to do, what do they like to do, and how do we have to modify the regimen in order to help them achieve that. So those are the objective things that we interact with them in the clinic.

And then on top of that, there's a number of subjective variables that I think are also important influences on treatment decisions—what's the patient's preference,

how do they want to be treated, what can they deal with on a regular daily or weekly basis, what's their support network around them, what kind of chronic pain issues do they have, what's their experience with current and past treatments. And so taking that all together, I think gives us a much more holistic approach to how we manage patients, and this helps guide how we choose the individual regimens.

Dr. Young:
Alright, well, Dr. Pipe, thank you very much for that very comprehensive discussion about factor VIII products, factor VIII levels. And I think it's clear that our thinking about factor VIII targets has evolved over time, and as we get better and better products, it continues to evolve, going from really what's the minimum protective levels to providing factor VIII levels that can really optimize long-term outcomes but also give patients a better quality of life. So thank you again for helping us walk through how clinicians can apply these principles in everyday practice.

Dr. Pipe:
Sure. Thanks.

CHAPTER 3

Dr. Young:
In this segment, we're going to shift into rebalancing agents and specifically how they work, what the current evidence shows, and how clinicians are thinking about integrating them into real-world care. We'll start with an overview of the mechanisms of action, move into the clinical trial data and patient selection, and then we'll spend time on the practical questions that clinicians tend to have—safety, monitoring, treatment burden, and what day-to-day implementation actually looks like.

With me for this segment is Dr. Robert Sidonio. Dr. Sidonio is a Professor of Pediatrics at Emory University School of Medicine, and he's the Medical Director of the Hemophilia of Georgia Pediatric Center for Bleeding and Clotting Disorders at Emory University in Atlanta, Georgia.

The objective for this segment is to evaluate current evidence on rebalancing agents and describe practical considerations for integrating them into individualized hemophilia care.

So why don't we get started with the first point of discussion, Robert, which is when we say rebalancing agents in hemophilia, what are we actually referring to? And how is this approach different from other therapeutic classes of drugs for hemophilia?

Dr. Sidonio:
Yeah, thanks for having me. So currently, back—we'll start back when you were training—all we had was replacement therapies, and so you were missing something, you replaced it with clotting factor concentrate. We've developed other products that mimic those products that allow subcutaneous administration. And then now that we are quite aware of the coagulation cascade, we can actually take a look at it and realize what we can alter. And so we can either do that through small interfering RNA technology, specifically targeting antithrombin, and then we can also mitigate or reduce the amount of tissue factor pathway inhibitor through monoclonal antibodies. And there are two drugs that utilize that mechanism. All of this improves thrombin generation in the end, which ultimately is the goal.

Dr. Young:
Alright, thank you for that.

So the next point of discussion is about the evidence. So what does the evidence tell us so far about clinical outcomes with rebalancing agents? In other words, what have the clinical trials shown in terms of the impact on bleeding rates, particularly joint bleeds and things like that?

Dr. Sidonio:
Yeah, so I'll just take one at a time. So let's start with fitusiran, which is a small interfering RNA, and its goal is to reduce the amount of antithrombin in the patient and thus improve thrombin generation. So it's approved for hemophilia A and B, with and without inhibitors. And we know through the clinical trial series—and it's the largest clinical trial series for hemophilia, mainly because they had issues initially with lots of AST, ALT elevation and cholecystitis, and then most importantly thrombosis—once they realized that if they targeted an antithrombin range of 15 to 35%, we are able to mitigate most of those risks and be able to provide a safe drug for patients. The great thing about this is it demonstrated this can be given in most patients every 2 months, and the efficacy is as good as a clotting factor concentrate. So that's the ATLAS clinical trial series.

We can shift now to concizumab, and that was the Explorer clinical trial series. So this is an anti-TFPI antibody, and this drug is given subcutaneously daily. It's indicated for 12 years and older for hemophilia A and B, with and without inhibitors. And during this clinical trial series, they noted a significant improvement in hemostatic efficacy. It does require daily administration. One of the things they realized is that they were going to need some lab surveillance, and because of this, a mitigation plan was placed. There were multiple nonfatal thrombotic events, and after the mitigation plan was in place, there were no further events. So that's one of the anti-TFPI drugs.

And finally, the last one was marstacimab. It's the BASIS clinical trial series, also an anti-TFPI drug targeting 12 years and older hemophilia A and B without inhibitors, potentially with inhibitors in the future. This drug does not require lab surveillance. It's designed slightly differently. And during the conduct of the clinical trial, they didn't develop any thrombotic events, but during the long-term extension, there was one thrombotic event and one thromboembolic event.

Outside of this, all of these drugs have significant improvements in hemostatic efficacy, a reduction of target joints, and certainly all of this comes with improvement in quality of life.

Dr. Young:
Alright. Thank you. Thanks for the comprehensive answer.

I think for this next question, you've covered quite a lot of that information in the answer before, because the question here is, you know, what are the key risks clinicians need to understand? And what does risk mitigation look like in practice? But I think since you've discussed already that the thrombotic events are really the key thing that we're trying to avoid, maybe you can discuss in a little bit more detail how these three rebalancing agents manage that with respect to these risk mitigation strategies.

Dr. Sidonio:
So I think one of the things that's really interesting is these drugs are getting so good at achieving such optimal hemostatic efficacy that we're going to continue to see some thrombotic events during clinical trial. All of the novel therapies in the last 10 years have had thrombotic events during the clinical trial series.

So fitusiran realized that a target antithrombin goal would mitigate most of those risks, and so they have a strict algorithm in which you start off at 50 mg every 2 months, and then you check the level, and then you adjust. Most of the people end up with the same regimen

or only one dose adjustment, and then you may have to check it once a year, once every other year, depending on the age of the patient.

When it comes to marstacimab, there is no lab surveillance required at this time. There could be in the future, maybe when we're talking about younger children, but right now they don't have that option. You do have the option of dose escalation as well. And they're currently looking at the thrombotic events, which are likely mostly related to the dosing of the bypassing agent used.

And then finally concizumab, because of the number of events that happened early in the clinical trials, they developed an ELISA test, and there's a specific target that allows you to adjust the dose up and down depending on what the level is. And so far, this has really mitigated the risk of thrombosis.

Dr. Young:
Alright. Thank you for that. Could you also briefly discuss management of breakthrough bleeding in these patients? I realize that there's not a lot of support or data for marstacimab and concizumab, but certainly for fitusiran there is a strategy that is used. So maybe you can just briefly describe how to manage the breakthrough bleedings with each of these three drugs.

Dr. Sidonio:
Yeah, just like you said, I could start with marstacimab and concizumab. There isn't exact dosing that's recommended. This is one of those things I think a lot of us are going to get together and try to come up with the best practice based on what's been done.

We know that the dosing and the frequency is going to be much lower for both concizumab and marstacimab. This has been demonstrated in the trials, in which most of the patients require one or two reduced doses of clotting factor concentrate or bypassing agents.

And fitusiran has a little bit more detail on how to manage it. It's available on their websites, but in general, the dosing is reduced and the frequency is reduced. And some people see this as an issue. It actually could be a tremendous cost savings, and as you know, when you're giving lower doses and you're giving half the dose, that's a significantly lower volume, which is much better to administer and certainly a better administrative burden for the patient.

Dr. Young:
Yeah, I think the key thing with fitusiran is to understand and know the bleed management and guidance. It's in the prescribing information, it's on the website for the drug, and really when you prescribe fitusiran to a patient, you have to change their breakthrough bleed prescription. That's the next thing you do, because you don't want them to be using larger or really more traditional doses of factor replacement or bypassing agents, because that does risk thrombosis. So you probably need to kind of pull back the factor they have at home or at least get them to understand that they need to use a lot less.

Dr. Sidonio:
And I think this is where you would bring them back early. We've talked about this before. You're not going to prescribe it and say, I'll see you in a year. You're going to prescribe it, and you have to have some contact with the patient afterwards so they truly understand the new dosing regimen that you've prescribed.

Dr. Young:
Great. Thank you very much. So from the patient perspective, we know that these are all subcutaneous, but there are some key differences. You've mentioned a little bit of that already in terms of the practical implementation. But can you talk a bit about the dosing frequency for each of these, because they're quite different, and then maybe a little bit about how they're administered? Do all come in these kind of fancy pens? So yeah, maybe let's discuss that a little bit.

Dr. Sidonio:
You know, when it comes to choosing between the different products, it's great. In hemophilia, we have lots of options, and so this allows the patients and the physicians, the parents if they're younger children, to help decide what they value most. And so if you value the least amount of administrative burden, that might be fitusiran. Most of the patients are on every 2 months, a very small injection. And, you know, this injection certainly can be done at home, it can be done in the office if needed, or a nurse can be sent out. It does require some lab surveillance early on, but that's pretty minimal, and there's a central lab in which you get that lab. And after the first few months, there's not much lab surveillance required. So if that's what you value, that product is probably the best for you.

And it depends. Otherwise, you look at the other products. So marching down to the least frequent is marstacimab, which is weekly. This is a similar strategy to most of the therapies in hemophilia. Many of the newer ones are weekly. It is subcutaneous, it doesn't require lab surveillance, and so this may be a good option. It comes—all of these come—with really nice pen devices which make it really easy. There's nothing to titrate. You give the dose, and that's it.

And then finally, there are many people that want full control of their dosing, and so concizumab is given daily. It does require a lab surveillance in the beginning, but you check it in the first 4 to 8 weeks as recommended. But there are some patients that really like this control. They know when there's a surgery going to happen, they can decide if they want to continue or stop it, so it allows some control of this.

And if you've seen these devices, the volume is extremely small. The needle is about as small as it gets. And so in general, all these products are great, and it just really comes down to what you value most in the management.

Dr. Young:
Thanks for that excellent answer. So as you had mentioned earlier, these products are currently approved for patients older than 12 with hemophilia A or B, and fitusiran and concizumab also for patients with inhibitors, marstacimab at this point not for patients with inhibitors, although that's probably coming fairly soon. So I guess one of the questions is how do we decide which patients are the right profile, I guess you could say, for a rebalancing agent? And you can go through the classic candidate for these and then maybe some other candidates. So yeah, please, what types of patients do you consider for rebalancing agents?

Dr. Sidonio:
It's a great question. So let's start with like a hemophilia B patient, right, a young male with hemophilia B. It could be a young female as well, but we're talking about a young man with hemophilia B. And so the hemophilia A patients have benefited from a plethora of novel therapies. They obviously have two most popular medications, Altuviiio and Hemlibra, being prescribed. So in hem B, this population felt like they hadn't had the benefit of having these novel therapies. So now they have all three options available to them. And so for hemophilia B, I think these rebalancing agents are a great option for them. Certainly, they have extended half-life IX products that are pretty good. But as you know, there are a lot of patients that struggle with the emotional toll of administration, and some of them just want a break from IV therapy, and I can't blame them for that. So I think that's a really good option.

Certainly hemophilia B with inhibitor, like you mentioned, fitusiran and concizumab would be excellent options for them to help manage and mitigate the bleeding that's associated with that. Those are certainly options.

I think it gets more challenging when you talk about hemophilia A and inhibitors. Certainly right now, emicizumab and Altuviiio are the most popular prescribed drugs. They are great options for patients that have limited safety concerns, but you know, there are patients that don't respond to those products for whatever reason, maybe they developed anti-drug antibody, though that rarely happens, or for whatever reason they want to try a different mechanism of action. And so certainly these are available for patients.

If you're older, you may like the idea of doing concizumab because you can very precisely titrate the dosing for that. And so a lot of it is going to be just sort of shared decision-making and what the patient and the physician value.

Dr. Young:
See, and I think for hemophilia A, as you said, emicizumab has really got the lion’s share of the market for good reason, being a subcutaneous drug and generally an effective drug. But one big difference is that emicizumab comes in a vial and syringe method, and the volume can get quite large in bigger patients. And so I think if a patient is doing well from a bleeding standpoint, well, obviously if they're not doing well from a bleeding standpoint, you're going to switch them over no matter what. But if they're doing well from a bleeding standpoint, then you know, they still may struggle a bit with the administration experience, kind of as I call it, and these pen devices may really overcome that.

So I think there are hemophilia A patients on emicizumab where I might show them the pen, discuss the pen, and see if they're interested in switching.

Of course, there are issues with switching, and we don't have time to get into that, but anytime you start somebody on one of these drugs, if it's not working, they can always go back to what they were on before.

Dr. Sidonio:
Yeah, these are really nifty devices, real simple to use, so yeah definitely.

Dr. Young:
So once you decide a patient is a candidate, what does starting and maintaining therapy look like in practice?

Dr. Sidonio:
Yeah, yeah. As I mentioned, you know, fitusiran has a standard starting dose, 50 mg every 2 months, and then you check a level. And it's important for people to realize they need to use the antithrombin assay that's been provided by the drug company to manage it. Oftentimes, when the level is normal, most labs can measure that pretty accurately, but when there's a reduction, you want to use the

same assay that was used in the clinical trial. So you would dose adjust per their algorithm.

Marstacimab requires a loading dose 300 mg, and then weekly it's 150 mg with the option to uptitrate, no lab surveillance. And then concizumab is dosed at 1 mg/kg on the first day, and then day 2 it's at 0.2 mg/kg, and then you're checking it around 4 weeks or so and you're targeting a level, and they have adjustments per their algorithm as well.

Dr. Young:
Yeah, so the key point there is that marstacimab and fitusiran for patients older than 12 are flat dose. There's no impact on the patient's weight with respect to the dose or any adjustments, whereas concizumab is weight based. And as you mentioned, it does come in a neat little pen. The difference is the concizumab pen has a dial so patients can dial their own dose.

Dr. Sidonio:
Yeah.

Dr. Young:
So finally, as patients move through different stages of life and treatment, how do you practically reassess the prophylaxis plan kind of as you go and determine if a different strategy is needed, such as when we're talking about rebalancing agents? So as you're following your patients over time, when might a discussion of a rebalancing agent come up?

Dr. Sidonio:
Yeah, and it's a great question. You know, I take care of a lot of children with bleeding disorders, and there are things that are changed. Obviously, if they go off to college, go on to trade school, they're traveling overseas, doing study abroad, many of them want the easiest management plan. And as you know, oftentimes there's a lot of rigor with the parents monitoring and doing surveillance and ensuring that the child, a teenager at the time, is following the prophylaxis plan, and so that can totally fall apart if they go to college. They have a lot of things going on and they're trying to look at their independence and find out who they are. And so I think this is a good time to give them an option in which they have very limited administrative burden.

And so that's why you want to go through all these options with them. Most of us have the little sham devices that we can show the needles, and this is a good opportunity for them to decide what they feel is important to them. They can make a decision. We know that these all are relatively safe and efficacious drugs, and so it allows them to choose, which I think is nice. It gives them a little bit of that understanding.

And certainly, as they get older, some people may look at they want to ensure that reduce the risk of thrombosis. That might become something more important as a patient becomes much older, but at the same time, you also want to have a medication that's simple to administer, particularly if a nurse has to come out and do it. And as you know, the veins get more and more difficult to access as you get older and certainly are difficult to access as a very young child.

And so I think it's just constantly talking to the families and the patients and seeing what's important to them, and then looking at their comorbidities and deciding if you need to mitigate the risk of thrombosis even more.

Dr. Young:
Great. Thank you very much. So Dr. Sidonio, thanks for all of that. It was really helpful. I think what's clear is that our options—our subcutaneous options—have greatly expanded. We had only emicizumab for 8-9 years, and now we've got three relatively new drugs that we categorize as rebalancing agents that are expanding the prophylaxis landscape. And what's important to take away, as we've been discussing, is each of these is really different in terms of their dosing. Even there's two different mechanisms of action, some require monitoring, some don't, some are weight based, some are not.

And so, to the audience, you do need to understand and learn about these nuances between the drugs so that you can do the best job for your patients and think about which option might be the best one for a specific patient. And there's always the option to try one, and if it doesn't work, there's always the option to switch to others as well. So thanks all for listening. And Dr. Sidonio, thanks for walking us through how you approach this in the real world.

Dr. Sidonio:
Yep, thanks for having me.

Dr. Young:
Thank you all for listening to this podcast. I guess I could summarize it by saying that joint preservation is really the key goal in hemophilia care, and we've learned today about how you can assess joints in terms of both diagnostic imaging and clinical exams. And then we discussed two strategies to preventing long-term joint disease, including treatments with factor VIII therapies, as well as treatments with rebalancing therapies.

So I hope all of this you can take into account as you go back to your clinical practice, and remember that your clinical practice is going to be best served working with your fantastic multidisciplinary team.

So thanks again for listening. I hope it was helpful and educational. And take good care.

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