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Ian Winburn: Hello, and welcome to Hemcast, a podcast series designed to help to keep you up to date with advances in science, technology, and clinical care in the rapidly evolving world of hemophilia.

Coming up in this episode, we explore the complexities of hemophilia care in 2021 and beyond—and I speak to some of the world’s leading experts in the field to gain their insights.

Cedric Hermans: We also have the ambition, you know, to take full control of the disease hemophilia, by achieving zero bleeds in the largest number of patients.

Gerry Dolan: One of the key concepts of a lot of complex or acute medical interventions in hemophilia is to remove hemophilia from the equation, [Interviewer: Yeah], so the simplest way is to actually effectively normalize their factor levels, and so they can be treated as any other patient.

Keith Gomez: Rather than treating patients as a large single group of individuals with, say, a disease type, we know that, within that group, there are lots and lots of individual variations in how, for example, the disease might manifest and how someone might respond to treatment.

Ian Winburn: We are living in a very exciting time in the evolution of the diagnosis and treatment of hemophilia. As said in the 2020 WFH Guidelines, in the past 5 years, there has been unprecedented progress made in the development of new therapeutics for hemophilia, as well as a huge shift in the principles and philosophy of hemophilia care.

This evolution of hemophilia treatment has brought about the advancement of capabilities to tailor treatments for patients, accounting for important factors, such as lifestyle and potential comorbidities, and most importantly, individualizing care to the needs of each patient. In this episode of Hemcast, we’ll take a look at the state of hemophilia care in 2020 and 2021 and we’ll focus in on considerations for the management of hemophilia patients within the ICU. We’ll finish by discussing how big data can be used to tailor hemophilia treatment and the

possible impact this could have on precision medicine and hemophilia. So, to give us an overview of hemophilia care in the current era, I welcomed back Professor Cedric Hermans, Head of the Division of Haematology, the Hemostasis and Thrombosis Unit as well as the Haemophilia Centre of the Saint-Luc University Hospital in Brussels, Belgium.

Ian Winburn: So, I'm delighted now to be joined by Professor Cedric Hermans and, Cedric, we've spoken many times before on *Hemcast*, but, as we all know, 2020 has been an unprecedented year, due to the ongoing COVID-19 pandemic, but setting that aside, when you, sort of, look back over the past, sort of, 5, 10 years, what do you feel have been some of the biggest changes in hemophilia care to date?

Cedric Hermans: Well thank you, Ian, thank you for the opportunity to join you. Well, clearly, things are changing quickly, and I would say that, you know, our practice has mainly been changed by, you know a different spirit, you know. Now, there is much more enthusiasm, optimism than before, and also a lot of ambitions that can now become reality. You know, we know that prophylaxis is now the standard of care, we know that prophylaxis is now accessible to more patients, and we also have the ambition, you know, to take full control of the disease hemophilia, by achieving zero bleeds in the largest number of patients. So, this would reflect, I think, my current perception of the situation.

Ian Winburn: Yeah, and I suppose all those things, when they combine together, they've helped us to achieve in hemophilia the fact that people who live with hemophilia are living longer today than they were, for example, 10, 20 years ago, and there's many reasons, as we know through the community, why that would be, but I suppose that brings up its own problems and with that you know, how can we best manage the multiple comorbidities that are becoming associated with those people who live with hemophilia, living that little bit longer?

Cedric Hermans: Well, I think what is needed here is try to put together the multiple expertise that are required. You really need a holistic approach to the patient, and also, again, you need a lot of optimism and enthusiasm because what we have seen, even in my place, is that you could even revert some situation, you could improve the joint status, you could, you know, even initiate prophylaxis later in life. So, this is achievable, possible, but you really need a team with a lot of expertise and also you need a patient who is highly motivated, with a high trust in the team, because for some of these patients, you know, the last few decades have been very difficult because there were not that many options and because of that they have, for some of them, developed, you know, all the consequences of hemophilia, so it takes time to convince these patients that it's worth investing a little bit more of time and energy in their disease.

Ian Winburn: Yeah, and you sort of mentioned your team and the teamwork and I think when we reflect back on this highly unusual year, for you and your team, how have you managed your practice over the past sort of 9 months or so? How have you evolved it in such a way whereby you're still able to deliver that super high standard of individualized care that you wanted for your patients?

Cedric Hermans: Well, it's clear that, you know, with the many restrictions that we have had during the first wave, but obviously recently with the second wave, clearly you know, it was very difficult for us to run our complex and multidisciplinary clinics. We have tried to do that, but it's clear that that was not possible, so some clinics have been delayed, some surgeries have been delayed, but I think that more or less we have been able, again, with a great team spirit and good collaboration and understanding of the patient to manage this more or less efficiently. And also, we could value, you know, new technologies, and also do our best to keep in contact with them on a regular basis. So, this is what we have tried to do.

Ian Winburn: Yeah. I know specifically we've spoken before about telemedicine, but has your experience of telemedicine sort of changed over the past 6 months or so? Has your experience of virtual clinical practice also evolved? Or, how has it been for you and your team, bringing virtual meetings to clinical care and clinical practice?

Cedric Hermans: Well, you know, it was, to some extent, a necessity, especially at the peak of the pandemic, to interact with our patients virtually. So, that has been useful. We have tried to value this, although honestly, I think the technology that we now have in place in my center should certainly be improved, but, again, I think this is complementary to the face-to-face review clinic. I think it's nice to keep in touch with the patient to make sure that things are fine, that everything is under control, but I don't think that it will fully replace, you know, especially when we have this kind of multidisciplinary clinic, you know, and you are seen by the physio, by the nurse, different doctors together, you know, that really creates a unique atmosphere that cannot be duplicated virtually. But honestly, I think it's complementary, because sometimes, especially with some patients, we do not see them that frequently, so to avoid, you know, long periods of not interacting closely, the telemedicine could be useful. My concern also is for older patients who might not have the expertise or do not have, you know, all the tools that are now required for telemedicine. So, something has to be done to avoid that these older people who clearly would benefit probably the most are not left aside. So, I think the initiative will be welcome here and this is an issue that I believe has been raised in many places, so I don't know how that will be solved, but clearly something has to be done.

Ian Winburn: So, Cedric, now my final question, and I suppose when we reflect back on 2020, and what a tough year it's been, of course our thoughts also now stretch to the future, and where do you think everyone's attention should be focused right now when we're thinking about the future, and innovation, and ultimately improvements that we hope will be round the corner for those patients who live with hemophilia?

Cedric Hermans: Well, it's clear that there are many innovations around, some of them will probably be more successful than others, this is clear, this is, again, very stimulating, but the question will be, you know, and this is increasingly difficult to select, you know, the best treatment options for each patient, so I think this is really the next challenge for the next few months and few years. So, each of these new treatment options have strengths and weaknesses, certainties and uncertainties, and you will have to navigate with this and make sure that we do this in an optimal way and provide the appropriate guidance to each of our

patients, because some of these treatment options might be very attractive, might seem very attractive, but, you know, do they really represent what we hope for the future of hemophilia? So, we need to be cautious, interpret all this with a great caution, and clearly have very open discussions with our patients, but it's clear that for our patients we have much more opportunities than before.

Ian Winburn: Yeah, and exciting times ahead, Cedric, so look without further ado, I just want to thank you for your time, as ever, I know how busy you are in between your clinic, and your research, and it's wonderful to have you join us again on *Hemcast*, and thank you very much, wishing you a great day, stay safe.

Cedric Hermans: Thank you, Ian, thank you for the opportunity to join you again on this, on this platform. Thank you, bye bye.

Ian Winburn: A great summary from Cedric there. It's wonderful to hear his positivity and enthusiasm for how far hemophilia treatment has progressed over the years and the innovations to come, as well as his useful advice on managing those patients who are living longer thanks to advances in hemophilia care.

Looking back to the 1970s when freeze-dried powdered concentrates containing factor VIII and IX became available, this revolutionized hemophilia care and enabled people with hemophilia to self-infuse at home, alleviating trips to the hospital for treatment.

But as we know, visits to the hospital, and indeed the intensive care unit, are inevitable. Hemophilia must therefore be managed in the complex environment of a busy intensive care unit and often alongside other complex medical considerations.

To understand more about the optimal management of hemophilia patients in this setting I talked with Dr Gerry Dolan, Consultant Haematologist at St Thomas' Hospital, London in the UK, and Haemophilia Centre Director at St Thomas' Comprehensive Care Centre in London.

Ian Winburn: Gerry, thank you so much for joining me to discuss the management of hemophilia in the intensive care setting. So, I know there have been numerous circumstances by which a person who lives with hemophilia may unfortunately need to be admitted to the intensive care unit, so I wonder whether you'd be able to, sort of, walk me through what that process looks like?

Gerry Dolan: Well yes, it is an interesting aspect of care for patients, particularly when we see the increasing age of our patients. One of the big successes of hemophilia therapy over recent decades, particularly with the development of recombinant concentrates, is that our patients are living longer because they've got safe, effective treatment. So, I mean I guess there's 2 ways in which patients, by which patients find themselves in ITU [intensive treatment unit]. One is perhaps we know from a major elective surgery which is going to require intensive support afterwards, and that gives us the opportunity to plan with the intensive care teams so that we

have a clear written plan, that we negotiate with the medical staff, the nursing staff in intensive care, understand each other's responsibilities, and that usually goes pretty well. The second option, of course, is that patients may find themselves in ITU through, you know, no warning, maybe a road traffic accident or maybe a major infection, even, you know, currently with COVID, and that scares patients a lot. So, I think from our point of view we need some sort of early warning system, so we do recruit the patients in that, we make sure that they and their families know that if they're coming anywhere near a hospital that they should ring us, and alert us to that situation, so there's no delay in communication. And then we actually, you know, in big centers like our own, we do actually have a pretty good relationship with intensive care anyway, perhaps not through hemophilia but through other aspects of hematological support for ill patients, and I think that's a key concept, building relationships, and you know, one reassuring thing is intensive care staff are generally quite open to collaboration and understanding the requirement for advice and support.

Ian Winburn: So, you know, you touch on this very close collaboration between ICU and hemophilia care teams, and you know, it's particularly important, you know, at all times, but it's particularly important now during COVID times as well, but maybe putting COVID aside for now, can you sort of tell me what have been the key aspects to, sort of, maintaining and managing this close relationship that you have between ICU and hemophilia care teams?

Gerry Dolan: Well, I mentioned planning, but actually also very regular personal visits to intensive care, so we make sure that the hemophilia consultant who is on duty will visit at least once a day, but often more often, then the hemophilia nurses take the responsibility for liaising with the other nurses to make sure that the factor concentrate is administered at the correct times, in the right way, and one aspect which is often a little bit forgotten is that, of course, with severe patients, you know, communication between hemophilia centers and severe patients is generally pretty good, but for moderate and mild it's not always because these patients do not bleed very often, they don't present very often, but they still require pretty intensive hemostatic support in that setting. So, again, regular personal contact is important here. And then also, you know, it's sometimes very difficult to plan around all the interventions that may be required in intensive care, maybe the patient may need ventilation or tracheostomy or intubation or different lines and how do you manage factor replacement in that very changing environment.

Ian Winburn: But moving as I say onto, sort of, focusing a little bit here and now, and sort of in the midst of the COVID-19 pandemic, are there any additional considerations for hemophilia patients admitted to the ICU with—?

Gerry Dolan: Well actually many of our patients are already concerned about COVID-19, and one of the "commonest" questions is am I more at risk of developing severe COVID-19 experience, and the short answer and consensus among the physicians is no, not as a direct result of hemophilia, but clearly in an intensive care setting, their management may be more complex unless we are closely involved. One of the key concepts of a lot of complex or acute medical interventions in hemophilia is to remove hemophilia from the equation, so the simplest

way is to actually effectively normalize their factor levels, and so they can be treated as any other patient, it takes a lot of the anxiety, make sure they get the appropriate treatment, and there's no delay in getting appropriate treatment, but of course there are some myths and legends amongst, you know, in medicine in many different circumstances, and one of them is that hemophilia patients don't get thrombosis or can't get thrombosis, which of course is not true, and then particularly in the setting where you are replacing the deficient factor then why could they, or why should they not get thrombosis if there is a big enough challenge?

Ian Winburn: Well, thank you, Gerry, for your time and we wish you well.

Very informative to hear from Gerry there about the additional considerations for the management of hemophilia patients within the ICU. Collaboration with the ICU team and regular visits by the consultant or nurse seem to be the key elements in the effective management of patients, whether that is a planned hospital visit for surgery or a trip without warning. This is essential, particularly in the current health care environment.

So, I want to change tack slightly now to look at what is termed "big data". In this era of genomic medicine, I wanted to learn about what big data is, and how this can be used to inform precision medicine and hemophilia. And I was delighted to have the opportunity to talk with expert Dr Keith Gomez from the Royal Free Haemophilia Centre and Thrombosis Unit, part of the UCL Medical School in London, UK.

Ian Winburn: Keith thank you so much for joining us.

Keith Gomez: It's my pleasure Ian.

Ian Winburn: Now, I want to really focus on big data, because I know that at a recent scientific meeting you presented really expertly on this topic. And for our listeners I wondered if you could briefly define what is big data, and what are its opportunities, and the opportunities it presents for overall medical care?

Keith Gomez: I think big data is a phrase that has come into our use in perhaps the last 5 years or so. And really what we are talking about is the accumulation of vast amounts of genomic and phenotypic data on thousands of individuals in databases.

And I think it's important to recognize that by databases we mean national and international collaborative databases. The, the reason why this is a bit different to what we've had before is because previously we have been used to collecting, say, genetic information on maybe a few hundred individuals within an institute or maybe in a national body.

But the problem with genetic data is that, that gives us relatively little insight into how those genetic changes impact upon disease. Because most genetic changes that are important are relatively rare. And so you need to see tens of thousands and sometimes hundreds of thousands of individuals, a mixture of normal individuals and those who have got the disease that you're interested in before we can start to work out what those variants are doing in terms of causing disease.

I think the second part of your question was, how do we then use that or what benefits does that give us? Well, I think in medicine the key point is that term “precision medicine”. And what we are thinking about there is really rather than treating patients as a large single group of individuals with a, say, a disease type, we know that, within that group, there are lots and lots of individual variations in how, for example, the disease might manifest and how someone might respond to treatment.

And what precision medicine is about is recognizing those differences and then tailoring treatment accordingly. And obviously it’s by having a really good understanding of the genetic causes of that disease and how that interacts with the clinical manifestations that we are then able to tailor the treatment accordingly.

So, I think big data is really a key requirement to enable precision medicine for our patients.

Ian Winburn: Ok, no, that’s really helpful, and thank you Keith for being so clear with your description there. I think, when I think about precision medicine and big data, I can definitely see how it could be used to identify sort of, cross-disease components of genetic risk. Can you explain this, sort of, more in the context, though, of hemophilia?

Keith Gomez: So, if we think about hemophilia then I think we have been used to thinking about it as a monogenic disorder. It is a monogenic disorder, mostly the key thing is what the variant is in the factor VIII or the factor IX gene. And that’s certainly true for severe hemophilia and you can more or less define the entire phenotype by knowing what the factor VIII level is, for example, and the factor VIII variant.

But if you think about other types of hemophilia, the more mild and moderate types, then we recognize straightaway that actually the factor VIII variant is a, is still a key part of it, but it also depends very much on other patient characteristics.

How much they, for example, do sport or other external activities where they might have trauma.

We realize now that that starts to play a big role in how much they bleed. And we also recognize that there are other genetic components that also influence this.

So, for example if we take factor VIII, we know that the level of factor VIII in our bodies is very largely dependent also on von Willebrand factor. And so, we now know then that genetic variation in the von Willebrand factor gene can influence our factor VIII levels.

So, we know that for mild hemophilia, understanding the influence of other genetic factors is very important for understanding the phenotype.

So mild and moderate hemophilia we can see that is important. Severe hemophilia, I think the thing we have to remember, of course, that our treatment strategies are now very, very much geared towards converting the phenotype in a patient with severe disease to mild disease. So, although they start off with severe disease, in reality for a large part of their time when they are with us, they are actually, have a milder phenotype, and so, effectively then, they fall into the category I have just described where it is understanding all those other components that becomes important. So, you can see then that it is not just the mild to moderates, it is really all of our patients. If we treat them in the way that we intend to, that we need to understand all of these different components that influence the bleeding phenotype.

Ian Winburn: Yeah, again really helpful. I think you know, you've very much underlined there the, the potential really for big data. But, I suppose like always there is that balance. And what challenges do you see are associated with big data analysis? And, you know, is there a risk of misinterpretation?

Keith Gomez: Well, there is that, and I think that's one of the key things that we have been, we have had to put in process steps to make sure that that doesn't happen. I think before we think about interpretation, I think the first challenge really is simply about accumulating the data. And there's, as someone who has been involved with some of the genomics projects that we have been having over the last 5 or perhaps longer years, maybe 10 years now, we can see that once we started collecting genomic data, one of the first things we realized was that we were asking for an awful lot of data capture.

And of course, that takes time and effort, and that's not necessarily something that is easy for a clinician or any health care professional to do while they are seeing a patient in clinic and they've got several other things to think about.

So, accumulating the data is, I think, the first challenge. How do we actually get all this deep phenotypic data? And how do we do that in a timely way? And the simple answer to that, well I don't think there is a single answer to that, but I think one thing that has worked well is if we have dedicated teams who effectively approach the patient once they've been referred from say within a clinic, and then capture the data in a, in a pro forma manner that basically allows it to be entered correctly into the database.

And that's the process that's been adopted in the UK, and I think it's the process that's been adopted in some of the other big projects around the world. So, essentially the clinician simply has to identify the patient, and then the patient agrees, and then they're essentially notified to the data collection team who then collect the data. So, I think that's the first challenge.

And then at the other end, obviously the data then gets analyzed, and then you're quite right the idea is at the other end you then get a report or some kind of feedback coming back to the clinician. And then you're absolutely correct that interpretation becomes the key part of that. Now again, whereas, it's to do really with the complexity of the data of course, once you've introduced a much larger data set, then complexity comes with that and so what we need is to

have very advanced and effective bioinformatics that lies behind the databases or indeed alongside the databases to interpret that data and filter out, if you like, the important bits of it and the less important bits of it. Scoring, if you like.

And so we've had now schemes of classification to classify variants, classify their effect on phenotype, and we need, we've adjusted the ways in which we report that data back to the clinician, so that essentially it becomes, in the same way for example we classify hemophilia into mild, moderate and severe, we now classify variants into likely pathogenic, pathogenic, variants of uncertain significance, and benign.

And it really is, it's the ones that are not benign that we are interested in. But, clinicians do need to then be aware of that classification and what the different categories mean. And there is undoubtedly a need for some education about that to help people understand that and how they would use that in their, in their clinical practice.

Ian Winburn: Ok, well thank you so much, Keith. You know, again, a wonderful summary about how clinicians can best contribute to big data, but also what some of the challenges are. My final question, really, I want to ask you to look into your crystal ball really, and sort of predict in 10 years' time, you know, how much do you think the utilization of big data will have really impacted precision medicine and hemophilia?

Keith Gomez: Well I think one of the things we can say about hemophilia, if we take stock at the moment, we can look at our treatment options that we have now in 2020, and they are very, very different to what they were even 5 years ago, and certainly 10 years ago. Because if we go back to when many of us started working in this area, treatment essentially consisted of factor concentrate. And there were a few different types of factor concentrate, but pretty much that was it.

We now have different half-lives of factor concentrate. We have treatments, which are not factor concentrate at all, but still provide a phenotypic effect. And all of that new treatment, all of the new treatment options that were only really possible because we had a thorough understanding, or we developed thorough understanding of the molecular basis of hemophilia. That's great for hemophilia A and B, well A more than B, I think, I think B perhaps is still a little bit behind there.

And then, if we look at hemophilia itself, then while we do have, you know, while these treatments options are a big advance on what we had, we're still not, they're not perfect. They still have issues to do with side effects, for example, and some patients still, for example develop inhibitors or get thrombosis with some treatments. And understanding exactly where the "sweet spot", if you like, is where precision medicine will come in. And I think with precision medicine if we get that right in 10 years' time, or 5 years' time, then really our aim should be to normalize the phenotype, and I hope that's where, that's where we will get to.

Ian Winburn: Well, thank you so much Keith for sharing that, and also, you know, for really shining a light on what we may have in the future. And it is exciting times ahead. So, without further ado, you know Keith, it's been great having you with us. Thank you for your time and your energy and your honest answers, and we look forward to speaking soon.

Keith Gomez: Thank you very much, Ian. It's my pleasure to talk. Thank you.

Ian Winburn: Fascinating insights from Keith on the exciting advancement of precision medicine in hemophilia care. Keith described a future in which big data, generated from databases of genomic and phenotypic data, can be used to tailor treatment to the patient for optimal outcomes, which is a very exciting prospect indeed.

And with that all that remains is to say, we hope you've enjoyed this edition of Hemcast. My thanks to Gerry Dolan, Keith Gomez, and Cedric Hermans for their time and expertise.

And until next time, goodbye.

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