WFH VIRTUAL CONGRESS 2020

JUNE 14 –19, 2020

A WEEK IN REVIEW

Irish Haemophilia Society

Contents

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CONNECTING THE GLOBAL **BLEEDING DISORDERS COMMUNITY**

WFH VIRTUAL SUMMIT
June 14-19, 2020

Introduction

Due to the Covid-19 pandemic, the WFH International Congress this year, which was due to take place in Malaysia, was organized virtually in June as a Global Summit.

The event was very successful. We did lose the ability to interact face to face, to meet speakers, to discuss new information together. However, we gained the opportunity for people who would otherwise not have been able to attend due to time or finance constraints to attend. It was also great to see that registration was free of charge, enabling any member of the Society who wished to attend, to do so.

As you would expect, the programme was varied and multidisciplinary with a particular focus on Gene Therapy, Novel current and future therapies. It was good to see a growing emphasis on traditionally overlooked areas of von Willebrands, rare bleeding disorders and women and bleeding disorders receiving more attention.

Over the course of the week, there were 55 sessions with 8551 participants from 159 Countries from across the globe. This attendance included; 1817 haematologists, 1758 from industry, 889 people with bleeding disorder and 477 nurses

This is a just a snapshot of the week but we hope you find it interesting and informative.

Barry

von Willebrand Disease – A Closer Look

Speakers: Paula James, Professor, Queen's University, Jeanette Cesta, Executive Director, vWD Connect Foundation, Cody Kester, Board member, Hemophilia Foundation of Arkansas, Baiba Ziemele, President, Latvia Hemophilia Society.

Dr Paula James gave an overview about vWD and its treatment options. vWD was discovered in 1926 by Dr Eric von Willebrand. It is the most common bleeding disorder, yet it is greatly undiagnosed. It occurs in 1 in 1000 individuals. Unfortunately there are still many barriers in the way of diagnosing vWD including a lack of knowledge about the condition, a lack of understanding of normal vs abnormal bleeding particularly with gynaecological and obstetric bleeding and there is a lack of access to resource and tools for self-education and self-assessment. vWD in women is approximately twice that recorded in men, most likely due to menorrhagia. Patients with vWD may experience excessive, mainly mucocutaneous bleeding including easy bruising, epistaxis, oral cavity bleeding, heavy menstrual bleeding, gastrointestinal bleeding as well as prolonged bleeding after haemostatic challenges such as dental work, childbirth and surgery.

Dr Paula James developed a website called 'Let's Talk Period' to raise awareness for vWD. The site has a nursing toolkit which contains free resources to help you share knowledge about menstruation, abnormal bleeding and bleeding disorders with patients and colleagues.

It is important to know which type of vWD a person has because treatment is different for each.

- **Type 1 vWD** is the most common form. People with Type 1 vWD have lower than normal levels of VWF. Symptoms are usually very mild. However, it is possible for someone with Type 1 vWD to have serious bleeding.

- **Type 2 vWD** involves a defect in the vWF structure. The VWF protein does not work properly, causing lower than normal VWF activity. There are various Type 2 vWD defects (2A, 2B, 2M, 2N). Symptoms are usually moderate.

- **Type 3 vWD** is usually the most serious form. People with Type 3 vWD have very little or no VWF. Symptoms are more severe. People with Type 3 vWD can have bleeding into muscles and joints, sometimes without injury.

General treatment of vWD includes birth control pills or tranexamic acid. The gynaecological department can offer hormonally coated IUD which is coated in progesterone to decease menstrual blood loss, endometrial ablation or hysterectomies. Treatments that are specific for vWD include Desmopressin (DDAVP), a synthetic hormone which stimulates the body to release VWF. However, it does have side effects including headache, allergic reactions, decrease in blood pressure, facial flushing, stomach pain, nausea and an increased heart rate. Treatment with DDAVP without reducing fluid intake may also lead to fluid retention and dilution of salt in the blood. It is important for patients to fluid restrict for 24 hours after given a dose of desmopressin.

DDAVP works mainly for Type 1 patients. If the VWF is defective as it is in type 2 vWD then the VWF released will be similarly defective after DDAVP. Since type 3 patients have no VWF, DDAVP will be ineffective to release VWF. The response for DDAVP is also short lived. VWF concentrates are another form of treatment through intravenous injections, which replaces the missing VWF and FVIII in the blood and helps blood to clot. Some concentrates are plasma derived. Regular infusions of VWF concentrate helps to prevent bleeding, improve joint health and provide an individualized tailored schedule. Recombinant von Willebrand Factor (rVWF) is the newest version available. rVWF only contains VWF and for acute bleeds it must be combined with rFVIII (Recombinant Factor 8). However, this is not available worldwide yet.

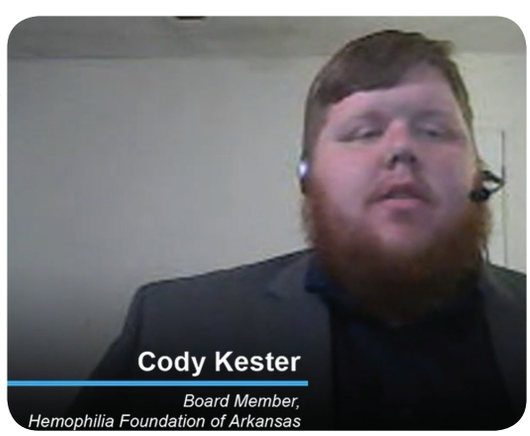
Jeanette Cesta focused on relationships and living with vWD. The shared goal for vWD individuals is to improve their quality of life. There is a need to address the psycho-social side as well as the medical side. Strong relationships contribute to the health, happiness and wellbeing of people and strong self-esteem can be linked with relationship satisfaction. The things to consider with the impact of living with vWD and self-esteem include independence, body image, marginalization, financial issues and genetic issues. People with vWD struggle to be validated and to not be marginalized in the health care system. If you are faced with a medical challenge that nobody else can support, it will be hard to approach the challenge and

find solutions. Body image is related to the physical attraction you have in a relationship. People with vWD suffer from a lot of bruising or for women, extended periods, which can make a person feel uncomfortable. You can also be limited in reaching your body goals as there can be limitations around exercise for vWD patients. For a person with vWD they can rely on a support system and feeling dependent in a relationship cannot be the best foundation for a balanced relationship.

Parents will also face the issue of independence with their children. Parents want their kids to be strong and independent, but they also have the natural instinct to protect. This can lead to worries about their child's transition into adulthood in relation to taking care of themselves with vWD, to learn about their medications and to liaise with their medical providers. Educational support is needed for vWD patients as children with vWD will become adults who will be responsible for the care of themselves and possible future children. The disclosure of VWD at the beginning of a relationship also plays a big factor in terms of intimacy and trust between partners.

Genetic counselling is vital for couples looking to start a family if there is family history of vWD. Furthermore, it can be expensive to live with a chronic illness leading to financial strains that can be stressful in a relationship. Workplace and schooling can also be majorly impacted. vWD may hold a person back from their dream college course and career choices. Bleeding episodes interrupt school and work life leading to a lack of attendance. This can be a conflict against being successful in what you desire to achieve in life. All these issues can be aided by enhancing the lives of vWD through validation, support networks and encouragement but mainly by being there when the person with vWD needs a helping hand. A motto from the vWD Connect Foundation quotes "it is not complaining, it is reporting." Jeanette Cesta stated this is important as vWD will not be fully understood until people start to come forward and report their symptoms. Patients should have great communication with their medical providers to achieve this.

Cody Kester shared his personal experience about a man living with vWD. Before being diagnosed, the substantial bruising had led to him being put into child protection services where his parents had to fight for guardianship. Cody was eventually diagnosed with Type 3 vWD. There was no family history, therefore his vWD was developed from genetic mutation. As a child he had several ports which lead to several infections. One of these infections left him in a coma for two weeks, resulting in him failing his final year in primary school. In High School, due to concern and lack of awareness about vWD he was separated from his classmates and only had four hours of school a week and he was taught the same lessons every year. However, this did not stand in the way of him applying for college. With his family support and encouragement, he went to an adult education centre and self-tutored himself. This hard work paid off and he was accepted into college and graduated with an Honours degree.



Baiba Ziemele shared her experience as a woman with vWD. Her life was majorly impacted. Diagnosis and treatment are lacking in Latvia. She was restricted as a child from playing sports due to fears of her vWD. This fear was because of the lack of knowledge about the disorder. Her sister had no treatment plan for when she was expecting her first child, throughout her pregnancy or during her labour. As a result she developed postpartum bleeding. Baiba still does not know what type of vWD she has. She recently had to take a trip to Estonia to carry out her vWD tests and she is now waiting to be told her correct diagnosis. Doctors in Latvia are not fully educated on vWD. When her father had taken ill, Baiba had to explain to his doctors about his bleeding disorder. This should not be the case. Baiba stresses that listening, and hearing are key for people with vWD, proper and timely diagnosis is vital, they should have access to health care services and availability of treatment options should be provided and be easily accessible.

vWD is an important bleeding disorder where patients benefit from accurate diagnosis and effective treatment. From shared experiences, skills and resources between other countries we can aim and strive for sustainable vWD care globally.

Julia

Treatment Choice in an Era of Change

Speakers: Johnny Mahlangu, Professor of Haematology, University of the Witwatersrand and NHLS, David Paige, National Director of Health Policy, Canadian Hemophilia Society, Brian O'Mahony, CEO of the Irish Haemophilia Society

Professor Mahlangu outlined how the standard of care we have used in the last several decades is to replace the missing clotting factor in order to rebalance haemostasis and replacement therapy has taken us far in the management of haemophilia. However, there are several unmet needs with recombinant products used to treat haemophilia A and B. Firstly, they are immunogenic and secondly, they need to be administered intravenously (IV). IV infusions are burdensome and because of the frequency the treatment needs to be administered, patients' veins can sometimes be destroyed, for example standard half life (SHL) Factor VIII (FVIII) needs to be given two to three times a week. Also, while a normal level of factor (peaks) is achieved, this then drops off (troughs) and these trough levels are the weak point that can lead to inadequate bleeding protection.

Some of these bleeds are clinically evident, but not always. In a study it was shown that a number of patients do have soft tissue and osteochondral changes that are consistent with subclinical bleeds. Subclinical bleeds lead to joint damage. Another study showed that 26% of bleed free joints had haemosiderin deposit (iron deposits) and 83% of patients had subclinical musculoskeletal damage. A study of patients with moderate haemophilia A showed that patients over the age of 40 years taking on demand treatment had a much higher number of joint bleeds compared to those on prophylaxis. But what was surprising was that those on prophylaxis still had some bleeds.

All of this is evidence that the current treatments may not meet all our requirements. The new re-balancing therapies promise a number advantages as they are administered subcutaneously, they are suitable for haemophilia A and B patients and they are suitable for patients with or without inhibitors. Several re-balancing therapies are under development, Concizumab has completed phase 1 clinical trials but phase 2 is temporarily on hold, Marstacimab2 has completed phase 2 and is proceeding to phase 3, Fitusiran has completed phase 1 of development and SerpinPC is in the preclinical phrase.

These re-balancing therapies are developed to address some unmet needs and while re-balancing therapies may offer several advantages over replacement therapies, these benefits should be weighed against the potential risk of swinging haemostasis balance towards thrombosis; thrombosis has been reported in a small number of patients in currently ongoing clinical studies.

David Page examined what a patient/caregiver considers, personally contacted 17 patients/caregivers with haemophilia A and B from around the world and asked them what current and developing treatments they would consider using. The patients ranged in age from new-born to 85 years old, the majority had severe haemophilia, 15 patients were male and 2 were female. The group varied greatly in age, activity level, bleeding issues etc. Of those asked six said they would choose Gene Therapy, of these two chose it as a long-term choice along with a different short-term choice. Six chose Emicizumab, three as a first choice, one as a second choice and two as a short-term option. Three patients chose prophylaxis FVIII, one chose on demand FVIII, one chose Sub-cu FIX, one chose Extended Half-Life (EHL) Factor IX, one chose Fitusiran and one had no idea what he would choose as he was so overwhelmed by everything.

Some of the positive considerations when choosing a treatment included, sustained factor levels, improved quality of life, no need for IV access and avoiding a port in young children. Some of the negative considerations included the duration of Gene Therapy expression, its long-term safety, if some patients will be eligible and the lack of research into inhibitor patients, female patients and children. The man who could not choose and was overwhelmed by all the options, was worried the new therapies have not been tested in many people for very long and his physician hasn't even mentioned options, he is not sure his physician knows much more than he does.

Brian O'Mahony's presentation concerned the issues of patients fears, expectations and decision drivers when considering Gene Therapy. The core-Hem multi stakeholders project which brought together patient experts, scientists, clinicians, payers and gene companies came up with 6 outcomes that were important, the level of factor expression, the duration of that expression, the impact of gene therapy on acute pain, healthcare utilisation cost of gene therapy, the impact on the mental health of the patient and the annual bleed rate. Another outcome which will be important when looking at the cost of gene therapy on an annual basis will be the decrease in the use of coagulation factor concentrates and therapies if replaced by gene therapy.

Even with current modern therapies, there are many unmet needs in haemophilia care, such as joint damage despite prophylaxis, poor health-related quality of life, some sense of social isolation, both acute and chronic pain, psychological difficulties as a result of anxiety and depression, a negative impact on work and education, treatment convenience, inhibitor development and high life time treatment costs.

Fears - Fears and concerns people have is that it may not work, you may take gene therapy and you might get limited expression or no expression and there have been people on clinical trials who have had no expression. The expression is not predictable, the duration of expression may be limited and currently we do not know what it is, ideally it would be a lifetime therapy, but many people feel it should be at least a ten years. Is there a long-term risk of cancer and if the expression is too high there is a risk of thrombosis? Then there are economic fears, you may not have access to gene therapy, due to costs or requirements in some countries for co-payment. In some countries if the person with haemophilia (PWH) has a high co-payment, they must pay up to 20% of their treatment costs, this would not be tenable with a treatment like gene therapy. The impact of vector shedding, is it possible to infect family members?

It is an irreversible therapy, once it is in your system it does not come back out. If you do not achieve reasonable expression and duration of expression you may have used up your one opportunity of gene therapy now and perhaps for the near future and retreatment is currently not possible with the same vector. Cross reactivity may prevent re-treatment with any AAV vector, so if you are treated with an AAV based gene therapy and are positive for one antibody that may prevent them being treated with several of the gene therapies. And re-treatment, even if it's possible may not be economically viable. An EHC survey was carried out at a conference in 2017, of the 40 participants the following results were reported before the participants had an education session on gene therapy. 22 had a fear of adverse events, while most did not specify what fear, 7 feared cancer, 2 feared risk of inhibitors, 3 feared infertility and 2 feared irreversible therapy. Despite this when asked 'do you think your life will be better in the future with gene therapy?', 30 replied yes and 5 replied no.

Expectations - Expectations in relation to gene therapy expression has changed. In 2006 it was expected that gene therapy would be an annual infusion, in 2014 an annual stable factor expression of 5% was a good outcome, by 2020 views on factor expression have moved on. At the recent WFH roundtable on gene therapy an informal study of 12 PWH was carried out and most felt that the ideal factor expression would be in the normal range (50-100%) and they wanted a life without the need for coagulation factor concentrates. They said the minimal factor expression acceptable would be 10-15%, the ideal factor expression would be more than 50% but at least 20-40% where you would only require coagulation factor concentrates for major trauma or surgery. In terms of duration of expression, this would ideally be for a lifetime and many feel it should be at least 10 years or 5-10 years. Expectation would be that re-treatment would be possible after 5-10 years, that the companies have 5-10 years to sort out that problem to allow for possible re-treatment with the same or a different vector.

Constant significant factor expression should result in the decrease in chronic pain, improvement in damages to joints over time due to less sub clinically bleeding, ability to do normal activities such as working, walking, cycling, swimming etc and

the opportunity to lead a more active and balanced lifestyle. The freedom from constantly having to consider haemophilia, to have to pre plan activities, do I take my prophylaxis in the morning or evening, having to respond immediately to a trauma, ensuring you have factor when travelling and being aware of the nearest treatment centre. Many young adults want to travel and work aboard but are being denied this opportunity because some countries see them as being an economic burden on that country. Gene therapy is not a genetic cure, it will not reverse existing serious joint damage, it will not make you more active and it does not mean you can undertake very risky activities or sports with total impunity. However, it may lead to a reduction in anxiety and depression, as positive feelings can produce a new outlook on life. But emotional support may be needed to deal with feelings of loss of identity or community, uncertainty of duration of expression and loss of past opportunities.

Decision Drivers - The unmet needs leading to decision drivers include the intrusiveness of chronic therapies, the need to be aware of peak and trough levels, joint morbidity and physical challenges, the impact on mental health, loss of work productivity and social inclusion and disability paradox, PWH overestimate their health related quality of life by 17%. Decision drivers based on their personal experience of living with haemophilia include their number of bleeds, existing state of their joints, current activity level and barriers to increase activity, poor venous access, needle phobia, tired of having to live with severe haemophilia and wanting to experience life without it. Another decision driver will be the existing therapies available to them, gene therapy will be looked at in relation to their current treatment and the impact of other as yet un-licensed novel therapies and they will look at their quality of life and weigh against the additional benefits and risks of gene therapy. Age will also be a deciding factor, for young adults who have good joints, gene therapy could maintain those joints, increase their quality of life, make them more active and give them more employment and travel options.

For older adults who may already have significant joint damage, that damage may not be reversed but it may improve the chronic pain and may offer more mobility. Children with severe haemophilia are the obvious target for gene therapy eventually to avoid the requirement for ongoing therapy, avoid joint damage and allow for a more active life. Of course you cannot give gene therapy to children at the moment as their livers are not developed and although the age for gene therapy may come down from 18 years to 15 years to even 12 years in the next number of years, it is unlikely to be available for younger children during that time. When gene therapy is licensed you will have some people who will be queuing to try it, while other people will be very cautious, they will want to wait for a significant period of time or they won't take the option of gene therapy at all, but mainly people will be in the middle, they may wait 1 or 2 years to see what world evidence there is compared to clinical trial data. But more people will take up gene therapy when there is world evidence of safe, stable, and predictable factor expression levels.

Typical questions PWH's may have before deciding to enter a trial are, what trial should I participate in? What are the results, if any from earlier phases of the trial? What is the reputation of the trial team? What vector is being used and what is the prevalence of pre-existing vector antibodies? Will pre-existing antibodies automatically rule out a trial participation or have strategies been developed to address this issue? What vector dose is being infused and what is the anticipated range of factor expression? Is a higher vector dose worthwhile if the objective is a higher factor expression? Am I comfortable taking a prophylactic course of steroids if that is part of the protocol? Also, what duration of trans gene expression is expected? PWH's must look at the lowest limit of duration expression outcome they would like to see, but they must also think if I don't get that outcome what is the minimum outcome I would be prepared to tolerate and they must be mentally and physically prepared for that minimal outcome.

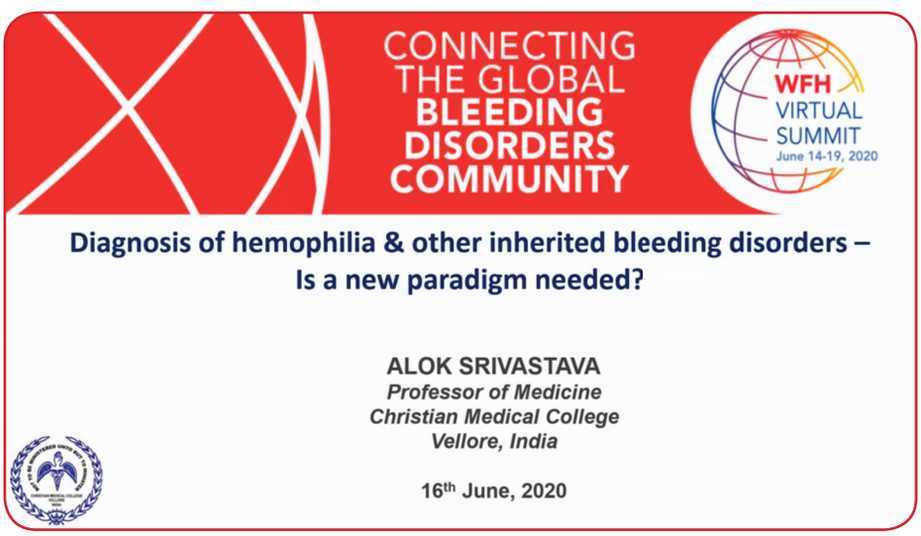
In Ireland at the I.H.S. annual conference in March this year, Brian was able to announce that the first person in Ireland had been treated with a gene therapy vector. The I.H.S have actively educated its members about gene therapy for a number of years and have been looking at several gene therapy trials.

Nina

Diagnosis of Haemophilia

Medical Plenary with Dr. Alok Srivastava

Dr. Alok Srivastava spoke about the challenges in relation to the underdiagnosis of haemophilia across the world. Data from the 2017 WFH Annual Global survey confirms that 315,000 people were diagnosed in that year. Of those 315,000 people diagnosed, there was no clarity in relation to severity for 200,000. However, when he took a closer look at the survey it appears that those who had clarity around severity were identified as being from higher income countries. Data published in 1999 confirmed that 78,000 people with haemophilia had been identified, which increased to 210,000 being identified in 2018, This is a change of 204% during this 9-year period, which is very significant.



Data extracted from the 2018 WFH Annual Global survey documented that only 2-3% of people were diagnosed in two countries in Africa. Indeed, there are many reasons for low numbers, however, this issue still needs to be addressed. After three or four decades of extremely hard world globally, 75% of people still remain underdiagnosed. Dr. Srivastava put it to his audience that this model was therefore a failed paradigm. The current diagnostic model has failed to achieve its goals, which is food for thought.

There are many reasons that many people go undiagnosed. With the current model in higher income countries, when a child presents to a clinician a clinical assessment is made and the child will be then referred to a treatment centre where the child undergoes testing. However, in lower income countries, there are many issues that prevent people seeing this through. There are issues around travelling to the centre, loss of time in work, the cost of transport to the centre and indeed many treatment centres are more than 100's of kilometres away and poor health infrastructure. In some countries testing may not be available, therefore there may be years of delay in diagnosis. Also, in some underdeveloped countries there are no labs to do the testing and this is an extremely difficult situation.

The challenges around diagnosis are many, however, the inclusion of assessment tools may be a welcome modification which could be adopted across the world, particularly in low income countries. However, these difficulties will continue to challenge the diagnosis of inherited bleeding disorders in many parts of the world. Dr. Srivastava feels that the best idea is to create a new model which simplifies clinical assessment which should be fairly easily achieved by using the self-assessed tools. Dr. Srivastava suggested moving away from the current system and moving to point of care testing devices. Dr. Srivastava spoke about a device called a 'Clot Cip' which is a disposable device, that requires only 10ml of whole warm blood, that has good correlation in people with haemophilia with or without inhibitors. This device could supplement full testing at a later stage.

Finally, Dr. Srivastava said that an updated cost-effective model with improved point of care devices, central haemostasis laboratories for diagnosis and continuing to increase awareness would help with the current challenges of people going underdiagnosed.

Debbie

Physical activity for joint health and wellness

Speakers: Adolfo Llinas, Orthopedic Surgeon, Fundación Santa Fe de Bogotá; Pamela Narayan, Executive Committee Member, Medical Advisory Board Member, Hemophilia Federation of India (HFI) & Chavez Edgecombe, Bahamas Hemophilia Foundation

Adolfo Linas explained yes there is an association between people with haemophilia and lower bone density. "Why people with haemophilia have lower bone density?" He noted there are 3 different reasons. Carriers have more than double the chance of developing Osteoporosis. He also explained prevention of osteoporosis such as factor replacement therapy administered on a regular basis to prevent bleeding and decrease mineral density, diet, physical activity, limitation of tobacco and alcohol and limitation of the duration of immobilization. He explained the intake of medications that modify the biology of the osteoclast must be taken with care to avoid excessive accumulation of minerals that may result in brittle bones. And that there is a new role in the multidisciplinary haemophilia care team: the bone metabolism expert.

Pamela Narayan spoke about 'Rehabilitation versus Wellness', explaining the difference between wellness and rehabilitation. Wellness is something that we can achieve actively and consistently. Rehab is actively restoring someone to good health through the process of therapy or training to achieve a certain goal. 85% of bleeds in a person with haemophilia occur in the muscle and joints. Pamela explained that very few people will look to a wellness program after rehabilitation. The reason people don't look to Wellness is anxiety about their future, a lack of support and a feeling of unknown towards wellness as a therapy. She showed a patients account of how they used wellness physical therapy to keep himself well. She explained that rehab is a prequel to wellness. All muscular skeletal specialists should set out a goal and she recommended using the smart goal acronym. For people to achieve wellness she recommends they should try Tai chi and yoga. She explained there is barriers to wellness such as for treaters; lack of resource, time, money, facilities, lack of symptoms and lack of appropriate assessment gold settings. For a person with haemophilia the barriers are it can be inconvenient, lack of symptoms, forgetfulness and lack of time. Overall Palmer's message was that rehabilitation programs should lead to Wellness and rehabilitation is necessary for one to be fit to engage in wellness. Engaging in a wellness program is key to a long term muscular skeleton health.

Chavez Edgecombe was born in the Bahamas with Haemophilia. He moved to Canada and after some time had to get a total knee replacement. After the replacement he set about regaining his strength. He found this difficult and painful. But having consistent factor and exercising more things got better.

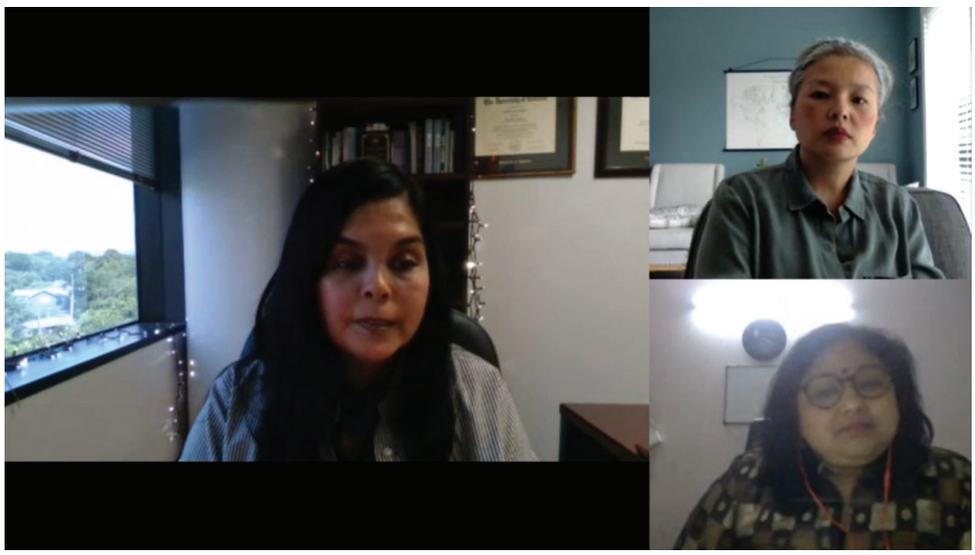
He came up with a strategy for muscular skeleton care:

1. Know your body
2. What do I want to accomplish
3. Start light and start small

People should get creative with your exercise as it can be done at home or the gym. Start by choosing target joints. For him best practices for strength for his right elbow was pushups, bicep curls and dips. For mobility he used different stretches such as shoulder touch, center chest palm, arm pull, bicep curl. To strengthen his right knee, he practiced biking and step ups. For mobility of his right knee he used resistance bands and biking. To strengthen his ankle he practiced calf raises and different variations. and for mobility he practiced moving his ankle in 360 degree turns. For swelling and bleeds he practiced R.I.C.E.

Robert

Healthy Living



This session looked at the strategies for healthy living and shared advice on, building self-confidence / self-esteem, healthy ageing and sexuality.

Speakers: Sabrina Farina, Social Worker, Texas; Lynn Driver, USA & Richa Mohan, Consultant Clinical Psychologist & Director

Sabrina Farina examined Trends in Ageing. Over the last number of years there has been a big mindshift as to how people view ageing, which now shows it to be positively cool to be ageing. Globally the population aged 65 and over is now growing faster than any other age groups. As we age we are susceptible to chronic diseases. Consider using one pharmacist, can look at the whole picture including over the counter meds. Consider speaking to a geriatrician in conjunction with your treatment centre.

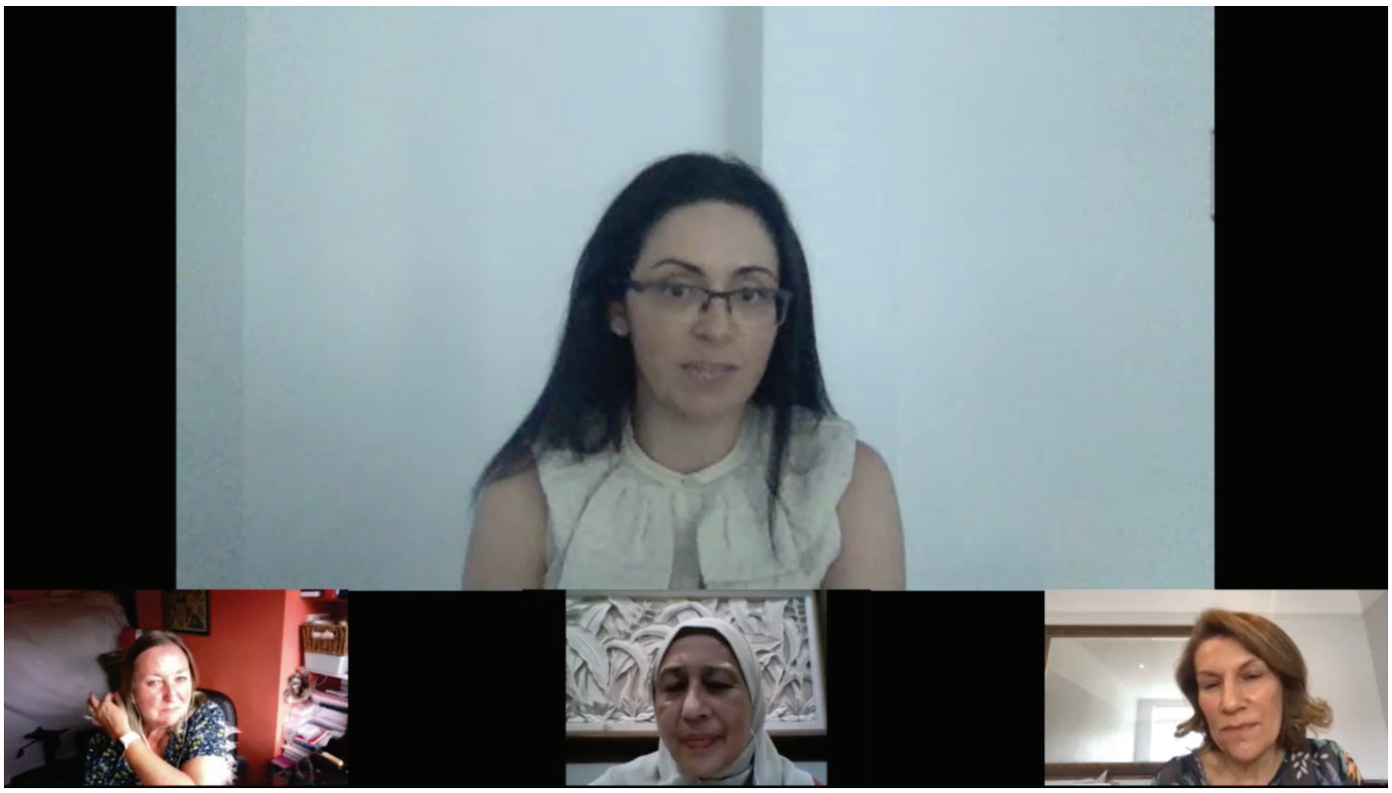
What are best practices for successful ageing? Reduce the risks of falls by improving strength, balance, coordination and flexibility. Make modifications to your home. Get a home assessment done. Arrange an emergency home medical alert system. Healthy ageing also means being able to plan and address brain health, break a sweat, be a lifelong learner, try new things, learn a new language, quit smoking, challenge yourself. Ageing doesn't mean we lose our feelings of love, compassion, belonging, these feelings never go away regardless of our age.

Lynn Driver spoke about how important it is to have a good healthy lifestyle. Living with symptoms of illness and in constant pain, patients experience lots of procedures, time is lost from work and school, changes in social support and self-esteem, mental health issues such as anxiety and depression. Hygiene, nutrition, lifestyle, environment, living, income, self-medication. Self-care is a priority. It's important to have a good diet, being mindful of emotional eating. Drink lots of water, it hydrates and boosts your immune system. Physical activity is important, just move. Even if you are just in your chair, just move. Sleep hygiene, studies say getting enough sleep is very important. Practice relaxation techniques, slows down heart rate, lowers blood pressure, maintains blood sugar levels. Example: square breathing: this is deep breathing, holding for 4 seconds.

Sexuality is not about who you have sex with or how often, it is about emotion, behaviours, it connects your mind and body. Issues that people with bleeding disorders have when it comes to sex include pain, periods lasting weeks, joint and muscle weakness. A recent survey showed that people with bleeding disorders experienced dissatisfaction with their sexual life due to their bleeding disorder. It's important to make sure you are comfortable, that you communicate with your partner. Practice safe sex and know your genetics. The UK Society have published a booklet on comfortable sexual positions you can have with your partner for people with bleeding disorders.

Richa Mohan spoke about self-esteem and healthy living. Self-esteem refers to a positive overall evaluation of oneself, a basic human need. Respect from others, self-love, self-confidence, unable to grow. Our own thoughts and perceptions of ourselves, how other people react to us, our own experiences at home and work, all affect healthy self-esteem. When one has a low self-esteem, one puts little value into his/her opinions and ideas. They believe others are more capable and more successful. When you have a healthy self-esteem, it means they have a balanced, accurate view of themselves. Living with a chronic medical condition is often accompanied with low self-esteem, a diminished sense of personal worth. However, people do not realise that the condition can be dealt with proactively. Building blocks include security, selfhood, affiliation, mission, competence which means self-esteem can be changed. Some of the tools used include, positive imagery, goal setting, peak performance, behave confidently, be with people who treat you well. When you value yourself, you are more resilient and better able to weather stress and setbacks.

Debbie



Women Ageing Gracefully

An Overview of ageing and the issues that are pertinent to women

Speakers: Dr Michelle Lavin, Clinical Lead for coagulation haematology research in the Irish Centre for Vascular Biology, Royal College of Surgeons, Dublin; Dr Rezan Abdul-Kahir Consultant Gynaecologist, Royal Free London NHS Foundation Trust and Dr Jameela Sathar, Senior Consultant - Haemotology, Ampang Hospital.

The main challenges for women as they age are the menopause, surgery, cardiovascular diseases, bone and joint issues and cancer. All these challenges are present for all women, but if a woman has a bleeding disorder, this can add to the complexity of her treatment, as bleeding disorders may influence treatment choices and require planning for surgery. Patients with von Willebrands Disease (vWD) can see their factor levels increase with age, those with mild vWD can often be 'removed' as having a bleeding disorder, but there is no evidence that this factor level increase removes their risk of bleeding, so we have to be very cautious about altering people's diagnosis as they age.

Access to age appropriate care is essential, but are our haemophilia treatment centres (HTCs) equipped to deal with this, do we have access to combined care and is the HTC the best place to deliver that care as many age related issues are general medical conditions, so should the haematology service be going out further into the successful ageing clinics and be providing combined care in that setting rather than bringing successful ageing to the HTC. Finally, research on women with bleeding disorders as they age is needed, there is very limited data on these patients. Women need to be included in all research; they cannot be an afterthought.

Perimenopause/Menopause – the peri-menopausal period is a very important time for women and to understand why this is an issue for many women, especially those with a bleeding disorder, it is important to remember hormonal changes occur at the onset (menarche) and end (menopause) of your menstrual life. Everyone's periods are regulated by hormones that are released, as women approach the end of their menstrual life these hormones will come out of sync with each other and periods can become more unpredictable, heavier and irregular. It is important for clinicians to support and prepare women with a bleeding disorder (WBD) for these changes and challenges they will face as they age. If a woman's hormone levels are very high that can be suggestive of menopause however there is no reliable blood test to say a woman is in the menopause and it is usually a combination of symptoms and signs that confirms it.

New onset heavy menstrual bleeding may occur at the onset of the peri-menopausal period and it is important that women are offered gynaecology input if this is required. A fact that is often lost with haemophilia treaters as they are not as familiar with this time is that contraception is still needed after periods end, for younger women who are less than 50 years when

they have their menopause, contraception is advised for 2 years and for those women who are over 50 years contraception is advised for 1 year. This is a time when a uterine device can often be helpful because it controls heavy periods and offers contraceptive cover.

Many physicians will be familiar with hormone replacement therapy (HRT) and we know that HRT can increase the rate of blood clots and sometimes general physicians who are aware a woman has a bleeding disorder will be reluctant to offer HRT to these women, where in fact it is more the women who have a thrombosis rather than a bleeding disorder are unsuitable for HRT.

Bone/Joint Issues – after the menopause, women are at greater risk of reduced bone mineral density. We know that woman can have problems with bleeding into the joints the same as men, so joint damage such as arthritis, arthropathy and reduced/weakened bones is another problem woman face as they age. In male patients with haemophilia, there has been evidence of reduced bone strength and reduced vitamin D levels, but it is not clear if this impacts on women who are carriers of haemophilia. If orthopaedic surgery is required, again haemophilia treatment centre (HTC) input is essential to safely guide these patients through this operative challenge. Prevention is important with good adherence to physiotherapy, ensuring a healthy body weight and keeping active as we age will help prevent the risk of poor joint health.

Cardiovascular Disease – the risk of heart attack, stroke and high blood pressure become more common as women age. With cardiovascular disease if someone develops a heart attack or irregular heart rhythm, treatment is often anti platelet agents or anti coagulation, both of which will increase the bleeding risk. So, it is very important that an individual assessment is carried out for a woman with a bleeding disorder (WBD) and the patient must be at the centre of this with all her medical teams involved in that decision making process and her treatment long or short term must be followed up closely. Risks can be reduced by managing high blood pressure, controlling obesity and reducing the risk of diabetes, particularly in WBD.

Surgery – As we age there is an increase in the need for surgery and an increase in the complexity of these surgeries, which carry an increase bleeding risk, but they also have a higher risk of thrombosis. In many cases we are providing pro thrombotic treatment to patients before the surgery. Again, HTC input is needed to balance the risk of clotting and bleeding in each individual patient. In Type 1 vonWillebrands Disease (vWD) patients with milder base line levels we see an increase of their von Willebrand factor levels as they age, but what is unclear is how to optimally manage these patients for surgery and to what level these patients should be treated to reduce their bleeding risk.

Cancer - Unfortunately, as everyone ages, the rates of cancers will also increase, and these bring with them inherent complexities for women with bleeding disorders.

Gastrointestinal (GI) – gut bleeding is often a new issue that arises with age, particularly in patients with more severe types of vWD, this affects both men and women and can be very difficult to manage.

Panel Discussion - some points of interest:

- We need to start capturing any data we can on women throughout their menstrual life. When women are included in studies, how their menstrual bleeding is affected by prophylaxis is usually an afterthought and often listed under 'other bleeding'. From the outset studies are not designed to look at menstrual bleeding, to capture the severity and duration. As woman age, data in relation to the different treatments being used, the challenges women face is needed, the data for these really isn't there for women with bleeding disorders.

- The clinical approach is towards men, clinicians when they treat haemophilia patients may forget about the women, they should ask about female relatives such as sisters etc, as we want these women to come forward. But we need to educate the men about bleeding issues for women through our clinics and through patient support groups and to target women themselves with educational booklets and talks.

- Women who are carriers can have low factor levels themselves and should be classed not only as carriers but as a person with a bleeding disorder. It is known that carriers with normal factor levels can still have bleeding issues. Factor assay tests can be misleading, women can have normal haemostatic levels, but have a very definite bleeding phenotype. It is important to use bleeding assessment tools and listen to women about their bleeding issues. In some countries if you only have a carrier diagnosis and not a bleeding diagnosis you may not be able to access necessary care. We need to look at removing these barriers to allow women to have full access to care.

- Gynaecologists and haematologists need to work together to jointly treat women as they approach menopause, at this stage heavy menstrual bleeding can be as a result of hormonal changes and gynaecology issues such as fibroids and may not just be the woman's bleeding disorder. It is important to investigate changes to menstrual bleeding issues to ensure that an underlying condition such as cancer is not missed.

- A woman who is heading towards a hysterectomy to treat heavy menstrual bleeding should be assessed for an underlying bleeding disorder first before this surgery is considered.

- The type and severity of a bleeding disorder impacts on menstrual bleeding, nearly all patients with severe von Willebrands Disease will have heavy menstrual bleeding issues.

- Women with mild haemophilia can have joint bleeds, but don't always take these bleeds seriously as they are not as severe as their son's bleeds, they often downplay their own joint bleeds, and this can lead to long term joint health issues for these women. Clinicians don't see as many joint bleeds in women as men and therefore maybe they are not checking for joint bleeds as much.

- As von Willebrands factor levels (vWF) rise in women as they age, those who have a vWF level of between 30-50% when they are in their twenties and thirties, are more likely to have a vWF level of above 50% in their fifties. When it comes to a patient who has been diagnosed with a bleeding disorder earlier in life and who's levels are now 'normalised' in later life, it is important to remember that bleeding for this older age group can still be an issue and they should remain as a person with a bleeding disorder and continue to be monitored.

- Heart valve abnormalities and gastrointestinal bleeding can be connected, there is a condition called Heyde's Syndrome were patients who were noted to have very tight aortic valves would be at risk of spontaneous bleeding from their gut. This was because if your blood is trying to push through a very tight heart valve, there is more turbulence, your body normally thinks turbulence is where you have damage to your blood vessels and that causes vWF to unravel and start to attach to platelets and to attach to the blood vessel walls. Because of this a patient can end up with an acquired von Willebrands Disease. If you have a patient with a bleeding disorder who has a tight heart valve it may be better to treat sooner to help prevent GI bleeds.

Nina

von Willebrand Disease & Women's Issues

Speakers: Lubna Zafar, Consultant Haematologist, Fauji Foundation Hospital, Rawalpindi, Robert Sidonio Pediatric Hematologist/Oncologist Emory University, and Roseline d'Oiron, Clinician Investigator, Centre Hospitalier de Bicetre

This session explored the research of the best scoring abstract authors in the category of von Willebrand Disease (vWD) and Women's Issues.

Dr Lubna Zafar explored 'The Menace of Menorrhagia in females with Inherited Bleeding Disorders'. The objective of this study is to identify the pattern of clinical presentation of bleeding in females affected with inherited bleeding disorders. This retrospective study was carried out on 90 females registered with haemophilia Treatment Centre (HTC) of HPWS Rawalpindi, Pakistan. The age range of the patients was 1.5 - 60 years, with various inherited bleeding disorders. 45 patients have vWD, 34 patients have Glanzmann's thrombasthenia (GT), 3 patients have Bernard Soulier Syndrome (BSS) and 8 patients have Rare Bleeding Disorders (6 of factor X, 1 each IX and factor I).

In vWD, nose, gum and skin bleeding were seen in 91%, 75.5% and 75.5% patients, respectively. In post menarche females 93% had menorrhagia. Only 2% had gastrointestinal bleeding and joint bleeding. In patients with GT and BSS, nose, gum and skin bleeding were seen in 83.7%, 64.8% and 75.6% respectively. Menorrhagia was seen in 88.4% post menarche patients and joint bleeds in 24.3% patients. In patients with Factor X, Factor IX & Factor I deficiency, menorrhagia was seen in all (100%), followed by nose, gum and skin bleeds in 75%, 87.5% and 87.5% respectively. Joint bleeds were present in 37.5% patients. Urinary, muscle and intracranial bleeds were not seen in any patients. Menorrhagia, nose, gum and skin bleeds were seen in the majority of patients.

The management of menorrhagia is a challenge. Some patients present with heavy cycles at the beginning and settle gradually with treatment whereas other patients needed more active management due to the difficulty controlling the bleeding. The treatments used were tranexamic acid, fresh frozen plasma, oral contraceptive pills, primolut N and von Willebrand Factor (vWF). vWF availability and affordability in Pakistan is a major problem. The impact of menorrhagia on the lives of girls / women is a concern as many suffer silently. Many women suffer from martial problems for those who do marry, due to lack of knowledge about vWD, frequent absence from school or dropouts, social isolation, low self-esteem and not being able to get married due to taboo linked to vWD, difficulty in conceiving, excessive bleeding during childbirth and puerperium, anaemia, anxiety and concern about the child having a bleeding disorder.

Dr Zafar concluded that menorrhagia is the most common symptom followed by mucocutaneous bleeding in females with bleeding disorders. Joint bleeds are not very common. Muscle, urinary gastrointestinal and intracranial bleeds are rare. Finally,

practical guidelines for management of menorrhagia in resource constrained countries will alleviate this burden.

Robert Sidonio discussed 'Treatments and Outcomes of Bleeds in Women and Girls with Factor VIII and IX Deficiency. The study included female patients who had at least two clinic visits and underwent medical or surgical interventions for haemostasis management for bleed events between April 1, 2012 and November 15, 2018. Patients with other coagulation disorders were excluded with the exemption of low vWF of 40-50%. The study showed that four out of seven women required haemostasis management peripartum and five out of seven women required management postpartum. Factor VIII and Factor IX concentrate were utilized in the majority of patients. It is known that Factor VIII levels rise during the 3rd trimester of pregnancy. Antifibrinolytic agents may also be used. Some patients were still using plasma derived products and a fair number required iron supplements. When it came to surgeries, the treatments used were desmopressin and Factor VIII and Factor IX concentrate; these were used extensively as well as antifibrinolytics.

Twenty-three women and girls with factor deficiency experienced spontaneous, traumatic or joint bleeds that required haemostasis management. About 39% of the patients had joint bleeds recorded and evaluated by the providers over the course of the study. The locations of the joint bleeds were the right and left knee, the right ankle and the right elbow. When it came to haemostatic management for bleeding events for spontaneous, traumatic and joint bleeds, including nose bleeds, and soft tissue joint bleeds, as expected factor concentrate was more heavily utilized as well as desmopressin for those who are responsive. "Some patients did lean on antifibrinolytic agents and plasma products for some particular reason unknown to us", quoted Mr Sidonio.

Overall, most women and girls with factor deficiency present to HTC's in the context of a family member's Haemophilia or for genetic counselling. Heavy menstrual bleeding and spontaneous traumatic bleeds were common reasons to visit the HTC for those with Factor VIII deficiency.

79% of the patients in this study were diagnosed with mild Haemophilia. The median factor level for the overall population at the time of diagnosis was 32%. For birth, surgery, traumatic and spontaneous bleeds haemostasis management consisted primarily of factor concentrates. Medical interventions generally led to decreased or stopped bleeding. Other modalities such as antifibrinolytics, desmopressin or transfusion were used depending on the extent of bleeding symptoms. Women and girls with factor deficiency (WGFD) experience significant bleed events. Understanding outcomes of current management strategies for WGFD treated at HTC's contributes to optimizing treatment approaches for this patient group in clinical practice and may guide future studies.

Roseline d'Oiron presented 'Age at diagnosis is delayed in women/girls with Haemophilia (WGWH) compared to men/boys with Haemophilia (MBWH): a FranceCoag report'. The age at diagnosis of low Factor VIII and Factor IX in carriers of Haemophilia had been unfrequently reported in large cohorts. Delays in providing such diagnosis impairs appropriate management for prevention and treatment of bleeding episodes. The FranceCoag is the French registry that is dedicated to all congenital bleeding disorders and included girls, boys, women and men with Haemophilia who have Factor VIII or Factor IX deficiency of less than 40%. The current study aims to compare the age distribution, the age at diagnosis and the circumstances of diagnosis of WGWH and MBWH included in FranceCoag by type and severity of Haemophilia. FranceCoag encompasses one of the most important and well-characterized cohorts of women with Haemophilia reported to date. Among the 420 females with Factor VIII/Factor IX deficiency in the cohort, 12 (2.9%), 12 (2.9%) and 396 (94.3%), had severe, moderate and mild forms, respectively. The principle finding is that mild Haemophilia is diagnosed 6 years later in WGWH compared to MBWH. The median age at diagnosis, 16.91years, of mild Haemophilia in WGWH occurs much later than the median current age of menarche in France which is 12.8 years. In mild haemophilia, circumstances of diagnosis differed between females and males. A family enquiry was the main reason for diagnosis in these WGWH (69.6%) but not for MBWH (30.0%). Diagnosis made for bleeding episodes and incidental findings represented 12.5% and 14.8% in WGWH by comparison to 27.7% and 40.2% in MBWH, respectively.

The delayed diagnosis in WGWH by comparison to MBWH emphasizes the need for better strategies to identify sooner the girls with a bleeding disorder in families with Haemophilia.

Julia

Quality of Life

Topic: The gain to pain

Speaker: Prof Lorimer Moseley, Clinical Neurosciences, University of South Australia.

A case study was presented of a man with a nail up through his boot. The doctor treating the man stated that the slightest movement of the nail was causing the man excruciating pain, in fact it was so painful that the man had to be sedated with powerful analgesics. Eventually they got his pain low enough that they could cut off the boot and as they removed the boot, they discovered that the nail had gone between two toes and had not caused any tissue damage and immediately this man's pain vanished. So, is pain there to detect an injury? If it is in this case the system failed, there was no injury, but the man was in extreme pain that could only be settled by powerful drugs.

It is a remarkable situation that a person could have no injury but severe pain. Prof Moseley was amazed by this and went to a local hospital; he was sitting in the waiting area and his job was to observe patients who walked in to compare the apparent gruesomeness of trauma and then to evaluate their pain and try to understand this relationship. While completing this survey a patient walked into A & E with a hammer stuck in his neck, there was blood coming down the front of his shirt and the injury looked gross, but he seemed very relaxed. Prof Moseley said to him 'there is a hammer in your neck mate' and he said 'yeh, yeh I know'. Prof Moseley was trying to make sense of this, he thought the patient was so calm he had taken some drugs, like morphine, so he asked him had he taken anything, the patient said 'yes, on the way here I stopped at a café for an egg and bacon roll', but no drugs. Prof Moseley thought maybe this is stress induced analgesic or maybe the patient is an idiot, but then the patient cracked a joke, he went around the waiting room with his elbow behind his back saying ' what am I?', eventually everyone said we don't know, he said 'I am a hammer head shark'. The patient invented this joke, he wasn't stupid, he was clearly a clever guy.

The next option is that something is stopping pain messages arriving to the patient's brain, this was the old way we would think about pain, it is being generated in the body and messages sent to the brain to detect an injury. Prof Moseley thought the brain is just clearly not able to cope with this, the patient is in shock, but then the patient hit his knee off a coffee table and was in agonising knee pain for a small bump on his knee. So, here is this guy with a severe injury but no neck pain but has pain with a minor knee injury. If the purpose of pain was to detect injury, but this doesn't happen, something else must be going on. Most people will understand their pain according to it being an indicator of tissue health, if pain gets worse the tissue health is worse, that is a common, intuitive and sensible idea. Is that how it works? Think about your own pain experiences, most of our own pain experiences occur outside of injury. The longer we have pain, we know that most people will start to shift their pain from being a protector to pain being a measure of tissue health and we have very good evidence that it is not.

We have very good evidence that the purpose of pain is protection. As an example of this, they did an experiment, they have a finger squeezing device and they get the person to wind up the pressure on the finger until they get pain, for example 3 out of 10. We record the pressure, but they didn't know what the pressure was and then we get them to come in with a friend and we ask the friend to control the pressure device and the pressure device will stop at exactly the same pressure, but invariably the pain is greater, it is the same signal being generated but the pain is greater. Then if we remove their friend and get someone else to do it again, the pain is greater again. In these situations, the event to the tissue is the same but the pain is different, and we make sense of that because the apparent risk is different. The brain weighing everything thinks I am more at risk with this person I don't know in charge of the pressure device than if it was me, so the brain takes that into consideration and produces more pain because it is the pain that stops you and gets you out of that situation.

In the 1960's scientists discover that the same hot probe produces very different effects, from making an animal jump to not evening making it flinch. This was really compelling data that the purpose of pain is not detection of something, not telling you what you have done, the purpose of pain is to protect you, to prevent you from doing something that might end up being dangerous. We now know that pain is not a measure of injury or tissue health but a measure of how we are trying to protect ourselves from a scenario. So, the contemporary understanding of the purpose of pain is it provides a protective buffer and that buffer is honed over evolution over many generations, but it is also honed over your experiences in life, your genetics and the course you have taken through life experiences.

We used to understand pain as a signal from the body, we don't understand it like that anymore we understand pain in this way, anything that suggests you need protecting takes pain up, and anything that suggests you don't takes pain down. Many

back pains are brutally painful even if we cannot find an injury to them, in fact some back pain that feel exactly the same and do have good evidence of acute injury e.g. a fracture, but they don't feel anymore painful necessarily because so many things are being considered when the brain produces pain. If you have an injury that is severe enough to be pain free, it must be catastrophic, catastrophic injuries, life threatening injures are often pain free. Because the brain is not producing pain to tell you what you have done, it is producing pain in order to motivate you to do something to protect yourself. Much of what is happening in the brain is outside our awareness, pain is produced based on what the brain knows, it is impossible for a human brain to ignore information such as a clinical diagnosis from its decisions around how well it protects you.

There are always many contributions to anyone's pain, there are no exemptions to this, our pain is always a conscious feeling that emerges from the brain that protects us according to all the available information that is coming in and all the information already stored there. This is a protective buffer which can be quickly and substantially modified by a whole range of things. In the 1980's scientists discover that the longer you have pain, the more sensitive your pain systems gets, your body becomes over protected by pain. This is very important if you have pain over a period of months or years and this learning process gives us a gauge of pain, so the pain system is gained and amplified. Is your pain system overprotective? Start to rethink your pain today, for more information on this go to www.tamethebeast.org.

Topic: Sleep, Why we need it.

Speaker: Bhajan Singh, Clinical Professor, University of Western Australia.

Normal sleep is a rapidly reversible state of responsiveness, motor activity and metabolism. Sleep consists of four distinct stages, first is rapid eye movement (REM) sleep, which normally occupies one fifth of sleep time. This is followed by three stage of non-REM sleep called N1, N2 and N3, which represent progressively deeper stages of sleep. We typically cycle through these stages of sleep several times, with each cycle lasting about 90 minutes, awakening can occur between cycles. Sleep architecture changes across the life span, the total sleep time decreases between childhood and adulthood, then remains verily stable from the age of 30 years onwards. However, the periods of wakefulness during the sleep period called 'wake after sleep onset' increases with age so that sleep becomes less efficient as we age. First it is thought that sleep is important for restoration and repair, this is supported by several changes during sleep such as the increase in the secretion of growth hormones.

The second idea is that sleep helps to conserve energy, thirdly sleep is thought to be important for memory consolidation. It is likely that patients with severe haemophilia have impaired sleep due to pain caused by bleeds and joint damage. It is known that of patients with chronic pain, two thirds experience poor or unfreshing sleep. There is a direct relationship between paid and sleep, pain contributes to sleep problems, and sleep problems contribute to pain due to decreased activity levels, by affecting mental health and by changing the perception of sleep. Studies have shown that sleep deprivation has been known to increase pain perception. Inadequate sleep, even moderately inadequate, impairs performance and cognitive ability. Cognitive impairment associated with sleep deprivation is similar whether it is achieved by a single night of sleep deprivation or partial sleep restriction over a week. Studies in sleep deprivation have shown that impaired sleep leads to an increase in motor vehicle accidents, fatal occupational accidents and errors in healthcare delivery.

Inadequate sleep has also been associated with cardiovascular disease, a study found that both short sleep, that is less than six hours per night or long sleep that is great than nine hours per night were associated with increases in incidences of myocardial infarction, of 20% and 34% respectfully. Inadequate sleep has a detrimental effect on the immune system. A study found that inadequate sleep was associated with an impaired antibody response to influenzas vaccination, it showed that adequate sleep is needed for optimal resistance to infections. Several studies suggest a link between inadequate sleep is also associated with increased mortality, the lowest risk of mortality was in those who slept for 7 hours per night. Inadequate sleep has been associated with several other adverse effects including reduced quality of life, an increase in anxiety, obesity and metabolic disorders such as diabetes mellitus.

However, the causality of inadequate sleep in promoting obesity and metabolic disorders has not been established. To optimise good sleep, the following should be followed, regular wake/sleep habits, regular daytime exercise, regular bedtime routine, avoid electronic equipment in the bedroom e.g. TV., avoid bright light from iPads, mobile phones etc. for one hour before sleep, avoid caffeine and alcohol at night, for haemophilia patients take analgesic medication for pain relief if required. Cognitive behaviour therapy is a highly effective strategy for managing insomnia and has benefits that outlast any benefits of hypnotic drugs, however intermittent use of hypnotic drugs may be required such as during a crisis.

Nina

Digital Technologies & personalised care to manage joint health

Speakers: Angela Forsyth, Director, REBUILD Program, Diplomat Specialty Infusion Group; Len Valentino, Chief Executive Officer, National Hemophilia Foundation; Deon York, Board Member, World Federation of Hemophilia & Alfonso Iorio, Professor, McMaster University.

Dr. Len Valentino spoke about cellular effects of bleeding in joints. Bleeds can contribute to joint arthropathy. Looking at the ankle joint, focusing on the true ankle joint, subtalar haemorrhage significant swelling. When you get reoccurring bleeding into a joint there is a progressive arthropathy destruction of the joint and of the synovial membrane and synovial cell filtration. Joint bleeding results in cartilage degradation accompanied in decrease of 25% of bone markers as well. Implications show a progressive increase in arthropathy with the most severe occurring in the last few decades of life. Ankles seem to be the first joints that develop arthropathy after a median time of 10 years. The burden of joint bleeding on patients, a significant difference in physical component summary score was observed for more than two target joints compared to those who had none. Decreased range of motion there is progressive burden of disease.

Angela Forsyth spoke about joint rehabilitation and joint function. Importance of individual monitoring for the preservation of joint health in haemophilia. Sometimes despite advances on technology we still need to focus back on basics. In the findings of some studies it indicates more of a willingness to self-monitor they find their disease more controllable, as is haemophilia if the proper care is available. Numerous apps are available for downloading that self-monitor focusing on logging details about bleeds, treatment, rehabilitation. Recognising subtle changes in joint health. Increased skill level in patients in the age of telemedicine, with possibly less face time. Even with medical advances and new therapies, there is still the potential for joint bleeds, although less frequently. We need a different range of motion to perform everyday tasks. We must discuss and develop self-monitoring strategies for joint health in haemophilia.

Dion York spoke from a patients perspective and said every bleed matters. Dion who is from New Zealand said that for the most part he has had good access to therapy and counts himself lucky, barriers do exist but many of them have been removed thanks to treatment and family. He was diagnosed at 15 months after a cut on his tongue. He has sampled lots of treatments including prophylaxis from 18 years of age. Sometimes there is a disconnect with what you know and what you practice. Sometimes we find stupid reasons not to treat quickly and if on prophylaxis it can be rare to experience a bleed. From an early age he can remember the pain of a bleed. Severity of a bleeding disorder doesn't matter, a bleed is a bleed. On digital technologies, reporting treatment is important and the team is alerted asap and what that bleed means for your health, it may mean you need physiotherapy. Paper records have now moved on to electronic records via apps, very well thought out apps with patients in mind which is great. Best apps out there are those that included the involvement of patients. Ensuring

adequate training on clinician and patients' side is important. The time it takes now to record treatment is minutes compared to years ago. Supports prompt treatment, experience of bleeding may impact your decision to treat quickly. We all know the longer you leave it the worse the bleed will get. Digital technologies can help you get on top of your help, it is realistic and helps manage the condition.

Professor Alfonso Iorio spoke about how to achieve zero bleeds:

- Effective treatment
- Access to treatment
- Measuring outcomes
- Individualised treatment
- Understanding needs
- Measuring adherence

He also feels technology is important in achieving zero bleeds. Digital technology allows us to obtain data and therefore determine individual needs of people with haemophilia and assists with maximising adherence which is very important. Telemedicine these days because of COVID-19 means doctors are not seeing our patients anymore. Can we do everything remotely? We can't do everything but we can do a lot by telemedicine. There is a lot that can be told by listening and talking to each other. Many now say clinicians have more time now with their patients. Digital tools are the backbone of modern society, have multiple applications for healthcare, including communication, data generation, gathering and overcomes the geographical barriers.

Debbie

WFH Educational – Community WFH Twinning Programme

Durinbg this session on WFH Twinning Programmes, the WFH announced the recipients of 'Twins of the Year' for 2018 and 2019 as follows:

2018 & 2019 HTC Twins of the Year

- The award for 2018 went to Ivory Coast & Belgium.
- The award for 2019 went to Indonesia & Netherlands.

2018 & 2019 HOT Twins of the Year

- The award for 2018 went to Kenya & Scotland .
- The award for 2019 went to Madagascar & Brittany.

Dr. Niamh O'Connell, Consultant Haematologist from the National Coagulation Centre (NCC) in Dublin spoke about being twinned with the treatment centre in Amman in Jordan. The team from the centre in Dublin visited Amman in 2018 & 2019. Dr. O'Connell feels that both countries are well matched. Already some goals have been achieved. Jordan have a very active patient organisation which makes it easy to work with. There is no language barrier which really helps with the communication. The team has received fantastic support from WFH and from the I.H.S. In 2018 they met with patients, clinicians, and were able to evaluate the comprehensive care that they are providing in Jordan. They visited a number of treatment centres in Amman. The team from the NCC also visited Amman in 2019, were honoured to participate in patient reviews, worked with multidisciplinary teams, visited labs, did onsite training and took part in a symposium. In November 2019 the team from Amman visited the NCC. Currently the NCC are doing training with Jordan using virtual technology, which takes place once a month.

Debbie

ASH ISTH NHF WFH guidelines on the diagnosis and management of VWD

Speakers: Nathan Connell, Chief of Hematology, Brigham and Women's Faulkner Hospital, and Mark Skinner, President, Institute for Policy Advancement Ltd.

This session focused on the guidelines for the diagnosis and management of von Willebrand Disease (vWD), which are due for publication later this year.

There is a limited awareness of vWD, even within the healthcare community, leading to further challenges for patients and healthcare providers (HCPs) including delays in diagnosis and uncertainty about optimal management. In an effort to address these issues, guidelines on the Diagnosis and Management of von Willebrand Disease were developed through a collaboration between the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the World Federation of Hemophilia (WFH), and the National Hemophilia Foundation (NHF). These guidelines followed a systematic process, led by the University of Kansas Medical Center, intended to meet recommendations of the Institute of Medicine. Recommendations were formed by guideline panels that included experts in vWD from multiple disciplines, methodologists, and patient representatives.

The Institute of Medicine in 2011 redefined clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."

On May 5th, 2015, Dr Paula James, Professor in Queen's University, wrote a proposal to the Medical Advisory Board of WFH on behalf of the vWD and Rare Bleeding Disorders Committee for vWD guidelines. During these discussions, similar conversations were happening within ASH and ISTH. A report was also published in November 2014 from the National Haemophilia Foundation Strategic Summit on vWD that called for a 'well qualified and authoritative organization, or a consortium of such organizations, should develop a new or updated evidence based clinical practice guideline on vWD'. International clinical vWD guidelines were also identified as the number one need at the WFH International vWD Symposium in 2017. All the partner organizations graciously agreed to work together on one project and in 2017 the project was approved. In the summer of 2018, a global scoping survey was carried out to identify the priorities for the guidelines, and in August 2018 the first, in person meetings, were held with the panels. Between August 2018 and January 2020 an enormous amount of work was performed to do the systematic reviews and to put together the evidence on which the recommendations were based on. From April 2020 – May 2020, public comments were received. These guidelines are on track to be published by December 2020.

Nathan Connell, Clinical Chief of Hematology, Brigham and Women's Faulkner Hospital, Boston and an Assistant Professor of Medicine, Harvard Medical School, gave a preview of the guideline recommendations. He stated, "these guidelines are a collaboration effort that is global in its scope". All the organizations that were involved in coming together have a commitment to improving the quality of life in patients with vWD. Sharing expertise and resources ensures quality, credibility, and wide dissemination and implementation of the guidelines. Patient input was critical to the project and was obtained through membership panels to ask them what was going to be important to them and the rest of the bleeding disorders community. The objective of the guidelines is to facilitate clinical decision making regarding the diagnosis and management of vWD to contribute to better health outcomes, increase access to appropriate diagnostic testing and therapeutic options, increase quality of life and health equity, identify research priorities and guide health care providers, patients, payers and other stakeholders to focus their areas in vWD and advocate for vWD.

There were two panels, one for diagnosis and one for management, that included clinicians, researchers and patients. It was geographically diverse representing 10 countries and 4 continents. Academic and community haematologists, methodology experts, content experts from other relevant fields such as gynaecologists and paediatricians were involved in the project. The patient representatives were diverse with respect to gender, type of vWD, disease severity and disease experience. Throughout the project there was a strict conflict of interest disclosure and management to ensure these guidelines are as robust as possible. When the guidelines are published later this year, it will include what is considered a strong and a conditional recommendation. This is different depending on if you are a patient or a clinician. For patients most would want the intervention if it is a strong recommendation. And for clinicians they should be thinking that most of their patients should receive the intervention. A conditional recommendation shows many patients would want the intervention, but many would not. And this is where it goes to the clinicians for a joint decision as different choices will be appropriate for different patients depending on their preferences and values. The guidelines right now are still draft guidelines that are going through clarification based on public comments.

The first preview Nathan Connell gave was to do with diagnosis. The question was 'in patients with an abnormal vWD screen, which included the antigen activity and Factor VIII and are suspected of type 1 vWD, should the diagnosis cut-off be at level less than 30% or below the reference range of the lab?'. The panel recommended a von Willebrand Factor (vWF) level of less than 30% regardless of bleeding and a vWF level of less than 50% in patients with abnormal bleeding, should confirm the diagnosis of type 1 vWD. The panel had additional statements to make in relation to this recommendation. When we talk about vWF levels it could be about either the amount of vWF protein in the blood or the activity i.e. how well it functions. Patients with levels between 30 and 50% and no abnormal bleeding should be diagnosed with low vWF. A concomitant (second) bleeding disorder should be considered in patients with vWF levels between 30-50%. And if the level is not 50% in the lab then the local lab lower levels should be used. The themes that emerged from surveys of panel members and discussions included:

- The panel placed priority on not missing cases and ensuring appropriate access to care.
- Many of the treatments for vWD will benefit patients with bleeding regardless of the underlying cause.
- While patients are interested in the results of the assay, they prefer clear diagnostic thresholds to provide a definitive diagnosis.
- The vWF antigen and activity are continuous variables with a continuous increase in bleeding risk with lower levels.

The second preview Nathan Connell gave was in relation to prophylaxis. The question was 'in patients with vWD with a history of severe and frequent bleeds, should we use routine prophylaxis with vWF concentrate or no routine prophylaxis i.e. treatment on demand?'. The panel recommended that in patients with vWD with a history of severe and frequent bleeds, long term prophylaxis rather than no prophylaxis should be used. The evidence to reach this decision showed that routine vWF concentrate prophylaxis reduced the risk of bleeding, prolonged the time to experience a bleeding event, reduced epistaxis, and reduced the risk of bleeding episodes, hospitalization, and heavy menstrual bleeding. The key considerations included:

- The value of prophylaxis depends on the frequency and severity of the bleeds
- Shared decision making to review risks and benefits is important
- There will be likely variability in values and preferences amongst individual patients
- The availability of educational material for clinicians and patients to highlight both the potential benefits and harms of long-term prophylaxis is important.

Dr Connell stated that long term prophylaxis is likely to be acceptable and feasible to implement, and this recommendation is likely to increase equity. The research priorities that came out of the evidence review were that there is a need for a large randomized controlled trial on the use of prophylaxis vs on-demand therapy, particularly in patients with mucosal bleeds. Studies are needed on the use of prophylaxis for heavy menstrual bleeding, gastrointestinal procedures and the impact on quality of life. We also need studies on plasma derived vs recombinant vWF concentrate for prophylaxis. Furthermore, we want to know how antifibrinolytics such as tranexamic acid may be helpful with prophylaxis for mucosal bleeding. And whether the role of concurrent anti-angiogenic therapies with prophylaxis will be beneficial for gastrointestinal bleeding. Concurrent anti-angiogenic are therapies designed to help stabilize blood vessels that are fragile.

In terms of the next steps, publication should be by the end of 2020. This will be the first hurdle and once the guidelines are published, raising awareness among clinicians, patients, advocates and caregivers about these guidelines is vital so they can decide what would be best to implement in terms of local practice. It is important to have education about these new guidelines and adoption of guidelines into clinical practice but recognize that different resource settings are going to need different types of implementation efforts and tools. For the guideline dissemination strategies, the collaborating organiza-

tions will explore the development of several clinical, educational and patient facing tools to support the implementation of the vWD guideline recommendations. There will be a process to determine the most appropriate tools and resources in conjunction with the guideline chairs and panellists. And the tools will need to be developed practically within the country that will be using the tool.

The recommendation on the threshold for type 1 vWD diagnosis and the recommendation for prophylaxis in the management of vWD are expected to have a considerable impact on the lives of people with vWD.

Mark Skinner President, Institute for Policy Advancement Ltd. gave us an insight into how they got patients involved throughout the guideline process. The way the process started was the NHF and the WFH, developed a robust list of potential patients that either had previously expressed interest or that they thought had a diversity of knowledge that they could bring to the panel. The patient representatives are from multiple parts of the world and are a mixture of male and female. Both patients and caregivers were included as well as individuals with vWD. There were some criteria that had to be met which as a result, excluded individuals from participation on the panel but they had other ways to participate which is why the public comment period was very important. Age, gender and geographic diversity certainly enriched the panel.

An international survey was carried out to highlight and understand the differences of what is important to patients as well as what is important to health care professionals so that they make sure the guidelines serve all of the constituaries. Patients were then included in ranking and drafting the guidelines. The guidelines are built on PICO questions. PICO process is a mnemonic used in evidence-based practice to frame and answer a clinical or health care related question. It helps to identify a patient group of interest, an intervention such as treatment or diagnostic tests, compare it to other tests or treatments and look to see what happens to patients as a result of those interventions. Targeted panel training and workshops were provided. And patient preferences were sought throughout.

Within any guideline process and timeframe public/community engagement is key. The geographically and socioeconomically diverse respondents suggest a broad based desire for increased attention to vWD guidelines. Involving a broader stakeholder community from an early stage in guideline development ensured that the different values and priorities were well represented in the development of recommendations. The collaborating organizations involved also used their social media platforms and their networks to generate response and enthusiasm. During the public comment in April and May, they received comments from 38 countries, and 15% of the comments about the guidelines were from patients. The global community engagement and participation in this process helps to improve the guidelines and contribute to the effectiveness of them and hopefully they will also contribute to the clarity of the final publication. We hope that the guidelines will positively influence patients personal care decisions and practices. Time will tell but with communities supporting collaboration and implementation of these guidelines, we will work together to hopefully achieve this.

Julia

Gene Therapy: The Unfolding Story

We are still learning about gene therapy. Each patient experience is different and gene therapy is not for everyone, either by choice or by exclusion because of antibodies. What can we expect if we ARE eligible – what is it like to participate in the GT trials? What is it like to be a patient once you have gone through the treatment? What if it does not work for me (one and done) – can I try other future therapies?

John Pasi, Professor of Haemostasis from UK spoke about managing expectations from a haematologist's perspective. This is going to become an exceptionally important issue in years to come. No doubt that gene therapy is the holy grail for haemophilia and we now see that after 25 years of promise its now a reality. We are in a time of great expectation and opportunity but we still must remember efficacy and safety. It's not always about the numbers, there are different layers and we need to know there are many hurdles along the path. Many patients want to know all about it and the major hurdle is eligibility. Seropositivity, comorbidity, inhibitor history, availability are the 4 main eligibility issues. Many patients are not going to be eligible and as a doctor it's very hard to tell patients as it's so disappointing for people if they are not eligible. The expectation that it's going to be marvellous is extremely high, as potentially this is a cure. However, this is not always the case. We must be cautious. Everything is focused on factor level in gene therapy. We must focus on a minimum realistic expectation in relation to factor levels. Managing uncertainty like the reliability of the gene therapy working, how sure are we that it will continue to work? Our knowledge is based on clinical trial data to date only. We must also remember that no bleeding doesn't mean joint disease is going to go away. Information for patients must be realistic and cover the range of uncertainty and we must remember that average is not the same for everyone.

David Page, Canadian Haemophilia Society is 66 years old, has severe haemophilia B, has arthropathy in 7 joints, is quite mobile, has pain which is increasing year by year, is pretty good at resting, is in good health, does gardening and weight lifting, is still working, has had one ankle infusion, one knee replacement, is on prophylaxis – extended half life - but despite that has breakthrough bleeding, over last 3 years had about 12 bleeds per year, veins are not good, participated in clinical trials previously, major motivation was selfish going onto a clinical trial, to cut down on bleeding and maintain joints, special interest was the only way to access gene therapy and the clinical trial was the only chance to have gene therapy. Adverse events are possible but feels are quite low.

Garrett Hayes, Youth Leadership Institute, USA has severe haemophilia A, is from Texas, 21 years old, active runner. His perspectives are that he is waiting on the next generation of gene therapy, prophylaxis has been the standard treatment, is fortunate to have this, is a little unwilling to jump into gene therapy, his approach is result based, successful with current treatment on 13 years no really pressing reason to take a risk to change this. Although we do need people to take that jump, he is unwilling at the moment. Uncertainty with gene therapy around long term impact. Pretty sceptical person generally.

Rob Schroeder, from USA is aged 52, in September 2018 was treated on gene research therapy trial. His reason to sign up was that he felt to be free of bleeds was very inviting. He has had infused ankles, other than that very active, very well controlled with longer acting prophylaxis therapy. Retiring over next 12 years at some point, has good insurance. Couldn't have been more pleased with the results. His biggest side effects was boredom, haven't had a bleed since 2018, not even sure what factor level is at the moment. Zero complaints.

Enrique David Preza Hernandez from the Mexican Haemophilia Society has haemophilia A with inhibitors, his first treatment was when he was 5 years old, on demand therapy, at 13 he got inhibitors and at 18 he had intercranial bleed. He used 'RICE 'a lot, at 24 he received one dose of bypassing agent which made things better but wasn't enough, then No-Voseven but still had serious bleeding, thyroid was removed due to cancer. Even though it has been hard he still has achieved a lot of things. He started on Emicuzimab, and feels it was a life changer. Life is good at the moment. Can he have a better life with gene therapy? He is unsure.

Debbie

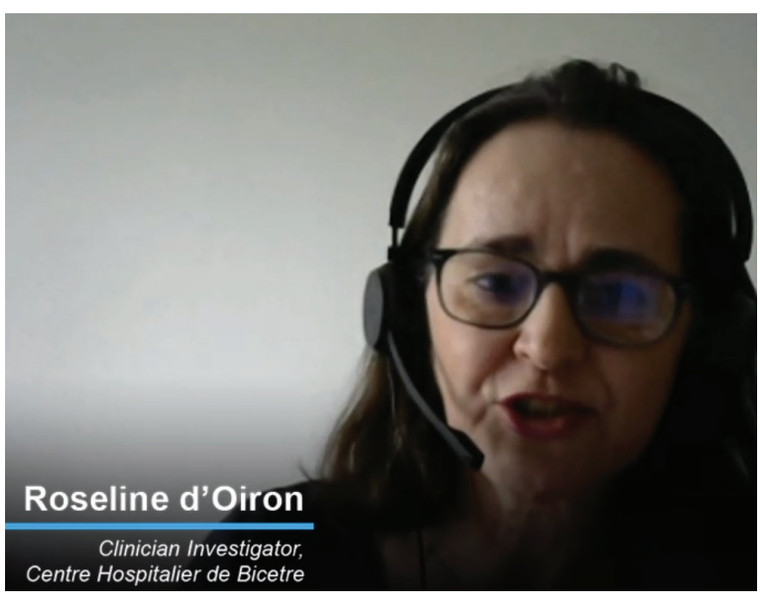
Women & Girls with Haemophilia

The aim of this session was to address issues of women and girls with hemophilia (WGWH) integrating here female carriers with low levels of Factor VIII (FVIII) or Factor IX (FIX)and/or bleeding experiences.

Women & Girls with Haemophilia – Importance of early diagnosis

Speaker: Roseline d'Oiron, Clinician Investigator, Haemophilia Centre, Bictre Hospital, France.

Men with haemophilia are not the only ones with bleeding issues, women bleed too. When it come to women & girls with haemophilia (WGWH) there are two diagnostic tests required, the first test is to establish the women/girls own factor levels and the second test is to determine her carrier status. About one third of carriers of Factor VIII (haemophilia A) and Factor IX (haemophilia B) deficiency have below 40% factor levels themselves. And we know that about one third have abnormal bleeding experiences however of these we know that some carriers with low factor levels do not bleed and reversely some of them do bleed despite the factor that they have is normal levels. Heavy menstrual bleeding and post-partum haemorrhaging (PPT) are the most common type of bleeds. It is said that haemophilia in females is extremely rare, this is true for those with moderate or severe forms of the deficiency, however mild deficiencies are not rare at all in carriers. Studies of over 700 families showed that for everyone male with haemophilia there are five potential carriers in the family, of this about 1.5 will be actual carriers.



Although it is known that a third of women/girls have haemophilia, a study of several national database registries showed that in all the registries less than a third of patient registered were female, although in the last year these numbers are increasing. The diagnosis of females with severe or moderate haemophilia is delayed compared to males, a study of 22 females to 22 males showed that females with severe haemophilia were diagnosed 6.5 months later than the males and females with moderate haemophilia were diagnosed 39 months later than the males. A study of 442 females and 442 males with mild haemophilia, showed that the females were diagnosed just over 6 years later than the males, the average age males were diagnosed was 10 years old compared to nearly 17 years old in females. Diagnosis for females at this age is well past the age of menarche, when girls first begin their periods, which meant that menarche could not be anticipated for those who were diagnosed so late. One explanation for this late diagnosis could be the confusion between the two separated diagnostic tests required for females with a history of haemophilia in their family, the factor level test and the genetic test. While factor level tests can be done at a young age, the age for genetic testing is done at an older age and this varies depending on the country. A lot of the women will present for genetic testing only when they are planning a pregnancy or are already pregnant, which is not the ideal situation.

Epidemiology & Variability in Phenotype

Speaker: Dr Sarah O'Brien, Paediatric Haematologist-Oncologist, Nationwide Children's Hospital, USA

Case Study #1: a 12-year-old girl was referred for heavy menstrual bleeding which lasted 7 days, she had also experienced easy bruising however did not bleed excessively after a tonsillectomy. The girls mother also had a history of heavy menstrual bleeding and had suffered post-partum haemorrhages. The maternal grandfather has mild haemophilia but is not followed up in a haemophilia treatment centre. It never occurred to the young girl's mother that her family history of haemophilia could be related to her and her daughters bleeding issues. Lab tests showed the young girls Factor VIII levels were 53%.

Case Study #2: a 14-year-old girl was referred for heavy menstrual bleeding which started when she was 11 years old. She

has an intrauterine device fitted but was still experiencing heavy break through bleeds, which required oral contraceptives to manage. There was no family history of any other bleeding disorders. Her Factor VIII level was 44% but her von Willebrand levels were in the normal range, after weening her off her oral contraceptive for several months, her levels were tested again and this time her Factor VIII level was 25%. She has undergone genetic testing and has a likely pathogenic mutation and other family members are currently undergoing testing.

A study in several countries of 168 haemophilia carriers was carried out and it found that the average ISTH-BAT (bleeding assessment) score in these women was 5.7 compared to 5 or below for women without a bleeding disorder. The most commonly reported symptoms were heavy menstrual bleeding, oral cavity bleeding, post-partum haemorrhage and excessive bleeding after tooth extraction. It showed that women who were carriers had a higher prevalence of bleeding symptoms. Another study was carried out on 145 carriers, these carriers were not attending the hospital for care for themselves, they just happened to be accompanying a male relative to his visit. While their bleeding score was not as high as the first study, their bleeding was still significantly different than matched controls.

Females with severe Factor VIII or Factor IX deficiency experience hemarthrosis (joint bleeds) with a similar frequency as compared to affected males of the same severity. More recent evidence has highlighted that joint bleeding also affects a much broader portion of the carrier community, with reported frequencies varying from 4 – 19%, carriers may also experience sub-clinical joint bleeding.

A major challenge in the care of WGWH is the wide variability in both baseline factor levels and the bleeding phenotype. A response of haemophilia A carriers to desmopressin (DDVAP) may provide an insight into why factor level is not predictive of bleeding. A study of 25 obligate carriers showed while their vWF increased throughout the 2-hour period post-DDVAP, their Factor VIII peaked and then decreased. In a recent study comparing carriers and healthy controls, carriers had a reduced response to DDAVP. Women with abnormal ISTH-BAT scores had a significantly lower Factor VIII response compared to those with normal bleeding scores. These DDAVP studies suggest an insufficient Factor VIII response to haemostatic stress is the cause of the bleeding. The bleeding phenotype in WGWH is highly variable and cannot be clearly predicted by factor level or genotype.

Management of Delivery

Speaker: Dr Andra James, Obstetrician/Gynaecologist, Duke University Medical Center, USA

During pregnancy in all women Factor VIII levels increase, while Factor IX levels do not increase significantly. What does this mean for haemophilia A & haemophilia B carriers? Haemophilia B carriers Factor IX levels do not increase by much and haemophilia A carriers while their Factor VIII levels do increase, they will not reach the levels achieved in other women. Therefore, haemophilia carriers are likely at a higher risk of bleeding at delivery than other women. The bleeding risks at delivery include obstetrical or uterine bleeding, this is the abnormal bleeding from the tiny vessels within the postpartum uterus, caused by the failure of the uterus to contract, this accounts for 80% of post-partum haemorrhaging (PPH). Surgical bleeding due to incisions, lacerations, ruptured vessels including bleeding from birth trauma or incisions from caesarean delivery accounts for 15-20% of PPH. And systemic bleeding due to inadequate haemostasis which could be due to platelet dysfunction, low levels of clotting factor, metabolic dysfunction, hyperfibrinolysis and certain medications. 3% of all women experience immediate PPH in the first 24 hours after deliver and 1% experience delayed PPH after 24 hours.

There is not a great deal of data in haemophilia carriers, but what data there is suggests a much higher rate of PPH in women with haemophilia, with rates ranging from 10-30% which is significantly higher than the 3% rate for immediate PPH and 1% delayed PPH. Male infants with haemophilia are at risk of bleeding at the time of delivery and in the USA 35% of these born with haemophilia will have their first bleed within 30 days of birth, half of these were due to circumcision, almost a quarter were due to head bleeds of which half were intracranial bleeds. It appears the risk of intracranial bleeds depends on the method of delivery, data taken from 882 vaginal deliveries and 283 caesarean deliveries show that in affected male

infants, 3.1% vaginal births and 0.4% caesarean births resulted in intracranial bleeds. This is a 9-fold risk increase for vaginal deliveries. Is there a significant difference in the general population of the method of delivery and intracranial bleeds?

Data from USA shows they found the risk of intracranial bleeds from unsuccessful spontaneous vaginal deliveries, those requiring forceps, vacuum or caesarean increased the risk of intracranial bleeds by 2-fold or 4 and caesarean delivery appears to be potentially protected with a relate risk of 0.7%. To prepare during pregnancy or even prior to conception for a delivery, we can identify the foetus who is potentially at risk. Women need to be informed of the potential risks and the diagnostic options. Genotyping can benefit possible and obligate carriers; it confirms the diagnosis in possible carriers but also provides beneficial information for obligate carriers which can be used in preimplantation genetic testing of embryos and prenatal diagnosis of a potentially affected male foetus. As females are unlikely to have severe haemophilia, determining the sex of the foetus prior to delivery is important, testing can be done by DNA testing in the first trimester or by ultrasound in the second trimester. A multidisciplinary team is needed to prepare for the delivery to prevent and manage any bleeding during and post-delivery. In the delivery of a foetus with known or possible haemophilia, a caesarean can be performed prior to delivery to reduce the risk of intracranial bleeding and if the patient does not wish to have a caesarean invasive procedures during a vaginal delivery should be avoided.

Nina

von Willebrand Disease (vWD)

Diagnosis: Mike Laffan, Professor of Haemostasis and Thrombosis in the Department of Haematology at Imperial College, London, UK, and Director of the Hammersmith Hospital Haemophilia Centre, London, UK

Diagnosis of vWD begins with the clinical assessment for the bleeding phenotype, and then made by laboratory investigation to investigate for the presence of haemostatic defects.

von Willebrand Disease is 'A bleeding disorder resulting from deficiency of von Willebrand factor activity.' von Willebrand factor (VWF) is a blood glycoprotein involved in haemostasis. vWF's primary function is binding to other proteins, in particular Factor VIII, and it is important in platelet adhesion to wound sites i.e. primary haemostasis. vWF monomers are assembled into giant multimeric forms so each of these multimers have multiple binding sites for platelets and collagen. These are very important aspects of vWF for its function, to create the greatest adhesive capacity and haemostatic activity, stated Professor Laffan. These large multimers circulate in the blood and some of them will carry Factor VIII while Factor VIII is inactive in circulation; Factor VIII degrades rapidly when not bound to vWF. When vWF is exposed in endothelium during an injury to blood vessel, it binds to collagen. When coagulation is stimulated, the platelet receptors get activated. vWF binds to these activated receptors. vWF binds to platelet Glycoprotein Ib (gpIb) receptor; this binding occurs under all circumstances but is most efficient under high shear stress i.e. rapid blood flow in narrow blood vessels.

In patients with vWD, the most common sites of haemorrhage include mucous membranes, usually nosebleeds, bruising on the skin, and menorrhagia and postpartum haemorrhage in women. Bleeding during or after surgical procedures is possible,

and muscle and joint bleeding occur in more severe type of vWD. Some patients require prophylaxis to prevent recurrent bleeding, particularly in the setting of joint damage. Although menorrhagia is common in women, those with vWD are more likely to have menorrhagia with blood clots greater than 1 inch in diameter, bleeding that requires a pad or tampon change more than hourly, and low serum ferritin levels.

vWD can be difficult to diagnose. Laboratory diagnosis requires a series of assays of vWF quantity and function, and Factor VIII activity, with no single straightforward diagnostic test available to either confirm or exclude the diagnosis. A vWF antigen test is carried out to determine the level of vWF in your blood by measuring a particular protein. It only assesses vWF presence and does not assess vWF function. You may have a lot of protein but not a lot of activity. vWF activity: these tests measure how well the von Willebrand factor works in your clotting process, and Factor VIII level: this shows whether you have abnormally low levels and activity of Factor VIII. Having measured the activity, the problem of deciding on the level of vWD deficiency arises.

vWF is the most variable of proteins in the blood. Professor Laffan showed a population-based study that vWF varies over a six-fold range in normal individuals. There are three groups of people. The first have normal levels where the vWF: RiCo (von Willebrand factor activity – ristocetin cofactor) activity is above 50% and these people should not have a bleeding disorder related to vWD. People who have levels below 30% who we can reliably predict will have a problem from their vWF deficiency will have vWD. The people in the middle whose levels are between 30-50% have low vWF. Many people with vWF in this range do not have a bleeding problem therefore we cannot simply label them as having vWD on the basis of their slightly low levels below the normal range. Because vWF levels are known to vary significantly over time, effectively masking the disease, recent guidelines have recommended repeat testing to ensure consistency in levels prior to assignation of a diagnosis. Stress, such as in an anxious adult, very recent exercise, acute or chronic illness, pregnancy, and the use of oral contraceptives may falsely elevate vWF and Factor VIII levels.

Next, Professor Laffan showed us a graph of treatment of vWD with rvWF concentrate. The graph explains how administrating a pure vWF concentrate to a patient with no vWF at all, is relatively easy to get the vWF protein and vWF activity up to 100%. rvWF is administered without recombinant Factor VIII (rFVIII) if baseline Factor VIII is sufficient to ensure haemostasis (≥40-100 IU/dL). vWF concentrates are reliable and useful, they replace vWF in the blood, but their quality needs to be thought about. If concentrate contains Factor VIII people should be aware of excessively high levels. Most people with vWD have minor bleeding problems and only require on-demand occasional treatment for bleeding episodes or surgery. But some patients do have repeated bleeding episodes making it worthwhile to administer prophylactic injection of Factor VIII and vWF.

Treatment of Women: Dr Jameela Sathar, Senior Consultant – Haemotology, Ampang Hospital. Dr Sathar provided an overview of the special considerations in treating women with vWD. Interdisciplinary management of childbirth and prophylaxis in the postpartum period are needed to reduce the risk of postpartum haemorrhage.

Dr Jameela Sathar, stated the physiological changes in women are ovulation, menstruation and childbirth. These can lead to serious complications for women with vWD. During ovulation, the rupture of the ovum (egg) being released can lead to bleeding. A structure called a corpus luteum is formed after ovulation, which secretes progesterone to prepare the endometrium for implantation of the ovum that has been released. But if the implantation does not occur, the corpus luteum shrinks and menstruation happens. Menstruation usually lasts for 5-7 days but for women with vWD, menstruation could last weeks. Heavy menstrual bleeding (menorrhagia) is reported as the main symptom in 90% of women with vWD. It is excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or quality of life.

Women may have to undergo unnecessary surgical interventions such as emergency laparotomy for ovulation bleeding or early hysterectomy for unexplained heavy menstrual bleeding. Hence clinicians should expect women have a bleeding disorder or vWD, if she presents with heavy menstrual bleeding since menarche, she requires blood transfusion, she has recurrent pelvic pain as well as prolonged mucosal bleeds and there is a family history of bleeding in vWD. Heavy menstrual bleeding can lead to anaemia with symptoms of fatigue, paleness, lack of energy and shortness of breath. Some women and girls with vWD also experience dysmenorrhoea, abdominal pain and ovulation bleeding, haemorrhagic cysts and endometriosis. Endometriosis is a painful condition in which endometrial tissue, the tissue that lines the uterus, forms in the abdomen or other parts of the body. This results in chronic pain, dysmenorrhea, dyspareunia, and subfertility. This has a major impact on a woman's life including her work, social functioning and sexual relationships.

For women with vWD to attain a healthier quality of life, a holistic or comprehensive care approach to her health care is essential. Women should be treated at a Haemophilia centre with a multidisciplinary team and counselling should be provided. With diagnosis and appropriate treatment, these problems can be dramatically reduced and sometimes even eliminated.

Women who have menorrhagia or abnormal vaginal bleeding need a full gynaecological consultation before treatment to understand any gynaecological issues. Treatments for heavy menstrual bleeding include tranexamic acid, antifibrinolytic drugs which can reduce bleeding by slowing the breakdown of blood clots, oral contraceptives which also aid ovulation bleeding, an intrauterine device (IUD), releasing the hormone progesterone which reduces bleeding, desmopressin (DDAVP), and Factor VIII, clotting factor concentrates.

For pregnancy planning, ideally, this should begin before conception. Women contemplating a pregnancy should be aware that they may be at an increased risk of bleeding complications during pregnancy and are definitely at an increased risk of postpartum haemorrhage (PPH); in the nonpregnant state, uterine blood flow is approximately 100 mL/min. At term, uterine blood flow reaches 700 mL/min, therefore posing a risk of postpartum haemorrhage in all women but especially in women with vWD. PPH may occur up to six weeks post-delivery. Women with bleeding disorders, especially those with severe disorders, are at risk of primary and secondary PPH. Primary PPH is blood loss of more than 500ml in the first 24 hours after delivery. Secondary PPH is excessive bleeding occurring between 24 hours and six weeks post-delivery. Management of PPH in women with bleeding disorders requires close collaboration between haematologist, obstetricians and anaesthetists.

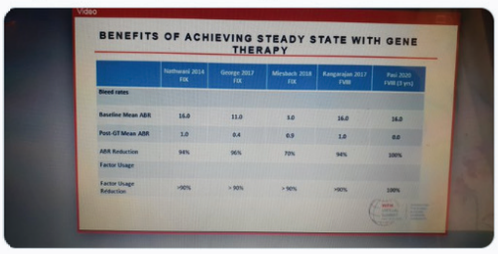
Treatment options should be planned during pregnancy. Invasive management of delivery with ventouse or rotational forceps should be avoided because of the risk of bleeding for the potentially affected neonate. Prior to conception or during pregnancy, women should also be offered the opportunity to speak with a genetic counsellor regarding the inheritance of vWD and with a paediatric haematologist regarding the evaluation of the infant after delivery. In terms of management of childbirth, women with type 1 vWD with levels equal to or greater than 50% and no history of severe bleeding do not require special treatment at the time of delivery. Women with type 3 vWD, type 2 vWD or type 1 vWD with levels less than 50% or a history of severe bleeding should be referred for prenatal care and delivery to a centre where, in addition to specialists in high-risk obstetrics, there is a Haemophilia Treatment Centre and/or a haematologist with expertise in haemostasis. Blood loss must be managed with IV iron therapy and avoiding unnecessary transfusions if possible. During labour, delivery and the postpartum stage prophylactic replacement therapy can maintain factor levels above 50%. This must be maintained for a minimum of 3 days after vaginal delivery and 5 days after a C-Section.

This abnormal bleeding can have implications for daily living and are associated with a reduced quality of life in vWD patients. A qualitative study showed several psychosocial issues in women with vWD. Among them are irritation and inconvenience, pain associated with bleeding, feeling self-conscious about odour, experiencing social embarrassment from staining through clothes and furniture, avoiding activities i.e., work and social related, unable to afford sanitary pads, therefore leading to infections from the unhygienic conditions of using towels or newspaper as an alternative and only 4 out of 10 women will consult their doctor; this can be due to social taboos. Reaching out to these women is vital. This can be achieved through organizing women's group, providing education with workshops and combining the gynaecology and obstetric clinics with haemostasis clinics, i.e. joint clinics.

Conclusion: Women with vWD need to be identified early to manage their ovulation, menstruation and pregnancy/childbirth appropriately. Women with type 1, 2 and 3 vWD with levels of <50% or a history of haemorrhage should deliver in a specialized centre. IV iron therapy is important to correct iron deficiency/anaemia. Psychosocial support should also be provided.

Julia

Brian O Mahony @Brianhemophilia · Jun 15
Nice slide from Johnny Malungu @wfhemophilia Summit on benefits of s:eady state factor level post Gene Therapy



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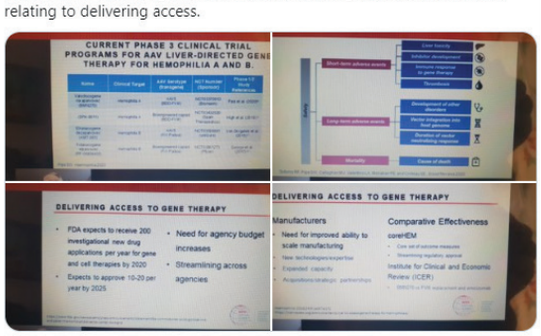
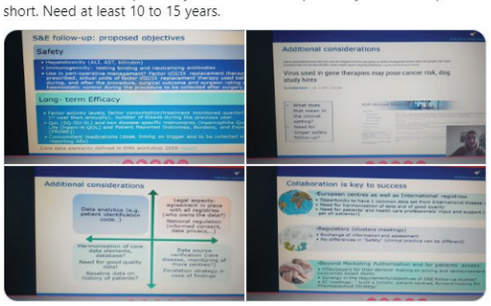
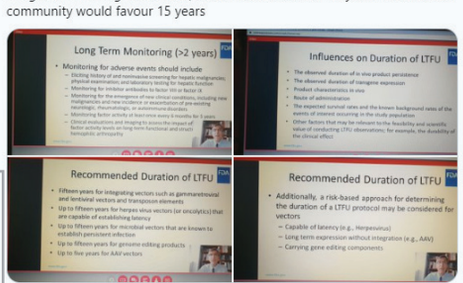
Brian O Mahony @Brianhemophilia · Jun 15
Steve Pipe on Gene Therapy @wfhemophilia outlines current Phase 3 trials, possible short and long term adverse events and gives his view on issues relating to delivering access.



Brian O Mahony @Brianhemophilia · Jun 16
Voltz from EMA @wfhemophilia Summit. States they may look for 10 years follow up post Gene Therapy. I believe patients will be happy with this. At least annual follow up already routine in haemophilia. 5 year follow up too short. Need at least 10 to 15 years.



Brian O Mahony @Brianhemophilia · Jun 16
Marks from FDA @wfhemophilia Summit on Gene Therapy follow up. Proposed follow up for AAV vectors is 5 years but given possibility of integration with high dose AAV, could make a case for 15 years. I believe our community would favour 15 years

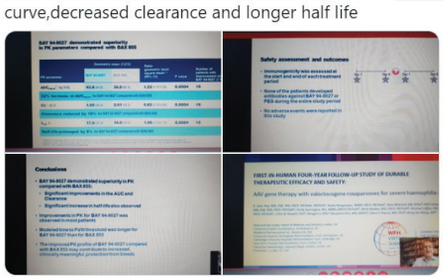


Brian O Mahony @Brianhemophilia · Jun 16
Delighted to see Carol Kasper recieve the @wfhemophilia Lifetime achievement award. I had the great pleasure of working with Carol for the 6 years she was VP Medical. Dedicated, knowledgable, enthusiastic, humble. Loved encouraging younger Doctors. An inspiration @WinetCarol

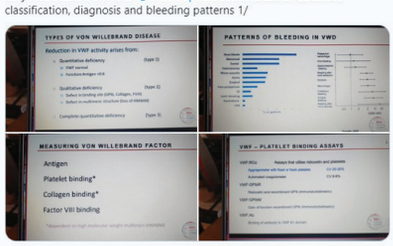
> **Mark Skinner** @MSkinnerDC · Jun 16
> Carol Kasper receives the 2020 WFH International Lifetime Achievement Award – Hemophilia World News news.wfh.org/carol-kasper-r... Carol's dedication, compassion, leadership and scientific contributions over a lifetime of service have impacted all of our lives. THANK YOU Carol!

Brian O Mahony
@Brianhemophilia

Mancuso @wfhemophilia Summit states that crossover study showed that EHL FVIII Jivi had a better PK profile than Adynovi with greater area under the curve,decreased clearance and longer half life

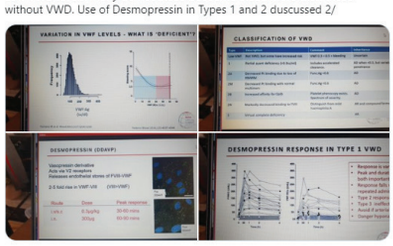


Brian O Mahony @Brianhemophilia · Jun 17
Very nice session on VWD @wfhemophilia Summit. Laffan discusses classification, diagnosis and bleeding patterns 1/



2 4 16

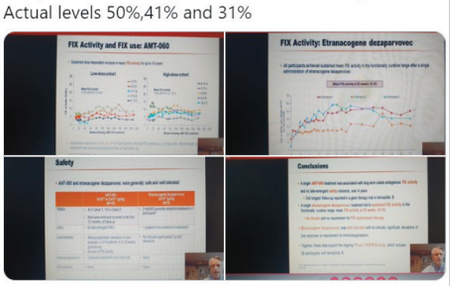
Brian O Mahony @Brianhemophilia · Jun 17
Laffan also discusses what deficiency is. Normal level at least 50%, bleeding common if less than 30%. Grey area is between 30% and 50%. Classified as Low VWD levels. Many do not bleed but some bleed more than those without VWD. Use of Desmopressin in Types 1 and 2 duscussed 2/



1 2 4

Brian O Mahony
@Brianhemophilia

Pipe @wfhemophilia Summit speaks about Uniqure AMT-060 and Phase 2B AMT-061 FIX Gene Therapy. 060 showing stable expression at 5% and 7.5% after 4 years in 2 doses. 061(Padua) in 3 PWH in dose finding study shows mean expression of 41% after 1 year. Actual levels 50%,41% and 31%

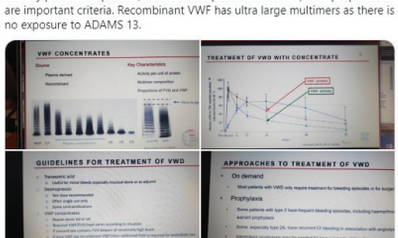


Brian O Mahony
@Brianhemophilia

Session on Quality of life shows @HCDEconomics slide on impact on EQ-5D-5L of different numbers if target joints. Can not imagine having 9 target joints. (I have 4. According to graph my QOL utility value should be 0.65. I put it at about 0.85.)@wfhemophilia

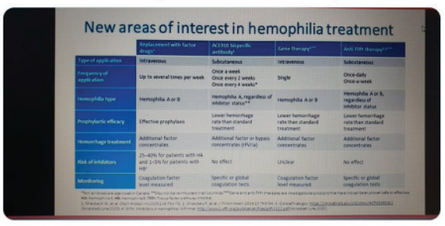
4:12 PM · Jun 17, 2020 · Twitter for Android

Brian O Mahony @Brianhemophilia · Jun 17
Laffan also discusses plasma derived and recombinant VWF concentrates. Activity per unit of protein,multimer composition and FVIII/VWF proportions are important criteria. Recombinant VWF has ultra large multimers as there is no exposure to ADAMS 13.



Brian O Mahony
@Brianhemophilia

Very nice summary slide from Miesbach @wfhemophilia Summit summarising the new treatment optiins



Brian O Mahony @Brianhemophilia · Jun 18
Delighted ti see Steve getting this award. A great Lab Scientist and a great teacher

> **WFH** @wfhemophilia · Jun 18
> The WFH presents this year's International Healthcare Volunteer Award to Dr. Steve Kitchen, for his dedication in sharing knowledge on #laboratory science with healthcare professionals globally. On behalf of the #bleedingdisorders community, Thank you! wfh.org/en/about/awards

1 2 16

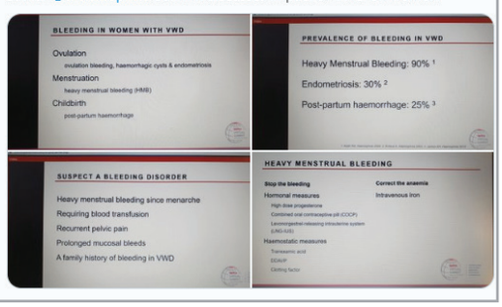
Brian O Mahony @Brianhemophilia · Jun 19
Delighted FereyDoun Ala from Iran and Yuri Zhuylov from Russia recieve the Presidents Award @wfhemophilia Both remarkable men who have made major contribution to their haemophilia communities over many years. I have had the pleasure of working with both men in their countries 1/

1 1 7

Brian O Mahony @Brianhemophilia · Jun 19
Yuri worked for years to increase access to treatment in Russia suceeding in having factor added to Federal budget. Photo is from Moscow visit in 1994- my first visit abroad as WFH President. Federyoun has worked tirelessly and kept Iran at forefront of our thoughts always.

7

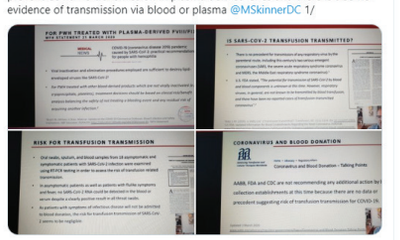
Brian O Mahony @Brianhemophilia · Jun 17
Sathar @wfhemophilia Summit discusses impact of VWD on women.



@HAEMOPHILIAIRL

@BRIANHEMOPHILIA

Brian O Mahony @Brianhemophilia · Jun 19
Skinner @wfhemophilia Summit points out that current viral inactivation will prevent Covid-19 transmission in plasma derived CFCs and there is also no evidence of transmission via blood or plasma @MSkinnerDC 1/



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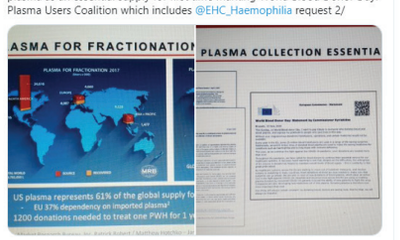
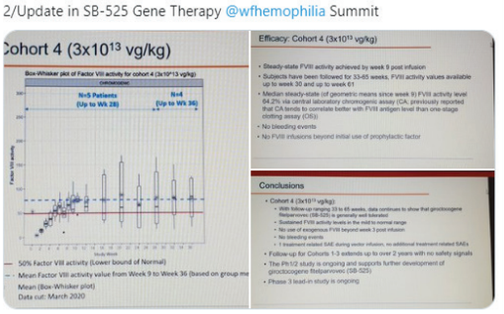
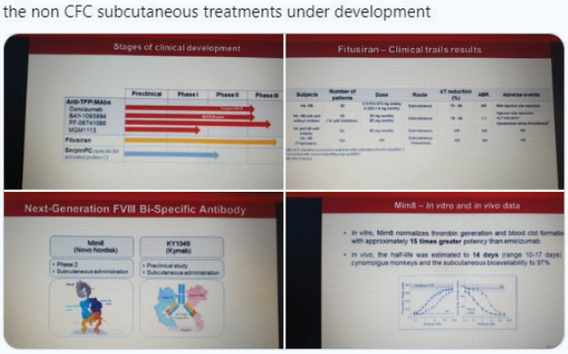
Brian O Mahony @Brianhemophilia · Jun 19
Skinner refers to plasma supply and global reliance on US plasma. Mentions this week's statement by EU Health Commissioner who refers to plasma as an essential supply for first time marking World Blood Donor Day. Plasma Users Coalition which includes @EHC_Haemophilia request 2/



Brian O Mahony @Brianhemophilia · Jun 18
2/Update in SB-525 Gene Therapy @wfhemophilia Summit



Brian O Mahony @Brianhemophilia · Jun 19
Peyvandi @wfhemophilia Summit outlines stage of progress with some of the non CFC subcutaneous treatments under development



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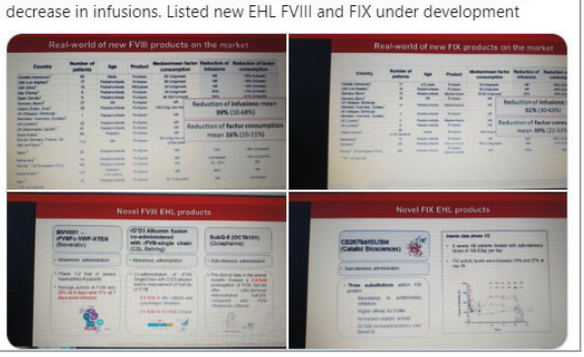
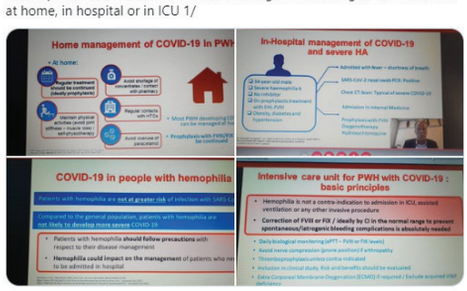
Brian O Mahony @Brianhemophilia · Jun 19
Peyvandi @wfhemophilia Summit overview on novel therapies. Use of EHL FVIII led to 16% mean decrease in CFC units used and 40% decrease in number of infusions. For FIX, led to 39% decrease in CFC used and 51% decrease in infusions. Listed new EHL FVIII and FIX under development



Brian O Mahony @Brianhemophilia · Jun 19
Hermans @wfhemophilia Summit on Clinical management of Covid-19 in haemophilia. Cedric outlines different management strategies for treatment at home, in hospital or in ICU 1/



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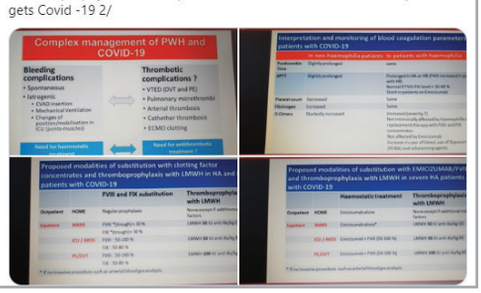
Brian O Mahony @Brianhemophilia · Jun 19
Hermans also discusses laboratory coagulation parameters, use of thromboprophylaxis and implications of use of emicizumab when person gets Covid -19 2/



Brian O Mahony @Brianhemophilia · Jun 19
Many thanks to all the Staff and Board @wfhemophilia for the Global summit. I missed seeing friends and colleagues in person but this was a practical alternative. Enjoyed many of the sessions. See you at at WFH 2022 in Montreal.

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