WILEY Haemophilia

ABSTRACT

00-INVITED PRESENTATION SUMMARIES

TU-PL-G – WFH VP Medical's Address | New horizons within sight for haemophilia

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Introduction: Haemophilia treatment has long been hampered by the shortage of products. Even today many countries lack a continuously supply and patients are left without any choice. It was therefore understandable that treatment choices were made based on shortage models. Therefore, patients had no access to treatment at home and treatment was only delivered after long delays and more often not at all. Only countries in the developed world with health-care systems that reimbursed the costs of treatment were able to start prophylaxis-based treatment regimens. Prophylaxis aimed at the prevention of bleeds is now globally accepted as the superior therapy. To prevent joint disease prophylaxis should be started very early, preferably after no more than 1-2 joint bleeds.[1] Patients having access to primary prophylaxis are growing up without or with very limited joint problems. The Swedish and the Dutch groups have published the most comprehensive data on long term outcome with life-long prophylaxis.[2]
Now the landscape is changing dramatically. The explosion of new products for the treatment of haemophilia will hopefully benefit all patients and change the current landscape from shortage, allowing only limited dosing in prophylactic regimens, to one of plenty. The first step that increased clotting product volumes was the introduction of recombinant products in the early nineties. Higher dosing for prophylaxis became possible for patients living in countries that could pay for the high costs. Some countries now even use up to 10 IU per capita, while the worldwide median per capita use is still only 0.83 IU.[3]
The development of inhibitors in 25-30% of the patients during the first 50 exposure days is still a major side-effect of treatment.[4] Although debate is ongoing regarding different risk profiles between products, the higher dosing which became possible after the introduction of recombinant products might have played an important role.[4] It is important to better investigate the impact of high dosing in order to prevent unnecessary inhibitor development.
Extended half-life (EHL) products became available only a few years ago and were developed to decrease the burden of infusions for patients and improve adherence to prophylaxis.[5,6] Especially for haemophilia B, EHL products have a clear benefit because they enable once-weekly dosing. For haemophilia A, especially in children, reducing dosing should be done very cautiously. It takes a long time before the deleterious effect of increased bleeding in children becomes visible. Parents might be persuaded that higher through levels with the same dosing and frequency of EHL is preferable.
The justification for higher through levels came also from the notion that adult patients on full prophylaxis may still report bleeding.[7] Especially in the light of gene therapy, where a single infusion may give long-term cure, it is important to know which level to aim for. Stakeholders now suggest that the current prophylactic dosing is too low. Interestingly, the Swedish prophylactic regimen of 20-40 IU/kg factor VIII 3 times a week, which for decades was perceived as too high and too costly, now, in the landscape of plenty, is considered inferior.
Moderate haemophilia, with factor VIII/IX levels between 1% and 5%, is an interesting "natural" model and therefore has recently received renewed attention. In the search for the preferred level to prevent bleeding completely, the publication of a study on long-term bleeding in 75 patients with moderate haemophilia has received much attention.[9] At a median age of 37 years, the bleeding frequency in these patients was 2.0 (IQR 0.8-3.7) bleeds per year. This result is very similar to those presented earlier for long-term outcome in severe haemophilia on life-long prophylaxis.[2] With moderate haemophilia, no bleeds were observed with factor VIII levels over 10%, which now seems to become accepted as the "new normal". Since self-reporting of bleeds in patients with bleeding conditions has its limitations, it is important to consider data on the effect of these reported bleeds on long-term joint arthropathy. In the moderate haemophilia study, at the age of 37 years, 82% of patients scored <10 out of 126 points of the Haemophilia Joint Health Score (HJHS), and reported no limitations in activities.[9]
Regarding severe haemophilia, Collins et al. reported that the annual bleed rate increased by 2.2% in children aged 1-6 years, and by 1.4% in adolescents 10 years and over and adults up to 65 years, for every hour spent with a factor VIII level below 1%.[10] We often concentrate on the burden of infusions, while the relief of parents who know their child is protected from bleeding and without pain is often disregarded.
In the developing world, up to 10% of children with severe haemophilia suffer from intracranial bleeding, a very rare condition in children on primary prophylaxis.[11] It is therefore very promising that the developing world has now embraced low-dose prophylaxis in children, with excellent results on bleeding, allowing performing

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activities and normal school participation. We have to strive to attain that all patients with haemophilia profit from improved care and that they have access to all new and existing therapies. Access to treatment will cause the developments of inhibitors, however, and we need to support access to immune tolerance induction and to bypassing agents in these areas too. The WFH is ideally positioned to play an active role in this process.

Many new therapies have become available which allow for subcutaneous dosing.[11-13] This will further facilitate the life of patients and improve adherence. Gene therapy is very promising and will lead to a cure for haemophilia.[14-15] In the meantime, patients deserve direct access to treatment. The ultimate goal is to prevent joint disease and the only way to reach that is by preventing bleeding from birth onwards. This holds true for both severe as well as moderate haemophilia A and B. As there are now sufficient products, "no bleeds" is attainable for all. The community has to play an active role in advocating access and at the same time demand lifelong data collection to address existing and new safety issues.

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TU-PL-MED | How to measure outcome in hemophilia: Perspective from patient, physician and payer

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Why Do We Need Outcome Assessment? Different Perspectives: In general, assessment of outcome is used for evaluation of treatment. For *patients*, it has to do with the burden of bleeding and arthropathy, followed by short-or long-term impairment in activities of daily life and participation in usual social roles. For the *physician or caregiver*, the goal is to minimise patient burden and optimise treatment, both at patient level in day-to-day care and at group level in research. From a *payers'* perspective, it is about optimising cost-effectiveness of both treatment with clotting factor concentrates (CFC) and supportive treatment. This includes assessment of both clotting factor consumption and hospital visits/stays. *Policy makers* have to plan care and health care budgets and will perform analyses of cost-effectiveness and/or cost-utility of treatment, based on quality of life, direct medical costs and work participation. A comparison with level of care and/or outcome with other countries can be especially helpful for decision making in these areas (1).

Make Sure to Cover All Aspects of Outcome: To cover all consequences of a disease, outcome assessment should follow a comprehensive schema, such as the WHO proposed International Classification of Functioning, Disability and Health (ICF) (2). This model describes the different interactive components of the main disease-disability pathway: Body Functions and Structures,

Activities, Participation, and Environmental and Personal factors. Health related quality of life is considered as a concept overarching all components of the ICF (2). Therefore, outcome assessment should include both measurement of the physical aspects (i.e., bleeding, joint status) and assessment of activities and participation.

Short or Long-Term Outcome? Intensive Treatment or Not?: In haemophilia, repeated or severe joint bleeding is followed by soft tissue changes in synovium and/or cartilage, which may be partly reversible.(3) In this stage, limitations in joint function and activities/participation may occur and are usually reversible. The next stage is the occurrence of mostly irreversible bony changes. Early joint changes, especially, may not be associated with limitations in joint function and/or activities and are therefore difficult to detect. In patients with severe haemophilia treated with early prophylaxis, bleeding rates are usually very low and joint changes are prevented or extremely delayed. In contrast, patients without access to CFC experience crippling arthropathy, often during childhood.

Consequently, the choice of outcome tool is affected by the intensity of treatment. The usual measure of short-term outcome is bleeding; bleeding is affected not only by severity of haemophilia, but also by trauma and current joint status. Accordingly, bleeding frequency should be observed for a minimum of 6-12 months. In the absence of prophylaxis, haemophilic arthropathy/bony changes may occur over a few years, in those treated with intensive prophylaxis however, it may be take several decades to develop. With early prophylaxis, the focus is more on soft tissue changes.

Balancing Time and Burden: Can We Define a "Core Set" of Outcome Tools?: Assessment of *joint health* can be done by physical examination and various imaging techniques. Physical examination scores have been developed, and the Haemophilia Joint Health Score has been most extensively studied. It was specifically designed to pick up early joint changes but requires 30-60 minutes' examination by a trained physiotherapist/physiatrist/professional. Imaging varies between point of care ultrasound, X-ray and MRI, each with their specific strengths and limitations. For osteochondral (i.e., advanced) changes, the X-ray scored according to Pettersson (4) is most well established; it is fast and cheap. MRI is somewhat controversial; it can image both soft tissue and osteochondral changes but is impractical for routine use as access is limited, it is very time consuming (±20 min/joint), and expensive. Ultrasound can be used to assess soft tissue changes and, to a degree, changes in cartilage and bone, using specifically designed scoring systems such as HEAD-US (5) or JADE. Preliminary data suggest good diagnostic accuracy when compared to MRI in patients with limited arthropathy. However, ultrasound is operator dependent and its value in clinical care still needs to be established. Measurement of *activities* can be done using questionnaires (especially the paediatric and adult Haemophilia Activities List ((ped)HAL)) or observation based tools (6). The Functional Independence Scale for Haemophilia (FISH) was developed and validated specifically for use in patients with more advanced arthropathy. Measurement of *participation* is partly covered by the (ped)HAL, and experience with specific participation questionnaires has been limited so far (6). Assessment of participation in school and/or work is currently not included in any of the widely used activity-related questionnaires. Recently, an international multidisciplinary group made consensus recommendations on which tools to use for outcome assessment in clinical care and research (7). Annual assessment of bleeding and physical examination (preferably HJHS, minimum range of motion), medical care (CFC consumption, surgeries, hospital visits, hospital stays), days lost from school/work, and paid employment were considered mandatory. Assessment of activities was recommended, while imaging was considered optional for clinical care and recommended for research. However, it is not established whether this set of parameters is sufficient to evaluate haemophilia care, and if it can be shortened.

Experience With a "Core Set" of Outcome Tools in Rheumatoid Arthritis (RA) and Other Rheumatic Diseases: In RA, similar problems with assessment of disease activity and joint status occur. Similar to haemophilia, the need for more detailed outcome assessment/detection of more subtle changes has increased with the improvement of treatment. Over the last 20 years, there has been an international effort to identify, validate, and use a "core set" of outcome parameters for care and research in RA, as well as for childhood arthritis, childhood myositis, lupus and other rheumatic disease. International consensus groups have, additionally, developed and validated criteria by which an individual can have been said to have benefited from treatment (responder criteria) and to have had a flare in disease activity. This work can be used as a model for further development of a core set out outcome tools to evaluate the benefits of treatment for persons with haemophilia.

M-MED03-03 | The diagnosis, clinical assessment and management of FXI deficiency

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Factor XI (FXI) is a plasma serine protease which plays an important role in the propagation phase of blood coagulation and formation of a fibrin clot in response to bleeding [1]. FXI deficiency is an autosomally inherited disorder characterised by non-spontaneous bleeding usually in the setting of surgery, trauma, childbirth or menstruation [2-5].

Many individuals are asymptomatic until haemostatically challenged and for this reason diagnoses are made throughout childhood and adulthood. Diagnosis is made by measuring plasma FXI:C levels in patients with a significant bleeding history, family history or with a prolonged activated partial thromboplastin time (APTT) although not all FXI deficient individuals have a prolonged APTT. The mode of diagnosis has altered over time with the majority of diagnoses currently being made via abnormal pre-operative coagulation screens or through family screening rather than through presentation with

bleeding symptoms [6]. This has resulted in many patients being diagnosed with FXI deficiency without ever having been haemostatically challenged and with an associated loss of the valuable bleeding history which this provides.

Clinical assessment of patients with FXI deficiency currently consists of taking a bleeding history, measuring FXI:C levels and ruling out an additional bleeding disorder in those with an extensive history of haemorrhagic symptoms.

Bleeding assessment tools can be used to describe a patient's bleeding history but bleeding scores hold no diagnostic value in the setting of family screening and have not been shown to be predictive of bleeding in this disorder [7]. No clear correlation has been demonstrated between clinical bleeding risk and FXI:C level, FXI antigen level, APTT or genotype [2, 3, 8, 9]. Variation in haemorrhagic tendency is observed between patients with the same FXI:C level and also between individuals within families who share the same *F11* gene mutation [3]

Individuals with partial FXI deficiency (FXI:C 15-60 IU/dL) as well as those with severe deficiency (FXI:C <15 IU/dL) can have a significant bleeding tendency but there is notable phenotypic heterogeneity within this disorder [3, 10, 11]. Some patients with severe deficiency do not have excessive bleeding, even after trauma or surgery whilst others with partial deficiency report significant haemorrhagic symptoms [3].

A number of possible reasons for this perceived phenotypic heterogeneity have been suggested [12]. Firstly, FXI deficiency has a predilection for causing bleeding in sites of high fibrinolytic activity following surgery or trauma. Individuals who have never been haemostatically challenged at these sites run the risk of being incorrectly classified as "non-bleeders". Secondly, inconsistency exists between patients and between physicians as to what defines significant bleeding symptoms. Much variability is seen between research definitions of "bleeders" and "non-bleeders" making studies difficult to compare [3, 9, 13-15]. Thirdly, contrasting reports exist about association between genotype and bleeding tendency in FXI deficiency. Studies that have found an association used data from Jewish patients with high frequencies of the same mutations [2] compared to studies using ethnically diverse FXI-deficient individuals with many different types of mutations [3]. Finally, it is has been proposed that the haemostatic balance provided by other coagulation factors may have more impact in mild bleeding disorders such as FXI deficiency. This has resulted in the evaluation of global haemostasis assays in this disorder [13, 15-17].

Studies of the ability of the thrombin generation assay to identify bleeding phenotype in FXI deficiency have been inconsistent [13, 15-17] with results shown to be dependent on sample type tested [16]. Although this assay shows promise it cannot be introduced into the hospital laboratory until a fully automated machine with standardised technique and reagents (sensitive to the coagulation defect present in FXI deficiency) becomes available. Plasma clot formation and lysis assays have been reported to distinguish bleeding tendency in individuals with severe FXI deficiency [15]. Similar results have recently been obtained in a larger study including patients with partial FXI deficiency [18] offering another potential assay to be developed for clinical use.

Treatment decisions in FXI deficiency are currently based on bleeding history, FXI:C levels, presence of FXI inhibitors, type and area of surgery proposed and whether or not risk factors for thrombosis and volume overload are present [19]. Recent guidelines have recommended that FXI-deficient individuals with a FXI:C level of <10 IU/dL, an additional coagulopathy, a past history of excessive bleeding or who were undergoing dental extraction, genitourinary or oropharyngeal surgery should be classified as high risk of bleeding. Tranexamic acid was recommended for all minor bleeds and minor surgery in high risk individuals and for all bleeds and surgery in low risk individuals. In high risk individuals with severe bleeding or having major surgery the use of FXI concentrate (10-15 U/kg) without tranexamic acid or Solvent Detergent -Fresh Frozen Plasma (SD-FFP) (15-25 mL/kg) with tranexamic acid was recommended [20].

Two plasma derived FXI concentrates are currently available but only in some countries [21, 22]. Thrombotic episodes have been reported in association with their use, with a predilection to those with predisposing risk factors for thrombosis and the elderly [23-25].Thrombosis has not been reported with FFP treatment however, there is an increased risk of other transfusion related complications including volume overload [19]. Recombinant FVIIa (15-30 μg/kg) has been used in individuals with inhibitors or in those declining plasma-derived products [26, 27]. This is also a treatment option for FXI-deficient individuals with severe IgA deficiency [19].

The improvement of care of FXI-deficient patients requires the development of measures that can predict bleeding phenotype and enable the identification of individuals who need treatment at times of haemostatic challenge. Tests which determine optimal type and dose of FXI replacement as well as accurately monitoring and guiding treatment decisions peri-operatively are required in order to offer patients individually tailored and more precise treatment of their disorder.

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W-LAB03-02 | Genotype versus phenotype in von Willebrand disease diagnosis

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von Willebrand disease (VWD) is the most common of the inherited bleeding disorders. It affects females to a greater extent than males as there are additional bleeding phenotypes that affect only this group; these include menstruation that can result in heavy menstrual bleeding (HMB) and post-partum bleeding. The tendency to bleed can be from mild-severe and is inherited in most individuals as an autosomal dominant disorder. It has been estimated that approximately 1 individual per 10,000 is affected by VWD sufficiently to seek medical attention. Different treatment options are available to patients depending on their VWD type and symptoms. These include use of desmopressin for individuals with type 1 VWD and also for some with type 2N. Patients with types 2A, 2B and 2M and those with type 3 VWD will generally receive clotting factor concentrate that may contain both VWF and FVIII. Additional products such as fibrin sealant, aminocaproic and tranexamic acid may also be utilised.

Phenotype Analysis: A history of mucocutaneous bleeding symptoms highlight a possible VWD diagnosis. The disorder may have already been diagnosed in family members, or may occur *de novo*, resulting from a new variant. The ISTH BAT (1) facilitates assessment of symptoms to determine extent of bleeding for 12 different symptoms and is used in the diagnostic process at some centres. VWD diagnosis utilizes a number of different assays. These determine quantity of VWF antigen (VWF:Ag), a measure of VWF activity, which until recently was determined using the VWF ristocetin cofactor assay. This has now been replaced in many laboratories by newer tests having reduced coefficients of variation; VWF:GPIbR and VWF:GPIbM (assays that are based on either ristocetin-induced

binding to a recombinant wild-type (WT) GPIb fragment or assays based on spontaneous binding to a VWF gain-of-function mutant GPIb fragment) (2). FVIII:C is also assessed. Additionally, determining extent of collagen binding and propeptide levels may add further information to help determine variant type (3) along with ratios of VWF antigen:activity.

Recently, plasma levels associated with diagnosis of VWD have been reduced to ≤30 IU/dL (an exception is type 2B, where levels may be up to 100 IU/dL). Patients are grouped into six main classes; type 1 (approximately equivalent levels of antigen and activity), types 2A, 2B and 2M where antigen is greater than activity (antigen:activity ratio <0.6), 2N where levels of FVIII:C are reduced, similarly to those in mild haemophilia A, and type 3, where patients have undetectable antigen levels.

Although these distinctions between patients having different VWD types can be made fairly readily in a good proportion of patients, they do not alert the clinical team to consequences of specific variants that may result in e.g. an inhibitory antibody or in anaphylaxis.

Federici et al (4) examined whether the ISTH bleeding score (BS) could be used as a predictor of requirement for treatment in adult VWD patients. 796 Italian VWD patients were assessed to see whether the European type 1 VWD BS (5) had utility to predict spontaneous bleeding requiring replacement with desmopressin and/or concentrates containing VWF or FVIII:C. 75 (9.4%) required management of 232 spontaneous bleeding events. A BS of >10 along with VWF:ristocetin cofactor activity <10 U/dL predicted risk of bleeding, however only a BS >10 correlated with a multivariable Cox proportional hazard model.

Genetic Analysis: Analysis of sequence variants can help to define VWD type, where the variant has been previously categorized, or falls into a known VWD type through its specific VWF location. The main analyses undertaken are NGS and Sanger sequencing, followed up by dosage analysis for large deletions, duplications and deletion/insertion variants, if necessary.

A proportion of VWD patients are at risk of inhibitory antibody development and occasional individuals may develop anaphylaxis. The main at-risk group are those with type 3 VWD (VWF:Ag <1 IU/dL) where estimates of 7.5-10% prevalence are stated for inhibitory antibodies (5-6). A single individual with type 2B VWD has recently been reported to have an antibody (7). Defining the specific sequence variant can provide further information regarding any known risks associated with the specific variant(s) present in the affected individual. Deletions (n = 12), null alleles (n = 5) and frameshifts (n = 2) and other undefined variants (total n = 35) were compiled from the literature by James et al, (6), amongst whom 21 developed alloantibodies and 10 reported anaphylaxis.

Two large studies encompassing all von Willebrand disease types were published by Veyradier et al, and by Batlle et al in 2016 (8-9). These studies provide an up-to-date analysis of the genetic variants found in 1000 index cases along with additional family members. These studies include many new VWF variants including novel deletions and duplications.

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W-LAB03-01 | Diagnosis of inherited bleeding disorders in the genomic era

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Inherited bleeding disorders (IBD) affect up to 1 in 10,000 individuals for the most common disorder, von Willebrand disease, to only eight reported cases worldwide of alpha-2-antiplasmin deficiency. Those with an identifiable abnormality can be divided into disorders of coagulation factors (87%), platelet count and function (8%) and the fibrinolytic system (3%). The remaining 2% are unclassifiable (1-3).

Next to bleeding symptoms, patients with an IBD can manifest abnormalities in other organ systems, warranting an accurate and complete diagnosis that reflects the underlying molecular pathology. This includes predisposition to renal impairment, deafness or acute myeloid leukaemia (4).

Despite the fact that IBD can be diagnosed through a combination of careful clinical assessment and laboratory assays of varying degrees of complexity, there are many where conventional approaches are inadequate. Improvements in phenotyping assays have enhanced the diagnostic toolbox, however genotyping offers the most precise diagnosis for some of these conditions.

In the past, obtaining a genetic diagnosis was often challenging. It was not always clear which genetic tests could be undertaken. These tests were based on Sanger sequencing, and were costly. Furthermore, the assays were time consuming. Genes were tested sequentially rather than in parallel, which meant that for some patients, it could take years to reach a diagnosis. Thanks to the development of targeted sequencing platforms, many genes can now be analysed routinely in a timely fashion. Thanks to the relative ease of use of these platforms, their use should be incorporated into the work-up of patients with an IBD.

The traditional stepwise testing approach may require multiple hospital visits to discuss test results and to add additional investigations. The cost of these interventions, which may require the patient to attend a specialist laboratory, and the consequent delays in diagnosis are compelling reasons for introducing genetic testing much earlier in the diagnostic process.

In order to make sense of the vast amount of data generated by NGS and particularly by whole genome sequencing (WGS) in a manner that is clinically useful, a multi-disciplinary approach is essential, involving clinicians, bioinformaticians and genetic scientists.

One such panel is the ThromboGenomics (TG), a targeted NGS panel, that has been developed in Cambridge, UK (5). Version 3.0 of the platform contains 78 genes with a confirmed role in bleeding/thrombotic disorders. These include coagulation pathways and platelet disorders due to defects important for platelet formation, morphology or function. By selecting only genes with an established role in inherited coagulation, platelet and thrombotic disorders, clinical utility is enhanced. The technology allows rapid addition of new genes once they have been approved by the Scientific and Standardization Committee (SSC) for Genomics as described below. To date, more than 1450 samples have been processed by the TG pipeline.

The speed at which investigations can be undertaken, and the reducing WGS costs, will promote its role. In parallel, ongoing bio-banking efforts for peripheral blood samples and analysis of genome-wide markers will allow linkage of genetic loci to specific phenotypic traits. When a clinical question, such as the cause of abnormal bleeding arises, a bioinformatics pipeline will analyse genes related to IBD for pathological variants.

In summary, we suggest the next approach for the investigation of patients with a suspected inherited bleeding disorder should be as follows (6):

1. Detailed history taking including
    a. Clinical assessment of presence and severity of bleeding symptoms using the International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool (BAT) (20), to generate scores from bleeding history.
    b. Age of symptoms onset.
    c. Family history; it is important to consider autosomal recessive inheritance of disorders in asymptomatic carriers, especially when parents are consanguineous.
    d. Platelet disorders can be part of multi-system disorders. A full physical examination may give clues facilitating diagnosis. In addition, a systems history should be taken.
    e. Diet, and certain products including herbs and caffeine can affect platelet function. In addition, malnourishment can result in factor deficiencies.
    f. Current medication
2. First-line investigations are available at most centres treating patients with an IBD that include a full blood count, APTT, PT, TT, Fibrinogen, VWF antigen and VWF activity. If a platelet disorder is suspected, platelet morphology and light transmission aggregometry should be undertaken.
3. Second-line testing is dependent on the outcome of previous testing. If a coagulation defect is suspected based on abnormal clotting studies, this could be followed up with specific factor assays. If all factors are normal, factor XIII and Alpha-2-antiplasmin deficiency should be excluded. Findings can be confirmed using NGS. If a platelet disorder is suspected, rather than second-line testing, which is costly and time-consuming, NGS should be used.
4. A multidisciplinary team meeting to discuss patients, having input from clinicians, biomedical staff, geneticists and bioinformaticians. If there is ambiguity, or further phenotyping is required, then additional third-line tests could be suggested. The outcome should be documented and conveyed to the patient.

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W-LAB03-03 | Genetic analysis of haemophilia carrier status

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As a medium income country from Latin-America, laboratory procedures for genetic analysis of haemophilia in Argentina are characterised by its cost-effectiveness, covering virtually all requirements to offer genetic counselling to affected families that include reliable carrier diagnosis. The aim of this section is to demonstrate our set of applied molecular approaches for genotyping the *F8* and *F9* genes, achieving carrier diagnosis in haemophilia A (HA) and haemophilia B (HB), respectively; additionally, to discuss the technical approaches to analyse and understand the molecular basis of haemophilia symptoms expressed in carriers and in those having genetic mosaicisms.

In families with at least a case with severe-HA, our laboratory algorithm for *F8*-analysis starts with the investigation of haemophilia inversion hotspots, the *F8* intron 22 inversion (Inv22) and intron 1 inversion (Inv1) causing 35-50% and 2-5% of severe-HA cases, respectively. Analysis of Inv22 and Inv1 are performed by inverse shifting-PCR (IS-PCR) and includes simultaneous detection of all *int22h*-associated rearrangements including deletions (Del22), duplications (Dup22) and *Bcl*I-related variants (1) (IS-PCR version 2016). Non-inversion *int22h*-mediated rearrangements (i.e., Dup22 and Del22) are rarely, or not, detected in a Haemophilia Gene Testing Laboratory as none of them expresses haemophilia. Hemizygous Del22 associates with *in utero* lethality while heterozygous females show extremely skewed-XCI (X-chromosome inactivation) and recurrent abortions of male foetuses. Dup22, comprises a structurally normal copy of *F8*, associates with recognisable facial features and mild cognitive deficiency in hemizygous males while heterozygous Dup22 females show extremely skewed-XCI (2).

Thereafter, the screening *F8* or *F9* large deletions are performed in a sample from the hemizygous patient by applying PCR amplification schemes including 38 and 12 amplimers, respectively, and sets of genomic tags up- and downstream of each gene until defining the limits of sequence loss. Carrier detection of large deletions may be achieved by either analyzing a deletion-specific PCR product across its 5′ and 3′ breakpoint junctions (3), or by a gene dosage approach using quantitative real time-PCR (qPCR) using an X/autosome amplification ratio and samples from control males and females to assess deletion carrier probabilities (4).

Small *F8/F9* mutations including insertions or deletions of <10 bp and nucleotide substitutions are primarily detected by high-resolution conformation-sensitive gel electrophoresis (CSGE) and characterised by Sanger sequencing (5, 6).

Finally, the significance and potential phenotypic impact of the observed *F8/F9* genotype in the hemizygous or heterozygous state should be critically investigated and provided in the genetic report.

A crucial topic to understand haemophilia expression in carrier females relates to the phenomenon of XCI. The assessment of XCI takes advantage of the epigenetic methylation marks associated with the transcriptional silencing of genes *AR* (on Xq12) (7) and *RP2 loci* (on Xp11.3) (8). Although in most cases XCI is a random process, roughly resulting in an average of half of the cells having paternal (or alternatively maternal) X-inactive; in rare cases, for different complex causes (discussed in Puck & Willard (9)), XCI may be skewed, shutting down expression of the targeted X chromosome in all cells from a tissue under analysis. In haemophilia carrier females, the former scenario associates with about a half of normal factor VIII activity (FVIII:C) levels while the latter (carriers with skewed-XCI) may associate with either normal FVIII:C levels or with significantly reduced FVIII:C, which may cause haemophilia symptoms, depending on the gamete phase between the *F8*-mutation and the preferentially active-X. In contrast to this theoretical framework, an unexpected absence of correlation between FVIII:C and XCI levels in blood leucocytes from haemophilia carriers was published (10). In order to address this correlation, we designed a linear binary model (V-model) taking into account, the experimental and biological variability of FVIII:C existing in non-carriers in which XCI (either skewed or random) does not play any role (11). Applying the V-model, Radic et al (2015) analysed the FVIII:C-XCI correlation in a series of 38 heterozygous carriers of severe *F8* mutations *versus* 20 non-carrier controls and concluded that the theoretically natural correlation (i.e., extreme XCI-extreme FVIII:C) cannot be statistically excluded as the underlying mechanism of haemophilia expression in carriers (11). The tissue to interrogate for XCI to infer its state in hepatocytes (FVIII and FIX secreting cells) is of crucial importance. In our experience, the ideal tissue to achieve this indirect estimation is through studying cells collected from urine (desquamated from bladder and ureter inner epithelia), as they derive from endoderm (the same embryonic layer as liver derives from) and there are no arguments to predict a significant departure from its original XCI state. On the other hand, peripheral blood leucocyte samples hardly resemble the relevant liver's XCI mosaic level as they are derived from embryonic mesoderm and are subjected to selected clonal expansions and retractions associated with immune system activity, which raise the XCI skewing rate with the female's age (12).

The molecular tools necessary for detection and assessment of genetic mosaicisms from suitable tissue samples as surrogate for inferring the state of the relevant tissues in haemophilia patients and carriers are of importance to estimate the haemophilia-phenotype expression and the variant heritability associated with the gonads. In addition, we have reported an interesting case of a combined somatic-gonadal mosaic involving the maternal grandfather of a severe-HA affected patient with a 2 kb *F8*-promoter deletion in whom the percentage of mosaic cells measured in urine and peripheral blood closely align with FVIII:C levels and the ratio of carrier to non-carrier offspring, respectively (13).

In conclusion, carrier diagnosis in haemophilia can be successfully achieved in developing countries covering the provision of all crucial molecular information required to offer accurate genetic counselling.

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01-ACQUIRED COAGULATION DISORDERS

M-MP-001 (694) | Severe bleeding diatheses in two patients with autoantibodies against factor XIII A subunit

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Introduction and Objective: Acquired factor XIII (FXIII) deficiency due to autoantibody is a rare, severe bleeding diathesis. Autoantibodies may develop against the catalytic A subunit of factor XIII (FXIII-A) or the carrier B subunit (FXIII-B). The aim of the study was the diagnosis and characterization of anti-FXIII-A autoantibodies in two elderly patients.

Methods and Patients: FXIII activity and antigen levels were measured by ammonia release assay and by ELISAs, respectively. The Nijmegen Bethesda assay and 50% inhibitor concentration (IC50) provided information on the strength of the inhibitor. The binding constants were determined by surface plasmon resonance. The truncation of FXIII-A by thrombin was monitored by Western blotting. The inhibition of Ca^{2+} induced FXIII activation and active FXIII (FXIIIa) were assessed by activity assay.

Results: An old woman (82; patient1) presented with occipital hemorrhagic stroke without bleeding history. Hemostasis screening tests were negative; FXIII activity was below the limit of detection. The Bethesda-Nijmegen assay revealed an anti-FXIII inhibitor with a titer of >16 Bethesda unit (BU). An IC50 value of 170.1 μg IgG/mL and a $K_a \sim 10^8\ M^{-1}$ indicated effective FXIII neutralization. The antibody bound to rFXIII-A_2 and FXIII-A_2B_2 with high affinity and accelerated the decay of supplemented FXIII concentrate. The main effect of the autoantibody was the inhibition of FXIIIa. After two months, due to combined therapeutic modalities the autoantibody disappeared and FXIII activity elevated. An elderly (75) man (patient2) developed severe intramuscular bleeding. The patient had 3% FXIII activity, un-measurable FXIII-A_2B_2 and FXIII-A antigens in the plasma. Western blotting revealed the presence of FXIII antigen in the plasma, the autoantibody interfered with the immunoassays. Platelet FXIII activity and FXIII-A antigen were normal. The autoantibody titer was 63.2, the IC50 was 50 μg/mL. The patient's IgG bound to FXIII-A_2B_2 and to FXIII-A_2 with equally high affinity ($K_a \sim 10^9\ M^{-1}$). Immunosuppressive therapy decreased the autoantibody titer, but due to recurrent bleedings the patient passed away.

Conclusion: The anti-FXIII-A autoantibody in patient1 exerted a combined effect (neutralizing and accelerated clearance). In patient2 the primary effect was the inhibition of FXIIIa.

M-P-002 (471) | New option of hemostatic treatment for acquired hemophilia A by single injection of emicizumab, FVIIIa mimicking bispecific antibody, irrespective of epitope specificity

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Introduction and Objectives: Acquired hemophilia A (AHA) results in severe, often life-threatening bleeding, and the management of bleeding has been difficult. Emicizumab improves the impairment of coagulation function in congenital HA patients irrespective of inhibitors. However, the effect of emicizumab on AHA patients in the presence of intrinsic FVIII and autoantibodies is unknown. In this study, we assessed the *ex vivo* effects of emicizumab on AHA taking advantage of the long half-life of PK profile of emicizumab with single dose of the drug. Materials and Methods

The clinical course of AHA could be divided into early acute hemostatic treatment phase (~4 weeks) requiring bypassing agents, and the subsequent hemostatic treatment and prophylactic phase (4 weeks~). According to the PK of emicizumab, we evaluated hemostatic potential of emicizumab *ex vivo* with in thrombin generation assay triggered by tissue factor (1 pM) using plasmas of AHA including low and high dose points of emicizumab.

Results: We obtained plasmas from 16 AHA patients with various epitopes of autoantibodies {8 pts [A1/A2/ light chain (LC)], 4 pts (A2/LC), 2 pts (LC), 1 pt (A1), 1 pt (A1), 1 pt (LC)} after informed consent. Medians (range) of FVIII activities and FVIII inhibitor in all cases were 4.5 (<1.0-33) IU/dl, and 43.3 (2.2-266) BU/ml, respectively. Medians (range) of FIX and FX activities in all cases, except one case which was not determined, were 77.3 (24.3-124) IU/dl and 61.5 (26.5-127) IU/dl, respectively. Improvements of peak thrombin by the addition of emicizumab were expressed as recovery rates (RR). Both of high (30~50 μg/ml) and low (2.5-20 μg/ml) concentrations of emicizumab, which reflecting early and late phase, respectively, improved the peak thrombin in all cases dose-dependently [Medians (range) of RR; high 100% (35-233%), and low 44% (20-77%), respectively], irrespective of the epitopes. Even for the patient with low FIX and X activities (24.3 IU/dl and 26.5 IU/dl, respectively), emicizumab improved the peak thrombin dose-dependently.

Conclusions: Emicizumab could effect on AHA as well as on congenital HA. Single dose of emicizumab could be effective from early to late phase in AHA based on markedly longer half-life of PK.

M-P-003 (499) | An evaluation of hemostatic abnormalities in patients with hemophilia according to the activated partial thromboplastin time waveform

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Introduction and Objectives: The activated partial thromboplastin time (APTT) is generally used as routine laboratory clotting time assays, however, they only show the time. APTT is useful for diagnosing the presence of lupus anticoagulant (LA) and coagulation factor deficiency in the intrinsic pathway such as hemophilia and acquired hemophilia A (AHA). Optical end-point coagulation analyzers can visualize the clot reaction curve as the APTT. The usefulness of the waveform of APTT in various diseases has been evaluated recent years. We analyzed the APTT waveform in hemophilic patients with and without inhibitor, AHA, those with von Willebrand disease (VWD), those positive for LA and those treated with warfarin to examine the relationship between the hemostatic abnormalities and the parameters of the APTT waveform.

Materials and Methods: The APTT waveform was examined in 30 healthy volunteers, 22 hemophiliacs without inhibitor, 6 hemophiliacs with inhibitors, 3 AHA, 6 VWD, 22 LA and 20 patients treated with warfarin.

Results: The correlation with the FVIII activity was highest for the height of acceleration peak. The peak time of acceleration, velocity and 1/2 fibrin formation, and the width of acceleration and velocity were significantly long and the height of acceleration were significantly low in hemophilia patients. The height of velocity was significantly low in hemophilia patients with inhibitor. There were no significant differences in the APTT waveform between hemophilia patients and the patients with LA, but the peak of acceleration and 1/2 fibrin formation were significantly longer, and the height of acceleration and velocity significant lower in hemophilia patients with inhibitor than in the patients with LA. Wave changes in the APTT were observed in all 22 patients positive for LA, while a biphasic waveform was observed in hemophilia patients with FVIII activity <10.0%.

Conclusions: The APTT waveform is useful for the analysis of hemostatic abnormalities in patients with hemophilia.

M-P-004 (707) | The result of Chinese acquired hemophilia registry (CARE): Conditions and challenges

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Introduction and Objectives: Acquired hemophilia A(AHA) is a rare bleeding disorder caused by autoantibodies to coagulation FVIII.

Patients remain at risk of severe hemorrhage with a high rate of mortality until the inhibitor has been eradicated, so early recognition, rapid diagnosis and proper treatment is necessary to improve the outcomes of bleeding. Optimal choice of therapy is controversial, and there is little available data in China. We analyzed information on 187 patients from 25 centers. The efficacy was compared between each treatment regimen about both hemostasis and immunosuppression.

Materials and Methods: The CARE was designed as a nationwide multicenter registry, conducted retrospectively before October 21, 2012 and prospectively from then on. We got back the data from participating centers in the form of CRF. All analyses were performed using SPSS 22.0 for Windows.

Results: Between October 21, 2012 to December 2016, a total of 187 patients were enrolled in the CARE by 25 centers in 15 provinces. It showed lower incidence in children and teens, but the preponderance of male in aged people and female in child-bearing age. The underlying conditions such as tumor, autoimmune disease, and infectious disease were analyzed. Longer than most results in previous studies, the mean time from first bleeding to definite diagnosis we calculated was 92 days. Bleeding was controlled in 54 patients treated with bypassing agents (94.7%) and 15 patients (71.4%) treated with replacement therapy (P = .03).There were 2 thrombotic events in relation to the use of aPCC. The mean time from definite diagnosis to immunosuppressive was as long as 13 days. We divided immunosuppressive treatment regimens into 4 categories: steroids alone, steroids and cyclophosphamide, rituximab based regimens and others. Combination of steroids and cyclophosphamide showed a higher CR ratio (66%) than other regimens.

Conclusions: Lack of knowledge about acquired hemophilia among Chinese physicians makes it difficult for early diagnosis and treatment. The risk factors include age, tumor, autoimmune disease, pregnancy, infection, etc. The optimal hemostatic treatment is bypassing agents but we should pay attention to the occurrence of thrombotic events. Patients treated with steroids and cyclophosphamides are more likely to achieve CR. But for those who had taken steroids and cyclophosphamide for underlying diseases before, addition of rituximab could improve the CR ratio.

02-AGING

W-FPMED01-002 (176) | Elevated HJHS scores in healthy adult males without hemophilia

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Introduction and Objectives: Although not yet validated in adult hemophilia subjects, the Hemophilia Joint Health Score (HJHS) is increasingly used in reporting joint status in this population. The HJHS-Validation in Adult Patients Study (HJHS-VAPS) has a primary aim of establishing the convergent and discriminant construct validity of the HJHS 2.1 in adults. The secondary aim is to define age-related HJHS scores in healthy adult males. This preliminary report describes HJHS scores in healthy subjects.

Materials and Methods: Healthy males age ≥18 years were eligible. Four age-matched strata were prespecified. Subjects with comorbidities (i.e. rheumatoid arthritis, neurologic disorders) that may independently affect the HJHS score were excluded. Subjects with mild sequelae from injury or other mild non-specific degenerative conditions were not excluded.

Results: 49 subjects were completed to date: 12 aged 18-29; 9 aged 30-40; 12 aged 41-50 and 16 aged >50 years. Median HJHS scores (ranges) for all 6 joints (maximum score 124) were 2.5 (0-13) in those 18-29 years; 4 (0-15) in those 30-40 years; 3.5 (0-6) in those 41-50 years and 9 (2-20) in those >50 years. HJHS scores increased as a function of age, Spearman's rho = 0.40 (P = .005) (moderate correlation). One subject had an HJHS score of 20 and 11/49 subjects (22%) had HJHS scores >10. The knee most often accounted for increased scores; the presence of crepitus was the most frequent abnormal item. The majority of HJHS items had some abnormal findings in those subjects with knee scores >0.

Conclusions: Age-related, joint-health changes may result in elevated HJHS scores in healthy adult males. Correctly interpreting HJHS scores in older individuals with hemophilia requires a better understanding of expected findings in healthy individuals. The current study will help define HJHS reference ranges by age once the target accrual of 120 subjects is reached.

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M-P-010 (164) | Ischemic events are rare among aging patients with hemophilia: Results of a cross-sectional study from at centers treating hemophiliacs in Japan

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Introduction and Objective: The aging hemophilia population has been confronted with age-related comorbidities, such as ischemic events. We conducted a multicenter observational study to analyze the incidence of risk factors for major ischemic events.

Materials and Methods: An Inclusion criterion was adult hemophiliacs (all severities) who were 30 years old or older and had been treated at one of five hemophilia treatment centers in Japan. The treatment modality (on demand or prophylaxis), HIV and HCV status, history of ischemic events, entire medical and medication history, smoking habit, blood pressure, and blood test data were collected during 2016. This study was approved by each hospital's medical ethics review board.

Results: In total, 360 hemophiliacs were registered until October 2017. The baseline characteristics are shown in the Table. Only one patient had an ischemic event in his medical history (angina pectoris). None of the patients had experienced stroke or myocardial infarction. The prevalence of hypertension was 18.1%, 34.3%, 51.4%, and 69.6% for patients aged 30-39, 40-49, 50-59 and 60 years or over, respectively. The prevalence of hyperlipidemia, CKD and diabetes in all age were 19.4%, 18.3% and 8.6%. These risk factors increased with age. However, underweight individuals were relatively infrequent across all age groups, and obesity was observed in around 30% of the patients in the youngest age group. The current smoking habit was about 20-30% in all aged group. No correlations between these risk factors and hemophilia-related variables (A/B, severity, inhibitor and treatment) were observed.

Conclusions: Despite the presence of risk factors, a low incidence of ischemic events was observed in our cohort. Japanese people without hemophilia reportedly have a relatively low rate of ischemic events. Whether the present results can be attributed to Japanese ethnicity or a hemophilia-related matter remains uncertain. Data collection is ongoing.

Table: Baseline characteristics of our study population.

	Number of patients (%)
Hemophilia	360
A	308 (86%)
B	52 (14%)
Severity	
Severe	251 (70%)
Moderate	47 (13%)
Mild	62 (17%)
Age	
Mean (range)	44 (30-83)
distribution	
30-39 years	105 (29%)
40-49 years	137 (38%)
50-59 years	72 (20%)
60-69 years	31 (8.6%)
70-79 years	10 (2.8%)
80-89 years	5 (1.4%)
Prophylactic treatment	191 (53%)
Severe	173 (90.5%)
Moderate	11 (5.8%)
Mild	7 (3.7%)

Conflict of Interest Disclosure: A. Nagao has received honoraria for speaking from Baxalta, Bayer, Bioverativ, CSL Behring, Chugai, Novo Nordisk, Pfizer and Torii. N. Suzuki received honoraria for lecturer fees from Bioverativ, Bayer, Baxalta, Pfizer, Novo Nordisk, CSL Behring, and Sysmex Inc. H. Takedani has received honoraria for speaking or participated in scientific advisory boards or symposia from Baxalta/Shire, Bayer, Biogen, Bioverativ, Chugai Pharmaceutical, CSL Behring, Kaketsuken, Novo Nordisk and Pfizer, and grands from CSL Behring. N. Yamasaki has received the advisory and lecture fees from Bioverativ, Bayer, Baxalta, Torii and Sysmex. Y. Chikasawa has received the advisory and lecture fees from Bioverativ, Bayer, Baxalta, Pfizer and Novo Nordisk. A. Sawada has received lecture and speaker fees from Novo Nordisk, Bayer, Baxalta, Bioverativ, CSL Behring, and Torri Yakuhin. T. Kanematsu had no interests which might be perceived as posing a conflict or bias. K. Amano hold concurrent posts as professors for the department of Molecular Genetics of Coagulation Disorders without additional salary; is a board member of the Factor Eight Inhibitor Bypass Activity Post Marketing Surveillance Study Board in Japan organized by Baxalta; has received honoraria for speaking from Baxalta, Bayer, Biogen, Kaketsuken, Novo Nordisk, and Pfizer; has received honoraria for consulting with Baxalta, Bayer, CSL Behring, Kaketsuken, Novo Nordisk, Chugai and Pfizer; and has received unrestricted grants supporting research from Pfizer, outside the submitted work. K. Fukutake hold concurrent posts as a professor for the department of Molecular Genetics of Coagulation Disorders supported by CSL Behring without additional salary; is advisory committee member of Chugai Parm. and consultant of Chugai Parm., SRL Inc. and LSI Medience; has received research funding from Baxalta, Bayer, Biogen/Bioverativ, CMIC, EPS, Hitachi, Kaketsuken, Novo Nordisk, Ortho, Pfizer and Sysmex; has received honoraria for consulting, speaker or advisor from Abbott, Baxalta, Bayer, Biogen/Bioverativ, Chugai Pharm./Roche, CSL Behring, Japan Blood Products, Kaketsuken, MSD, Novo Nordisk, Octapharma, Ortho, Pfizer, Roche Diagnostic, Sekisui Medical and Torii Pharm. S. Higasa has received the advisory or lecture fees from Bioverativ, Bayer, Baxalta, Novo Nordisk, CSL Behring, Kaketsuken, Chugai, and ViiV Healthcare. T. Fujii has received research funding from Pfizer, Novo Nordisk, Bayer, and the advisory or speaker fees from Bioverativ, Bayer, Baxalta, Pfizer, Novo Nordisk, CSL Behring, Sekisui Medical, Torri Yakuhin, Kaketsuken, Chugai, Nihon Pharmaceutical, Japan Blood Products Organization, and ViiV Healthcare. T. Matsushita received honoraria for lecturer fees from Bioverativ, Bayer, Baxalta, Pfizer, Novo Nordisk, CSL Behring, and Sysmex Inc. T. Suzuki has received the advisory and lecture fees from Bioverativ, Bayer, Baxalta, Pfizer, Novo Nordisk, CSL Behring, Sekisui Medical, Werfen, Kaketsuken, Chugai, Nihon Pharmaceutical, Japan Blood Products Organization, Kyowa Medex, and MSD.

03-CLINICAL RESEARCH AND CLINICAL TRIALS

M-FPMED02-003 (681) | Low annual bleeding rate with regular replacement therapy at lower doses in children with severe hemophilia in India: A multi-center study

Aby Abraham[1]; Shashi Apte[2]; Cecil Ross[3]; Biju George[4]; Vikram Mathews[4]; Alok Srivastava[1]

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Introduction: Lack of sufficient clotting factor concentrates (CFC) prevents regular replacement therapy or prophylaxis in developing countries in severe hemophilia. We have prospectively evaluated the effectiveness of prophylaxis at lower doses in young children with severe hemophilia A.

Patients & Methods: Children between 3-7 years with severe hemophilia A (FVIII <1%) without inhibitors and a HJHS score of <5 were offered prophylaxis with a pdCFC (KLOTT™) at a dose of 10-15 IU/kg 2-3 x/week, depending on weight and response. Their bleeding rate over 12 months prior to initiating prophylaxis was documented. All bleeding was documented while on prophylaxis, with special emphasis on joint or muscle bleeds. Inhibitors were monitored every 5-10 exposures.

Result: A total of 32 children were treated with this protocol. Their median age was 5 (3-7) years. The median number of exposures to CFC prior to study entry was 4 (0-314). The median annualized bleeding rate (AdBR) prior to prophylaxis was 3 (0-15). On prophylaxis with a median dose of 16 IU/kg twice weekly, the median AdBR was 0 (0-3) at a median follow-up of 10 months (1-14). No patient had any target joint at study entry or during the course of the study. No patient had any muscle or CNS bleeding during this period. Three patients developed transient inhibitors (low titer 1.1 BU, 2.5 BU & 2.0 BU respectively) after 7, 17 and 100 exposures. These resolved within 4-12 weeks with continuing prophylaxis and have remained negative since. None of the other patients developed inhibitors after a median of 85 exposures (9 to 124). Compliance was complete except for two patients who withdrew after 9th & 11th doses for personal reasons and one patient who missed two prophylaxis doses.

Conclusion: Data from this prophylaxis program shows that regular replacement of CFC even at low doses of ~15 IU/kg x2/week reduces the AdBR very significantly to <3/year. These results can be even better if such therapy is started earlier in life for these children and dosage optimized to reduce bleeding in each individual patient to a level which will give the best long-term results.

M-FPMED02-004 (550) | BAY 94-9027 provides effective long-term prophylaxis in pediatric patients: Interim results of the PROTECT VIII Kids extension study

Gili Kenet[1]; Tina Biss[2]; MacGregor Steele[3]; Camila Linardi[4]; Despina Tseneklidou-Stoeter[5]; Kapil Saxena[4]

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Introduction and Objective: BAY 94-9027 is an extended–half-life PEGylated recombinant factor VIII (FVIII). In the PROTECT VIII Kids trial, BAY 94-9027 was efficacious for the prevention and treatment of bleeds in children with severe hemophilia A. We report interim long-term efficacy and safety data from the PROTECT VIII Kids extension.

Methods: In PROTECT VIII Kids, previously treated patients (PTPs) aged <12 years with severe hemophilia A received BAY 94-9027 prophylaxis twice weekly (25 IU/kg), every 5 days (45 IU/kg), or every 7 days (60 IU/kg). Patients completing ≥50 exposure days (EDs) and ≥6 months in the main study or a 12-week safety substudy (part 2) that enrolled PTPs aged <6 years could continue in the optional extension for an additional ≥50 EDs.

Results: Fifty-nine of 73 patients treated with BAY 94-9027 in PROTECT VIII Kids continued in the extension (median [range] age at enrollment, 5.0 [2.0-11.0] years). At data cutoff (August 2017), patients had a median (range) of 1312 (351-1521) days in the trial (main study or part 2 plus extension). Patients in the extension received prophylaxis twice weekly (n = 20), every 5 days (n = 21), every 7 days (n = 8), or switched frequency during the extension (variable frequency; n = 10). Median (range) dose/infusion was 52.1 (19-62) IU/kg. Median annualized bleeding rate (ABR) for total bleeds was 1.7 for all patients and 1.0, 1.2, 2.6, and 3.3 for those treated twice weekly, every 5 days, every 7 days, or at variable frequency, respectively. Median ABR for joint bleeds in all patients was 0.7. During the extension, 3 patients (5.1%) experienced adverse events (AEs) reported as treatment related and classified as mild (n = 1), moderate (n = 1), or severe (n = 1). One patient discontinued because of a nonstudy-drug–related serious AE. No confirmed FVIII inhibitors or persistent anti-PEG antibodies were seen; no patients had sustained levels of detectable PEG in plasma.

Conclusions: Long-term treatment (>3 years) with BAY 94-9027 prophylaxis was efficacious and well tolerated in pediatric patients with severe hemophilia A.

Conflicts of Interest: Gili Kenet: has received research support from Bayer, received honoraria from Bayer for lectures, and participated in an advisory board for Bayer; Tina Biss: no relevant conflicts of interest; MacGregor Steele: has received honoraria from Bayer; Camila Linardi: employment, Bayer; Despina Tseneklidou-Stoeter: employment, Bayer; Kapil Saxena: employment, Bayer.

T-FPMED02-002 (600) | BAY 94-9027 PROTECT VIII studies: Observation of pharmacokinetic steady state for 60-kDa PEG demonstrates the existence of elimination processes for PEG

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Introduction and Objective: Efficacy and safety of extended–half-life PEGylated recombinant factor VIII BAY 94-9027 has been observed in patients with severe hemophilia A using dosing intervals of once to twice weekly for up to 563 exposure days (EDs). Preclinical data showed that excretion processes (urine, feces) exist for high-molecular-weight polyethylene glycol (PEG; ≥30 kDa), including the PEG 60 moiety of BAY 94-9027. No PEG-related adverse events or cellular vacuolation were observed in BAY 94-9027 preclinical studies. Plasma PEG 60 concentration-time profiles after once-weekly administration of the BAY 94-9027 therapeutic dose in humans (4 µg/kg) were simulated based on single-dose administration of a lifetime equivalent dose of PEG 60 in rats. Simulations predicted that steady-state plasma levels of PEG 60 will be reached following a year of treatment with BAY 94-9027. Plasma PEG levels were measured during the PROTECT VIII trials to verify these predictions.

Materials and Methods: During the main study, plasma PEG levels were measured in adults/adolescents (PROTECT VIII) at baseline and 3 subsequent visits (including final visit) and in children (PROTECT VIII Kids) at baseline and after ≥50 EDs; levels were measured every 6 months in ongoing extensions. PEG levels were determined using size exclusion chromatography and mass spectrometry (MS)-MS.

Results: Plasma PEG levels were available for 120 adults/adolescents (age at enrollment, 12–62 years) and 52 children (age, 2–11 years). Median (range) total time in the study was 3.9 (0.8-5.2) years (223 [23-563] EDs) for adults/adolescents and 3.6 (1.0-4.2) years (281 [97-406] EDs) for children. Nearly all PEG measurements were below the lower limit of quantitation (0.1 mg/L); borderline positive results during the extension were observed in 3 patients (maximum level, 0.119 mg/L), but all 3 patients had ≥2 negative follow-up measurements.

Conclusions: A very low dose of PEG is delivered to patients with prophylactic BAY 94-9027 treatment. Very low and steady-state 60-kDa PEG plasma levels are observed in patient samples, which demonstrates the existence of an elimination process for PEG 60.

Conflicts of Interest: All authors are Bayer employees.

T-FPMED02-004 (353) | Do EHL products meet patients expectations (the HOPE study)?

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Introduction and Objectives: Clinical trials have demonstrated the efficacy of extended half-life (EHL) clotting factor products. Little is known about patients' expectations before switching to these products, and whether those expectations are met.

Materials and Methods: Adverts were placed in UK haemophilia centres and on social media seeking parents of children and adults with haemophilia who had been counselled on switching to an EHL factor. Responders were invited to participate in semi-structured telephone interviews to discuss their expectations. First round interviews were analysed in "real time" using modified grounded theory methodology. Interviews were then repeated 6 months later.

Results: Fifteen mothers of children with a mean age of 5.8 years (range 1-14) and eight adults mean age 36.7 years (range 16-26) were interviewed. Two adults with haemophilia B received on-demand treatment, remaining adults and children were on prophylaxis, including one child with mild haemophilia and a severe bleeding phenotype. Three themes emerged: a desire for improved factor levels, enhanced convenience and improved vein health. After 6 months, 21 participants agreed to a follow-up interview. Six patients had not switched to an EHL product, whether by choice (2/6) or as the result of a medical decision (4/6). Among those who switched, 14/15 (93%) described increased confidence knowing they had higher factor levels: 12/15 (80%) scored confidence in EHL products at 8-10 (Likert scale 0-10). Bleed rates were reduced; most reported no bleeds. Six mothers and three patients described reduced treatment burden, but four mothers reported difficulty in remembering treatment days (this was viewed positively as it meant haemophilia was forgotten): one father had lost confidence due to less practice in treating his child. Pain was described as reduced due to fewer bleeds, or "niggling" joints (in adults).

Conclusion: The perception of increased factor levels with EHLs is important to patients and caregivers, increasing their confidence in treatment, and reducing pain and treatment burden. However, there may be a need for more personalised approaches to working with patients and families who struggle with change.

The HOPE study was funded by Sobi.

W-P-000 (517) | Evaluation on effects of early home treatment of bleeding in hemophilia patients

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Introduction: In Vietnam, most treatment of bleeding episodes is delivered only in specialized hospitals. Patients often have to travel long distances to receive treatment with consequent significant delays and increased morbidity.

Objectives: Evaluation of the effectiveness of early home treatment of bleeding for hemophilia patients.

Study Subject: 60 patients with severe hemophilia A, without inhibitor, living around Hanoi were randomized into two groups: 30 in hospital treatment (control group) and 30 in the home treatment (study group).

Study Design: A prospective, controlled, six-month follow-up study was conducted. The parameters collected included demographics, bleeding symptoms, bleeding treatment rate, treatment outcomes, costs, total days off from schools/work.

Results: There were 1317 bleeding episodes in both groups, of which 83.8% were joint bleeding, 9.3% were muscle bleeding. In the study group, 90.1% of the bleeding was successfully treated at home, and 9.9% were hospitalized due to severe bleeding and exhaustion of home treatment supplies. The median time from first signs of bleeding to factor concentrate injection in the study group was 1 hour (10 minutes to 15 hours), significantly more rapid than the control group (6 hours; 1 hour to 144 hours). The mean duration of one bleeding episode in study group was 1.5 ± 1 day (1-12 days) shorter than in control group at 2.7 ± 2.1 days (1-22 days). The median factor VIII used for each bleeding episode were 500 UI (250-12,000 IU) in the study group, significantly less than those in the control group of 10,000 IU (250-24,000 ui). The mean cost/patient/6 months for study group was 148.7 ± 77.3 million VND (36.2-355.1 million), lower than control group at 205.3 ± 106.6 million (31.7 ± 466 million). The median number of work/school-leaving days due to treatment was about 2 days (0-48 days), lower than the control group which was 41.5 days (5-83 days).

Conclusions: Home treatment is a safe and effective treatment that helps patients get treatment early and reduce costs, reduce dependency. There were not detected defects in the in the coagulation hemostasis (general indications of coagulation tests (APTT, TV, PTI, fibrinogen).

W-P-001 (404) | Safety of long-term prophylaxis with BAY 94-9027: Interim results of >5 years of treatment in the PROTECT VIII extension trial

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Introduction and Objective: BAY 94-9027 is a B-domain–deleted extended–half-life recombinant factor VIII (FVIII) conjugated with a single 60-kDa (30-kDa branched) polyethylene glycol. In the PROTECT VIII study, BAY 94-9027 provided effective protection against bleeds and was well tolerated with twice-weekly, every-5-day, and every-7-day prophylaxis in patients with severe hemophilia A. We report interim safety data from the PROTECT VIII extension study evaluating long-term outcomes in patients using BAY 94-9027 prophylaxis for >5 years.

Materials and Methods: Previously treated patients aged 12 to 65 years with severe hemophilia A were enrolled in PROTECT VIII, in which they received BAY 94-9027 for 36 weeks on demand or as twice-weekly (30-40 IU/kg), every-5-day (45-60 IU/kg), or every-7-day (60 IU/kg) prophylaxis. Patients could subsequently participate in an extension study with the same or a different regimen. Adverse events (AEs), anti-PEG antibodies, inhibitor development, renal safety, and plasma PEG levels were evaluated during the extension phase.

Results: One hundred twenty-one of 134 patients from PROTECT VIII continued in the extension study receiving BAY 94-9027 either on demand (n = 14) or as prophylaxis (n = 107). At data cutoff (August 2017), patients aged 15 to 67 years at time of analysis (median age, 39 years) had a median (range) of 1420 (297-1903) days in the trial since enrollment and a median (range) of 223 (23-563) exposure days. Prophylaxis patients were treated either twice weekly (n = 23), every 5 days (n = 34), every 7 days (n = 23), or switched frequency during the extension (n = 27). Overall, 8 patients (6.6%) experienced treatment-related AEs during the extension classified as either mild (n = 3), moderate (n = 4), or severe (n = 1). Two patients (1.7%) experienced 3 SAEs considered to be treatment-related that led to study discontinuation (elevated liver function tests; thrombocytopenia and back pain). Transient low-titer anti-PEG antibodies were detected in 8 patients but were not correlated with clinical events. No patients developed FVIII inhibitors or had sustained levels of detectable PEG in plasma. No changes in renal function were observed.

Conclusions: During the ongoing PROTECT VIII extension, BAY 94-9027 prophylaxis was well tolerated for >5 years, and no patients developed FVIII inhibitors.

Conflicts of Interest: Shadan Lalezari: Consultant for Bayer, Teva Pharmaceuticals, PfizerMark T. Reding: Served on advisory boards for Bayer, Bioverativ, Genentech, Novo Nordisk, and Shire; and on speaker bureaus for Bioverativ and Shire. The University of Minnesota receives research funding on behalf of Dr. Reding

from Bayer. Dr. Reding was an investigator on the PROTECT VIII study. Heng Joo Ng: No conflicts of interest to declare; Despina Tseneklidou-Stoeter: Bayer, Employment; Camila Linardi: Bayer, Employment.

W-P-002 (102) | Evaluation of balance by technobody balance device in patients with hemophilic arthropathy

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Introduction: Disturbance of balance caused by arthropathy results in further bleeding in joints due to accidents. In this study, we aimed to investigate deterioration of the balance and the risk of falling in PWH and compared our findings with those in control group (CG).

Methods: 34 PWH on prophylaxis [27 hemophilia A (3 with inhibitors), 7 hemophilia B, 33 with severe, 1 with moderate disease] whose target joints were knee or ankle included in the study. They are evaluated using Gilbert score (GS), pediatric Functional Reach Test (FRT), Time up and go Test (TUG) and Technobody Balance device in order to show static, dynamic and functional balance, and Pediatric Berg Balance Scale to show risk of falling. The results were compared to those in CG (34 males) who stratified according to age.

Results: There was no difference in two groups for age (15.6 ± 3.3 years in PWH and 15.7 ± 3.3 years in CG) and body mass index. Target joints were knee in 27 and ankle in 7 PWH. Each patient had only one target joint. According to GS, arthropathy was slight in 11, moderate in 16, and severe in 7 PWH. There was a trend toward worse results in patients with severe arthropathy for TUG, FRT and Berg balance scale but no significance difference for static test with balance device. Comparison of test results between two groups was similar for TUG and FRT, however, Berg score which shows impaired balance was significantly low in PWH. When the static balance test applied with the balance device, the oscillations from the centre of pressure (c.o.p) of the PWH were statistically higher than those in CG ($P < .05$).

Discussion/Conclusion: Our study revealed PWH have impaired balance due to arthropathy in lower extremity. Therefore, they are more vulnerable to falling due to loss of balance. Within PWH, patients who had severe arthropathy are more prone to danger of falling compared to the other patients with arthropathy. These results strongly support primary prophylaxis in PWH in order to prevent joint damage and disturbed balance. Technobody Balance device could be used to investigate balance in PWH.

W-P-003 (106) | Does the use of an online screening tool affect referral outcomes? Preliminary results of the Let's Talk Period project

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Introduction: Classification of bleeding symptoms as normal or abnormal is a challenge for both patients and physicians but is critical in the diagnosis of an inherited bleeding disorder. Letstalkperiod.ca is a website (with aligned social media posts) which includes an online Self-Administered Bleeding Assessment Tool (Self-BAT) which is freely accessible and assesses past and present bleeding symptoms and generates a quantitative Bleeding Score (BS).

Objective: The goal of this study was to examine details of new patients seen in a tertiary care Hematology clinic in Kingston, Ontario, Canada, to determine if referral due to an abnormal Self-BAT BS (normal ≤5 for women, ≤3 for men) was more likely to lead to a diagnosis of an inherited bleeding disorder and require more clinical intervention than those referred without the prior use of the Self-BAT as a screening tool.

Materials and Methods: This was a retrospective, observational study. After obtaining REB approval, chart review was performed for patients assessed for suspicion of an inherited bleeding disorder during a 12-month period.

Results: 61 patients (57 female) were identified for inclusion with a mean age of 44 years (range 18-76). 9 were referred by their primary care provider due to a positive Self-BAT BS, 52 were referred because of bleeding or bruising symptoms, abnormal labs or family history. Clinical assessment at the initial visit included the expert-administered Condensed MCMDM1-VWD BS (normal ≤3). Individuals referred for a + Self-BAT BS had higher expert-determined BSs than those referred for other reasons (median BS = 8, range 6-11 vs. 3, range −2 to 14, $P = .003$). Patients referred for a +Self-BAT BS required intervention due to bleeding issues more frequently (i.e. iron supplementation, referral to Gynecology, ENT; 7/9 (78%) vs. 15/52 (29%) $P = .008$) and showed a trend towards being diagnosed with an inherited bleeding disorder more often, 2/9 (22%) vs. 3/52 (6%), $P = .100$.

Conclusion: Preliminary results of this ongoing study suggest that the Self-BAT at letstalkperiod.ca may be a useful tool for patients and physicians in identifying those in need of referrals to hematology clinics for assessment and management of bleeding symptoms.

W-P-004 (168) | Individualized prophylaxis can contribute to decreasing annualized bleeding ratio (ABR) in adult persons with hemophilia A

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Introduction: Prophylaxis is universally recognized as the standard treatment in persons with hemophilia (PWHs). However, the prophylaxis

regimens often change according to their ages, weights, activities, pharmacokinetics of the factor agents, and annualized bleeding ratios (ABRs) in the real world. There have been few reports analyzing the efficacy of the prophylaxis (so called "Individualized") changed from traditional one. The aim of this study was to clarify the impact of individualized prophylaxis on ABR in PWHs who have changed their prophylaxis regimens. And then, we also discussed whether individualized prophylaxis was superior to "conventional" one or not in the point of ABR.

Materials and Methods: The subjects were adults with hemophilia A, who received prophylaxis and experienced modification of their prophylactic regimens in the observation periods. The persons who did not continue the modified regimens over 6 months were excluded because the period was too short to evaluate the efficacy. The change before and after modifying the regimen was investigated on ABR and trough level of coagulation factor VIII activity (FVIII:C).

Results: The subjects were narrowed 14 persons included 3 moderate and 11 severe hemophilia. Their average of age was 46 y.o. and that of weight was 66 kg. All of them used standard rFVIII agents before the regimens modified. Only one of them received Canadian dosing regimen and 7 had twice-weekly prophylaxis. The average of single dose was 28.9 U/kg and that of weekly dose was 66.0 U/kg. In modified regimens, they changed 37.0 U/kg and 73.3 U/kg, respectively. Seven of them changed from standard agents to extended half-life ones. The ABRs after modifying regimens decreased from 3.5 to 2 (median), and there was a statistical significance between them ($P < .01$). On the other hand, the trough levels before and after modifying the regimen were similar (1.5% vs 2.0%, median, $P = .089$). Although 4 of them had target joints, they became no longer target joints in 2 PWHs.

Conclusions: Modifying the prophylaxis regimens and making the prophylaxis more individualized can contribute to decreasing ABR in PWHs. It may bring about increasing their activity and improvement of their quality of life eventually.

Teruhisa Fujii has received research funding from Pfizer, Novo Nordisk, Bayer, and the advisory or speaker fees from Bioverative, Bayer, Baxalta, Pfizer, Novo Nordisk, CSL Behring, Sekisui Medical, Torri Yakuhin, Kaketsuken, Chugai, Nihon Pharmaceutical, Japan Blood Products Organization, and ViiV Healthcare. Naoya Yamasaki has received speaker fees from Bioverative, Bayer, Baxalta, and Novo Nordisk. Tomie Fujii state that she has no conflict of interests.

W-P-005 (698) | The correlation between overall haemostatic potential with bleeding severity in haemophilia A

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Introduction: It is observed that patients with haemophilia A and similar FVIII levels show different bleeding severity. The mechanism behind this variability is not completely clear, but it seems that other factors of the complex haemostatic system may have influence. Aim: We have studied the importance of global haemostatic assay in assessment of bleeding severity in patients with haemophilia A in order to obtain additional, clinically useful information.

Materials and Methods: Seventy-six patients with haemophilia A and 30 healthy males representing a control group were included. Depending on FVIII:C levels haemophilia A patients were grouped as severe (<1 IU/dl), moderate (1-5 IU/dl) or mild (>1-<40 IU/dl). According to the number of spontaneous haemarthrosis patients were grouped as clinically severe (>3 haemarthrosis/year) or clinically mild (≤3 haemarthrosis/year). Global haemostasis was assessed by overall haemostatic potential assay (OHP).

Results: OHP level in a group of 56 patients with severe haemophilia A was heterogenous, from undetectable to normal values (ranged from 0 to 6.7), despite the identical FVIII: C level <1 IJ/dl. OHP level was significantly lower in patients with clinically severe (n = 56) comparing to clinically mild (n = 20) form of haemophilia A, with OHP values 0.39 ± 1.02 and 2.76 ± 2.62 respectively. The heterogeneity of OHP values is also observed in relation to the clinical severity of the disease. Undetectable or markedly reduced OHP values were measured in 54/56 (96.43%) patients with clinically severe haemophilia A (ranged from 0 to 1.58) but also in 10/20 (50%) patients with clinically mild haemophilia A (ranged from 0 to 1.72).

Conclusion: It may be suggested that OHP assay may be additional test which could be of particular benefit for some patients with haemophilia A for evaluation of bleeding severity and tailoring the individual treatment approach.

W-P-006 (342) | Platelet rich plasma for synovitis treatment: 1 year follow up

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Introduction: Haemophilic synovitis is caused by chronic accumulation of blood in the joint. Conservative treatment does not prevent bleeding. We began using PRP for haemophilic synovitis treatment due to its anti-inflammatory properties, and because it contains chondrogenic factors. The aim of this study was to describe the evolution of chronic haemophilic synovitis treatment by means of PRP injection into the joint after one year follow up.

Patients and Methods: 39 patients with 66 chronic synovitis joints were treated and one year followed up. 38 patients were haemophilia type A and 1 type B (32 severe, 6 moderate, 1 mild). Four patients had inhibitors. Mean age was 25 years old (8-48). 38 were located in the knee (57.6%), 15 in the elbow (22.7%) 13 in the ankle (19.7%) joints. Patients were evaluated for Joint perimeter measure, visual analogue scale (VAS), number of bleeding episodes (BE), Haemophilia Joint Health Score (HJHS), range of movement (ROM)

before treatment and 3 months, 6 months and 12 months after treatment. PRP was obtained by intravenous blood centrifugation for 8 minutes at 1600 rpm and were injected into the joint cavity of each patient.

Results: The average volume of blood extracted was 15 ml (10-35). The average volume of PRP injected was 4 ml (2-9). The average platelet count was 420 10^3/ml (200-850). All patients reported pain relief, the average VAS before treatment was 5, patients reported pain relief 3, 6 and 12 months after treatment ($P < .001$), decrease in joint bleeding episodes was statistically significant ($P < .001$) 3 months, 6 months, 12 months after treatment. The HJHS before treatment vs. 3 months, 6 and 12 months after treatment was also statistical significant ($P < .001$). Joint perimeter measures also improved 3 months, 6 and 12 months after treatment and was statistically significant for ankle and elbow joints ($P = .011$, $P = .008$). The range of movement (flexion and extension) improved in all patients but wasn't statistically significant.

Conclusion: All patients reported benefit of the PRP therapy. The improvement was very important in the first 3 months and continues until one year up follow up.

W-P-007 (604) | Demographics of haemophilia in the Ivory Coast in 2017: Data collection in the setting of the WFH twinning program

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Introduction and Objectives: In sub-Saharan African countries, haemophilia is largely under-diagnosed and under-treated. In 2015, the WFH Global Surveys reported 79 cases of severe and moderate haemophilia in the Ivory Coast. Since 2014, both HTCs of the Cliniques universitaires Saint-Luc (Brussels, Belgium) and the Centre Hospitalier Universitaire (CHU) of Yopougon (Abidjan) have established a close partnership in the frame of the WFH twining program. The goal of the present study was to collect accurate, detailed and systematic demographics of the Ivorian haemophilia population.

Methods: Data were prospectively collected on site during multidisciplinary visits in 2017. The evaluation included an in-depth individual face to face interview, the establishment of a pedigree, a clinical examination with a joint assessment performed by an experienced physiotherapist, a biological work-up including clotting factor VIII and IX measurements and systematic screening for inhibitors. The full protocol was approved by Ivorian and Belgian EC and is registered on ClinicalTrials.gov (NCT03054662).

Results: The cohort included 67 persons with haemophilia from 47 different families: 55 severe, 6 moderate, 1 minor haemophilia A (HA) and 4 severe, 1 moderate haemophilia B. With regard to ethnicity, they were classified as Akan (28), Krou (16), Mandé (12), Gour (6) and others (5). Patients geographically clustered in Abidjan (26) and in the southern half of the country. Family history of haemophilia was found in 69%. Pedigree analysis identified 49 deaths in affected relatives (16 after circumcision, 9 intra-cranial haemorrhage, 5 oral bleeding, 10 other bleeding and 9 unknown causes). The median age (range) at evaluation was 12.4 years (1.6-63.4) and at diagnosis 3 years (0.0-45.0). Circumstances of diagnosis were family screening (8), spontaneous (17) or traumatic (18) bleedings and circumcision (24). Anemia (haemoglobin <12 g/dl) was present in 41/63 (4 missing data) patients. 2 PWH were HCV+ and 1 HBV+.

Conclusion: The twinning offered a unique occasion to provide robust data from the Ivorian population with haemophilia. These data are extremely valuable to make decisions locally on appropriate interventions, allocate resources and evaluate their impact. A priority should be to increase haemophilia's screening in order to avoid deaths due to ignorance of the condition.

W-P-008 (684) | Surgical prophylaxis using long acting factor concentrate in a cohort of haemophilia patients

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Introduction and Objective: Long acting factors are attractive in the management of haemophilia because of less frequent administration. These drugs have been used extensively in prophylaxis and appear promising with regard to support during surgery. This retrospective study looks at the use of extended half-life (EHL) recombinant factors in patients with haemophilia A who underwent surgery at a single centre provided through the WFH humanitarian aid program.

Patients and Methods: Patients with haemophilia who underwent major surgery, either as elective or as emergency, with EHL rFVIIIFc as the clotting factor concentrate (CFC) for haemostasis were included in this study. All these patients were negative for inhibitors. The recovery factor assays were done with a one stage APTT method. The CFC support was continued till suture removal, usually 10 days. Other supportive measures included tranexamic acid, at physician discretion.

Results: A total of 21 patients underwent surgery. There were 19 patients with severe haemophilia A, 1 each with, moderate and mild haemophilia A. The median age was 32 (8-68) years. Out of the 21 procedures, 16 (76.2%) were orthopaedic surgeries, 2 (10.5%) were abdominal surgeries and 1 (5.2%) each was parotid surgery, neurosurgery and skin graft. The orthopaedic surgeries included pseudotumour excision (n = 3), open reduction and internal fixation of fracture (n = 4), corrective osteotomies (n = 5), amputation (n = 2), arthrodesis (n = 1), and curettage (n = 1). The median recovery assay prior to surgery was 101% (63-226). The median trough levels for

post-operative days +1, +3, +5, +7 were 55% (21-139), 47% (29-228), 45% (25-104), and 26% (20-112) respectively. The median total factor used was 151 (123-563) IU/kg for once daily dosage and 388.5 (182-707) IU/kg for twice daily dosage respectively. Nine patients required transfusion of 1 packed red cell each as per expected blood loss in those surgeries. No other blood product transfusion was required. None of the patients developed inhibitor during the perioperative period.

Conclusions: EHL rFVIIIFc can be used safely for major surgery in haemophilia at modest doses with effective haemostasis. Given the longer T ½, with more experience it should be possible to reduce doses further without losing efficacy.

W-P-009 (578) | Continued benefit demonstrated with BAY 81-8973 prophylaxis in children with severe hemophilia A: interim analysis of the LEOPOLD Kids extension study

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Introduction and Objective: BAY 81-8973 (Kovaltry®) is a full-length, unmodified recombinant human factor VIII (FVIII) for prophylaxis and treatment of bleeds in patients with hemophilia A. Safety and efficacy of BAY 81-8973 in children, adolescents, and adults were established in LEOPOLD trials. This analysis reports interim data from LEOPOLD Kids extension study for patients with ≥100 exposure days (EDs) to BAY 81-8973.

Materials and Methods: In LEOPOLD Kids, boys aged ≤12 years with severe hemophilia A and ≥50 EDs to FVIII received BAY 81-8973 (25-50 IU/kg) ≥2 times/wk for ≥50 EDs. Patients completing the main study could enroll in an ongoing extension for ≥100 EDs.

Results: Of 51 patients who completed the main study, 46 entered the extension (aged <6 years, n = 22; aged 6-12 years, n = 24). Patients were treated for a median (range) of 1494 (175-1989) days and accumulated 546 (67-1011) EDs in the extension. Median (quartile [Q]1; Q3) dose per prophylaxis infusion was 37.7 (33.1; 41.8) and 30.9 (29.1; 34.9) IU/kg for younger and older patients, respectively; annual prophylaxis dose was 4984 (3679; 6529) and 4089 (3283; 5555) IU/kg. Median (Q1; Q3) annualized number of total bleeds was 1.95 (0.21; 4.18) and 1.79 (0.49; 2.95) for younger and older patients, respectively; annualized total bleed rate was 2.95 (0; 6.02) and 0 (0; 6.38) for these patients in the main study. Median (Q1; Q3) annualized total bleeds within 48 hours of prophylaxis infusion was 0.82 (0; 1.74) and 1.02 (0.12; 1.63) in younger and older patients in the extension. Response was excellent/good in 337/405 bleeds (83.2%); data were missing for 22 (5.4%) bleeds. Most bleeds (93.5%) were mild/moderate and were spontaneous (42.4%) or traumatic (53.6%). One patient experienced a mild treatment-related serious adverse event (transient very low FVIII inhibitor titer concurrent with acute infection and positive immunoglobulin G anticardiolipin) and remained in the extension. No change in therapy was required, and the patient was clinically well.

Conclusions: Data from LEOPOLD Kids extension show that BAY 81-8973 provides safe and effective long-term prophylaxis in children with severe hemophilia A, confirming safety results observed in the main study.

Conflicts of Interest: Gili Kenet has received research support from Bayer, received honoraria from Bayer for lectures, and participated in an advisory board for Bayer. Valentina Uscatescu has nothing to disclose.

Bryce A. Kerlin has received research support from CSL Behring and has served as a consultant for Bayer and Novo Nordisk. Despina Tseneklidou-Stoeter and Nikki Church are employees of Bayer.

W-P-010 (737) | BAY 94-9027 prophylaxis improves quality of life: Haemo-QoL-A data from the PROTECT VIII study

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Introduction and Objective: BAY 94-9027 is an extended–half-life PEGylated recombinant factor VIII product. Reduced infusion frequency may translate into improved quality of life (QoL) for patients with hemophilia A; QoL data from the phase 2/3 PROTECT VIII study were evaluated to investigate this hypothesis.

Materials and Methods: In PROTECT VIII, 134 previously treated males aged 12–65 years with severe hemophilia A received BAY 94-9027 on demand or as prophylaxis twice weekly (30–40 IU/kg), every 5 days (45–60 IU/kg), or every 7 days (60 IU/kg) for 36 weeks. QoL was assessed at baseline and week 36 using Haemo-QoL-A (disease-specific tool; range, 0–100) and Health Utility Index Mark 2 (HUI2; generic tool, range, 0–1; higher scores indicate higher QoL for both instruments).

Results: Baseline Haemo-QoL-A scores were lower in patients treated on demand before the study (n = 41) versus patients who received prophylaxis before enrollment (n = 77). Regardless of previous treatment, a consistent and positive trend was observed towards improved QoL for all patients who received prophylaxis during the study (n = 97; median total Haemo-QoL-A change at week 36 vs baseline, +2.5); no QoL improvement during the study was observed in patients treated on demand. Greater improvements in total score (minimal important difference [MID], 6–7) and all domains, particularly the physical functioning domain (MID, 9–11), were seen in patients with previous on-demand treatment who received BAY 94-9027 prophylaxis (n = 21) and was more pronounced in the every-7-days group (n = 5; median change at week

36 vs baseline, +13.8 [total score] and +13.3 [physical functioning]), resulting in a median total score (75.1) that was only slightly lower versus patients who received previous prophylaxis (80.9). For HUI2, although no meaningful change over time was observed for the prophylaxis group as a whole, MID (0.03) was exceeded in patients who previously received on-demand treatment and switched to every-7-days BAY 94-9027 prophylaxis (n = 5; median change from baseline, +0.11).

Conclusions: In patients previously treated on demand, QoL improved during BAY 94-9027 prophylaxis. Most improvement was observed in patients treated every 7 days, which suggests that every-7-days treatment is the preferred regimen for patients who were not receiving prophylaxis treatment before the study.

Conflicts of Interest: Shadan Lalezari is a consultant for Bayer and Teva Pharmaceuticals and has previously consulted for Pfizer. Camila Linardi and Monika Maas Enriquez are employees of Bayer.

W-P-011 (677) | A prospective randomized double-blind trial of celecoxib versus acetaminophen in haemophilic arthropathy

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Introduction and Objective: Cyclooxygenase-2 inhibitors have been used to treat pain of haemophilic arthropathy. However, there has been no prospective study comparing these drugs with conventional analgesics in haemophilic arthropathy. This study aims to prospectively evaluate the efficacy of celecoxib compared to acetaminophen in a randomized double blind clinical trial in patients with severe haemophilia.

Patients and Methods: Patients with chronic haemophilic arthropathy, aged between 11-60 years having VAS (Visual analogue score) of at least 4 with activities were enrolled in the study. The extent of arthropathy in the affected joints was assessed by plain Xray. In addition to VAS, HJHS (haemophilia joint health score) and FISH (functional independence score for haemophilia) were done at study entry and at 1 week and 6 weeks. Patients were randomized 1:1 to acetaminophen or celecoxib. They were given either oral celecoxib 200 mg/day (children 100 mg/day) once daily or oral acetaminophen 4000 mg/day (children 80 mg/kg/day) in 4 divided doses for a period of six weeks. The patients and investigators were blinded to the study drugs.

Results: A total of 43 patients were included in the study. There were 21 patients in the acetaminophen arm and 22 in the celecoxib arm. The median age was 27 (11-51) and 25 (13-37) years, respectively. There were 19 patients with haemophilia A in both arms. The median Petterson score was 6 (1-12) and 8 (1-11) in the 2 groups (P = .12). The median VAS at study entry was 7 (4-10) and 6.5 (4-10) in each arm (P = .83). The median VAS at 1 week (5 [0-9] & 5 [2-7] P = .65) and at 6 weeks (4 [0-8] & 4 [2-7] P = .90) showed improvement in both arms. There was no significant difference in the median HJHS and FISH at 0, 1 and 6 weeks.

Conclusions: Both acetaminophen and celecoxib are effective in achieving comparable analgesia in patients with pain from chronic haemophilic arthropathy. Both drugs were very well tolerated. There was no breakthrough pain requiring additional medication in either arm. The lesser frequency of administration and therefore possibly, better compliance with medication will favour celecoxib.

W-P-213 (667) | Topical application of tranexamic acid after dental extractions does not induce systemic plasma levels

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Introduction and Objectives: Antifibrinolytic therapy, either topically or systemically, is often used as adjuvant therapy to achieve adequate hemostasis in patients with inherited bleeding disorders (IBD). We intend to present the preliminary results of an ongoing study which aimed to analyze the systemic absorption of tranexamic acid (TXA) topically used as adjuvant therapy for bleeding control in IBD patients undergoing dental extractions (DE).

Materials and Methods: A prospective, multicenter, phase II study enrolled 26 IBD patients whom needed DE. Thirty-five DE procedures were randomized into two groups: study group – an 8% bioadhesive gel of TXA (Kin Exogel, Kin Lab, S.A., Spain) was topically applied over the surgical site after DE, t.i.d., for 07 days. Control group – 10 mg/Kg of TXA was prescribed t.i.d. starting 01 day before DE and continuing for 7 days. Both groups received factor replacement therapy (FRT) according to the underlying disease at least 01 hour before DE. Peripheral blood samples were collected immediately before and 01 hour after DE. The measurement of plasma levels of TXA was performed using nuclear magnetic resonance spectroscopy.

Results: Only two patients presented bleeding who required FRT, both from the study group (P = .25). The plasma levels of TXA in the study group were below the limit of detection in both periods of blood collection. In the control group, the mean plasma level concentration of TXA was 1.26 mg/L (0.29-12.1), and 0.94 mg/L (0.23-10.9) before and after DE, respectively.

Conclusions: Topical application of an 8% bioadhesive gel of tranexamic acid after DE in IBD patients was safe and did not appear to induce significant systemic absorption. Complementary analysis of the samples by mass spectrometry will be performed in order to confirm these results.

04_CLOTTING FACTOR CONCENTRATIONS

W-FPYR-003 (320) | Detection and localization of intracellular FVIII in IPS derived endothelial cells from three Hemophilia A (HA)-patients with null mutations

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Introduction and Objectives: The mutation type plays a pivotal role during inhibitor development for severe` HA-patients. Null mutations like large deletions, nonsense mutations or Intron 22 inversions (I22I) have the highest risk for inhibitor development. For *F8* nonsense mutations the position of a pre-terminal stop codon (PTC) affects the immunogenicity against replacement FVIII, showing an inhibitor risk of 70% for the mutation R1941X located in the A3 domain of FVIII. We earlier discovered an abnormal intracellular trafficking of FVIII in IPS-derived endothelial cells from one HA-patient (P1-A3X) harbouring the PTC at position R1941X. To verify this mutational effect we reprogrammed a second patient (P2-A3X), harbouring the same mutation and added one I22I-patient.

Materials and Methods: Blood from three HA-patients (P1-A3X, P2-A3X, P3-I22I) and one healthy donor (Cm) were reprogrammed using episomal vectors. Stable IPS clones were differentiated into vascular endothelial cells (vECs) and CD144 MACS-separated to analyze intracellular FVIII (Immunostaining: FVIII A2 domain & vWF).

Results: Wild type vECs (Cm) show FVIII together with vWF strongly accumulated close to the nucleus and with some weak signal in the tips of the cell. P1-R1941X and P2-R1941X present a clear shift of FVIII into the tips of the cell with only weak co-localization with vWF. P3-I22I shows intense diffuse distribution of intracellular FVIII, but no co-localization with vWF.

Conclusions: The high-risk inhibitor mutation R1941X presents an abnormal intracellular trafficking of FVIII. However, the individual genetic background of each patient can influence the trafficking machinery. Future organelle co-staining and comparison to low inhibitor risk mutations will clarify if this abnormal trafficking is responsible for the high immunogenicity of this mutation.

T-FPMED02-001 (491) | Safety and pharmacokinetics of subcutaneously administered Factor IX variant ISU304/CB2679d in hemophilia B patients

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Introduction and Objective: Currently, Factor IX (FIX) products are administered into Hemophilia B patients intravenously. Although subcutaneous (SQ) is a preferred route of administration, low bioavailability and low potency of FIX products limited SQ administration. ISU304/CB2679d is a Factor IX variant showing 22-fold enhanced potency due to its resistance to ATIII inhibition, increased catalytic activity and affinity for FVIIIa, which enables SQ administration. This study is to evaluate the PK and safety of ISU304/CB2679d following intravenous (IV) and SQ dosing and to find a dose for daily SQ administration allowing near normal FIX activity (>40%) in severe hemophilia B patients.

Materials and Methods: Single IV BeneFIX of 75 IU/kg followed by single IV ISU304/CB2679d of same dose were given in Cohort 1. In Cohort 2 and 3 single IV ISU304/CB 2679d 75 IU/kg followed by single SQ ISU304/CB2679d (75 and 150 IU/kg, respectively) were administered. Cohort 4 was omitted. In Cohort 5 daily SQ dosing of ISU304/CB2679d for 6 days were administered. Not only PK parameters (C_{max}, T_{max}, $AUC_{0\text{-}t}$, $t_{1/2}$, CL, Vss, and $MRT_{0\text{-}t}$, K) and PD parameter (aPTT) but also safety parameters (adverse events, physical examination, vital signs, electrocardiogram, FIX inhibitors and anti-drug antibodies and laboratory tests for DIC and thrombosis) were monitored. Safety follow-up continued at least 2 weeks after last blood sampling for PK analysis. Data Safety Monitoring Board meeting and Data Monitoring Committee were held after completion of safety and PK analysis of each Cohort to determine progression into the next Cohort.

Results: In the cohort 2 and 3, subcutaneously administered ISU304/CB2679d showed and 1.4- to 4.8-fold prolonged half-life compared with intravenously administered ISU304/CB2679d (IV; 25.6 h~35.2 h (median = 27.2 h) vs SC; 36.2~124.3 h (median = 59.8 h). Following SQ injection, some patients experienced minor generalized or localized adverse events which were expected after SQ injection.

Conclusion: This interim result of Safety and PK profiles of SQ ISU304/CB2679d supports its prophylactic use for severe hemophilia B patients. Complete safety and PK profiles for all the cohorts, including daily dosing, will be reported.

M-FPMED01-001 (738) | Distribution of rFIXFc and FIX using in vivo PET imaging analysis in non-human primates

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Background: The pharmacokinetic (PK) profile of factor IX (FIX) is consistent with a two-compartment model where FIX largely distributes to a space outside of the plasma compartment (extravascular space). We have previously shown using SPECT imaging that the rFIXFc and rFIX biodistribution profiles in hemophilia B mice are consistent with the hypothesis that FIX can distribute to tissues outside of the plasma compartment, while glycoPEGylated-rFIX remains mostly in the plasma compartment due to the PEG modification. In this study we evaluated the distribution of rFIX and rFIXFc in nonhuman primates (NHP).

Methods: rFIXFc and rFIX were labeled at lysine residues using ^{124}I-SIB (succinimidyl iodobenzoate). Cynomolgus monkeys received a single IV bolus injection of ~2 mCi tracer dose of ^{124}I-SIB-rFIXFc (2 mg/kg) or ^{124}I-SIB-rFIX (1 mg/kg). Reconstructed whole-body PET/CT scans were used to generate maximum-intensity projection images and *in vivo* biodistribution was determined via regions of interest analysis.

Results: PET imaging in NHP showed an early distribution of ^{124}I-SIB-rFIXFc and ^{124}I-SIB-rFIX in the blood pool, heart, liver and kidneys. At later time points both rFIXFc and rFIX showed distribution to shoulder joints as well as other bone joints (wrist, ankle and jaw) with rFIXFc displaying significantly higher distribution to these areas, even at time points when FIX plasma levels were below the detection level. Both in vivo and ex vivo data showed blood pool clearance of rFIXFc and rFIX. TCA precipitation data showed >95% radioactivity was associated with the FIX.

Conclusions: The rFIXFc and rFIX biodistribution profiles in NHP are similar to those observed in hemophilia B mice and are consistent with the hypothesis that FIX can distribute to tissues outside of the plasma compartment. The significantly higher distribution of rFIXFc to joint areas compared to rFIX could potentially reflect retention at these tissues due to improved PK. While the role of extravascular distribution in prevention of bleeding and overall protection of joint health remains an area of investigation, this study is consistent with the observations in mice that demonstrated biodistribution differences for FIX variants suggesting plasma levels may not be comparable, or have the same meaning, across FIX variants.

M-MP-023 (447) | Molecular design of MG1121, a novel vWF-independent long-acting FVIII

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Introduction and Objective: Recently developed long-acting FVIIIs are still inconvenient because patients are administered two or three times per week even with these drugs. To overcome this, the half-life of FVIII should be extended at least three times longer than that of rFVIII in HA mice. We are exploring a novel vWF-independent long-acting FVIII by generating FVIII linked with the D'D3 domain of the vWF, which contains the FVIII binding domain, and then by conjugating it with PEG.

Materials and Methods: To reduce the size of the B domain and to conjugate PEG to it, we made several single-chain FVIIIs (scFVIII) having different truncations in the B domain. These molecules were transiently expressed in HEK293F cells, and the one showing best expression level was used for further development. We made eleven scFVIIIs having single amino acid substitution with cysteine in the B domain, PEGylated them and evaluated their PEGylation efficiency by SDS-PAGE. Amino acids linkers were used to connect the D'D3 monomer to C-terminus of scFVIII to prevent its binding to endogenous vWF. After conjugation with PEG, pharmacokinetic behavior of three PEG-scFVIII-D'D3s having different linkers were evaluated in HA mice. Four different PEGs (5, 10, 20, and 40 kDa linear) were conjugated, respectively, to scFVIII-D'D3, and then the pharmacokinetic behavior of these PEG-scFVIII-D'D3s were also evaluated.

Results: While lower than 1 IU/mL was achieved in the expression of three or less N-glycosylation sites containing scFVIIIs, five times higher expression was apparent in those having more N-glycosylation sites in their truncated B domains. Considering this tendency and PEGylation efficiency, we selected one optimal site where PEG can be attached. The half-life of PEG-scFVIII-D'D3 linked with 60, 120 and 300 amino acids linkers was 2.87, 3.50, and 2.45-fold longer than that of rFVIII, respectively. The half-life also increased by 1.65, 2.01, 3.00 and 3.48-times longer than that of rFVIII, as the length of PEG increased.

Conclusions: MG1121 possesses 3.0-fold more extended half-life compared to rFVIII. It has a great potential to overcome limitation imposed by vWF, so that it could become a novel FVIII chimera administrable on a weekly basis.

M-P-020 (406) | Use of high-purity factor X for on-demand treatment of bleeding episodes in factor X deficient patients: Results from a multicenter, retrospective, data collection study

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Introduction and Objective: A high-purity, plasma-derived factor X (FX) concentrate (pdFX) is licensed in the United States and Europe to treat congenital FX deficiency (FXD). Here we present long-term efficacy and safety results for pdFX for on-demand treatment of bleeding episodes in FXD patients who received pdFX on a compassionate-use basis.

Materials and Methods: An open-label, retrospective, multicenter, international study was conducted. Subjects with hereditary FXD who had received pdFX on a compassionate-use basis were given pdFX as routine prophylaxis, on-demand treatment, short-term prevention, and/or perisurgical hemostatic cover. The on-demand treatment population was defined as all subjects receiving ≥1 pdFX infusion to treat a bleed. Dosing was set at the discretion of the investigator and tailored to each subject. Efficacy assessments included the number of bleeds/year/subject, total dose/year/subject, dose and exposure days to treat a bleed, and investigator's efficacy assessment in treating a bleed (effective, not effective, or unknown). Standard safety data (adverse drug reactions) were collected.

Results: Of the 15 subjects in the study, 8 were in the on-demand treatment population; two of these subjects also received short-term preventative treatment. All subjects were aged ≥12 years. All 8 subjects reported ≥1 bleed; the mean number of bleeds/subject was 8.9 (range: 2–26), with a mean of 0.80 bleeds/subject/month. The mean pdFX dose/infusion/subject was 20.445 IU/kg (range: 13.60–27.66 IU/kg); mean total pdFX dose/subject was 237.1 IU/kg. Mean exposure days per subject was 10.4; mean duration in the study was 1.4 years. A total of 69 pdFX-treated bleeds were reported (35 menorrhagic, 22 traumatic, 8 spontaneous, 4 other or unknown); twenty were rated as minor severity, 4 were rated as major (2 traumatic muscle bleeds, 1 spontaneous renal bleed, 1 spontaneous subdural hematoma), and 45 were not rated. For all bleeds, the investigator assessed pdFX treatment as effective. No adverse drug reactions, safety concerns, infusion site reactions, tolerability issues, or inhibitor development were reported during pdFX compassionate use.

Conclusions: During long-term compassionate use, pdFX was shown to be safe and effective for the on-demand treatment of bleeding episodes in subjects with hereditary FXD.

M-P-024 (514) | Risk of inhibitor and purity of FVIII: the apparent paradox of plasma derived concentrates?

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During the last decades, the manufacturing of Factor VIII (FVIII) concentrates aimed enhanced safety by different methods including production and purification processes. These efforts have resulted in a dramatic reduction of the infectious risk of these treatments, independently of the type of FVIII (recombinant FVIII/rFVIII or plasma derived FVIII/pdFVIII). During the same period, the high risk of inhibitor development was not reduced. Surprisingly some recent studies based on large cohort of patients suggested the requirement to consider the risk of inhibitor individually for each type of concentrate, regardless of class. The international randomized study SIPPET found a lower incidence of inhibitors in PUPs treated with pdFVIII. Moreover, the FranceCoag group reported a lower risk in patients treated with the pdFVIII concentrate Factane® by comparison with two rFVIII. These observations suggest that differences in final formulation of marketed FVIII concentrates, induced by different production and purification processes, may modify their global immunogenicity. In our study we tested the variability of proteins related to FVIII activity express in IU, for the two pdFVIII and the three rFVIII, most used in France in last decade. We also checked the presence of protein residues in vials that could modify immunogenicity or interfere with the FVIII activity. Six different batches for each FVIII concentrate have been tested. Announced dose in UI and total quantity of proteins indicated by the manufacturer have been confirmed by chromogenic assay and by Bradford dosage Method, respectively. The contaminants proteins have been searched by LC-MS/MS proteomic analysis with nrLC-HESI-Q-Orbitrap and identified thanks to bioinformatics Mascot search in NCBInr database. Relative quantity of each protein has been calculated by Mathias Mann's label free method. We focus here on residual proteins in pdFVIII. The presence of proteins implicated in coagulation pathways was expected, but the high number of proteins, their diversity and the impressive amount of some of them were unpredicted. Interestingly, the presence of some contaminant proteins, known to interfere with immune regulation system could reduce the risk of inhibitor development of pdFVIII treatments. These results suggest a positive impact of low specificity of purification process that characterizes pdFVIII.

M-P-025 (714) | Real-World expenditures associated with Prophylactic Factor IX replacement in Severe Hemophilia B patients in the US: A comparison between standard and extended half-life products

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Introduction and Objective: Management of Hemophilia B requires intravenous factor IX (FIX) infusions. Recombinant extended half-life (EHL) FIX products have been introduced in the US that require less frequent infusions compared to the standard half-life (SHL) products. Consequently, EHL products in the US are priced higher per IU than SHL FIX products. We compared real-world expenditures in the US associated with treatment of Hemophilia B patients with EHL products (eftrenonacog alfa and albutrepenonacog alfa) versus recombinant SHL product (nonacog alfa).

Materials and Methods: A large US national specialty pharmacy dispensation claims database was used to calculate monthly factor IUs dispensed, and associated expenditures, for male severe hemophilia B patients (ICD-9 286.1/ICD-10 D67) receiving prophylactic FIX replacement who used nonacog alfa, eftrenonacog alfa, and/or albutrepenonacog alfa from April 2015 to September 2017. The wholesale acquisition cost specific to each month for each product was used. Monthly averages were calculated for each patient considering the months in which the first and last prescriptions occurred, and intervening months. Descriptive statistics were used to analyze results. Medians for expenditures and IUs dispensed were used to accommodate for the skewness of data distribution.

Results: 177 patients were identified who received at least one of the three products – 110 patients were dispensed nonacog alfa, 74 patients eftrenonacog alfa, and 30 patients albutrepenonacog alfa. The albutrepenonacog alfa group had a higher proportion of patients <18 years of age (66.7%) compared to nonacog alfa (56.4%) and eftrenonacog alfa (40.5%) groups. Median (interquartile range [IQR]) monthly average IUs dispensed were higher with nonacog alfa (25,492 [28,038]) versus eftrenonacog alfa (17,331 [16,142]) and albutrepenonacog alfa (10,325 [8855]). However, median [IQR] monthly expenditures were lowest for nonacog alfa ($33,973 [38,912]) compared to eftrenonacog alfa ($51,388 [48,003]) and albutrepenonacog alfa ($43,882 [37,635]).

Conclusions: This real-world data analysis showed higher expenditure among US severe Hemophilia B patients receiving EHL prophylaxis compared to SHL. The relatively few number of individuals receiving EHL products limit the conclusions that could be drawn, but these analyses reflect the early experience with these agents in the US.

M-P-029 (228) | Bayesian pharmacokinetic individualization of prophylaxis with recombinant factor VIII in severe or moderate hemophilia A

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Introduction and Objectives: Knowledge of the individual's pharmacokinetics (iPK) using Bayesian analysis with 2-3 samples could help to individualize prophylactic therapy with recombinant factor VIII (rFVIII) in severe/moderate hemophilia A patients (HA) and minimize risk of bleeding.

Material and Methods: Retrospective study in HA with Advate® prophylaxis (January 2014-September 2017). A Bayesian model (myPKFit®) was employed to get iPK profile using FVIII trough levels retrospective data. PK parameters analyzed were: clearance (Cl); steady state volume (Vss); half-life ($t_{1/2}$); trough level at 48/72 h (TL); and time to reach rFVIII<1% (T1%). Kruskal-Wallis test (R®) was used to compare PK parameters and clinical variables: age, dose/kg, annualized joint bleeding rate (AJBR), Gilbert score.

Results: Eighteen patients were analyzed. Mean age was 36.7 years (SD:13.3; range:16-70) and 144 PK monitoring were made. Mean PK values (SD) were: Cl 3.0 (0.6) mL/h/kg; Vss 52.2 (7.3) ml/kg; $t_{1/2}$ 13.9 (2.5) h; TL at 48 h 4.6 (2.7) IU/dL, TL at 72 h 1.7 (1.5) IU/dL and T1% 75.8 (17) h. The median dose/kg was 62.4 (12.9) IU/kg/week and mean Gilbert score of 17 (12.1). Along the last year, 7 patients (38.9%) reported joint bleeds (JB), with a mean of 0.6 JB/patient/year, instead prophylaxis. A significant association between AJBR and $t_{1/2}$ was noted ($P = .017$) when $t_{1/2}$ was categorized in short (<p25 12.3 h), normal (p25-p75) and long (>p75 15.4 h). In 3 patients JB were related to low TL48 (TL72 not evaluable) and short $t_{1/2}$ (#1:$t_{1/2}$ 10.2 h, TL48 0.8 IU/dL; #7:$t_{1/2}$ 11.8 h, TL48 2.9 IU/dL; #9:$t_{1/2}$ 11.3 h, TL48 1.9 IU/dL). However, several JB were reported in 3 patients with high Gilbert score and severe arthropathy (Gilbert #11:28, #13:23; #17:36), whereas their estimated TL and $t_{1/2}$ were appropriated (#11:$t_{1/2}$ 14.1 h, TL48/72 5.4 and 1.7 IU/dL; #13:$t_{1/2}$ 16.5 h, TL48/72 9.4 and 3.4 IU/dL; #17:$t_{1/2}$ 16.5 h, TL48/72 6.6 and 2.4 IU/dL).

Conclusions: Bayesian estimate with myPKFit® allows to know the iPK profile and could be a useful tool to individualize prophylaxis, along with physical activity and bleeding pattern. Patients with short $t_{1/2}$ are more prone to bleeding and a personalized prophylaxis would be adequate, although other factors such as articular state also influence the AJBR. We are running a personalized 1-year program to identify and treat the causes of poor bleeding control in HA prophylaxis.

M-P-030 (334) | Real world experience of Elocta in paediatric patients with severe haemophilia A in Ireland

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Introduction and Objective: The standard prophylaxis for all paediatric patients with severe Haemophilia A was Advate. Since May 2016, Elocta has been offered to children with severe haemophilia A fulfilling the following criteria: no history of FVIII inhibitor, >50 exposure days to factor VIII concentrate and three or more infusions of factor VIII concentrate weekly. The aim of this study was to compare bleeding history of those patients while on Advate and Elocta. The specific objectives were to identify if patients developed inhibitors, the weekly consumption of factor dose/kg and if bleeds were spontaneous or traumatic joint or non-joint bleeds.

Method: Twenty two children met the criteria to switch and were offered the option to switch. Data was collected one year pre and post commencement of Elocta. This data was collected from the patient Electronic Health Care Record System (ClinTech). Bleeding episodes included head Injuries, joint bleeds, lacerations, fractures, epistaxis and mouth bleeds. All were reported by the parents to the nursing/medical staff and required treatment with Elocta. Results

Twenty two patients aged between 2-16 years agreed to change their treatment of choice from Advate to Elocta. On review of the year pre commencement of Elocta, fifteen children had a total of twenty eight bleeding episodes. Of these bleeds, three were spontaneous, twenty four were traumatic, and one unknown cause, of which, eleven were joint bleeds and seventeen non-joints bleeds. The year post commencing Elocta identified ten children having a total of eighteen bleeding episodes. One was spontaneous, fourteen were traumatic and three of unknown cause, of which, thirteen were non-joint bleeds and five were joint bleeds. The overall median usage of Advate was 118 iu/kg 2.8 times per week. The overall median usage of Elocta was 105 iu/kg two times per week.

Conclusion: Overall this study found that there were no reactions to Elocta, no patients developed inhibitors, no patients requested to switch back, overall average usage decreased by 13 iu/kg/week, and less bleeding episodes on the longer acting factor. With fewer IV administrations, the quality of life has improved for these patients and their families.

M-P-031 (269) | Scottish experience introducing extended half-life factor concentrates in Haemophilia A and Haemophilia B patients

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Introduction & Objectives: Extended half-life (EHL) factor concentrates are a recent advance in Haemophilia treatment. Longer half-life products have the potential to offer less treatment days and higher factor trough levels which appeals to both patients and haemophilia treaters. We evaluated the use of EHL factor concentrates in Scotland.

Material & Methods: Haemophilia Treatment Centres submitted data on their experience of switching patients to EHL factor concentrates. Data included which EHL factor concentrates they had been switched to, dose, dosing interval, trough levels and bleeding rate since changing. Details of previous treatment were collected for comparison.

Results: 11 adults and 4 children with Haemophilia B switched to EHL factor concentrates (13 Idelvion and 2 Alprolix). 4 patients have been established on fortnightly dosing, 10 on weekly dosing and 1 on every 4th day prophylactic regimes with trough factor IX levels between 0.05-0.13 IU/ml. All but one patient have less treatment days per year on EHL factor concentrates. Physical disability made standard half-life product prophylaxis unfeasible for this one patient; however this has been overcome by extended dosing intervals with EHL factor concentrate. There has been no increased bleeding rate in Haemophilia B patients who have switched to EHL factor concentrates. There was a net annual cost of £82,072 switching all 15 Haemophilia B patients to EHL factor concentrates. 3 adults and 4 children with Haemophilia A switched to EHL factor concentrates (Elocta for all patients). Regimes vary from alternate days, twice weekly, every 4th day and weekly, with trough factor VIII levels between 0.01-0.06 IU/ml. Again the only patient to experience more treatment days on EHL factor concentrates switched from on demand treatment to prophylaxis.

Collection of bleeding rates for haemophilia A patients is ongoing and not yet available. There was a net annual cost of £99,308 switching all 7 Haemophilia A patients to EHL factor concentrates.

Conclusions: Across Scotland there is variation in how EHL factor concentrates are being used although all regimes achieve satisfactory troughs and there appears to be no increased bleeding rate.

M-P-032 (371) | Annualized bleeding rates: Their importance, implication and impact from a Regulatory perspective

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Introduction and Objective: Hemophilia, an inherited bleeding disorder, can lead to spontaneous and trauma-induced bleeds, especially in joints and soft tissue associated with various pain conditions. Every bleeding episode might have significant negative impact on joint status and quality of life of patients. Therefore, the reduction of bleeding episodes, calculated as the annualized bleeding rate (ABR), is often used as a measure for the efficacy of Hemophilia treatment. The calculation of an ABR might be challenging, depending on the definition of a bleed, treatment modalities, joint status and individual pain perception, time of follow-up and number of patients analyzed.

Materials and Methods: Definitions of ABR from clinical trial reports were compared. The PEI-Database encompasses anonymized data from >1300 patients receiving more than 85.000 Factor concentrate infusions investigated in 30 clinical trials. Factor concentrate administration following on-demand and different prophylactic treatment regimen and corresponding reasons for treatment (e.g. spontaneous or trauma bleed, pain, surgery, trial-related, follow-up) were analyzed. Additional parameters included in the investigation were: age, severity of Hemophilia, and consumption.

Results: The definition of ABR is various, which hinders a direct comparison of ABRs used within clinical trials for single products. The result of this analysis will provide guidance on the minimum standards that should be used in clinical trials performed for regulatory purposes.

Conclusions: To be able to compare ABRs, to enable conclusions on treatment regimes, products and potential benefit for specific patient cohorts a clear definition of parameters and characteristics is absolutely necessary.

M-P-033 (461) | Incidence of factor VIII inhibitor in Korean previously untreated hemophilia A patients

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Introduction and Objectives: Incidence of inhibitor in Korean hemophilia A patients is known as 21.6%. However inhibitor development by the origin of the factor concentrates is still under debate. We investigated inhibitor incidence by the origin of factor concentrates in Korean hemophilia A previously untreated patients (PUPs).

Materials and Methods: We retrospectively reviewed the medical records of 256 PUPs (plasma derived factor VIII (PdFVIII) 108 vs. recombinant factor VIIII (rFVIII) 148) who registered in Korea Hemophilia Foundation. Among them, 179 PUPs (PdFVIII 82 vs. rFVIII 97) were severe. Age at diagnosis was 4.3 years old, but severe patients were diagnosed at 2.5 years old. Inhibitor which had existed more than 1.5 years at the start of study was regarded as persistent inhibitor. Inhibitor more than 5 BU/mL was classified as high titer.

Results: Incidences of inhibitor in the total PUPs and severe PUPs were 18.4% and 24.6%. Ten patients among 108 PdFVIII PUPs (9.3%) developed inhibitors whereas 22 of 148 rFVIII PUPs (14.9%) developed inhibitors. Seventy-five PdFVIII users had ultimately switched over to rFVIII and after switching, 14 patents developed inhibitors including 6 persistent inhibitors. In total, 16.1% of rFVIII-injecting patients developed inhibitors. The titers of inhibitors developed after using of rFVIII were much higher than PdFVIII; 27.6 vs. 6.5 BU/mL.

Conclusions: Incidence of inhibitors in rFVIII-injecting PUPs was substantially higher than PdFVIII-injecting PUPs. Titers of inhibitor in rFVIII-injecting patients were also higher than PdFVIII-injecting patients.

M-P-034 (486) | Utility of converted factor VIII activity by thrombin generation assay for evaluation of clotting function among hemophilia A carriers

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Introduction and Objective: Heavy menstrual bleeding (HMB) and severe postpartum hemorrhage (SPH) in female carriers with hemophilia A (HA) are serious events. The precise evaluation of hemostatic function is essential for treatment, but FVIII:C does not always correlate with bleeding phenotype.

Materials and Methods: We investigated 6 symptomatic females (case 1: HMB, 2: frequent nasal bleeding, 3: HMB, 4: HMB, 5: SPH, 6: SPH) and 12 asymptomatic females (case 7-18) with heterozygous *F8* mutation (case 1, 2: splice site mutation, 3, 9: small ins/del outside poly A, 4-8, 14-18: missense, 10-12: nonsense, 13: intron 22 inversion) from 14 families of HA patient(s) in our hospital. The median values of FVIII:C, FVIII:Ag, VWF:RCo and VWF:Ag among them were 49 (IQR: 34.7-55.2), 45 (35.8-58.5), 81 (79.2-98.5) and 93 (66.3-105.8)%, respectively. Thrombin generation assay (TGA) triggered by tissue factor (0.5 pM) and ellagic acid (0.3 μM) was examined and the value of peak thrombin-height (PeakTh) was evaluated in the plasmas obtained from these females.

Results: PeakTh (mean ± SD) of symptomatic females was 402 ± 51 nM, lower than that of normal control (511-619 nM), whilst that of asymptomatic cases was 539 ± 55 nM within normal range. In order to compare the hemostatic potentials evaluated

by TGA and FVIII:C, the contrived standard plasmas consisting of FVIII deficient plasma and serial dilutions of rFVIII (0-1 IU/mL) were prepared, and we evaluated the hemostatic function of FVIII by TGA (TGA-FVIII) in each sample. TGA-FVIII (no less than 40%) was concordant with FVIII:C among asymptomatic females. In contrast, the values of TGA-FVIII were below 30% and a discordance between TGA-FVIII and FVIII:C was observed among symptomatic females but for case 3 (case 1: TGA-FVIII/FVIII:C 2.8/32%, 2: 17.2/34%, 3: 22.3/25%, 4: 4.9/31%, 5: 11.2/52%, 6: 19.2/43%). This discordance would be determined by wild-type/mutant FVIII ratio in the plasma affected by inactivation of X chromosome carrying non-null *F8* mutation.

Conclusion: We concluded that TG-based FVIII assay would be useful for precise evaluation of the hemostatic functions influenced by *F8* mutation among HA carriers.

M-P-035 (513) | An en-masse switch to extended half life recombinant factor IX replacement therapy in Irish adults with Haemophilia B

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Introduction and Objective: Prophylaxis with recombinant Factor IX (rFIX) prevents spontaneous bleeds in persons with severe Factor IX deficiency. In 2017, Ireland became the first country to conduct an en-masse switch of patients receiving FIX prophylaxis to an extended half life (EHL) rFIX (Alprolix®, Sobi).

Materials/Methods: Following ethical approval and written informed consent, data was collected from the National Haemophilia electronic health record on rFIX dose and frequency, weight, bleeding events and Haemophilia Joint Health Score (HJHS). Bloods were taken at baseline and at 3 months post switch for virology and FIX inhibitor status. Pharmacokinetic (PK) sampling was performed on standard half life (SHL) rFIX (at +48, +72 and +96 hours; all ±6 hours) and EHL-rFIX (+0.3, +1 hour and trough sample). Patients completed a quality of life PROBE questionnaire on day 0 and at +3 months of EHL-rFIX.

Results: Of 28 adults (median age 43.6 years, range 17.6-69.7) with severe FIX deficiency, 22/28 used SHL-rFIX prophylaxis routinely and 6/28 on-demand, primarily due to poor venous access. The median SHL-rFIX dose prescribed was 77.2 IU/kg/week (range 47.4-181.8) and the median ABR was 3.3 (range 0-20) in the preceding 12 months. All patients were FIX inhibitor negative at enrolment. All but 3 patients had elevated HJHS scores (median 24, range 0-53). All patients commenced prophylaxis with EHL-rFIX (mean 56.0 IU/kg/week, n = 24 or mean 96.9 IU/kg/fortnight, n = 4). Trough FIX levels were significantly increased on EHL FIX versus SHL FIX (mean 0.08 IU/mL versus 0.05 IU/mL) and 57% of patients experienced no bleeds in the first 3-6 months of treatment. A total of 17 breakthrough bleeds were reported in 12 patients following the switchover. Only 4 bleeds required more than one EHL-rFIX treatment. Improved patient experience was reported due to reduced treatment burden and mild side effects were reported, including headache (n = 1), dysgeusia (n = 1) and anxiety (n = 1).

Conclusions: In Ireland, prophylaxis with EHL-rFIX has been offered to all patients with severe FIX deficiency, with evidence of improved FIX trough levels and enhanced patient experience. Extension of the dosing interval for prophylaxis while maintaining protective FIX trough levels offers an opportunity to further reduce the treatment burden.

M-P-036 (546) | Allosteric activation of factor IXa by an antibody binding to the protease domain

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Introduction: BS-125 is a monoclonal antibody against activated factor IX (FIXa) that was identified during the development of a bispecific antibody aimed at mimicking the function of FVIIIa. We have previously shown that while not entirely specific, BS-125 is selective for FIXa over zymogen factor IX (FIX). Here, we provide a deeper characterization of this antibody and its interaction with FIXa.

Methods: The affinity and specificity of BS-125 towards FIX, FIXa, and FIXa with an active site inhibitor were determined using surface plasmon resonance. Biolayer interferometry was used to assess the calcium dependence of this interaction. The structure of a complex between the Fab portion of BS-125 and a truncated FIXa, comprising the EGF2 and serine protease domains, was solved by X-ray crystallography to 2.3 Å resolution. Furthermore, the effect of the bivalent or monovalent forms of BS-125 on FIXa activity toward an amidolytic substrate, as well as its effect on the rate of ATIII inhibition of FIXa, were tested.

Results: BS-125 was determined to bind to FIX, FIXa, and FIXa with an active site inhibitor with 8 nM, 1 nM, and 0.4 nM affinity, respectively. While binding can be observed in the absence of calcium, the interaction between BS-125 and FIXa was greatly enhanced by calcium. The co-crystal structure of the Fab-FIXa complex revealed that the BS-125 epitope overlapped with the FVIIIa epitope and the heparin binding site on FIXa. Furthermore, we found that BS-125 increased the rate of FIXa amidolytic substrate cleavage as well as the rate of FIXa inhibition by ATIII approximately 4-fold.

Conclusions: The ability of BS-125 to positively modulate the activity of FIXa towards a peptide substrate and ATIII are in line with the notion of allosteric activation of FIXa. This regulatory activity appears to be

intrinsically linked to a specific epitope on FIXa that is shared by BS-125, FVIIIa, and heparin. A FIXa antibody with greater specificity and the ability to increase FIXa activity may better mimic the characteristics of FVIIIa, and could result in a FIXa/FX bispecific antibody with greater efficacy.

M-P-037 (697) | A companion protein, click chemistry approach to extended half life FVIII

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Introduction: Standard methods for half life prolongation have been disappointing in FVIII because of its association with von Willebrand's factor (vWF) which imposes an approximately 18 hour half life on the molecule. We have developed a synthetic protein consisting of the D'D3 fragment of vWF, a linker and a full length human albumin. This molecule, CM110, can be tethered to FVIII using click chemistry. The resulting complex should then be divorced from the endogenous vWF and can use the albumin for half life extension.

Methods: CM110 was produced by transient transfection into Expi 293 cells and the protein was purified using a CaptureSelect HSA affinity column. CM110 was treated with 1 mM NHS-PEG12-transcyclooctene (NPT) for 1 hour at room temperature in 10 mM HEPES, pH7.4, 300 mM NaCl, 4 mM $CaCl_2$ then separated from unreacted NPT by Superdex 200 (S200) chromatography. B-deleted FVIII was treated with 1 mM maleimide-PEG4-methyl tetrazine for 1 hour at room temperature in the same buffer, then similarly purified by S200 chromatography. A 3 mg/ml solution of CM110 and 1 mg/ml derivatized FVIII was incubated at room temperature for 2 hours in 20 mM HEPES, pH 7.4, 150 mM NaCl, 4 mM $CaCl_2$ followed by S200 chromatography to isolate the CM110/FVIII complex (S8).

Results: FVIII was quantitatively converted into the S8 complex with a molecular weight of 540,000, a dimer of CM110 containing 2 molecules of FVIII. S8 retains activity in a chromogenic assay and corrects the APTT in FVIII deficient plasma. Preliminary experiments in mice expressing the human neonatal Fc receptor with an albumin knock out suggest a significantly improved half life.

Conclusion: Divorcing FVIII from the endogenous vWF can be effected by tethering D'D3 to the FVIII, enabling use of traditional half life extension techniques, such as albumin ligation.

M-P-052 (42) | Turoctocog alfa is stable during storage at 40°C and multiple sequences of temperature cycling

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Introduction and Objective: Patients with haemophilia can experience spontaneous or traumatic bleeds; therefore practical storage conditions, stability and portability of coagulation factor are critical to provide patients with increased flexibility. Turoctocog alfa is a recombinant FVIII for the treatment of haemophilia A. We examined the stability of turoctocog alfa when stored at 40°C for 3 months and when moved between storage conditions of 5°C and 40°C multiple times.

Materials and Methods: Long-term stability was tested by storing the product at 5°C ± 3°C/ambient humidity/darkness for 27 months followed by storage at 40°C ± 2°C/75% relative humidity (RH) ±5% RH for 3 months. The effect of repeated temperature changes was tested by storage at 5°C ± 3°C/ambient humidity/darkness for 24 months followed by cycling between 5°C and 40°C/75% RH up to 10 times; the drug product was then stored at 40°C/75% RH for 3 months (resulting in a total of 4 months at 40°C), and returned to 5°C to attain 30 months shelf life. All studies utilised the lowest, highest and one intermediate strength of turoctocog alfa (250, 1500/2000 and 3000 IU). Stability assessments included potency (investigated by chromogenic substrate assay), purity and oxidised forms (investigated using reverse phase high performance liquid chromatography) and water content (assessed by near-infrared spectroscopy).

Results: The potency of turoctocog alfa was maintained within the shelf-life specification limits for the product strength tested at high storage temperature and humidity conditions (Fig. 1). Up to 10 cycles of temperature changes and storage at 40°C did not affect potency. For both studies, product purity, oxidised forms and water content were stable; complying with the shelf-life specification limits.

Conclusions: Turoctocog alfa is stable when stored at 40°C and when cycled between 5°C and 40°C. These findings offer more flexibility to patients in their daily activities.

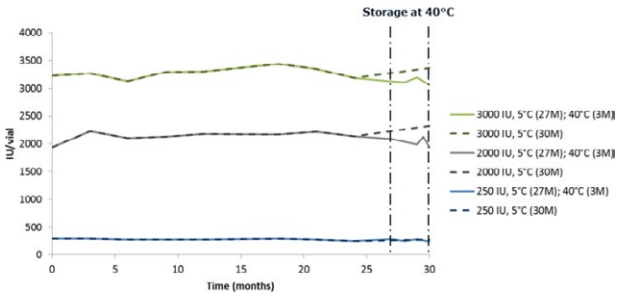


FIGURE 1. Potency of turoctocog alfa (250, 2000 and 3000 IU) stored at 40°C/3 months following storage at 5°C/27 months. Controls were stored at 5°C/30 months. The increase in potency observed for the 2000 and 3000 IU control samples at study end is due to analytical variation. M, months.

Conflicts of Interest: All authors are full-time employees of Novo Nordisk, and were so during the conduct of these studies.

M-P-053 (74) | Correcting hemophilia using in vivo therapeutic protein production by an Afibromer encapsulated gene modified allogeneic cell

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Introduction: Current hemophilia therapies require frequent protein infusions yet are unable to adequately address long-term sequelae due to compliance, peaks and troughs and immunogenicity. To overcome these drawbacks alternative delivery methods such as gene therapy are being investigated. The aim of this study is to determine whether the chronic delivery of blood clotting factors by implantation of gene modified cells producing factor is a more controlled viable alternative with significant upside for patients due to elimination of protein administration and better outcomes due to stable production levels.

Materials and Methods: We are investigating the secretion of blood clotting factors by a gene modified engineered cell line encapsulated with Afibromer™ polymer chemistry using a combination of in vitro (ELISA and activity assays) and murine hemophilia models.

Results: Proprietary cell line engineered to stably express high levels of hFIX or hFVIII and placed in Afibromer™ capsules maintain viability, are contact inhibited and have a long-life span. A time course experiment revealed a rapid secretion of hFIX or hFVIII through the capsules. Upon murine implantation hFIX is detected in the plasma at therapeutically relevant levels. We are currently performing long-term expression studies to monitor durable expression of hFIX or hFVIII in vivo and also performing efficacy studies in FIX- or FVIII-deficient mice.

Conclusions: Taken together, these data confirm the stable clotting factors secretion by our encapsulated engineered cells creating a viable alternative to protein delivery or gene therapy with several important advantages. This platform is amenable to patients suffering from blood disorders requiring chronic therapeutic protein treatment.

M-P-054 (663) | BAX 855 prophylaxis: Efficacy, safety, and immunogenicity in previously treated pediatric patients from the United States, Europe, and the Asia-Pacific region

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Introduction and Objective: Rurioctocog alfa pegol (BAX 855, SHP660) is an extended half-life factor VIII (FVIII) built on the full-length Antihemophilic Factor (Recombinant) protein and is approved for treatment of children and adults with hemophilia A (HA). We evaluated the hemostatic efficacy, safety, and immunogenicity of BAX 855 as prophylaxis in previously treated pediatric patients by geographic region.

Materials and Methods: In this phase 3 multicenter study (NCT02210091), pediatric patients with severe HA were enrolled in 2 age-based cohorts, (<6 years, 6 to <12 years) and received twice-weekly prophylaxis with 50 ± 10 IU/kg of BAX 855 for 6 months or ≥50 exposure days, whichever occurred last. Breakthrough bleeding episodes were treated with BAX 855, with dose determined by bleeding severity and type. Outcomes included annualized bleeding rate (ABR) and incidence of adverse events, including development of inhibitory antibodies to FVIII.

Results: 66 pediatric patients received ≥1 BAX 855 infusion. ABR was evaluated overall, by age group (<6 years, n = 32; 6 to <12 years, n = 34) and by geographic region, with 14/66 patients (21.2%) from Asia-Pacific countries and 52/66 patients (78.8%) from Europe and the United States (US). The point estimate for the mean ABR (95% CI) for all patients was 3.0 (2.2-4.2). ABRs were generally low across age groups and geographic regions (Table). Younger patients had fewer bleeding episodes than older pediatric patients overall and within regions. A mean ± SD of 94.1 ± 2.4% and 93.2 ± 5.5% of prophylactic infusions in the younger and older pediatric patients, respectively, adhered to the infusion schedule. No treatment-related serious adverse events were reported. No patients developed treatment-emergent neutralizing antibodies to FVIII. As expected for this age group, most patients (63/66; 95.5%) did not have hemophilic arthropathy.

TABLE 1 Annualized Bleeding Rate (95% CI) by Age and Geographic Region

	<6 years (n = 32)	6 to <12 years (n = 34)	Total (n = 66)
All regions	2.4* (1.5-3.8)	3.8* (2.4-5.8)	3.0* (2.2-4.2)
Asia-Pacific	n = 7 1.4 (0.5-4.1)	n = 7 2.5 (0.8-7.3)	n = 14 1.9 (0.9-4.1)
Europe	n = 14 2.1 (1.2-3.8)	n = 16 2.4 (1.4-4.3)	n = 30 2.3 (1.5-3.4)
United States	n = 11 3.1 (1.5-6.4)	n = 11 4.7 (2.4-9.2)	n = 22 3.9 (2.4-6.4)

*Historical mean (SD) ABRs were 4.3 (3.7) in <6 years group, 12.4 (27.3) in 6 to <12 years group, and 8.5 (20.0) in Total group.

Conclusions: BAX 855 demonstrated efficacy and safety in previously treated pediatric patients with HA regardless of geographic region. No patients developed neutralizing antibodies to FVIII.

Disclosures: TW is the site PI for studies sponsored by Shire, Bayer, Novo Nordisk, and Pfizer. ST, WE, and MS are all employees of Shire. OS has nothing to disclose. Funding for development of this abstract was provided by Shire Development LLC (Lexington, MA) to C4 Med Solutions, LLC (Yardley, PA), a CHC Group company.

M-P-082 (674) | Changes in bleeding and daily life with emicizumab prophylaxis: a questionnaire in patients with hemophilia A with inhibitors (PwHAwI) and their families in a long-term phase 1/2 study

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Introduction and Objectives: Long-term safety and exploratory efficacy of emicizumab prophylaxis in PwHAwI were demonstrated in a phase 1 study (JapicCTI-121934) and its extension phase 1/2 study (JapicCTI-132195). In the studies, the changes in bleeding and daily life of PwHAwI and their families as a consequence of emicizumab prophylaxis were also explored.

Materials and Methods: Patients (≥12 years) received emicizumab in three dose cohorts with 0.3, 1, or 3 mg/kg/week. Patients and their families were asked to answer an original questionnaire on a voluntary basis to describe the changes in bleeding severity, joint status, daily activities, and overall feeling compared with those before starting emicizumab prophylaxis.

Results: A total of 11 PwHAwI were enrolled in the studies. As of September 2016, nine patients (three for each cohort; aged 12-47 years) and four families (patient age: 12-22 years) answered the questionnaire. The median observation period was 2.9 years. Annualized bleeding rates under emicizumab prophylaxis were lower than those during the prior 6 months under previous treatment in all the patients with reduction rates ranging 49.3%-100%. In the questionnaire, improvements in bleeding and daily life compared with those under previous treatment were suggested (Table). Comments from patients or their families indicated less bleeding severity (*"A bruise doesn't turn a dark bluish-purple color, but remains light in color and resolves relatively quickly."* by patient), less time until bleeding stops (*"Bleeding after blood draws stops more quickly."* by patient), or expansion in the range of activities (*"He is now able to change his clothes and bathe on his own."* by family).

Conclusion: Emicizumab prophylaxis has the potential of improving bleeding-related symptoms and daily life activities in addition to reducing the bleeding frequency.

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M-P-083 (354) | Single centre experience of switching from standard half-life to extended half-life products in patients with severe haemophilia A and B

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Introduction and Objective: The availability of extended half-life (EHL) factor concentrates has provided an option of less frequent dosing for patients on prophylaxis. We present a joint adult and paediatric centre experience with switching patients from their standard factor concentrates to EHL products.

TABLE. Responses from patients and their families on the changes in bleeding and daily life

	Improved	Slightly improved	Unchanged	Slightly worsened	Worsened	No symptom applicable
Patients (n = 9) / Families (n = 4)]						
Change in bleeding severity	5/1	4/3	0/0	0/0	0/0	0/0
Time until bleeding stops	9/4	0/0	0/0	0/0	0/0	—
Joint pain	3/1	4/1	1/1	0/0	0/0	1/1
Joint swelling	3/2	2/0	2/1	0/0	0/0	2/1
Mobility or range of joint motion	2/2	4/2	3/0	0/0	0/0	0/0
Frequency in daily activity	4/3	4/1	1/0	0/0	0/0	—
Frequency in going out or exercise	4/3	4/1	1/0	0/0	0/0	—
Motivation to learn, work or do housework	3/2	4/2	2/0	0/0	0/0	—
Anxiety	6 / 4	3 / 0	0 / 0	0 / 0	0 / 0	—

Materials and Methods: Clinical and laboratory data on patients switched to EHL is presented. We collected information on treatment characteristics 1 year prior to and following the switch.

Results: A total of 32 patients were switched to EHL products at our centre. The distribution of patients was as follows: severe haemophilia A (SHA) n = 22: adults 13, children 9; severe haemophilia B (SHB) n = 10: adults 6, children 4. All patients with SHA were switched to Elocta. This switch was either their first exposure (adults n = 12; children n = 4) or following on from participating in the clinical trial for this product (adults n = 1; children n = 5). Patients with SHB were switched to either Alprolix n = 6 (adults n = 4; children n = 2) or Idelvion n = 4 (adults n = 2; children n = 2) of whom 3 patients had participated in the clinical trial for Alprolix. A modified half-life assessment was performed in most patients (n = 28) prior to the switch and after moving on to their EHL. The baseline half-life studies were helpful in identifying the EHL regimen to be prescribed. For patients with SHA, trough FVIII levels were measured in 15/22: 72 hour level in 7/22 and 96 hour level in 8/22. In all but one young child the FVIII level was >1.5 iu/dl. Trough FIX level at 168 hours was >2 iu/dl in all 5/10 SHB patients in whom it was performed. There was an overall reduction in cost of factor used following switch to EHL. Bleed data through Haemtrack entries were also collected and showed no increase.

Conclusion: Patients switched to EHL attained satisfactory trough levels on less frequent dosing with no increase in bleeding episodes. This has been especially beneficial in patients with difficult venous access in achieving reliable levels despite fewer injections.

05-COMPLICATIONS & COMORBIDITIESS

W-FPMED01-004 (288) | High rate of sustained virological response in patients with hemophilia and chronic HCV infection treated with direct acting antiviral agents

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Introduction: Chronic hepatitis C is the main co-morbidity in adult patients with hemophilia (PwH) treated with plasma-derived concentrates before 1990 and causes progressive liver fibrosis with increased risk of end-stage liver disease and hepatocellular carcinoma. Eradication of HCV is possible with antiviral therapies which were mainly represented by interferon (IFN)-based regimens until recently. PwH have been often considered "difficult-to-treat" because of several bad predictors of response as male sex, long duration of viral infection, HIV co-infection and high prevalence of HCV type 1. The advent of direct acting antiviral (DAA) drugs has provided sustained virological response (SVR) rates of 90% and above for many patient groups, however scarce data are available on the safety and efficacy of DAA drugs in PwH. In the last 5 years DAA were available for PwH in Italy and here we present the treatment outcome from a single center experience.

Materials and Methods: PwH and chronic hepatitis C sustained by any HCV type and of any age regularly followed-up at the Hemophilia Treatment Center of Milan were eligible for therapy with DAA drugs including those with compensated cirrhosis, HIV infection and/or previous failure to IFN-based antiviral therapy. Patients received DAA drugs with or without ribavirin for 12 or 24 weeks according to current guidelines. SVR was defined as persistent negative HCV-RNA at 12 weeks after treatment completion (SVR12).

Results: Eighty patients aged 27-84 years (median: 51) received DAA drugs between July 2012 and October 2017. The most prevalent HCV types were 1a (42, 53%) and 1b (22, 28%). Fourteen (18%) were HIV positive and 28 (35%) had cirrhosis. Forty-eight (60%) were non-responders or relapsers to previous interferon-based treatment. Ribavirin (800-1200 mg/day) was associated to DAA drugs in 48 patients (60%). HCV-RNA was undetectable at week 4 in 35/62 (57%) patients. At time of data analysis 70 patients (88%) had completed the 12-week post-treatment follow-up and SVR12 was achieved in 69 (99%). No patient had side effects related to DAA.

Conclusions: DAA drugs were safe and highly effective in PwH irrespective of HIV status, stage of liver disease severity and/or previous failure to IFN-based therapy.

M-MP-012 (407) | Reduced cardiovascular events in haemophilia – Results from a 5 year prospective study

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[1]*van Creveldkliniek – UMC Utrecht – University of Utrecht, Utrecht, Netherlands;* [2]*Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK;* [3]*Glasgow Haemophilia and Thrombosis Centre, Royal Infirmary, Glasgow, UK;* [4]*Arthur Bloom Haemophilia Centre, School of Medicine, Cardiff University and University Hospital of Wales, Cardiff, UK;* [5]*Katharine Dormandy Haemophilia Centre and Haemostasis Unit, Royal Free Hospital, London, UK;* [6]*Division of Haemostasis and Thrombosis, Department of Haematology, University Medical Centre Groningen, Groningen, Netherlands*

Introduction and Objective: Cardiovascular disease (CVD) mortality is reported to be lower in haemophilia patients than in the general population, but reports on non-fatal CVD are lacking. For cardiovascular risk management in patients with haemophilia, it is important to know the incidence of CVD compared to the general population. Earlier we reported an unfavourable risk profile (QRISK2) compared to the general population.

Materials and Methods: A prospective, observational study for CVD incidence of haemophilia patients (aged 30 years or older at inclusion) from The Netherlands and the UK. The incidence of CVD was compared to the expected 5 years incidence based on the QRISK2 – 2011 cardiovascular risk score. This score can be calculated in patients aged 30-84 years, without a history of CVD or use of statins. Cardiovascular events are according to QRISK defined as: Myocardial infarction (MI) Ischaemic heart disease (IHD), stroke, or transient ischaemic attacks. Peripheral vascular disease is not included. Also, there is no discrimination between haemorrhagic stroke and ischaemic stroke.

Results: 709 patients were included, 48% with severe haemophilia and a mean age of 49.8 years. For this review 514 complete datasets including a QRISK score were available. The expected number of events was 21.4 (4.16% (95% CI: 3.676%-4.629%), there were significantly less events observed: 7 (1.362% (95% CI: 0.389-2.529%)): 1 MI, 3 IHD, 2 strokes and 1 TIA. In the low risk subgroup (10 year risk <10%, n = 358) there was a significantly reduced number of events: expected 5.0 (1.409%; 95% CI: 1.287% -1.540%) vs observed: 0% (95% CI 0%-0%). In the medium risk group (10 year risk 10-20%, n = 91) there were significantly less events: 2 (2.20% 95 CI: 0%-5.49%), compared to an expected 6.4 events (7.03%; 95% CI: 6.73%-7.33%). In the high risk group (10 years risk of >20%, n = 65) there were 5 events (7.69%; 95% CI: 1.54-15.4) compared to an expected 10.0 events (15.31%; 95% CI: 13.91-16.4), not significantly reduced. There were 4 strokes: 2 fatal haemorrhagic stroke and 2 ischaemic stroke.

Conclusion: This prospective study showed a significant reduced incidence of CVD in PWH.

M-P-057 (526) | Natural history of hepatitis C in a cohort of HCV monoinfected haemophilia subjects

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Introduction and Objective: End stage liver disease (ESLD) represents the first cause of morbidity and mortality in HCV patients. Hepatitis C has a very high incidence among adult haemophilia subjects. Recently direct acting antiretrovirals (DAAs) have been proven highly effective for HCV eradication. Aim of this study is to follow the progression of HCV infection in a cohort of haemophiliacs in the DAAs era.

Materials and Methods: The study includes 133 HCV +/HIV- patients with congenital bleeding disorders with known seroconversion dates, alive on 1/1/2002, followed up until 1/6/2017. ESLD was defined as the first episode of liver decompensation or HCC diagnosis. Anti- HCV regimens included IFNa or pegIFN ± RBV between 2002-2015. In the new anti-HCV treatment era, different DAAs regimens were used, according to patients genotypes (>85% gen1).

Results: At the end of follow up (EOF), 114 pts (85%) remained alive. HCV infection was self limited in 32 (24%) or the patients. Among the 82 patients with chronic hepatitis C, 44 have received so far at least one anti-HCV regimen. 26 were treated with an IFNa regimen and 16 (61%) achieved SVR, while 18 of them received an IFNa free regimen with 100% SVR among those who completed treatment at the EOF (16/18). All patients treated with DAAs had severe fibrosis (F3) of cirrhosis (F4). No decompensation was observed among the treated population. 19 patients died during follow up, 8 of them (42%) from liver causes (2 ESLD, 6 HCC). Two patients developed HCC after they have cleared HCV.

Conclusions: Although haemophilia subjects have a long duration of HCV infection, they present with relatively low incidence of ESLD especially in those with SVR. The efficacy of DAAs schemes is not inferior compared to other risk groups. Early eradication of HCV before cirrhosis development would reduce the incidence of HCC.

M-P-013 (57) | The association between hepatitis C and elevated blood pressures in patients with hemophilia

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Introduction and Objectives: The higher prevalence of hypertension in patients with hemophilia (PWH) compared to males in the general population is not explained by the usual cardiovascular risk factors. Many PWH were infected with Hepatitis C virus (HCV), primarily through contaminated blood products. HCV infection is associated with cardiovascular risk in the general population, and our previous study had suggested a possible association between HCV and higher blood pressures (BP). Here we examine that hypothesis by retrospectively comparing PWH against a cohort from another population with a high prevalence of HCV.

Materials and Methods: We compared PWH (n = 571) from 4 sites in North America to a cohort of outpatients attending the Veterans Affairs Medical Center in San Diego (VINCI; n = 13,368). We fitted generalized additive models for systolic and diastolic BP (SBP and DBP respectively) on age, adjusted for BMI and race. Since age distributions of HCV+ and HCV- patients differed, we randomly selected subjects matched for age and race. Patients taking antihypertensive medications were analyzed separately.

Results: Patterns of BP distributions varied widely in both cohorts. In PWH, only HCV+ patients aged 25 to 50 years not taking anti-hypertensives had significantly higher DBP compared to HCV- patients. In older (>65 years) HCV+ PWH the reverse was found. SBP was not affected in any age-group in PWH. For VINCI subjects taking anti-hypertensives, DBP was significantly higher in older (>65 years) HCV+ subjects compared to HCV- subjects, and SBP was elevated in patients < 70 years. When comparing PWH and VINCI subjects, HCV- PWH without anti-hypertensives aged 25-55 years had lower SBP and DBP than VINCI subjects, whereas those >60 years had much higher values. There were no differences in the HCV- category taking anti-hypertensives. In the HCV+ category, irrespective of anti-hypertensives, PWH had lower SBP and DBP compared to VINCI subjects.

Conclusion: While there were large variations in BP patterns between PWH and VINCI subjects when compared by HCV status and stratified by antihypertensive use, there was little evidence that HCV infection status might explain the greater prevalence of high blood pressure among PWH.

T-P-009 (311) | The differences between intracranial hemorrhage in hemophilia A and hemophilia B and its outcome

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Introduction and Objectives: Intracranial hemorrhage (ICH) is potentially life threatening complications and may result in significant long-term morbidity in hemophilia. After this major bleeding there are no any recommendations for treatment of the acute phase and any consensus on the role of long-term factor replacement prophylaxis in the prevention of recurrences. The aim of the study is to assess ICH and its outcome in hemophilia A and hemophilia B.

Materials and Methods: The study includes 320 PwH who are pursued by our center since 1992. These patients were evaluated for ICH retrospectively. Type and severity of hemophilia, age of ICH, symptoms, cause and location of hemorragia, treatment (medical or surgical) of ICH and their outcome were recorded.

Results: Fourteen (4.3%) of all 320 PwH had ICH in the last 25 years. Eleven (4.2%) of the 258 Hemophilia A and 3 (4.8%) of the 62 Hemophilia B had ICH, but this difference was not significant. Among 14 PwH, 15 ICH (one of the patients had recurrent ICH) episodes were recorded and all of them are severe hemophilia. Median age of ICH was 2-years-old (range:0 days-30 years). Six (43%) out of 14 patients had a history of recent trauma. Out of 15 ICH; 12 intracerebral, 1 subdural and intracerebral, 1 epidural, 1 extracerebral frontal hemorragia were recorded. Convulsion was the most frequent symptom and 3 of the patients had no symptoms among them. All patients required factor replacement therapy, but at the beginning of the 1990's, 2 hemophilia A and 1 hemophilia B received FFP only. Neurosurgeons performed craniotomy for a 9-year-old hemophilia A patient and shunt placement for 1-month hemophilia B. Despite the treatment, 1 hemophilia A patient died due to the ICH. Four (36.3%) out of 11 Hemophilia A and 2 (66.6%) out of 3 Hemophilia B had late sequela.

Conclusion: Intracranial hemorrhage is the most serious complication in PwH and the early replacement therapy is essential. Prompt neurosurgical intervention will increase the chance of a better prognosis and it will protect the late sequelaes and deaths if needed. Although it requires more patients to assess, this study suggests that the rate of ICH does not change, but there is a difference in the occurrence of late sequel between Hemophilia A and B.

M-P-078 (368) | High risk of intracranial haemorrhage in adult mild haemophiliac patients: Data from the EMO.REC Registry

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Introduction and Objective: Intracranial haemorrhage (ICH) is the most serious event in patients with haemophilia (PWH) which leads to disability and in some cases death. ICH is more frequent in patients with severe haemophilia, aged <2 or >50 years while only few data are available for mild PWH. The aim of our study was to assess the incidence of ICH in a population of adult mild PWH, the risk factors for ICH, and the outcome.

Materials and Methods: All PWH with ICH were retrospectively (from 2009 to 2012) and prospectively (from 2013 to 2017) collected at 13 Italian Haemophilia Centres. The adult mild patients were subsequently evaluated and compared with the moderate/severe ones.

Results: 35 patients with ICH were recorded, 23 were adults, of whom 47.8% were affected by mild haemophilia. Mean age was 47 years, lower than non-mild patients (61 years). In 91% of the cases ICH were spontaneous, higher than in the other ones (75%). One patient had a low-titre inhibitor, same data recorded in the other group. 9 out of 11 mild patients suffered from hypertension (81.8%), while only 33.3% of non-mild subjects had this co-morbidity ($P < .05$). Smoke and alcohol intake were similar between two groups. All mild patients were treated with coagulation factors concentrates only on-demand at the time of ICH event, while 25% of the moderate/severe patients were on prophylaxis. 27.3% of the mild patients died, 66.7% in the other groups ($P = .09$). 50% of the survivors had a permanent disability. Prophylaxis after acute treatment was continued

life-long (9%) or for 2-6 months (45.5%) in mild subjects. Data confirmed in the moderate/severe group where only 25% of the patients continued the prophylaxis after the acute treatment, and 50% of the survivors had disabilities.

Conclusion: Incidence of ICH in adult mild PWH is high and similar to moderate/severe ones. The hypertension was proved to be the major risk factor for ICH in mild subjects, data not confirmed in the other group. 87% of the adult patients were on-demand treatment, 100% in case of the mild subject cases, which indicate the important role of the prophylaxis in preventing ICH.

06-DATABASES AND REGISTRIES

T-FPMTD01-003 (331) | Economic outcome of 14 years of factor tenders in Ireland

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Objective: In Ireland, since 2002, the Haemophilia Product Selection, Monitoring Advisory Board (HPSMAB) have been responsible for selecting and purchasing of coagulation factor concentrates on a national basis for the treatment of bleeding disorders. The HPSMAB consists of 3 haematologists, 2 members of the patient organisation and 1 haemophilia nurse, health ministry official, blood safety expert, a virologist and contract specialist and meets no less than six times per year. The aim of this study was to review the impact of the HPSMAB in creating efficiencies in terms of providing treatment that meet the highest standards of safety, efficacy, quality, security of supply and cost effectiveness.

Methods: A review of purchasing orders and tender documentation was carried out between 2002 and 2015, which included treatment for FVIII (including Immune Tolerance Induction), FIX, von Willebrands and FX. Savings assessed included cost savings from individual tenders, clinical trials and handling fees on all products. Costs avoided were based on comparison with pre HPSMAB system of purchasing and comparing the results with annual EU average costs.

Results: In this time, CFC use in Ireland increased from 3.87 IU/capita to 9.0 IU/capita for FVIII, and 1.84 to 2.84 IU/capita for FIX. The HPSMAB has driven an efficient procurement of the safest and most effective products and provided significant savings for the Irish healthcare system. There were 6 FVIII tenders, 9 FIX tenders (8 negotiated), 5 vWF tenders and 4 FX tenders. From 2002 to 2015, actual savings were € 73.66 million including € 22.74 million savings from removal of handling fees from the contract holder. Cost avoidance when compared to the previous model totalled € 162.18 million.

Conclusion: The HPSMAB has driven an efficient procurement of the safest and most effective products and provided significant savings for the Irish healthcare system which has resulted in a 232% and 54% increase in FVIII/capita and FIX/capita use, respectively, and very significant investment in haemophilia comprehensive care infrastructure.

T-MP-012 (91) | Prevalence of depression and anxiety disorders in patients with hemophilia: A nationwide cohort study

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Introduction and Objective: Because life expectancy has increased in persons with hemophilia (PWH), healthcare providers currently encounter and treat both acute bleeding events and chronic comorbidities, including psychological problems. Depression and anxiety disorders may affect the quality of life of PWH and their adherence to clotting factor replacement. This retrospective study analyzed the prevalence of and risk factors for depression and anxiety disorders among PWH.

Materials and Methods: We analyzed the data of 915 PWH retrieved from Taiwan's National Health Insurance Research Database between 1997 and 2013 by comparing variables to 3660 age- and sex-matched healthy individuals from a general population.

Results: The prevalence of depression and anxiety disorders was higher in PWH than in the general population (5.9% vs. 3.77%, odds ratio [OR] = 1.601, 95% confidence interval [CI] = 1.158-2.212). No difference in the prevalence was observed between PWH A and PWH B. In subgroup analysis, the prevalence was higher in PWH aged 18-40 years than in persons of the same age in the general population; however, the prevalence was not significantly different between younger and older groups. After adjustment for comorbidities, including hepatitis B, HIV infection, stroke, coronary artery disease, chronic obstructive pulmonary disease, and cancer, the prevalence of depression and anxiety disorders was still significantly higher in PWH than in the general population. However, after adjustment for hepatitis C infection, the prevalence did not significantly differ between the two groups (OR = 1.251, 95% CI = 0.855-1.830).

Conclusions: The prevalence of depression and anxiety disorders was high in PWH, particularly in the young adult to middle-aged groups. Hepatitis C infection was strongly associated with psychological disorders in PWH.

T-MP-013 (425) | The WFH World Bleeding Disorders Registry

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Introduction: The advancement of hemophilia care is limited by factors inherent to research in rare diseases, including small sample sizes, geographical dispersion of patients and clinically heterogeneous patient populations. Registries, with international collaboration between centres and countries, are an effective way to pool data to achieve the required sample size to conduct clinical research on rare disorders, such as hemophilia. By combining data from countries around the world, the WFH World Bleeding Disorders Registry (WBDR) will provide a large amount of real-world data on the patient clinical experience, which can be used to address important clinical questions and support advocacy initiatives. As a global organization with access to a network of 134 national member organizations, more than 1000 hemophilia treatment centres (HTC) and numerous patients in countries with varying levels of access to care, the WFH is uniquely positioned to develop such a registry. Following the success of a pilot study, implementation of the full scale WBDR is underway.

Methods: The WBDR is a prospective, global registry of patients diagnosed with hemophilia A and B. The goals are to enroll at least 200 HTCs from more than 50 countries, and at least 10,000 people with hemophilia, aiming for representation of patients from around the world. A data linkage strategy is being developed for countries with an established national patient registry. The WBDR database is being developed through collaboration between the WFH, Karolinska Institute and Health Solutions.

Results: Invitations to join the WBDR were sent to 126 HTCs between October-December 2017. These 126 invited HTCs represent 84 countries from all Gross National Income (GNI) categories: 20 (16%) high income countries (GNI A), 37 (29%) from upper-middle income countries (GNI B), 55 (44%) from lower-middle income countries (GNI C) and 14 (11%) from low income countries (GNI D). Patient enrolment will begin in January 2018.

Conclusions: Implementation of the WBDR has begun, with representation of all regions and economic levels of development. This global network of HTCs and patients will provide a large amount of real world data, on which evidence to improve the quality of care worldwide will be generated.

T-P-014 (82) | CBDR and MyCBDR advancing hemophilia nursing practice in Canada

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Introduction and Objectives: In Canada, Hemophilia Treatment Centers (HTCs) provide care and services to patients with bleeding disorders. The advancement of routine prophylaxis regimens allows patients to experience less bleeds and fewer unscheduled visits to HTCs. To adapt to these changes in hemophilia management, comprehensive care teams must implement new strategies to accurately monitor bleeding episodes, factor usage and adherence to treatment regimens. This requires detailed record keeping and adequate patient education to help care teams manage patients and individualize factor replacement treatment regimens.

Material and Methods: In 2015, Canada launched the Canadian Bleeding Disorder Registry (CBDR), along with MyCBDR, an internet-based infusion tracking application that allows synchronous communication with CBDR at HTCs across Canada. These collaborative platforms enable integration of data from both patients/caregivers and health care teams to better support hemophilia management across Canadian HTCs.

Results: Successful implementation of CBDR/MyCBDR has improved the efficiency of hemophilia practice and is a useful educational tool to promote treatment adherence and patient self-management.

Conclusion: Integration of CBDR/MyCBDR in HTCs can foster a rapid sharing of information between patients and their care team, providing the opportunity to improve best practices in hemophilia management.

T-P-015 (136) | Korea Hemophilia Foundation Registry Trends 1991-2016: Patient registry and demographics, with the changes of hemarthropathies, contagious diseases, and inhibitor incidence

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Introduction and Objective: The Korea Hemophilia Foundation (KHF) founded in 1991 has registered Korean hemophiliacs, and updated the cohort by establishing the network of medical information between affiliated clinics. We determined the KHF data of over 25 years' experiences with the changes of inhibitors incidence over 10 years in hemophilia A and hemophilia B.

Materials and Methods: Among the 2482 patients registered in the KHF, 2303 were alive at the end of 2015 because 179 patients had died; there were 1654 patients (71.8%) with hemophilia A and 409 (17.8%) with hemophilia B and 116 (5.0%) with von Willebrand disease (VWD).

Results: From 1991 to 2016, while the general South Korean population grew by 15%, the KHF registration patients grew about 200% (n = 2303). Registered hemophilia patients was approximately 1:20,000 males at 1995, which gradually increased over years, and up to 0.9:10,000 males at 2015, with 80% having factor VIII deficiency. The median life expectancy of hemophiliacs without inhibitors has increased to 65 years-old. The registered patients with VWD grew by 116; they are only one-eighteenth of the population of hemophiliacs. Contagious diseases have decreased markedly in the registered hemophilia patients. The incidence of inhibitors in hemophilia A has not increased in spite of the increased use of recombinant factor VIII (rFVIII) agents.

Conclusions: Although the KHF patient base has grown much faster than the general Korea population, some patients have still been left out, especially those with VWD. Therefore, a more efficient and nationwide registry system should be fixed for the provision of comprehensive management for this disorder. Decreased or nonchanged incidence of inhibitors in hemophilia A over time may warrant the use of rFVIII use.

T-P-016 (196) | Development of a prospective, outcomes-based bleeding disorders registry: A pilot study

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Background: Outcome-based data allows assessment of the quality of treatment provided to haemophilia patients, and is increasingly required by funding authorities. The existing National Haemophilia Registry in Singapore captures only incidence data. There is a need to develop a Bleeding Disorder Registry (BDR) which not only captures diagnostic data but also prospective information on bleeds, treatments and outcomes.

Objective: We describe the stepwise development of a prospective, outcomes-based BDR and highlight the milestones and challenges encountered during the initial pilot phase.

Methods: Development of the BDR was piloted in a paediatric hospital. Existing patient records were previously entered by a nurse into an Excel file in a standalone computer. A data manager was hired to manage the registry. A series of teleconferences were convened with haematologists, haemophilia nurse, data manager and an external vendor to design the data fields. Changes were tested serially in user acceptance testing (UAT) environments before being uploaded onto the actual live registry. Data fields included demographic variables, diagnostic details, details of individual bleeds and their management, doses of prophylaxis, clinic visits and annual outcome measures including annual bleed rate, Haemophilia Joint Health Score and compliance. A registry manual was developed with definitions based on published WFH or ISTH guidelines.

Results: The BDR took 6 weeks to go live. Data could only be entered if consent was documented online. Patient data was coded, with no visible patient identifiers to protect data privacy. Access was granted only to registered users by the site administrator. As of 7 months since the registry went live, 30 patient records (34% of registered patients) have been entered. While actual migration of existing patient data onto the registry took an average of 15 minutes, data verification from source documents was time-consuming and tedious. Patient data from ongoing visits was entered within 7 days, ensuring that data entry was timely and up to date.

Conclusion: A prospective, outcomes-based BDR has been piloted successfully in our institution. The eventual aim is for the BDR to become a national registry, with the ability to generate outcomes-based and factor usage data on a national scale.

T-P-017 (520) | Retrospective chart review of hemophilia patients registered at Haemophilia centers across Czech Republic (CR) since the past 6 years

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Introduction and Objectives: The global burden of Haemophilia is projected to be 187,183 cases in 2015; with a real burden of 1,076 patients in CR. This burden commands the need to understand evolvement of care over the years. A retrospective chart review allows examining patient records to apprehend clinical events and treatment modalities. This review aims to understand demographic and clinical characteristics, along with trends in management of Haemophiliacs registered at Haemophilia centers in CR.

Materials and Methods: A retrospective chart review was conducted using patient medical records from designated Haemophilia centers in CR, available through Czech National Haemophilia Programme (CNHP) registry (www.cnhp.registr.cz). The sample included patients registered at Haemophilia Comprehensive Care Centres and Haemophilia treatment centers across CR from 2011 to 2016. Data regarding demographics and clinical characteristics, Haemophilia care and resource utilization were obtained. Primary outcomes included distribution of demographic and clinical features

of Haemophilia A and B patients, and trends in treatment utilization among children and adults.

Results: Overall, 747 Haemophiliacs were registered within CNHP registry; with Haemophilia A cases accounting for 86.9%. There was no significant difference in demographics between Haemophilia A and B. Hepatitis C was the most common comorbidity among adults. More than 38% of registered cases had severe form of Haemophilia. During 2016, around 55% of registered Haemophiliacs needed treatment for clinically significant bleeds, while approximately 45% did not require treatment accounting to no bleeds. Prophylaxis has been shown to significantly decrease the number of bleeds in all age categories. Treatment included plasma derived and recombinant factors VIII and IX, with recombinant factors (75%) being the most preferred treatment in children and plasma derived factors (74%) in adults. There were 19 patients with active inhibitors in the registry of which four developed inhibitors in 2016.

Conclusion: This review helps understand Haemophilia characteristics and treatment approaches among children and adults in CR; thus, aiding to formulate right treatment strategies to improve the quality of life in these patients.

T-P-018 (643) | Establishment of a UK registry for haemophilia patients switched to extended half-life clotting factor concentrates: 1 year update

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Haemophilia A and B are X-linked inherited bleeding disorders characterised by low levels of factor VIII and IX respectively. Clinically low levels manifest as recurrent joint and muscle bleeds, or spontaneous and potentially fatal bleeding into any organ. The current UK standard of care for haemophilia patients is regular prophylaxis with either factor VIII or IX between 2 to 4 times a week to maintain a trough level of 1% affording protection against spontaneous bleeding events and resultant joint damage. New extended half-life coagulation factor concentrates (EHL-CFC) have been introduced into routine clinical care. These are cleared more slowly enabling either increased trough levels at the same infusion frequency or same trough levels at decreased infusion frequency reducing the treatment burden. Thus far, data on patients switched to EHL-CFCs have only been collected through participants in clinical trials who may not be representative of the UK population. The UK EHL Outcomes Registry was established to systematically collect data on all patients being switched across the UK in the 2 years post-switch. The principal goals of the registry are to collect quality of life (EQ5D, Brief Pain Inventory, HAEM-A-QOL & HaemoPrefer), physical activity (IPAQ), consumption and treatment information to identify the relationships between patient and treatment characteristics and outcomes as these new products become available. The study will also gather data on clinician perceptions and local practices for monitoring prophylaxis to develop future clinical strategies. The study opened to recruitment in December 2016; to date 15 centres have opened to recruitment with further sites in set up. 87 patients have been enrolled, at a median follow up post-switch of 7 months. The vast majority of patients recruited (98%) have severe haemophilia and 7% of whom had a previous inhibitor, commonly an exclusion criteria in trials. The principal reason for switching to EHL-CFCs was convenience of fewer injections (56%), though a number of patients had previously participated in a trial or requested to switch (24%). The study remains open to recruitment, and further analysis of the changes in factor consumption and quality of life for patients will be conducted as recruitment progresses.

T-P-019 (646) | Development and management of national registry in hemophilia care in Kenya

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Introduction: With hemophilia cases being evenly distributed and new diagnosis being made more often, there is need to have a well structured, easy to operate and accessible means of keeping track of these records from the Kenyan population of over 45 million people. Currently, there is a national hemophilia registry that has been in operation since the year 2013 and having more than 450 entries. This has been facilitated through the Kenya Hemophilia Association alongside other partners.

Objectives: To provide support in management and care for hemophilia patients; To inform the government on the required policies and their implementation for better hemophilia care in Kenya through the records obtained; To enhance inter-institutional network amongst hemophilia treatment centers in Kenya; Promotion of consultative forums, training and capacity building amongst hemophilia healthcare givers.

Methodology: Kenya Hemophilia Association-National Registry, was started in the year 2013 and is in operation across the three hemophilia treatment centers in the country; Mombasa, Nairobi and Eldoret. It has more than 450 entries currently and the process is ongoing. Every known diagnosis and all the encounters are recorded as necessary. Accessibility to the registry is limited to users depending on the functions of interest. It captures patients' demographics, diagnosis and treatment plan.

Results: The consumption of the registry to meet the objectives has come with its challenges. They include limited infrastructures in most parts of the country; registry is technology dependent, inadequate capacity to use technology amongst care givers, complexity in its usability and navigation, imbalance between the input and output and completeness of the records.

Conclusion: Access to healthcare by itself is a challenge in developing countries. In hemophilia care, having improved, well structured, accessible and user-friendly nation registries could play a very pivotal role in reverting this. A few lessons can be borrowed from the more established countries on developing, managing and maintaining national hemophilia registries. A World Hemophilia Registry perhaps?

07-GENETICS OF BLEEDING DISORDERS

M-FPMED01-005 (298) | Prevalence of mild factor XIII deficiency phenotype: Current update to the WFH sponsored CRGP study

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Introduction and Objectives: Inherited mild FXIII deficiency individuals (FXIII levels 20-60%) are usually asymptomatic unless exposed to trauma. Owing to the difficulty in detecting and diagnosing such individuals the accurate prevalence and the true clinical relevance of this disorder is not known. Under the WFH sponsored CRGP grant, we aim to screen approximately 1000 apparently healthy controls for their FXIII levels and their *F13A* and *F13B* genotypes in order to estimate the prevalence and potential clinical relevance/bleeding risk for this disorder.

Material and Methods: Plasma samples from the apparently healthy controls will be evaluated for FXIII antigen, FXIII activity using photochemical, incorporation and FXIIIAa (activated FXIIIA) generation assay. In individuals detected for mild FXIII deficiency next generation sequencing (Nextera rapid capture custom enrichment kits; Probe based; Illumina Work flow) with DNA extracted from peripheral blood is being done.

Results: A total 961 apparently healthy controls have been collected and showed normally distributed activity levels between 35.4-156% (mean: 117 ± 22.9%). Seven individuals showed mild FXIII deficiency (FXIII levels: 20-60%). Samples analyzed with generation assay showed FXIII activation rates ranging between 15.0-87.0 ΔRFU/Δt. Next generation sequencing of mild FXIII deficiency individuals showed the accumulation of a number of interesting coding variations within *F13A1* and *F13* genes like *p.Gly201Arg*; *F13B* gene (novel) with coding polymorphisms like *rs5985*; *F13A1* gene in the background. Variability in the bleeding phenotype of mild FXIII deficiency individuals was considerably more than the remaining population.

Conclusion: Mild FXIII deficiency appears to have a prevalence of 1 in 200 from the currently tested cohort. Most mild FXIII deficiency reported bleeding/bleeding related issues on deeper anamnesis. On a genetic level, mild FXIII deficiency appears to be the combined effect of heterozygous variation and background coding/non-coding polymorphisms rather than an isolated event caused by a single mutation. However, final conclusions can be made only after the complete cohort has been genotypically and phenotypically analyzed.

T-FPMED01-002 (757) | Whole Exome sequencing as a first-tier diagnostic test for haemostatic disorders

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Introduction and Objective: An increased susceptibility to develop bleeding complications because of genetic defects in one or more components of the haemostatic balance are typical characteristics in haemostatic disorders. Over one hundred genes/loci are known in the Online Mendelian Inheritance in Man (OMIM) database as genetic causes for haemostatic disorders. The Objective is to introduce Whole Exome Sequencing (WES) in our routine for haemostatic disorders. WES allows analysis of a large panel of genes in one single test making the test a time and cost-efficient approach.

Materials and Methods: First, genetic abnormalities were screened in a predefined haemostatic panel using WES. The haemostatic gene panel contains at this moment 132 genes proven to be involved in haemostatic disorders including genes involved in primary haemostasis (vessel wall and platelets) and secondary haemostasis and fibrinolysis. Second, if the haemostatic panel is negative, exome wide analysis was performed.

Results: 89 patients were tested with the diagnostic panel. 22 patients were diagnosed containing a pathogenic mutation causative for the disease and explaining the phenotype; 9 with an autosomal dominant mutation (VWF, RUNX1, MYH9, THPO, GFI1B, SLFN14, GP1BA), 2 with a homozygous autosomal recessive mutation (ITGA2B, P2RY12) and 1 with an X-linked hemizygous mutation (F8). 10 patients were heterozygous carriers of mutations in genes involved in primary/secondary haemostasis. Interestingly, 3 patients had either a combination of mutations in VWF gene and genes with an autosomal recessive heredity pattern or two autosomal recessive genes. 21 variants with unknown pathogenicity (VUS) were detected (18 patients).

Conclusions: The introduction of WES in our diagnostic routine was successful in 52 of our initial patient population which was higher than our conventional targeted gene approach (34%). Based on our

experience we expect to resolve more haemostatic disorders due to the detection of combinations of autosomal recessive abnormalities in primary or secondary haemostasis, fibrinolysis or combinations of each. Finally, we expect that WES may introduce a risk analysis approach by analyzing allele frequencies of VUS in other non-haemostatic cohorts compared to haemostatic cohorts.

W-MP-013 (332) | mRNA analysis and multiplex ligation-dependent probe amplification in hemophilia A patients without mutation in genomic DNA

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Introduction and Objectives: Hemophilia A (HA) results from mutations of F8 gene and knowledge of these mutations is helpful in predicting severity of bleeding, risk of FVIII inhibitors as well as detection of carriers. However, in 2-7% of HA patients no mutation is found by DNA-based molecular techniques.

Objectives: We performed messenger RNA analysis (mRNA) and multiplex ligation-dependent probe amplification (MLPA) assay to identify the genetic defects for HA patients without detectable mutations in genomic DNA.

Patients and Methods: From June 2006 to December 2016, there were 185 HA patients from 153 unrelated families who had undergone genetic testing in our hemophilia center, including 108 severe, 28 moderate and 49 mild type patients from 96, 22 and 35 unrelated families, respectively. Among this HA cohort, we found 14 patients from 9 unrelated families who had no detectable DNA mutation, including 10 patients with mild type from 6 unrelated families, two patients with moderate type from one family and two patients with severe type HA from two unrelated families. The median age of these patients was 22.5 years old with a range of 8-78. We assessed the 14 HA patients by mRNA analysis with reverse transcription-polymerase chain reaction (RT-PCR) followed by nested PCR first, and MLPA was then carried out.

Results: Twelve of the 14 (85.7%) patients without DNA mutation were found to have mutation by the mRNA analysis and MLPA, including 8 mild HA patients with splicing mutation of 90 bps from intron 18 insertion between exons 18 and 19 (E18ins90bpE19) caused by deep intronic variant of c.5999-277G>A, another three patients with skipped exon 19 and one with exons 8-14 duplication.

Conclusions: Our study demonstrates that combination of mRNA analysis and MLPA was an effective assay for HA patients who had no detectable DNA mutation. An 85.7% (12/14) detection rate was achieved. Deep intronic variant of c.5999-277G>A may be a hot spot for mild type HA without detectable DNA mutation.

W-MP-022 (763) | Hemarthrosis in FVIII-deficient mice causes systemic gene expression changes that are improved with FVIII prophylaxis

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Introduction and Objective: Hemarthrosis in patients with hemophilia (PWH) leads to inflammation and vascular changes in the joint that may promote re-bleeding. Little is known about the extent and nature of systemic responses to joint bleeding. Since the spleen is a major systemic immune-modulatory organ, we quantified changes in splenic gene expression profiles in FVIII-deficient mice with and without induced hemarthrosis, and determined the effects of prophylactic FVIII replacement.

Materials and Methods: Hemarthrosis was induced in FVIII-deficient mice by sub-patellar needle puncture +/- 100 IU/kg recombinant human FVIII (rhFVIII) intravenously 2 hours before and 6 hours after injury. Spleens were harvested on day 3 post-injury, as well as from uninjured mice (n = 3-5). RNA libraries were prepared using the NEBNext Ultra II Directional RNA Library Prep Kit and sequenced on an Illumina NextSeq500 platform (single-end; 75 bp reads). For analysis, the R BioConductor packages tximport, edgeR and limma were used to read in Salmon transcript files and the limma-voom method was used for differential expression analyses. Functional enrichment was performed using Signaling Pathway Impact Analysis.

Results: Pronounced alterations in splenic gene expression profiles occurred in vehicle-treated mice, with 8801 differentially expressed genes (DEG) and 23 perturbed pathways compared to uninjured mice. Significant differences were observed in multiple interacting pathways that influence inflammatory and immune processes, as well as cell survival and differentiation. These included cytokine-cytokine receptor interactions ($pGFWER = 2.5 \times 10^{-8}$), cell cycle (pGFWER = 0.009), and nuclear factor-κB (NFκB) (pGFWER = 0.0003) and chemokine signaling (pGFWER = 0.0003). Vascular endothelial growth factor (VEGF) signaling, and pathways encompassing focal adhesion and osteoclast differentiation from monocytes/macrophages, were also affected by hemarthrosis, and, we postulate, are linked to local joint changes. Notably, gene expression changes were markedly dampened with rhFVIII prophylaxis (1050 DEG and 2 pathways compared to uninjured mice). The cell cycle pathway remained significantly altered ($P = .0002$), while the other aforementioned pathways were comparable to uninjured mice.

Conclusions: Joint bleeding in hemophilic mice leads to profound changes in multiple systemic pathways, previously undescribed, as shown by gene expression profiling. This approach can be used to explore the mechanisms leading to progressive hemophilic arthropathy in PWH, and may lead to novel therapeutic targets.

W-MP-023 (773) | Effects of prophylactic clotting factor replacement on synovial gene expression after hemarthrosis in FVIII-deficient mice

Srila Gopal[1]; Bilgimol C. Joseph[1]; John Shimashita[2]; Padmaja Natarajan[2]; Steven R. Head[2]; Chanond A. Nasamran[1]; Kathleen M. Fisch[1]; Annette von Drygalski[1]; Esther J. Cooke[1]

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Introduction and Objective: Repeated joint bleeding in patients with hemophilia leads to hemophilic arthropathy (HA), which cannot be entirely prevented by clotting factor replacement. The mechanisms of perpetuated joint bleeding and HA progression are incompletely understood. To this end, we explored synovial gene expression profiles in FVIII-deficient mice with and without induced hemarthrosis, and examined changes with prophylactic FVIII replacement.

Materials and Methods: Hemarthrosis was induced in FVIII-deficient mice by sub-patellar needle puncture +/- 100 IU/kg recombinant human FVIII (rhFVIII) intravenously 2 hours before and 6 hours after injury. Synovium was harvested and RNA extracted on day 3 or day 14 post-injury, as well as from uninjured mice (n = 3-5). Libraries were prepared using the NEBNext Ultra II DNA Library Prep Kit and sequenced on an Illumina NextSeq500 platform (single-end; 75 bp reads). The R BioConductor packages tximport, edgeR and limma were used to read in Salmon transcript files and the limma-voom method was used for differential expression analyses. Functional enrichment was performed using Signaling Pathway Impact Analysis.

Results: A strong synovial transcriptional response occurred with hemarthrosis in vehicle-treated mice at day 3 (4672 differentially expressed genes (DEG), 5 perturbed pathways), and was not substantially dampened in rhFVIII-treated mice (3836 DEG, 2 perturbed pathways). Extracellular matrix (ECM) interactions and peroxisome proliferator-activated receptor (PPAR) signaling were similarly dysregulated in both groups (pGFWER < 0.01). At day 14, there was persistent transcriptional activity and pathway perturbation, but fewer DEG with rhFVIII treatment (vehicle: 2901 DEG, 7 perturbed pathways; rhFVIII: 1362 DEG, 8 perturbed pathways). Notably, differences in ECM interactions were highly significant with both vehicle (pGFWER = 1.7×10^{-11}) and rhFVIII prophylaxis (pGFWER = 1.4×10^{-10}), as were focal adhesion and PPAR signaling (pGFWER < 0.0001). At both time points, coagulation and complement cascades were significantly altered in vehicle-treated (pGFWER < 0.05) but not rhFVIII-treated mice.

Conclusions: Hemarthrosis in FVIII-deficient mice triggers profound changes in synovial gene expression and multiple signaling pathways that may play a role in HA. Since changes were incompletely mitigated by rhFVIII prophylaxis, we postulate that future pathway analyses will enable targeted drug discovery to intercept progression of HA.

W-P-014 (83) | Germline and somatic mosaicisms of factor VIII gene mutation identified in an asymptomatic grandfather

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Introduction and Objective: About one third of hemophilia A are sporadic. The origin of mutation and how the de novo mutation is transmitted were not well studied. We present a sporadic severe hemophilia A family, the origin of mutation was assigned to the proband's asymptomatic maternal grandfather who presented with germline and somatic mosaicisms of factor VIII gene mutation which might occur during early embryogenesis.

Materials and Methods: Clinical, laboratory and genetic studies were carried out routinely in a sporadic severe hemophilia A family. Linkage analysis was studied using the intragenic and extragenic markers of the factor VIII gene to determine the origin of the de novo mutation. A technique named amplification refractory mutation system-quantitative polymerase chain reaction (ARMS-qPCR) was used to detect the presence of somatic and germline mosaicisms.

Results: A sporadic severe hemophilia A with factor (F) VIII:C of <1 IU/dl, VWF:Ag 96 IU/dl and VWF:Act 90 IU/dl was diagnosed in a 5.5 years old boy. FVIII gene analysis identified a hemizygous mutation c.3637delA, p.I1213F fs*5 in the exon 14. His mother had a FVIII:C of 47.8 IU/dl, vWF:Ag 75.9 IU/dl and vWF:Act 74 IU/dl, FVIII gene analysis revealed a heterozygous similar mutation. His elder brother and 2 maternal uncles were all asymptomatic with normal FVIII:C level and normal FVIII gene. He had no maternal aunt. His maternal grandmother was deceased, while his maternal grandfather was asymptomatic and had FVIII:C of 122.8 IU/dl, VWF:Ag 169.5 IU/dl and vWF:Act 173.6 IU/dl. Interestingly, FVIII gene analysis showed a heterozygous similar mutation but with a mosaic pattern. The linkage analysis assigned the origin of mutation to this maternal grandfather. To confirm the possible mosaicisms, ARMS-qPCR was done and revealed that the % mutant in blood cells, oral mucosa cells and sperm cells from grandfather were 34.8%, 16% and 43%, respectively, indicating the presence of germline and somatic mosaicisms of FVIII gene mutation.

Conclusions: We present a rare case of germline and somatic mosaicisms of FVIII gene mutation in an asymptomatic maternal grandfather who transmits the disease.

W-P-024 (299) | A mutation potentially associated with X-linked intellectual disability (XLID) in hemophilia A carrier with skewed X chromosome inactivation revealed by whole exome sequencing

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Introduction and Objective: Hemophilia A is an X-linked recessive disease affecting primarily males, while females are typically asymptomatic carriers. However, in rare cases, female carriers present with hemophilia A due to skewed X-inactivation, i.e. complete inactivation of their X chromosome carrying the normal F8 gene, resulting in exclusive expression of their mutant F8 gene. Prenatal diagnosis for prevention of hemophilia A in such women is based on exclusion of male fetuses carrying the mutant F8 gene. However, since extreme skewing is associated with mutations in genes involved in X-linked intellectual disability (XLID), selecting male fetuses carrying the X chromosome with normal F8 gene, which is completely inactivated in the mother, may be associated with a significant risk of selecting fetuses with XLID. The aim of our study was to identify mutations potentially related to XLID in a female hemophilia A patient (an obligate carrier, daughter of a severe hemophilia A patient) with confirmed skewed X-inactivation (Factor 8~1%) treated and followed up by the Israeli National Hemophilia Center.

Materials and Methods: Patient's DNA was analyzed by whole exome sequencing (WES), followed by comprehensive bioinformatics analysis. Direct sequencing was used for confirmation of the mutation identified by WES and analysis of patient's family members for the identified mutation. X-inactivation was studied by HUMARA assay.

Results: In addition to being a carrier of her paternal F8 gene mutation (splice site, intron 5 c.670+2T>C), the patient was found to be a carrier of a novel frameshift mutation in the PGK1 gene encoding for phosphoglycerate kinase (PGK), which was inherited from her mother. Similarly to the patient, her mother demonstrated skewed X-inactivation of the chromosome bearing the mutant PGK1 gene. PGK deficiency is an X-linked disorder commonly associated with mental retardation; therefore, our findings are extremely important for patient's future pregnancy planning and warrant a similar study in 2 additional female hemophilia A patients treated at our Hemophilia Center.

Conclusions: Hemophilia carriers with skewed X-inactivation should be analyzed for mutations potentially causing XLID on their inactivated X chromosome prior to being offered prenatal diagnosis and/or PGD based on exclusion of their mutant F8 gene.

08-HEMOSTASIS TESTS AND ASSAYS

T-FPMED02-003 (315) | In vitro activity of concizumab in combination with activated prothrombin complex concentrate or rFVIIa as studied by thromboelastography and thrombin generation

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Introduction and Objective: Concizumab is a high-affinity, humanized, monoclonal antibody directed against the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI). It is currently in clinical phase 2 development intended for subcutaneous prophylaxis treatment of haemophilia A and B regardless of inhibitor status. Concizumab has demonstrated a concentration-dependent procoagulant effect in functional TFPI assays, including in the thrombin generation assay (TGA), in both pre-clinical experiments and in phase 1 clinical trials. In inhibitor patients, the current treatment options for potential breakthrough bleeds are on-demand by-passing agents; recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (pd-aPCC). Concizumab, rFVIIa and pd-aPCC are procoagulants and therefore it is important to investigate potential interaction.

Materials and Methods: The procoagulant effect of combining concizumab with rFVIIa or pd-aPCC was studied using thromboelastography (TEG) and TGA. TEG was measured in whole blood with a 1:200,000 dilution of lipidated tissue factor (Innovin®). Thrombin generation was measured in human platelet-poor plasma using a calibrated automated thrombogram system with 1 pM tissue factor and 4 μM phospholipids. In both assays, haemophilia A conditions were induced using an inhibiting polyclonal anti-factor VIII antibody. Compounds included concizumab, NovoSeven® (rFVIIa) and FEIBA® (pd-aPCC) tested at pharmacological concentrations alone or in combination (i.e., concizumab + NovoSeven® or concizumab + FEIBA®).

Results: Pharmacological concentrations of the individually tested compounds were, as expected, procoagulant and effective (increased peak thrombin in TGA and shortened clot time in TEG). Combinations of concizumab with NovoSeven® or FEIBA® caused a small increased procoagulant effect compared with concizumab alone, as expected when combining two individually effective concentrations. Notably, the combination of concizumab and FEIBA® in TEG did not reach a clot time shorter than what was observed for FEIBA® alone. Additionally, in TGA the combinations using relevant clinical concentrations did not generate an activity exceeding that of normal control plasma.

Conclusions: *In vitro* activity analysis of the combinations of concizumab with rFVIIa or pd-aPCC did not result in excessive procoagulant effects and thus no immediate concern for a careful clinical evaluation of the combination of these products in a controlled setting has arisen.

Conflict of Interest Disclosure: Authors are employed at Novo Nordisk A/S.

W-MP-028 (253) | Use of rotational thromboelastometry to monitor boys with severe haemophilia A and inhibitors on treatment with emicizumab

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Introduction and Objectives: Current treatment for bleeding in boys with severe haemophilia A with high titre factor VIII(FVIII) neutralising inhibitors is bypassing agents. Emicizumab is a humanised antibody that mimics FVIII with possible use in these boys as demonstrated by reduction in bleeds in phase III adult trials. Currently only an estimate of emicizumab activity can be derived from chromogenic FVIII measurement (FVIII:C). Rotational thromboelastometry (ROTEM) is used to monitor haemostasis in cardiac surgery and offers the possibility of use to monitor emicizumab activity. This study aims to investigate use of ROTEM as a tool to monitor haemostasis in boys with severe haemophilia and inhibitors currently on trial treatment with emicizumab.

Material and Methods: Blood samples were obtained for ROTEM when patients attended for screening, loading and steady state trial visits. Control samples were obtained from 5 healthy adults with no history of bleeding, thrombosis or medication. The ROTEM delta instrument was used and samples run using NATEM programme for up to 45 minutes. Clotting time (CT), clot formation time (CFT), alpha angle (AA) and maximum clot firmness (MCF) were recorded.

Results: 32 samples were obtained from 7 subjects. These included 4 screening, 17 loading phase and 11 steady state samples, these are summarised below. An improvement was seen in all ROTEM parameters and more prominently in CT and MCF compared to CFT and AA.

Conclusions: ROTEM parameters improve following the first emicizumab injection. This improvement was maintained through the period of observation. Our findings suggest that ROTEM may be used as a tool to monitor haemostasis in these patients.

Figure 1. ROTEM parameters for the controls and patients at various stages of treatment (median (95% CI))

	Clotting time (seconds)	Clot Formation Time (seconds)	Maximum clot firmness (millimetres)	Alpha Angle (°)	Chromogenic Factor VIII (IU/ dL)
Adult controls	489 (416 to 602)	180 (144 to 221)	55 (50 to 59)	57 (51 to 62)	n/a
Patients: Pre emicizumab (Bypassing agent treatment within 72 hours)	1272 (478 to 2412)	378 (79 to 567)	50 (12 to 68)	34 (7 to 49)	< 1
Patients: Loading phase emicizumab	757 (615 to 1152)	266 (240 to 379)	57 (49 to 60)	45 (36 to 49)	20 (13 to 21)
Patients: Steady state emicizumab	669 (529 to 913)	283 (226 to 375)	58 (54 to 59)	46 (39 to 52)	19 (17 to 24)

W-P-029 (540) | Comparison of analytical performances of the automated chromogenic and one-stage factor VIII assays

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Introduction and Objectives: Chromogenic factor VIII (FVIIIchrom) assay is still not widely used and is perceived to be more difficult to automate than the one-stage assay. Therefore, we aimed to investigate the analytical performance of the automated FVIIIchrom assay in comparison with the one-stage FVIII (FVIIIclot) assay.

Materials and Methods: FVIIIchrom assay (TECHNOCROM FVIII:C, Technoclone, Austria) was adapted for the Sysmex CS2000i coagulation analyzer (Siemens Healthcare Diagnostics, Germany), and compared with the performance of the FVIIIclot assay on the Sysmex CS5100 coagulation analyzer using reagents from Siemens Healthcare Diagnostics (FVIII deficient plasma and Actin FS). Within-run and between-run imprecisions were estimated according to CLSI EP15-A3 protocol, in normal and pathological range using Control plasma N (CPN) and Control plasma P (CPP), whereas the very low pathological range was tested using CPP prediluted 1/10 (approximate FVIII activity 3%). Measurement uncertainty (MU) was calculated at two concentration levels using reference materials. Method comparison was performed in 49 plasma samples with a wide range of FVIII activities including low, normal and high levels, using Passing Bablok regression, assisted by Bland-Altman analysis.

Results: Low within-run and between-run coefficients of variations (CVs) were obtained for both methods using CPN (within-run: FVIIIchrom = 0.7%, FVIIIclot = 2.0%; between-run: FVIIIchrom = 4.2%, FVIIIclot = 4.1%). Although for both methods similar within-run imprecisions were determined for CPP (FVIIIchrom = 2.5%, FVIIIclot = 2.8%), a remarkable difference for between-run CVs was obtained, being much lower for FVIIIchrom (3.4%), as compared to FVIIIclot (13.4%). Within-run CVs for CPP 1/10 were: FVIIIchrom = 5.8% and FVIIIclot = 3.7%, whereas between-run CVs were FVIIIchrom = 23.9% and FVIIIclot = 7.2%. Calculated MUs for FVIIIchrom were similar for both concentration levels (CPN: 18.7%, CPP: 18.0%), while for FVIIIclot higher MU for CPP (28.6%) than for CPN (12.8%) was obtained. Passing Bablok regression analysis demonstrated good agreement between the two methods with concordance coefficient of correlation 0.958 (95%CI: 0.933-0.974), a regression line slope 0.855 (95%CI: 0.784-0.942) and intercept 0.995 (95%CI: 0.117-3.464). Bland-Altman analysis showed mean difference of −5.8% between FVIIIchrom and FVIIIclot that was strongly represented in the higher measuring range.

Conclusions: Automated FVIIIchrom assay has demonstrated excellent analytical performance, including remarkable linearity (0.7-149.0%), making the method suitable and applicable to daily routine.

Table 1. Test	Method	Assigned potency (u/dL)	Survey 1 n	Survey 1 Median u/dL	Survey 1 CV (%)	Survey 2 n	Survey 2 Median u/dL	Survey 2 CV (%)
VWF antigen	All methods	116.0	205	110.5	7.5	222	115.0	6.1
VWF activity	VWF:RCo	84.0	78	79.4	20.3	37	80.9	19.7
	VWF:Ab*	–	25	94.4	10.1	40	96.7	8.0
	VWF:GPIbR*	–	11	99.0	5.5	55	93.4	8.0
	VWF:GPIbM*	–	12	82.2	12.7	44	87.0	8.5

*Immunoturbidimetric methods.

W-P-030 (553) | Assays for von Willebrand factor (VWF): A need for further standardisation?

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Introduction: Diagnosis of von Willebrand disease (VWD) requires precise and accurate assays of VWF activity. Historically these assays have been performed using platelet agglutination-based methods (VWF:RCo assays), and have been subject to high levels of imprecision and poor sensitivity. However, the introduction of immunoturbidimetric methods has led to a higher degree of within-method precision. The ISTH SSC plasma standard is a reference material with an assigned potency for VWF:RCo, and this plasma standard has been distributed in UK NEQAS BC proficiency testing exercises on two occasions, 5 years apart, where results obtained by large numbers of haemostasis laboratories have been compared to the assigned VWF:RCo value.

Methods: The SSC plasma standard (lot #4) was coded and sent to >200 centres for VWF assays, in May 2012 (survey 1) and May 2017 (survey 2). Median results and coefficient of variation (CV) were determined for each method group and are shown in table 1 – VWF activity methods are classified as described in *Bodo et al*, *Journal of Thrombosis and Haemostasis* 2015; 13: 1345-50.

Results:

Conclusions: The proportion of centres employing immunoturbidimetric assays compared to VWF:RCo assays increased from 38% in 2012 to 79% in 2017. Results with all 3 immunoturbidimetric methods were statistically significantly higher than results obtained with VWF:RCo assays ($P < 0.001$), and 2 of these 3 methods were >10% higher than the assigned potency for the SSC plasma standard. Importantly, the potency for this material was assigned using results from centres predominantly using VWF:RCo assay methods, and potency was assigned by calibration against a WHO International standard, itself calibrated using the VWF:RCo assay. The next lot of SSC reference plasma standard is currently undergoing calibration and it is important that the potency assignment of this new material incorporates values obtained with immunoturbidimetric methods.

09-INHIBITORS

M-LBMED01-XXX (326) | Recombinant activated factor VII: 20-year safety update including >5 million administered doses

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Introduction and Objective: Recombinant activated factor VII (rFVIIa) was first approved for use in Europe in 1996. This updated safety review summarizes data based on the use of greater than 5 million standard rFVIIa doses (90 μg/kg; calculated based on an individual weighing 40 kg) administered since approval in its licensed indications: congenital hemophilia with inhibitors, congenital factor VII (FVII) deficiency, acquired hemophilia, and Glanzmann's thrombasthenia.

Materials and Methods: A safety review of rFVIIa use in all licensed indications using data collected between 1996 and December 31, 2013 has been previously published. This update includes additional safety data collected since then, based on a systematic and periodic review of all cases reported cumulatively from spontaneous sources, scientific literature, and post-marketing studies and registries, up to December 31, 2016.

Results: In total, 217 individuals treated with rFVIIa have experienced 249 thrombotic events (TE) (including thrombophlebitis). TEs were reported in 91 individuals who received rFVIIa treatment for congenital hemophilia with inhibitors, the majority of which were venous (46/105, 43.8%). In acquired hemophilia, TEs affected 66 individuals, with approximately equal proportions being arterial (26/72, 36.1%) or mixed (29/72, 40.3%). In Glanzmann's thrombasthenia, TEs were reported in 11 individuals treated with rFVIIa, the majority of which were venous (9/15, 60%). TEs were also reported in 49 people with congenital FVII deficiency treated with rFVIIa, most of which were venous (30/57, 52.6%). Overall, 95 of the 217 individuals with TEs (44%)

recovered without sequelae or were recovering at the time of data collection. There have been no reports of thrombotic microangiopathy in any licensed indication. No neutralizing antibodies against rFVIIa were reported in congenital and acquired hemophilia with inhibitors or Glanzmann's thrombasthenia.

Conclusions: Recombinant FVIIa has shown a favorable safety profile over 20 years of use. This updated safety review shows that, despite substantial use, relatively few AEs and safety concerns have occurred when rFVIIa is used in relation to its licensed indications. Recombinant FVIIa has a favorable safety profile in approved indications and is well tolerated.

Conflict of Interest Disclosure: Ellis J Neufeld and Claude Négrier have served as consultants and advisory board members for Novo Nordisk. Soraya Benchikh el Fegoun, Alonso Rojas-Rios, and Stephanie Seremetis are Novo Nordisk employees and shareholders. David L Cooper is a Novo Nordisk employee.

W-FPMED01-001 (682) | Immune tolerance induction using a recombinant FVIIIFc (Eloctate): A report of early responses from India

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Introduction and Objective: There is limited data on use of extended half-life (EHL) CFC for immune tolerance induction (ITI). We have attempted ITI in a cohort of patients with hemophilia A and high titre inhibitors with some of the rFVIIIFc provided through the humanitarian aid program of the World Federation of Hemophilia. This report summarizes the early outcome in these patients treated in three centers in India.

Patients and Methods: Patients with hemophilia A and high titre inhibitor (>5 BU) given ITI with rFVIIIFc were included in this analysis. Past data was acquired from hospital records and personal interviews. For ITI, rFVIIIFc dose ranged from 50 IU/kg 3x/week to 200 IU/kg per day, depending on the weight, convenience and response as well as availability. Bethesda assay was done every 2-4 weeks. The endpoint of ITI was a negative Bethesda assay with a FVIII recovery of >60%. Patients received either FEIBA or rVIIa for breakthrough bleeds, as available.

Results: A total of 33 patients underwent ITI, 7 (21%) of whom had a family history of inhibitors. Their median age was 15 years (2-39). The median age at diagnosis of inhibitors was 12 years (1.8-38). Two patients (6%) were on prophylaxis and 7 patients (21%) had history of surgery prior to development of inhibitor. Seven patients (21%) had exposure to only plasma derived CFC. The median FVIII exposures was 18 (2-80) and duration of inhibitor prior to ITI was 1.4 years (0.1-20). The maximum inhibitor titre recorded was 20 BU (12-326). The median inhibitor titre at the time of starting ITI was 12 BU (0.6-332.8). At a median duration of ITI of 21 weeks (9-55), 14/33 patients (42%) achieved a negative inhibitor status. Among the responders, the median duration of ITI to achieve negative inhibitor status was 16 weeks (10-30). The median breakthrough bleeds during ITI was 1 (0-10).

Conclusions: These early data show that EHL rFVIIIFc can be effective in ITI with a significant number of responses being seen within 6 months. An updated status of response will be presented.

M-P-059 (455) | Agreement between a chromogenic modified Nijmegen-Bethesda Assay and a qualitative ELISA test in detection of Factor VIII inhibitors in plasma from Persons with Hemophilia A (PwHA)

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Introduction and Objective: An inhibitor response via antibody development to FVIII replacement therapies is the most significant complication of hemophilia A treatment today. An accurate diagnosis of FVIII inhibitors is essential in guiding patient management, however international proficiency studies have revealed high rates of variation between laboratories. Different reagents and methods used across labs account for the high variability. Thus, there is a need for standardization and improvement of the FVIII inhibitor assay. Considering the potential variation caused by application of FVIII-depleted plasma from different sources, a kit for a Modified Nijmegen-Bethesda Assay (MNBA) was developed in frozen format consisting of an Imidazole Buffered Bovine Serum Albumin (4% IB-BSA) to replace FVIII-depleted plasma, an Imidazole Buffered Pooled Normal Plasma (IB-PNP, FVIII 95-105%), a positive FVIII inhibitor control (0.8-1.2 BU/mL) and an inhibitor-free plasma negative control.

Materials and Methods: A total of 37 frozen clinical plasma samples from PwHA with history of FVIII inhibitor were heat-deactivated (56°C, 30 min.), centrifuged, and stored at less than −70°C before testing. After thawing, test mixtures (1:1 mixture of IB-PNP with either undiluted or IB-BSA diluted heat deactivated plasma samples) and control mixtures (1:1 mixture of IB-PNP:IB-BSA) were prepared and incubated for 2 h at 37°C followed by 10 min. incubation on ice. FVIII chromogenic activity of the test and control mixtures was determined on the Siemens BCS® XP analyzer. The residual FVIII activity (Test Mix/Control Mix) closest to 50% was multiplied by the sample dilution factor to calculate FVIII inhibitor titer in Bethesda Units (BU), and ≥0.6 BU/mL was applied as cutoff for a positive inhibitor as ISTH-SSC recommendation. Heat deactivated samples were also tested in parallel for anti-FVIII antibodies using an ELISA (Immucor Factor VIII Antibody Screen).

Results: The methods showed 100% negative agreement (n = 6; 54.1-100%, 95% CI), and 87% positive agreement (n = 31; 70.2-96.4%, 95% CI). The observed discrepant samples (n = 4 out of 37) were borderline positive by ELISA, negative by the chromogenic MNBA, and negative by another one-stage Pathromtin® SL clotting MNBA.

Conclusions: The chromogenic MNBA shows promise for laboratories seeking a standardized functional inhibitor assay suitable for clinical management or multi-center clinical studies of PwHA.

M-P-060 (109) | Determinants involved in the development of inhibitors in patients with hemophilia in Colombia: A nested case-control study

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Introduction: Hemophilia is an uncommon hemorrhagic disease, characterized by a deficiency of coagulation factors VIII (hemophilia A) or IX (hemophilia B).

TABLE 1. Characteristics of patients and controls with hemophilia and inhibitors against coagulation factors VIII and IX, Colombia, 2016.

Patients characteristics	Cases with inhibitors (n = 23)	Controls (n = 92)	p value
Age			
Mean age – years (SD)	29.3 (17.9)	29.6 (17.6)	.937
Age group (%)			
0-4 years	2 (8.7)	7 (7.6)	
5-14 years	4 (17.4)	12 (13.0)	
15-18 years	0 (0.0)	6 (6.5)	
19-44 years	13 (56.5)	46 (50.0)	
>45 years	4 (17.4)	21 (22.8)	
Family history of coagulopathy	8 (34.8)	56 (60.1)	.06
In self-infusion scheme	4 (17.4)	11 (11.9)	.489
Clinical variables			
Type of hemophilia - No (%)			
Hemophilia A	22 (95.7)	88 (95.7)	1.000
Hemophilia B	1 (4.3)	4 (4.3)	
Severity - No (%)			
Mild	1 (4.3)	22 (23.9)	.041*
Moderate	1 (4.3)	20 (21.7)	**.07**
Severe	21 (91.3)	50 (54.3)	**.001**
Age at diagnosis – years (SD)	3.5 (10.5)	7.4 (10.2)	.493
Currently in prophylaxis	10 (43.5)	52 (56.5)	.262
Type of prophylaxis - No (%)			
Primary	2 (20)	7 (13.5)	1.000
Secondary	1 (10)	23 (44.2)	.041*
Tertiary	7 (70)	22 (42.3)	.519
Presence of joint damage	17 (73.9)	50 (96.1)	.089
Number of affected joints			
None	6 (26.1)	41 (44.6)	.107
1 joint	1 (4.3)	13 (14.1)	.295
≥2 joint	16 (69.6)	38 (41.3)	**.015**
History of CNS injury	3 (13.0)	2 (21.7)	.054
Allergic reaction attributable to the factor	1 (4.3)	11 (11.9)	.455
Infectious comorbidity	5 (21.7)	13 (14.1)	.353
HBV infection	17 (73.9)	41 (44.6)	**.012**
HCV infection	4 (17.4)	18 (19.6)	1.000
Transfusion before 1990	11 (47.8)	39 (42.4)	.638
More than one transfusion in the last 5 years	6 (26.1)	21 (22.8)	.741
Immunization Program of Colombia	17 (73.9)	67 (72.8)	.916
Pharmacological variables			
Type of factor before entering the care program			
Unknown	13 (56.5)	29 (31.5)	**.026**
Plasmatic	2 (8.7)	36 (39.1)	.006
Recombinant	2 (8.7)	27 (29.3)	.041
Application days			
1 day a week	1 (4.3)	0	1.000
2 days a week	1 (4.3)	11 (11.9)	.455
Every other day	9 (39.1)	39 (42.4)	.777
Everyday	1 (4.3)	0	1.000

SD: Standard Deviation; CNS: central nervous system; HBV: Hepatitis B virus; HCV: Hepatitis C virus; * Not significant confidence interval.

Objective: To identify the variables related to the development of inhibitors in patients with antihemophilic therapy in Colombia.

Methods: Nested case-control study. Patients of any age with hemophilia, treated in a specialized institution from 30 cities of Colombia, and with a diagnosis of inhibitors against factor VIII or IX during 2016 were selected as cases. Four controls per case were obtained, matched by age and type of hemophilia. Sociodemographic, clinical and pharmacological variables were identified and analyzed. Multivariate analysis was performed. A $P < .05$ was determined as significant.

Results: From a cohort of 354 patients with a diagnosis of hemophilia, 23 cases with inhibitors and 92 matching controls were identified. The prevalence of patients with inhibitors was 6.5% and 95.7% had hemophilia A. The sociodemographic, clinical and pharmacological variables are presented in Table 1. The multivariate analysis showed that having severe hemophilia (OR: 13.4; 95%CI: 1.43-125.66), infection with hepatitis B virus (HBV) (OR: 4.21; 95%CI: 1.03-17.29) and not knowing which coagulation factor was used before entering the care program at the specialized institution (OR: 20.6; 95%CI: 3.32-128.10) were statistically associated with a greater probability of developing inhibitors.

Conclusion: There is no dependable strategy to predict the development of inhibitors. In Colombia inhibitor presence had low prevalence, mainly in patients with hemophilia A. The probability of developing inhibitors was higher in cases of severe hemophilia, with HBV infection and in those with unknown coagulation factors received before entering the care program of this institution.

M-P-061 (823) | Prevalence of FVIII inhibitors in cases with hemophilia A receiving "on-demand" therapy

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Objectives: Inhibitor development in Hemophilia A is one of the most dreaded treatment related complication which is encountered by Cases with Hemophilia A (CWHA) and treating clinicians. Financial constraints limit prophylactic FVIII replacement in India and hence majority of patients receive on-demand therapy. Limited literature exists on the prevalence, titers and clinico-pathological correlates of inhibitor development in CWHA receiving on-demand therapy. The present study was done to assess the prevalence of inhibitors in CWHA in North Indian population taking "on- demand" therapy.

Materials and Methods: Study group comprised of 280 CWHA. Detailed clinical parameters, treatment history, bleeding profile including family history were recorded. Diagnosis of Hemophilia A was confirmed by PT, INR, aPTT, mixing studies, FVIII bioassay, vWF Antigen assay. Inhibitors were screened using mixing based studies followed by quantification by Bethesda Assay and Nijmegen modified Bethesda Assay. Samples were collected from five cities in North India where a cost free supply of FVIII was available and effectively used in three of these cities.

Results: In the 280 CWHA, phenotype was severe 201 (71.8%), moderate 60 (21.4%) and mild 19 (6.8%), based on the FVIII bioassay. Inhibitor prevalence was 9.6% (n = 27) and seen only in the severe phenotype. Inhibitor titers ranged from 0.8-108.8 BU/ml. Six CWHA had low (<5 BU/ml) and 21 had high titers (>5 BU/ml). Analysis of various clinico-pathological parameters in Inhibitor positive versus negative cases was done. Bleeding in joints and ecchymoses was the most common manifestation found in the study population whereas when Inhibitor positive and negative cases were compared, CNS bleed and hematuria was found to correlate with inhibitor development. Overall, most common blood group was B (33.34%),followed by O (27.34%), A (24.34%) and AB (15%), however in inhibitor positive cases blood group O appeared protective while significant inhibitor formation was seen in A (12/27, 44.4%). The prevalence of inhibitors in a citywise distribution at 10.2%, 12%, 4.87%, 11.55% and 5.88% in city A,B,C,D and E which correlated with the mean consumption of plasma derived FVIII in terms of annual factor intake/patient in different regions.

Conclusion: FVIII inhibitors were found in 9.6% CWHA. Inhibitor development has been extensively studied in cases receiving prophylaxis, our study provides a perspective in CWHA on demand therapy.

M-P-062 (421) | Long-term outcomes of patients with severe hemophilia A and high titer inhibitors with partial tolerance after immune tolerance induction

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Introduction and Objective: Approximately 70% of patients with severe hemophilia A with inhibitors who undergo immune tolerance induction (ITI) are successfully tolerized and able to resume standard prophylactic regimens with factor VIII (FVIII). However, a portion of patients who do not meet criteria for successful tolerance remain responsive to factor VIII (FVIII) and report minimal bleeding symptoms on increased intensity FVIII dosing regimens. In this case series, we evaluated the long-term outcomes of patients at our institution with partial tolerance following ITI.

Materials and Methods: Patients aged 3-21 years with severe hemophilia A, a history of a high titer inhibitor, and a classification of partial tolerance after a ≥33-month period of continuous ITI were evaluated. Partial tolerance was defined by clinical response to FVIII and an inhibitor titer <5 BU/ml, FVIII recovery <66%, or FVIII half-life <7 hours. FVIII pharmacokinetics (recovery, half-life, and inhibitor titers), FVIII dosing regimens, and annualized bleeding rates (ABR) over a 12-month period were analyzed.

Results: Five patients considered to have partial tolerance, ranging from 3-15 years following their course of ITI, had historical peak

inhibitor titers of 42-819 BU/ml. FVIII recoveries ranged from 61 to ≥100% of predicted. Four of the 5 patients had a negative inhibitor titer. The remaining one patient had a low titer inhibitor of 0.6 BU/ml and was well controlled on 30 units/kg every other day. The 4 inhibitor negative patients required increased FVIII dosing regimens of 50-150 units/kg every other day for bleeding treatment and prevention. The mean ABR for this group was 1.4 with a mean joint ABR of zero over a 12-month period from July 2016-June 2017 on the increased FVIII regimens. None of the patients required a bypassing agent for bleeding.

Conclusions: This study demonstrates that a portion of patients with severe hemophilia A and high titer inhibitors are able to achieve a prolonged response to FVIII with high dose FVIII regimens and maintain function with low ABRs despite partial tolerance after ITI attempts.

M-P-071 (175) | Critical assessment of the methodologies used to collect data in congenital hemophilia with inhibitors: Lessons learned from a systematic literature review on recombinant FVIIa

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Introduction and Objective: Studies of hemophilia, with or without inhibitors, have limitations. Many of the studies are relatively small (with less than 100 participants), include limited numbers of bleeding episodes, and lack standardized definitions of outcomes, especially in congenital hemophilia with inhibitors (CHwI). A systematic review was therefore performed to provide more robust information on rFVIIa efficacy and safety in CHwI, with a secondary objective being to pool the data, if feasible.

Materials and Methods: We searched Embase®, MEDLINE®, and Cochrane Central Register of Controlled Trials (CENTRAL) databases using terms such as "congenital hemophilia," "human coagulation factor VII (activated)," or "novoseven" or "eptacog alfa" (cut-off date May 2, 2016). Two independent reviewers screen the retrieved abstracts, with discrepancies reconciled by a third reviewer. Full-text publications of selected abstracts were then reviewed in the same way for final inclusion.

Results: After screening the 1214 publications identified, 20 studies (13 observational and 7 randomized controlled trials) reported in 58 publications were selected for inclusion in the systematic review; the studies included 1221 participants, of whom 746 experienced 5981 bleeds treated with rFVIIa. Assessment of the study quality supported the feasibility of performing a meta-analysis. Tentative pooling of the data to perform a meta-analysis was done. However, variability across studies on the effectiveness criteria utilized, and limited safety data, did not allow such a meta-analysis. Regardless, the data extracted from the individual studies were valid and valuable. The most commonly reported rFVIIa initial dose was 90 μg/kg, repeated at a mean interval of 2-3 hours. Based on a qualitative review of limited safety data, rFVIIa had a favorable safety profile with a low risk of general adverse events as well as thromboembolic events.

Conclusions: The high degree of heterogeneity, and the absence of consensus on how effectiveness was evaluated, hindered the potential to pool results. The key lesson learned from this exercise is that recommendations and consensus on the data to collect in CHwI are required; one approach to rectify this could be to assess the feasibility of formulating an international registry for all present and future therapies.

Conflict of Interest Disclosure: Craig M. Kessler has participated in advisory boards and medical education activities for Novo Nordisk and has received funding for clinical research from Novo Nordisk. Andrew Worster has acted as a consultant for Novo Nordisk.

M-P-072 (580) | Outcomes of haemophilia A patients who develop inhibitors in Australia between 1996 and 2016

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Introduction & Objective: Management of haemophilia with inhibitor patients is complex. Immune Tolerance Therapy (ITT) is effective in eradicating inhibitors in the majority of patients. Spontaneous clearance of inhibitors has also been reported in patients who do not undergo tolerisation. The aim of this study is to review the treatment history of patients with a previous inhibitor that had now resolved.

Methods: Retrospective data was obtained from the Australian Bleeding Disorders Registry (ABDR) on Haemophilia A (HA) patients from all Haemophilia Treatment Centres (HTCs) with appropriate ethics approval. Patients were classified as inhibitor positive by an inhibitor titre of ≥0.5 BU/mL confirmed on two consecutive tests. Information was extracted on disease severity, age, inhibitor results, details of ITT and spontaneous remission.

Results: 244 HA patients (25.74% [173/672] severe and 8.22% [71/863] non-severe) registered on the ABDR developed an inhibitor between 1996 and 2016. Data analysis was performed on 141 HA patients (48 Historic/Overseas patients on whom treatment history was unable to be obtained, and 55 HA patients with a current positive test for an inhibitor were excluded from the study). 75/141 (53%) HA patients have been previously successfully tolerised, which included 18 with low-titre (≤5 BU/mL), and 57 with high-titre (>5 BU/mL) inhibitors. The average treatment dose of factor VIII concentrate was 80.7 IU/Kg (SD 23.3)

and tolerisation time (median) was 222 days for low-titre, while 96.3 IU/Kg (SD 37.2) and 334 days respectively for high-titre. 28% of patients were tolerised within 6 month and 32% within 12 months. Most patients received daily factor VIII infusions initially with subsequent reduction in frequency to every 2nd day or 3xWeekly. Spontaneous remission was observed among 66/141 HA patients, the majority of whom had low-titre levels. 12% of these patients (8/66) developed inhibitors again when re-exposed to FVIII concentrates.

Conclusions: The majority of patients with Haemophilia A with a historical inhibitor have previously undergone successful tolerisation therapy.

M-P-073 (493) | Differences between extended half-life isolated FVIII and natural FVIII/FVW complex concentrate against inhibitors

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Introduction and Objective: Factor VIII (FVIII) concentrates for the treatment of hemophilia are available as the natural complex of FVIII and von Willebrand Factor (VWF) purified from plasma (pd) or as FVIII without VWF prepared by monoclonal antibody purification or recombinant DNA technology (rFVIII). Recently, modified rFVIII products aimed to increase the half-life of circulating FVIII known as extended high life (EHL) concentrates, have been marketed. EHL comprise Fc fusion proteins and PEGylated FVIII. In this study the neutralizing capacity against inhibitors of a commercial EHL-FVIII concentrate was assessed in comparison to a natural pdFVIII/VWF complex concentrate.

Materials and Methods: FVIII inhibitors (IgG) were purified from a pool of plasmas from hemophilic patients with inhibitors by Protein G chromatography. Samples (1 IU/mL FVIII:C) of FVIII concentrates (natural pdFVIII/VWF complex and recombinant B-domain deleted FVIII Fc fusion protein [BDD-rFVIII-Fc] obtained from Human Embryonic Kidney cells) were incubated 1:1 with serial dilutions of IgG in the presence of 1 IU/mL pdVWF (i.e., without FVIII). In a second set of experiments, samples of pre-mixed isolated pdVWF and FVIII concentrates were incubated with the inhibitor. After 2 hours at 37°C incubation, residual FVIII:C was determined using a chromogenic assay. Inhibitor titer was determined through a Bethesda assay. Comparisons to normal plasma were performed using the unpaired Mann-Whitney test. Three independent runs were performed for each FVIII concentrate and plasma.

Results: Bethesda assay results showed a statistically significant difference ($P < .0001$) between BDD-rFVIII-Fc (16.77 ± 1.11 BU/ml, mean ± SD) and natural pdFVIII/VWF complex concentrate (10.97 ± 1.72 BU/ml). The pattern of results was similar when FVIII was pre-mixed with VWF before contact with inhibitors.

Conclusions: In agreement to previously reported data, an isolated EHL-FVIII concentrate showed significantly lower residual FVIII:C than a concentrate containing the natural FVIII/VWF complex, when challenged with a pool of FVIII inhibitors. This effect was also observed even after pre-incubation of FVIII with isolated VWF. This finding is similar for all isolated FVIII products studied so far, regardless their origin, molecular form, cell line involved or modifications to attain EHL.

Disclosures: The authors are employees of Grifols.

M-P-079 (713) | Follow up after inhibitor diagnosis in a non-severe haemophilia A cohort at the Royal London Hospital

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Introduction and Objectives: Anti-Factor VIII (FVIII) antibodies complicate management of non-severe haemophilia A (NSHA) patients treated with FVIII concentrates. Studies have demonstrated a lifelong inhibitor risk in some patients, with antibody formation being associated with significant bleed related morbidity and mortality. There is incomplete understanding of the natural history of inhibitors in NSHA, including apparent transience seen in some patients. We reviewed data of all NSHA patients diagnosed with an inhibitor at our centre to improve understanding of outcomes and time course of inhibitors.

Materials and Methods: A database search was conducted of all NSHA patients (n = 396) at the Royal London Hospital Haemophilia Centre. 5% (22/396) of NSHA patients had an inhibitor history. Data on treatment history and laboratory testing were reviewed for patients with available electronic records (n = 19).

Results: Inhibitors were registered at a median of 45 years (17-81) with a peak titre of 1.8 BU/mL (0.5-20.2). *F8* genotypes were recorded in 89% (17/19). Eight different *F8* mutations were represented with the most common (7/17) being Trp2229Cys. Inhibitors were either transient (n = 8), remained positive (n = 8; including 2 historical inhibitors) or were purely historical (n = 3). Baseline FVIII activity (FVIII:C) declined after inhibitor detection in 92% (11/12) with 73% (8/11) to <0.01 IU/ml and 82% (9/11) recovered >90% baseline FVIII:C at a median of 18 months. On-demand treatment was required for 75% (12/16) of patients with recent inhibitors (median episodes = 4; 1-12) and two switched to prophylaxis. After a recent inhibitor, 2/16 were re-challenged with FVIII concentrate with low-titre inhibitor re-emergence seen in 1, which became undetectable after switching to prophylaxis. After a historical inhibitor, 3/5 had been re-challenged with FVIII concentrate and late inhibitor

re-emergence occurred in 2. Inhibitor re-emergence was also seen in one patient treated with FEIBA (peak titre = 4.1 BU/mL).

Conclusions: Inhibitors became undetectable in 50% (8/16) of NSHA patients recently diagnosed with an inhibitor without treatment to induce immune tolerance. Whether these inhibitors are truly transient is not clear due to few patients (n = 5) receiving re-challenge with FVIII, with inhibitor re-emergence seen in three patients. Further prospective study of outcomes in patients with inhibitors in NSHA is required.

10-LABORATORY ISSUES

M-FPMED01-002 (321) | One stage and chromogenic assays discrepancy in the estimation of Factor IX recovery: What single hemophilia center can and what cannot do?

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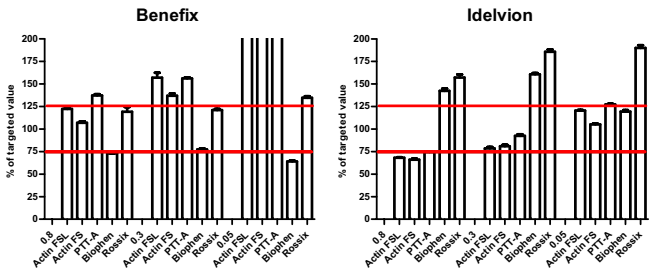
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Background: Both aPTT-based one stage (OS) and chromogenic substrate (CS) assays are used in the estimation of FVIII recovery, but CS assays for the determination of FIX have become available only recently. Therefore, data about potential discrepancies in hemophilia B are very limited. Extended half-life (EHL) products make this issue even more complicated.

Objectives: To investigate the recovery of different FIX concentrates using different OS and CS assays.

Methods: Standard (BeneFix) and EHL (Idelvion) FIX concentrates were spiked (0.8, 0.3 and 0.05 IU/dL) in FIX deficient plasma and tested by three OS (Actin FSL, Actin FS and PTT Automate) and two CS (Biophen and Rossix) FIX assays in triplicate.

Results: A small, non-significant difference was observed between OS assays using immunodepleted (Stago) or congenital (George King Biomedical) deficient plasmas and therefore all OS assays presented below were performed with immunodepleted FIX deficient plasma.



The results are presented as percent of targeted spiked value for each FIX concentrate. Red lines represent 75% and 125% since discrepancy of ± 25% may be considered acceptable. Conclusions

Our findings indicate discrepancies in the estimation of the recovery of FIX concentrates using different OS and CS assays. We suggest that each laboratory in hemophilia comprehensive centers should perform such an investigation with locally available FIX concentrates and assays and then decide on the potential combinations, since no laboratory is able to perform all assays. Manufacturers of factor concentrates may help by clearly stating in their concentrates' inserts which assays are used in potency assignments.

W-MP-031 (446) | A model for national proficiency testing programs in resource restricted countries and its impact on quality of haemostasis tests

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Introduction and Objectives: The objective of an external quality assessment scheme (EQAS) is to assist laboratories to produce reliable and accurate results in support of patient care. In resource restricted countries, lack of awareness and access due to financial constraints are the major reasons for laboratories not participating in an EQA scheme. We describe our effort at developing such a program in India and assisting other countries in developing their own.

Materials and Methods: Beginning in 2002, an EQAS was initiated supported by the UK NEQAS with samples for about 25 laboratories in India with CMC, Vellore being the coordinating centre. This program was supported initially through a grant from the Katherine Dormandy Trust and could provide samples free of cost for these laboratories which supported people with haemophilia. In 2004 this program was opened to all laboratories in the country along with production of stable, homogenous lyophilized material in India and data management at CMC, Vellore. The program now has grown to include >700 participants from around the country. Result entry and report dispatch is performed through a dedicated web portal at https://cmceqas.org.

Results: Besides offering a subsidized service in India, CMCEQAS has also extended support to several other countries: Philippines (2006), Thailand (2007), Sri Lanka (2009), China (2010) and South Africa (2014 – ongoing) involving between 10-20 laboratories in each country for a limited period of time ranging from 2-3 years after which they were expected to initiate their own programs.

Conclusion: We propose this as a model for resource restricted countries to establish their indigenous program that may then become sustainable on a long-term basis and will present data to show how it has helped improve the quality of haemostasis tests in India.

TABLE 1. Participant profile by program

	Number of surveys per year	Number of participants
Basic program		
PT	3	703
INR	3	703
APTT	3	703
TT	3	51
Fibrinogen	3	175
Advanced program		
Factor VIII:C	3	78
Factor IX	3	61
vWF:Ag	3	25
Ricof	3	9
Factor VIII Inhibitor	1	12
Lupus Anticoagulant	1	22

was obtained from each patient (washout of 72 Hs), and another 10 min after infusion of the FVIII concentrate indicated by the treating physician. Delta of the parameters were established as follows: Delta APTT: pre – post, Delta FVIII; Max1; Max2; Min2 in absolute value: post-pre. APTT-SP Instrumentation Laboratory (IL, 24-38 sec), FVIII:C one stage assay (50-150%), ACL TOP 300 IL.

Results:

When comparing Delta APTT vs Delta FVIII:C between the different products, there were differences between Advate and Koate-DVI vs kogenate-FS ($P < .05$). However, when comparing Delta Max1, Delta Max2, and Delta Min2 between the different products, there was no statistically significant difference.

Conclusions: Although patients with Kogenate-FS increased the FVIII: C more, there were no statistically significant differences with the other products in the velocity, acceleration and deceleration of the clot formation. This could mean that clinically this difference is not significant, but more samples and other studies would be necessary to validate these results.

W-P-032 (758) | Waveform of APTT in the treatment of Hemophilia

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Introduction: Throughout history, treatment therapy has evolved in people with hemophilia (PWH), as well as diagnostic methodologies. Currently there are optical coagulometers that have software that allows analyzing the morphology and parameters of the waveform of the APTT. The latter are Max1: velocity of the formation of the clot, Max2: acceleration of the formation of the clot and Min2: deceleration.

Objective: Evaluate if there are differences between the different products in the delta of the parameters APTT, FVIII:C, Max1, Max2 and Min2 obtained of pre and post infusion samples of PWH.

Materials and Methods: 47 PWH with FVIII:C <1% were studied (SHA), who received prophylaxis with plasma derivatives (Koate-DVI; N: 16), or with third-generation full-chain recombinant concentrates (Advate; N: 21, Kogenate-FS; N: 10). A pre-infusion sample

W-P-033 (356) | Truncated live calibration in one-stage adn chromogenic assays improves accuracy and precision

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Truncated live calibration in one-stage and chromogenic assays improves accuracy and precision. Current BCSH guidelines do not advocate use of stored calibration curves for factor assays. Assays should have at least three dilutions of test sample and results should fall within the range of clotting times on the standard curve. Calibration should occur with each run of test samples. A full calibration incurs cost in reagents and time but reliance on a stored calibration curve may lead to inaccuracy of results over time. We evaluated inclusion of a truncated (3 point) calibration curve alongside test samples by addition of a standard plasma, traceable to an International standard, in this system test. A correction factor was applied to QC sample results. The aim was to compare results using stored curves and correction factors in routine assays. Corrected and uncorrected results of two batches of internal QC plasma (P54

TABLE 1 Delta APTT vs Delta FVIII:C

	Delta APTT (seg)	Delta FVIII:C (%)	Delta Max1 (dAbs/dt)	Delta Max2 (dAbs/dt2)	Delta Min2(dAbs/dt2)
Advate N:21	49 ± 10	68.4 ± 26.8	196.862 ± 89.130	523.626 ± 147.020	188.835 ± 83.178
Koate-DVI N:16	50 ± 16	66.9 ± 22.3	175.086 ± 48.394	494.508 ± 123.190	172.637 ± 70.650
Kogenate-FS N:10	58 ± 11	94.5 ± 37.5	183.361 ± 49.043	518.686 ± 111.220	185.172 ± 68.799

TABLE 1 Corrected and uncorrected results

Clotting factor & QC (N)	Range of correction factor applied	Median uncorrected IU/dL, %CV	Median corrected IU/dL, %CV	% of samples with >10% difference in corrected and uncorrected
VIII:C1 P54 (28)	0.93-1.18	36, 7.8	37, 6.5	14
VIII:C1 P55 (5)	1.00-1.12	67, 4.1	69, 3.8	0
VIII:CR (165)	0.86-1.07	38*, 5.4	35*, 4.1	13
IX Actin FS P54 (35)	0.59-0.84	97*, 11.9	76*, 2.5	89
IX Actin FS P55 (26)	0.93-1.03	99*, 4.2	97*, 3.1	0
IX SynthaSil P54 (11)	0.76-0.98	82*, 7.4	75*, 2.0	36
IX SynthaSil P55, (22)	0.83-1.03	103, 6.0	98, 2.4	23
XI P54, (59)	0.87-1.13	56, 4.9	57, 2.6	5
XI P55 (30)	0.85-1.09	94*, 7.2	92*, 3.5	3
XII P54 (24)	0.59-1.04	112*, 23.1	1.01*, 3.1	46
XII P55 (12)	0.84-0.96	121*, 6.6	104*, 3.7	83
II P54 (19)	0.93-1.06	92*, 3.4	87*, 3.1	5
II P55 (14)	0.92-0.96	107*, 2.4	101*, 2.6	0
V P54 (14)	0.93-1.00	65, 2.5	64, 2.2	0
V P55 (16)	0.94-1.07	87, 3.5	86, 2.7	0
VII P54 (13)	0.85-1.00	124*, 2.8	114*, 2.9	3
VII P55 (17)	0.91-1.00	56*, 2.9	54*, 1.7	0
X P54 (10)	0.92-1.03	96*, 3.4	94*, 1.7	0
X P55 (16)	0.94-1.03	112*, 3.8	110*, 2.8	0

*Denotes statistically significant differences by Wilcox paired t-test between the uncorrected and corrected values.

and P55) were compared for factors II, V, VII, X, IX:C, XI, XII and one-stage and chromogenic Factor VIII:C (FVIII:C1, FVIII:CR). One-stage assays were performed using Siemens Standard Human Plasma, Innovin, Actin FS or SynthaSil (Werfen) with deficient plasmas; from Precision Biologic or Siemens. Chromogenic VIII was performed using Biophen Hyphen kit, Calibrator and QC. Correction factors were calculated as manufacturer assigned value/analyser obtained value for the standard during the assay. The %CV of uncorrected QC results ranged from 2.4-23.1%. The %CV of corrected results ranged from 1.7-6.5%. Application of correction factors decreased %CV in every factor assay (0.3-20%) compared with uncorrected results. The greatest improvement was observed in intrinsic clotting factors, particularly FIX and FXII. Extrinsic clotting factors demonstrated the least change between results.

A number of uncorrected results showed marked inaccuracy (see table). The use of correction factors consistently improved precision and accuracy of all factor assays and reduced the requirement for regular recalibration of the stored curve.

W-P-034 (556) | Mixing based inhibitor screening in hemophilia A: Challenges in interpretation

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Introduction and Objectives: Inhibitor development against FVIII in cases with Hemophilia A (CWHA) is most feared complication of FVIII replacement. Mixing based inhibitor Screening (MBIS) followed by quantification of inhibitor titers by Classical/Nijmegen Bethesda assay (CBA/NBA) is standard practice. MBIS, CBA and NBA are well described in literature and standard textbooks. However, cut-offs for positive MBIS for CBA/NBA are not clearly defined and are based on personal experiences and communication with other labs performing these assays. Present study aims at evaluating different cut-offs for MBIS before assaying inhibitors.

Material and Method: MBIS was performed by mixing patient's plasma and pooled normal plasma (PNP) in 1:1 ratio and performing APTT on fresh (F) and incubated (I) mix after 2 hours incubation. When difference (Δ) between two APTTs (Δ (I-F)) was ≥5 seconds, the case was considered positive. 36 CWHA with Δ (I-F) ≥ 5 seconds & 15 cases with negative MBIS were included in the study. CBA/NBA was used as gold standard to quantify inhibitors. NBA and CBA were performed at Δ (I-F) ≥ 5 seconds

and >10 seconds, respectively. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive value were calculated at both cut-offs.

Results: 29 of 36 cases were confirmed to have inhibitors on CBA/NBA. At cut-off Δ (I-F) ≥ 5 seconds, MBIS detected all 29/29 cases (both positive on CBA&NBA, range = 0.8-108.8 BU/ml). At cut-off >10 seconds, MBIS detected only 23/29 cases (positive on CBA only, range of 4.8-108.8 BU/ml). Diagnostics of MBIS showed sensitivity, specificity, PPV and NPV of 100%, 68.18%, 80.55% and 100% respectively at Δ (I-F) ≥ 5 seconds. At Δ (I-F) > 10 seconds these were 79.31%, 100%, 100% and 78.57% respectively.

Conclusions: As sensitivity of MBIS was 100% when Δ (I-F) was ≥5 seconds, we recommend this cut-off to perform CBA/NBA. At cut-off >10 seconds most low titer inhibitors (<5 BU/ml) could not be detected. We Propose that NBA should be performed when Δ (I-F) is ≥5 seconds (when low titer inhibitors are suspected) and CBA when Δ(I-F) is >10 seconds (when high titer inhibitors are suspected). Though Nijmegen assay shows a better specificity and intra- and inter laboratory variation, it is still vulnerable by several limitations related to assay characteristics (pH, temperature, and time of incubation) which should be in considered.

M-P-017 (156) | Reducing unnecessary coagulation testing in outpatients: A quality improvement project

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Introduction and Objectives: The prothrombin time (PT) and partial thromboplastin time (PTT) are often considered "routine" tests in the outpatient setting. They are frequently used as screening tests for bleeding disorders in unselected patients despite sensitivities ranging between 1 and 2%. For the most common bleeding disorder, a negative score on a bleeding assessment tool (BAT) has a NPV of 1. We developed a multimodal quality improvement study in the outpatient family practice unit with the primary aim of minimizing unnecessary coagulation testing and maximizing the appropriate use of a BAT.

Materials and Methods: We developed three interventions using plan-do-study-act (PDSA) cycles to achieve our goal. Cycle (1) involved stakeholder engagement, baseline assessment of ordering rates, development of educational tools and addition of the BAT onto the electronic medical record (EMR). Cycle (2) involved an audit to determine appropriateness of coagulation testing for patients on anticoagulants and subsequent targeted intervention. Cycle (3) will involve the removal of the PTT from the laboratory requisition.

Results: After Cycle 1, we saw a significant decrease in rates of PT and PTT ordering from 1.9 tests per 100 patient visits per month (for both tests) to 1.5 and 1.4 respectively; ($P < .001$ for both). With Cycle 2, we identified an inappropriate PT and PTT ordering rate of 11% and 36% respectively for patients on anticoagulants. We also identified that PT and PTT were being tested together despite being ordered individually; further investigation revealed that they were being erroneously coupled by the laboratory technicians. Since integrating the BAT on the family practice EMR, the majority of hematology referrals for bleeding have been accompanied by an appropriate BAT score.

Conclusions: From our quality improvement project in the emergency department, we learned that educational interventions alone are often not sufficient and a process change is required to achieve meaningful change. Here we found that PT and PTT tests are "culturally" linked by physicians and technicians alike. We also found that EMR integration of the BAT successfully guided hematology referrals for bleeding. We expect further optimization of coagulation testing by the end of Cycle 2.

M-P-018 (466) | Study of fibrin clot ultrastructure of varying concentrations of FVIII deficient plasma using scanning electron microscopy

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Introduction and Objective: Hemophilia patients may develop life-threatening bleeding problems; however, they may paradoxically develop clotting issues during therapy. Factor VIII concentrations ([FVIII]) influence thrombin concentration which impacts the local ultrastructure of plasma clot formation; we elected to use scanning electron microscopy (SEM) to examine ultrastructural changes of plasma clots with varying [FVIII]: 0%, 1%, 5%, 10%, 20%, 40%, 50%, 75%.

Materials and Methods: Normal pooled plasma (NPP) and FVIII deficient plasma were mixed to generate samples similar to hemophilia A patients with various degrees of severity. 20 μL NPP samples were transferred to 0.025 μm Millipore™ membrane. Clot formation was initiated with Factor IXa, phospholipids and $CaCl_2$. Clots were fixed with glutaraldehyde in 0.1 M phosphate buffer (pH = 7.4), stained with osmium tetroxide, dehydrated with gradient ethanol series, gold sputter-coated, and examined at 20,000× magnification. Three images were captured from randomized locations for each sample. Using area field of view of 205 μm^2, average fiber count and fiber width were measured using a custom Java-based software. Average values from each [FVIII] sample (n = 3) were recorded.

Results: As [FVIII] increased, fiber width decreased while fiber count increased. The 0% [FVIII] clot had an average width of 0.17 ± 0.07 μm and an average count of 17.28 ± 12.70, compared to 0.16 ± 0.05 μm and 35.61 ± 5.00 for the 75% [FVIII] clot, respectively. Plasma clots

with lower [FVIII] had fewer fibers that were thicker and potentially more susceptible to fibrinolysis than higher [FVIII] clots. In 0% [FVIII], few large fibers with scattered smaller fibers resulted in very porous non-cohesive clots, exposing the membrane.

Conclusions: Previous FVIII thrombin generation assay experiments have shown that decreasing [FVIII] is correlated to decreased thrombin. At low thrombin, clot formation is impaired along with compromised fibrin clot structure. Low thrombin concentration clots result in thicker and less abundant fibers. This may explain the observed results and display the importance of [FVIII] in relation to thrombin and hemophilia A. Our research examined clotting process from another perspective that may aid to understand clots in hemophilia A patients. This may set up the ground-work for further investigation into interactions with anticoagulants.

M-P-219 (141) | Thrombin generation response with the addition of bypassing agents in plasma of patients treated with fitusiran, an investigational RNAi therapeutic targeting antithrombin for the treatment of hemophilia

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Introduction and Objective: Hemophilia is a bleeding disorder characterized by a defect in the ability to generate sufficient thrombin for effective hemostasis. Fitusiran is a subcutaneously administered investigational RNA interference (RNAi) therapeutic targeting antithrombin (AT) to improve thrombin generation (TG) and promote hemostasis in patients with hemophilia A or B with and without inhibitors. Because breakthrough bleeds in inhibitor patients receiving fitusiran are treated with bypassing agents (BPAs, aPCC or rFVIIa), the combined effect of fitusiran-induced AT lowering and BPA administration on coagulation is of clinical interest. AT activity inhibition has been shown to increase the TG response to BPAs. The objective of the current study is to investigate the TG response to BPAs in plasma from hemophilia patients with pharmacologic, fitusiran-mediated AT lowering.

Methods: Platelet poor plasma was collected from patients with hemophilia A with or without inhibitors, both before and after treatment with fitusiran. This plasma was spiked ex vivo with BPAs aPCC (0.1, 0.25, 0.5 or 1 U/mL) or rFVIIa (0.75, 1.75 or 2.5 μg/mL). The resulting thrombin generation response was evaluated by Calibrated Automated Thrombogram (CAT) stimulated with 1 pM TF and 4 μM phospholipid.

Results: Plasma samples from 8 patients with hemophilia A (7 without inhibitor, 1 with inhibitor) were collected, both before and after treatment with fitusiran. The median residual AT activity in fitusiran-treated plasma was 22% (range 15-41%) of baseline. In ex vivo TG studies, fitusiran-induced AT lowering alone led to increased peak TG. Both aPCC and rFVIIa produced further linear increases in peak TG when added to fitusiran-treated patient plasma. In intra-patient comparisons, lower than typical doses of aPCC were sufficient to produce peak TG levels in fitusiran-treated plasma that were equivalent to those achieved with full aPCC dosing in pre-fitusiran plasma from the same donor. At the aPCC and rVIIIa doses tested in fitusiran-treated plasma, peak TG remained within the normal range observed in healthy volunteers.

Conclusions: These results provide evidence to support using reduced doses of BPA to achieve hemostasis in patients who experience breakthrough bleeding during fitusiran treatment.

11-MANAGEMENT OF BLEEDING

W-FPYR-003 (157) | DDAVP responsiveness and clinical outcome: A Canadian single center experience

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Introduction and Objective: DDAVP is used for treatment/prevention of bleeding in patients with non-severe hemophilia A (NSHA). DDAVP responsiveness is determined by measuring FVIII levels before and after administration of a test dose. Currently, no single definition of responsiveness exists. DDAVP response testing in patients with NSHA in the Southern Alberta Rare Blood and Bleeding Disorders Program (RBBD) was reviewed with the aim of classifying response and examining its relationship to clinical outcome after use.

Materials and Methods: The local electronic record system was used to identify adult patients (≥18 years old) registered in the RBBD, with NSHA (FVIII 0.01 iu/ml to ≤0.40 iu/ml) who underwent DDAVP testing between January 2007 and October 2017. Information collected included: baseline FVIII level, DDAVP test dose (mcg/kg), FVIII level at 1 and 4 hours, and clinical outcome after use. Test-response was compared to 6 reported definitions of DDAVP responsiveness to determine classification.

Results: DDAVP response testing was obtained for 50 patients with NSHA. 42/50 had mild HA (FVIII >0.05 iu/ml). Median baseline FVIII was 0.11 iu/ml. 9 (18%) patients received the full 0.3 mcg/kg dose. 41 (52%) patients received a standard dose (maximum 20 mcg), regardless of weight. 29 (58%) patients (all mild HA) had "complete response" by all 6 definitions. 9 (18%) patients (5/9 moderate HA) had "no response". 24% (n = 12; 3 moderate, 9 mild HA) of patients had a partial response (by ≥2 definitions). Of 12 patients with "partial response": 8 (67%) received DDAVP for dental procedures, minor surgeries and trauma with resolution of/no abnormal bleeding; 1 received DDAVP for a calf bleed with no improvement; and 3 (25%) never received DDAVP treatment. 2/9 patients with "no response" received DDAVP for minor bleeding/procedures with good effect.

Conclusions: Use of DDAVP for prevention/treatment of bleeding in patients with NSHA should consider both clinical judgement/situation and test-response. "Partial response" and "no response" classifications do not mean "no clinical effect"; rather, patients may benefit from DDAVP in certain clinical situations. Further investigation is needed regarding clinical outcomes following DDAVP use in patients with NSHA.

Disclosures: there are no disclosures.

T-P-026 (389) | Central line placement challenges and management heterogeneity in pediatric patients with hemophilia

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Introduction: Venous access in hemophilia A or B patients can impede prophylactic factor infusion or immune tolerance induction (ITI). Central venous line (CVL) placement eases this burden, improving opportunity for regimen adherence and expediting parental infusion independence. Despite reducing risk of bleeding from missed doses, peripheral infiltration, and child behavioral struggles, CVL related complications can also arise.

Objective: To investigate frequency of CVL complications within 30 days of placement and the association with age, type of hemophilia, presence of inhibitors, type of CVL, and factor replacement plan. To establish trends in rate of and perioperative planning for CVLs placed and duration of CVL use.

Methods: We conducted a single center IRB-approved retrospective investigation of all hemophilia A and B patients with central lines placed 2007-2017.

Results: 36 CVLs placed in 25 patients 2007-2017. All patients had severe hemophilia, 22 A and 3 B. Median age at first CVL was 1.1 years (0.66-6). Placement indications included anticipation of poor venous access 39%, failed peripheral access 36%, or start of ITI 25%. All patients had <50 exposure days at first CVL placement. 44% of CVLs had a complication within 30 days of placement. Post-operative and accessing related bleeding were the primary complications. No intra-operative bleeding, early line malfunction, infection/bacteremia, or thrombosis observed.

TABLE 1 CVL with and without complications

	CVL with complication (first 30 days)	CVL without complication (first 30 days)
Inhibitor		
Port-a-cath (PAC)	9	4
Co-insertion of peripherally inserted central catheter (PICC)	4	0
Broviac	6	0
Age at placement (median, range)	3 years (1.1-21)	6.6 years (0.9-19)
Hemophilia type		
A	7	3
B	2	0
Peri-op hemostasis		
Pre-op dose (median, range)	rFVIIa 270 mcg/kg (90-270)	rFVIIa 270 mcg/kg (n = 1) FVIII 100 IU/kg (50-150)
Pre-procedure factor level obtained	n = 1	n = 1
Post-procedure frequency (median, range)	q2hours, then spacing	rFVIIa q2hours, then spacing FVIII 6hours (3-12)
Post-procedure treatment (days)	7 days (3-14)	7 days (all)
Post-procedure hospitalization (days)	3 days (2-20)	2.5 days (2-3)
CVL longevity	1.5 years (0.4-6)	2 years (0.25-3)
Non-Inhibitor		
Port-a-cath (PAC)	5	13
Co-insertion of peripherally inserted central catheter (PICC)	0	0
Broviac	0	0
Age at placement (median, range)	0.9 years (0.7-1)	4.5 years (0.75-14)
Hemophilia type		
A	3	9
B	1	0
Peri-op hemostasis		
Pre-op dose (median, range)	FVIII 50 IU/kg FIX 100 IU/kg	FVIII 50 IU/kg (50-150)
Pre-procedure factor level obtained	n = 0	n = 7
Post-procedure frequency (median, range)	FVIII 6 hours (2-8) FIX 12 hours (n = 1)	FVIII 12 hours (4-12)
Post-procedure treatment	4 days (3-5)	6 days (3-8)
Post-procedure hospitalization	2 days (2-3)	2 days (1-7)
CVL longevity	2 years (1-4)	4.5 years (0.5-8)

Conclusions: Post-procedure bleeding/hematoma, typically after discharge, is our most common complication of CVL placement. Challenges with needle dislodgement, difficult access, and limited frequency of infusion seem to contribute. PICC co-placement to enable PAC healing and consistent factor infusion may reduce bleeding complications requiring re-admission. Elimination of pre-procedure factor levels was not associated with any intra-op or immediate post-op bleeding. PK to predict patient half-life is not routine prior to minor procedures in infant/toddlers but may better inform dosing and infusion frequency necessary to promote wound healing.

T-P-027 (283) | Successful hemostatic management for surgery in patients with congenital factor IX deficiency: A single center experience

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Introduction and Objective: Hemophilia B is an X-linked recessive bleeding disorder resulting from factor IX (FIX) deficiency. Prevalence of hemophilia B is one in 20,000 live male births, a quarter that of hemophilia A. While coagulation factor replacement is essential in surgical intervention in hemophilia B patients, evidence in support of the perioperative management is more lacking than hemophilia A. This study provides an updated evaluation of the safety and effectiveness of coagulation FIX concentrates in treating perioperative bleeding.

Materials and Methods: We reviewed the records of hemophilia B patients with inhibitors who underwent surgery between June 2006 and May 2017 using coagulation FIX concentrates at a single center. The first bolus of [80 IU/kg X 1.2-1.4] was given 30 min before surgery to achieve a preoperative FIX level of 80% under the supervision of a multidisciplinary hemophilia team of our institute. Approximately 50% of the initial dose was administered every 12 h and the dosing intervals were increased to 24 h.

Results: In total, 109 surgeries (93 orthopedic, 16 other) were conducted in 70 hemophilia B patients. The median age of the patients was 35.5 years (range, 6-78). The median duration of hospitalization was 14.3 days (range, 2–47), and median duration from operation to discharge was 11.5 days (1-42). Recombinant FIX concentrates were administered in all cases except 2 patients. The major surgical procedures, that were defined as one that required hemostatic support for periods exceeding 5 consecutive days, were 94 cases (89.5%). Median difference between preoperative and postoperative hemoglobin was 2.35 g/dL (range, 0-7.7). Total 18 cases of patients required packed RBC transfusion after surgery. In most cases, bleeding stopped or was well controlled; however, one patient expired after emergent surgery for intracranial hemorrhage. No thromboembolic event and development of antibody to FIX were observed in any case.

Conclusions: Good control of hemostasis can be achieved using FIX concentrates in hemophilia B patients who are undergoing surgery. Thorough planning is needed before elective surgery and more active and aggressive management may be needed for emergency surgery.

T-P-028 (536) | Achieving consensus for the management of bleeding from the mouth for people with haemophilia using a Delphi process

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There are currently low levels of evidence regarding the best way to manage bleeding from the mouth in people with haemophilia (PWH). In the absence of sufficient primary data to inform a contemporary guideline, a Delphi process was initiated with an international multi-disciplinary team (MDT) providing care for PWH. Aim; to use information from a Delphi process a to establish consensus on what constitutes best management of bleeding from the mouth.

Methods: A purposive sample of haematologists, dentists and specialist nurses with high levels of experience in providing care for PWH, were recruited via a call for interest. Eligible respondents took part in a two-round e-Delphi consensus process. In round 1 participants were presented with a list of 20 statements regarding management of bleeding from the mouth derived from the literature and current World Federation of Haemophilia (WHF) guidance documents. Participants anonymously assigned level of agreement with the statements using a Likert scale. In round 2 participants were provided with descriptive group statistics derived from round 1 and asked to re rank anonymously the same statements, citing specific reasons and/or evidence for their own stance if they were not in accordance with the consensus opinion in round 1.

Results: A 94% (n = 34) response rate was achieved across the 2-round e-Delphi process. The MDT participants included 12 haematologists, 15 dentists and 7 nurses drawn from 21 countries. Five consolidated practice statements were developed using

items which achieved a level of 80% consensus from the MDT and focused on: self-management, topical, local and systemic measures.

Conclusion: In the absence of high levels of evidence it was possible to achieve consensus best practice statements in relation to managing bleeding from the mouth, using a rigorous Delphi consensus methodology. Participants self-reported low levels of knowledge and confidence in managing a proportionate response to bleeding from the mouth. The process identified important gaps in the literature regarding effective routes of delivery of tranexamic acid to aid haemostasis in the mouth. Further work will include development of algorithms to address the knowledge and confidence gaps in health care professions managing care for PWH.

T-P-029 (300) | Clinical efficacy of recombinant factor VIII Fc fusion protein in hemophilia A patient receiving on demand treatment only, a cross sectional study

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Introduction and Objectives: Hemophilia A is X linked disease due to decreased levels of factor VIII and patients need replacement of factor VIII to maintain healthy life. Numbers of recombinant products are available with improved pharmacokinetics and less side effects. Recombinant factor VIII Fc fusion protein is a new drug with prolong half-life in patient receiving prophylactic treatment. Our study aims to evaluate the efficacy of this drug in hemophilia A patient receiving on demand treatment only.

Materials and Methods: Male patients of hemophilia A already receiving recombinant factor VIII (25 Units/kg) on demand, with no history of inhibitors (group I) were included in study. Patients were divided in three sub groups based on Factor VIII levels into severe, moderate and mild groups. Same patients were switched to recombinant factor VIII Fc fusion protein (25 Units/kg) (group II) and its efficacy was measured in terms of dose requirement, number of injections required per bleed, number of bleeds in six-month period, presence of inhibitors and side effects.

Results: In study 89 patients were included who were registered at Pakistan hemophilia welfare society, Rawalpindi. All patients were receiving recombinant factor VIII Fc fusion protein on demand. Both groups were compared in terms of dose requirement, number of bleed, injections required per bleed, and development of inhibitors. In both groups we observe significant reduction in dose from median value of 5750 units for group I to 4000 units for group II (*P* value .0468). Number of bleed in six-month period were reduced from 5.325 in group I to 4.5056 in group II (*P* value .0492). Number of injections required per bleed were reduced on average to one injection per bleed. No inhibitors were detected in any patient receiving recombinant factor VIII Fc fusion protein. Majority of patients did not experience any side effects except few patients who reported nonspecific arthralgias and headache.

Conclusions: Recombinant factor VIII Fc fusion protein has prolonged activity and results in reduction of total dose, number of bleed, and dose required per bleed. It has also shown reduced antigenicity in patients receiving on demand treatment.

T-P-030 (337) | Spinal epidural hematoma in hemophilia

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Central nervous system hemorrhages are an uncommon complication of hemophilia, occurring in only 2-8% of children.

Cases: A 15- month old boy with hemophilia A (factor VIII: Ag <1%, FVIII inhibitor <0.6 BU) admitted with the complaints of limited neck movements and difficulty of standing. Though cranial computed tomography was normal, magnetic resonance imaging (MRI) of the spinal cord demonstrated epidural hemorrhage between C4-T4 vertebrae which compress the medulla spinalis. Factor VIII concentrate replacement (50 U/kg q12 h first week and 25 U/kg q12 h second week) was given and control MRI of the spinal cord revealed remarkable shrinkage of epidural hemorrhage. He was discharged with factor VIII prophylaxis. A 6-year old boy with hemophilia A (factor VIII: Ag 0.25%, FVIII inhibitor: 3 BU) admitted with the complaints of walking difficulty and urinary retention. He dropped from his bike two days ago. MRI of the spinal cord showed epidural hematoma between L2-S3 vertebrae which cause spinal canal stenosis. Immediate factor VIII replacement and surgical drainage could not control the bleeding. FVIII inhibitor titer increased to 38 BU and recombinant factor VIIa (rFVIIa; 75 mcg/kg q3 h) was received. At the fifth dose, bleeding was controlled. MRI showed disappearance of cord compression. He was discharged with rFVIIa prophylaxis.

Discussion: Spinal epidural hemorrhage (SHE) is a rare, serious complication in hemophilia. The most common localizations are dorsal and dorsolateral sides of medulla spinalis and presented by back pain, sensory and motor deficits. Infants are not able to localize pain and the diagnosis can be underestimated especially in the lack of motor deficits and this may worsen the prognosis. Immediate diagnosis and aggressive factor replacement therapy can prevent surgery. In the first case aggressive factor replacement therapy was sufficient to control bleeding however in the second case despite aggressive therapy and urgent decompression, due to

high inhibitor titer bleeding could be controlled with rFVIIa. To prevent long-term sequels of SHE, diagnosis and treatment should not be delayed.

T-P-031 (824) | Characteristics and Influencing factors of Breakthrough bleeding in adult patients with severe hemophilia A receiving low- and intermediate-dose FVIII for tertiary prophylaxis

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Objective: To investigate the characteristics and influencing factors of breakthrough bleeding in adult patients with severe hemophilia A (SHA) receiving low- and intermediate-dose FVIII for tertiary prophylaxis.

Methods: Forty-nine patients (mean age 31.53 ± 7.33 years) with SHA receiving tertiary prophylaxis FVIII treatment were divided into low-dose group (n = 15) and intermediate-dose group (n = 34). The data including clinical bleeding phenotype (Pre-AJBR), 72 h FVIII trough activity, and Functional Independence Score in Hemophilia (FISH) were recorded in all the patients, and Hemophilia Steward APP was used to record the bleeding episode and the treatment data. All the patients were followed up for at least 6 months.

Results: In the low-dose and intermediate-dose groups, the number of joint bleeding (AJBR) episodes were 18.79 ± 13.03 and 9.28 ± 7.02 per year (P = .016), and the proportions of spontaneous bleeding were 75% and 48%, respectively. The proportions of patients with target joint were 80% and 44%, target joint bleeding occurred in 59% and 41%, and cataract bleeding after 0-12 h of prophylactic injection occurred in 4.86% and 5.18%, median breakthrough bleeding time of 40.08 h and 46.08 h (P = .008), respectively. The proportions of patients with 72 h FVIII trough activity <1% were 44.4% and 34.8% in the two groups, respectively. AJBR was negatively correlated with the preventive dose consumed (r = -0.57, P = .000, n = 49) and FISH, but positively correlated with Pre-AJBR in the two groups (P < 0.05).

Conclusion: Tertiary prophylaxis with low- and intermediate-dose FVIII were not sufficient to achieve the goal of preventing progression of joint disease in most of Chinese adult patients with SHA. Although the prophylactic dose was the most important effected factor of the efficacy, reducing the target joint, reasonable arrangements for restorations and injection time, shorten the injection interval, improve the clinical bleeding phenotype or Activity Ability and another non-factor approach may improve efficacy.

Keywords: severe hemophilia A; low and Intermediate-dose; prophylaxis; breakthrough bleeding.

T-P-032 (792) | Muscle hematomas in patients with hemophilia. Experience in a comprehensive hemophilia treatment center in Colombia

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Introduction and Objective: the most frequent bleeds in patients with hemophilia are hemarthrosis, soft tissue and muscle hematomas (MH). There is poor evidence to treat muscle bleeds, they could have more factor concentrate consumption than hemarthrosis. Treatment for this type of bleeds must be careful due to the high risk of complications such as infection, compartmental syndrome, need for surgical procedures, contractures, and disability. The main objective is to describe MH in a group of patients with hemophilia who were followed in a cohort, in a hemophilia treatment center in Colombia.

Materials and Methods: Descriptive study in a population of patients with hemophilia who presented MH in a period of 4 years. The qualitative variables are presented with absolute and relative frequencies. The quantitative variables with measures of central tendency.

Results: There were 93 muscle bleeds in 41 patients. It was the third cause of bleeds in our hemophilia treatment center. Median age was 13 years, 73 episodes were in children and 20 in adults, all were traumatic; 53 were in severe hemophilia patients, 32 in moderate and 8 in mild disease. There were nineteen episodes in 3 patients with hemophilia A (HA) with inhibitors and 74 bleeds in patients without inhibitors (52 in patients with HA and 22 in hemophilia B). The location of the hematoma was soleus (n = 29), forearm (n = 15), gluteus (n = 13) and thigh (n = 13). The majority of patients were treated in the outpatient clinic (n = 58), and 35 with hospitalization, mainly for those located in psoas, gluteus, and thigh. Patients with psoas, gluteus and leg bleed receive physiotherapy

TABLE 1. Analysis of break-through bleeding in the two groups.

Bleeding reason	Low-dose group (n = 15)	Intermediate-dose group (n = 34)	χ^2	P
Spontaneous bleeding	75%	48%	25.54	.000
Traumatic bleeding	25%	52 %	25.54	.000
Proportion of patients with target joint	80%	44%	5.417	.029
Target joint bleeding	59%	41%	6.859	.009

as part of treatment. 38.4% of bleeds resolved with 1 to 2 doses, 20% with 3 to 5 doses and 40% require 10 or more doses. Psoas and thigh were those with more factor concentrate consumption, with an average of 43.350 IU and 24.225 UI of FVIII respectively. No complications as compartmental syndrome or disability were observed in this group of patients.

Conclusions: MH was a frequent cause of bleeds in this group of patients, near 40% of episodes required 10 or more doses to control bleed. Physiotherapy should be considered for more patients as part of treatment.

T-P-033 (195) | The bleeding score: Useful in predicting spontaneous bleeding events in adults with bleeding of unknown cause?

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Introduction and Objective: Many patients with mild bleeding symptoms referred for coagulation investigation have no identifiable disease, even after comprehensive laboratory testing. These patients are often categorized as having bleeding of unknown cause (BUC). Evidence available to inform clinical management of BUC patients is currently limited. Recently, the bleeding score (BS) has been shown to be a good predictor of future bleeding events in von Willebrand Disease patients. This study aims to determine whether the BS predicts risk of future spontaneous bleeding events in patients with BUC.

Methods: A single-center retrospective chart review was conducted on BUC patients at the Adult Hemostasis and Thrombosis Clinic in Kingston, Ontario. The BS was collected, and patients with a BS ≥4 were included in the study. The following laboratory tests were collected: (i) complete blood count, ABO blood type, coagulation profile (INR, PT, PTT, TT, fibrinogen), ferritin; (ii) VWF antigen level, VWF functional assay and factor VIII level; (iii) platelet function studies; and (iv) additional factor assays if indicated. Information about spontaneous bleeding events (frequency, site, treatment) was collected from patient charts. Data was imported into IBM SPSS and analyzed using t-tests, chi-squared tests and logistic regression.

Results: A total of 94 BUC patients were included in the study. In this cohort, 47.9% of patients (45/94) had at least one spontaneous bleeding event. Menorrhagia was the most common type of bleeding event, while muscle hematoma was the least common. The mean (SD) BS of BUC patients with at least one bleeding event was 9.8 (3.2), which is significantly higher than those that did not have any bleeds [8.1 (3.9), $P = .022$]. In a secondary analysis including all bleeding events except menorrhagia, the BS was still significantly different between the two groups ($P = .019$), 10.8 (3.5) and 8.5 (3.9) for BUC patients with and without spontaneous bleeding events, respectively.

Conclusions: The BS in BUC patients with at least one spontaneous bleeding event was significantly higher than in those without a bleeding event. These results should be prospectively validated to confirm the relationship between the BS and future spontaneous bleeding events in this patient population.

T-P-047 (333) | Clinical effectiveness of recombinant activated factor VII in bleeding disorders

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Introduction and Objective: Recombinant activated factor VII (rFVIIa) received European approval in 1996. The aim of this summary is to review post-marketing effectiveness data from rFVIIa licensed indications of congenital hemophilia with inhibitors (CHwI), congenital factor VII deficiency (FVII CD), acquired hemophilia (AH), and Glanzmann's thrombasthenia (GT). Materials and Methods

This summary includes rFVIIa post-marketing data from registries and observational studies conducted by Novo Nordisk between January 1996 and December 2016. A large body of evidence was available on the number of bleeds, patients, and the effectiveness of rFVIIa for acute bleeding from 10 studies (5 registries, 5 observational studies), and 6 studies (4 registries, 2 observational studies) reporting on rFVIIa use for surgeries and/or invasive procedures.

Results: Registry data indicated that for acute bleeds, rFVIIa stopped up to 90% of bleeds in CHwI and 85% of bleeds in AH (with an independently conducted registry showing that 93% of bleeds in AH were stopped with rFVIIa). Registry data also showed "excellent" or "effective" outcomes in up to 92% of FVII CD bleeds, and was rated as effective in 91% of GT bleeds when rFVIIa was used alone. For surgery and invasive procedures, registry data showed that bleeding was stopped in up to 91% of procedures performed in CHwI, was rated as excellent/good in 77% and fair/partially effective in 9% of bleeds in AH, and prevented bleeding in 95% of surgical or invasive procedures in individuals with FVII CD. Observational study data showed that rFVIIa was effective in up to 96% of acute bleeds and 91% of surgical procedures in CHwI, while in AH, one observational study indicated that 89% of acute bleeds were controlled. In FVII CD, observational study data indicated that excellent/effective outcomes were achieved in 82% of bleeds and effective in 91% of bleeds associated with surgery/

invasive procedures. No observational study data were available for GT.

Conclusions: Post-marketing data collected over 20 years have consistently shown that rFVIIa provides effective bleeding control for its licensed indications (CHwI, FVII CD, AH, and GT), despite the varied underlying biology.

Conflict of Interest Disclosure: Ellis J Neufeld and Claude Négrier have served as consultants and advisory board members for Novo Nordisk. Soraya Benchikh el Fegoun and Stephanie Seremetis are Novo Nordisk employees and shareholders. David L Cooper is a Novo Nordisk employee.

12-MANIFESTATIONS OF HEMOPHILIA

W-FPMED01-003 (28) | Advanced magnetic resonance imaging of the osteochondral components in hemophilic joints reveals cartilage hemosiderin and correlations with clinical joint scores

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Introduction and Objective: The purpose of this study was to evaluate joints of adult patients with hemophilia (PWH) using conventional and quantitative ultrashort echo time (UTE) magnetic resonance imaging (MRI) sequences, and to determine if findings correlate with Hemophilia Joint Health Scores (HJHSs) and pain. Ultimately, this knowledge would improve our clinical understanding of hemophilic arthropathy.

Materials and Methods: 23 patients with hemophilia (42 ± 15 years; 18 type-A, 5 type-B) were recruited prospectively (9 knees, 7 ankles, and 7 elbow joints). Pain scores (Visual Analog Scale) and HJHSs were obtained before undergoing MRI at T3 using a conventional clinical MRI protocol and a 4-echo 3D-UTE-Cones sequence. MRI images were evaluated by a musculoskeletal radiologist and scored using the International Prophylaxis Study Group (IPSG) MRI scale. Additionally, UTE-T2* values of cartilage in weight-bearing joints (patellae and tali) were quantified. IPSG scores for all 23 joints were compared with pain and HJHS scores (excluding gait to allow analysis for the non-weight-bearing elbow joints) using Spearman rank correlation. UTE-T2* values of the 16 weight-bearing joints were compared with pain, global gait, and total HJHS scores. $P < 0.05$ was considered significant. Two patients subsequently underwent knee arthroplasty, which permitted linking of histological findings (including Perl's reaction) with MRI results.

Results: Pain scores demonstrated no correlation with any MRI measures. The MRI osteochondral subscores correlated with HJHS scores (rho = 0.6, $P < 0.01$), driven by osseous erosions (rho = 0.55, $P < 0.01$) and cysts (rho = 0.49, $P < 0.05$). There was no correlation between soft tissue subscores and HJHS. UTE-T2* values for cartilage correlated inversely with HJHS clinical scores (including joint total score, rho = -0.81, $P < 0.01$ and global gait, rho = -0.58, $P = .02$). This finding was unexpected since UTE-T2* values increase with worsening, not better joint status in osteoarthritis in non-hemophilia patients. Histological analysis of cartilage revealed hemosiderin within chondrocytes and macrophages, associated with some of the lowest UTE-T2* values.

Conclusions: HJHSs in adult PWH correlate strongly with osteochondral pathology on MRI, contributing to the validity of the HJHS to assess chronic joint deterioration in adults. In addition, UTE-T2* values may reflect hemosiderin accumulation in cartilage, as a new measure to quantify sequelae from chronic bleeding.

W-FPYR-002 (776) | Increased severity of joint disease in individuals with hemophilia A compared to hemophilia B as measured by the hemophilia joint health score

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Introduction and Objective: Chronic joint disease due to hemarthrosis is a frequent problem in individuals with hemophilia A and B (HA/HB), often leading to reduced health-related quality of life. The severity of joint disease and its rate of progression over time may reflect that person's bleeding phenotype more accurately than the baseline clotting factor level. The objective of this investigation was to determine the differences in joint disease severity among individuals across the age spectrum and with varying severities of hemophilia.

Methods: Individuals with HA or HB who participated in the University of Colorado's IRB-approved Hemophilia and Bleeding Disorders Prospective Inceptional Cohort Study (Hemo-PICS) were included in the analysis. Joint disease was quantified using the Hemophilia Joint Health Score (HJHS). Each subject's most recent HJHS was calculated as the sum of ankle, knee, and elbow exam scores. HA/HB severities were defined as severe (<1% factor VIII/factor IX activity), moderate (1-5%), or mild (6-30%). Simple linear regression was used to estimate the relationship of age and HJHS total score for each patient subgroup.

Results: 246 individuals with HA/HB were included. For both HA and HB, joint health worsened with increasing age; HJHS increases

were more pronounced depending on disease severity (mild < moderate < severe, Table 1). For all HA/HB severities, HJHS increased more with age in HA compared to HB. Those with moderate HB showed similar degrees of age-dependent HJHS increases as those with mild HB, whereas those with moderate HA showed increases that were higher than those with mild HA.

Conclusion: Joint disease is more severe in individuals with HA compared to HB. This difference was most striking for those with moderate HA and HB. For those with moderate disease, treatment recommendations should take into account measures of joint health such as the HJHS and not rely solely on baseline FVIII/FIX level.

TABLE 1. Relationship of Age and Hemophilia Joint Health Score for Individuals with Mild, Moderate, and Severe Hemophilia A and B

	n	HJHS Increase per 1 year Increase in Age	95% CI	p value for model fit
Hemophilia A				
Mild	60	0.31	0.22-0.40	<.0001
Moderate	36	0.65	0.43-0.87	<.0001
Severe	98	1.07	0.89-1.26	<.0001
Total	194	0.60	0.48-0.72	<.0001
Hemophilia B				
Mild	19	0.35	0.13-0.57	.004
Moderate	17	0.36	0.09-0.63	.01
Severe	16	0.85	0.40-1.30	.001
Total	52	0.42	0.24-0.61	<.0001

HJHS = Hemophilia Joint Health Score, CI = confidence interval.
Higher HJHS scores indicate increased severity of joint disease.

W-P-037 (58) | Musculoskeletal ultrasound reveals that patient-derived symptom assessment questionnaires are unreliable for the diagnosis of hemarthrosis in patients with hemophilia

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Background: Patients with hemophilia (PWH) experience painful joint episodes which may or may not be associated with new hemarthrosis. Point of care (POC) musculoskeletal ultrasound (MSKUS) is being utilized increasingly to rapidly detect hemarthrosis and direct management. The diagnosis of hemarthrosis can be complicated by patient and physician perception of non-specific symptoms such as warmth, pain and swelling. Patient-derived questionnaires describing pain sensations have been suggested for diagnosing hemarthrosis. We sought to validate a questionnaire developed by an experienced patient group and compare it against POC MSKUS to detect hemarthrosis.

Methods: We administered the patient-developed questionnaire comprising 20 questions (10 each associated with hemarthrosis and arthritis pain, respectively) to adult PWH experiencing acute painful episodes and reporting to the Hemophilia Treatment Center at the University of California San Diego. Patient and providers were blinded to question assignment and the order of the questions was randomly scrambled. We confirmed the presence (or absence) of bleeding by MSKUS. We performed univariate and multivariate logistic regression analysis to identify symptoms associated with bleeding.

Results: We evaluated 32 painful episodes, 14 retrospectively and 18 prospectively. The median patient age was 44 years; 25 and 7 had hemophilia A and B, respectively. The majority of episodes (18) were in patients with severe hemophilia. POC MSKUS detected joint bleeding in 17 episodes. Of the 20 symptoms queried, only 2 significantly correlated with hemarthrosis detected by MSKUS. The symptom of "irregular, non-progressive pain with movement or weight bearing" negatively correlated with hemarthrosis (OR = 0.20, 95% CI 0.04-0.90, P = .0365). The symptom of "when resting, pain eases by not moving" positively correlated with hemarthrosis (OR = 11.25, 95% CI 1.86-68.13, P = .0084) with a sensitivity and positive predictive value of 88% and 71%, respectively.

Conclusion: Our findings suggest that patient-developed questionnaires may not be reliable in diagnosing hemarthrosis in PWH. However, 2 of the 20 described symptoms had discriminatory capacity, and a larger prospective study is warranted to prove their validity and use in settings where POC MSKUS is not readily available.

W-P-038 (88) | Intracranial hemorrhage in young children with hemophilia: A report of hemophilia study Group of Taiwan Society of Hemostasis and Thrombosis

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Introduction: Intracranial hemorrhage (ICH) is a life-threatening complication of patients with hemophilia (PWH), especially in childhood, resulting in high rates of mortality and disabling sequelae. This presentation will evaluate the clinical characteristics, management and outcome of ICH in young children.

Methods: Enrolled patients with ICH from Hemophilia Study Group of Taiwan Society of Thrombosis and Hemostasis. Clinical features of PWHs, data of ICH management and outcomes were evaluated.

Results: 39 ICH events were found in 306 PWHs. 76.9%(30/39) Patients are Hemophilia A, and 92% (36/39) are severe type. 15 ICHs occurred in children ≤2 yrs (none of the children was on prophylaxis). Only 3 patients had ICH with inhibitors and one patient developed inhibitors several days after ICH. 94% patients were under on-demand therapy. Total 15 patients had ICH with

age below 2 years old. 6/15 (40%) presented as neonatal. In 9 (60%) bleeding was intracerebral. The causes of ICH included 46.7%(7/15) spontaneously, 20%(3/15) traumatic, 20%(3/15) delivered related and 13%(2/15) were unknown. 60%(9/15) patients received factor replacement after ICH and two of them received surgical removal of blood clot. 3 patients received supportive care only because hemophilia was not diagnosed. Of survivors, 46.7%(7/15) had neurologic sequelae and 40%(6/15) continued prophylaxis after treatment of ICH.

Conclusions: The results obtained confirm high incidence of ICH in PWH, especially in young children. High incidence of spontaneous ICH that may provide insight in areas of care that can be improved in the future.

W-P-039 (287) | Quality of life and hormonal profile in adult hemophilia-A in Northern India

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Introduction and Objectives: Haemophilia patients experience physical and psychosomatic issues affecting quality of life. The underlying pathophysiology for secondary factors is unclear. Our aim was to assess Quality of Life (QoL) domains and hormonal profile in adult patients with haemophilia-A and correlate the two.

Materials and Methods: In a cross-sectional study, 50 adult haemophilia-A males were assessed for QoL using Short Form-36 (SF-36) questionnaire and for hormonal profile (TSH, fT3, fT4, Testosterone, Cortisol, LH, FSH, iPTH, prolactin) using chemiluminescence assays.

Results: Out of 50 adult haemophiliacs, mean age 28.2 ± 10.4 years, 34 (68.0%) had severe haemophilia, 15 (30.0%) moderate and remaining mild. Mean annual bleed rate (ABR) was 14.8 ± 13.4, ranging 2-75. Mean SF-36 domain scores as shown in Table-1.

TABLE 1. Quality of Life, SF-36 Domain scores in adult haemophilia (N=50)

SF-36 Domain	Abbreviation	Score mean	Score SD, Stand. Deviation
Physical functioning	PF	63.90	±21.71
Role physical	RP	39.47	±39.59
Bodily pain	BP	45.28	±29.07
General health	GH	42.84	±26.05
Vitality	VT	63.80	±19.62
Social functioning	SF	70.50	±28.65
Emotional role	RE	51.99	±42.14
Mental health	MH	63.96	±18.36

The mean Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were 37.28 ± 9.54 and 47.17 ± 11.00 respectively. Thus, the scores were particularly low for general health, bodily pain and physical role. Hormonal profile revealed abnormal serum parathormone level in 16 (32%) subjects, with low in nine and high in seven subjects. Ten patients (20%) had low testosterone levels. High TSH suggestive of hypothyroidism was observed in 2 (4%) subjects. Serum testosterone levels were low in 10 (20%) subjects. Other hormones viz. Cortisol, FSH, LH, and Prolactin were normal in 92%, 80%, and 88% cases respectively. In our study statistically, significant correlation was seen between general health (GH) and fT3 (P = .005) and fT4 (P = .017). Further, there was statistically significant correlation between vitality (VT) and fT3 (P = .012) and between social functioning (SF) and fT3 (P = .005) and TSH (P = .032).

Conclusions: This study reveals considerable physical and general health morbidity amongst adult haemophilia-A patients, impacting their Quality of Life. Significant hormonal alterations occur and may play a role. These need further elucidation in order to improve the quality of life in haemophiliacs.

W-P-040 (544) | Mortality and morbidity in mild vs severe hemophilia A and B; 15 years' experience; retrospective multi-center outcome

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Introduction and Objectives: Intracranial haemorrhage (ICH) is not an uncommon life-threatening event occurring in patients with haemophilia (PWH) of variable severity and the outcome can also vary. Aim of this work is to study the incidence and outcome of ICH in mild and severe PWH in Egypt.

Methods: We used a standardized collection tool to obtain consented data from 2001-2016 on eligible haemophiliacs aged ≤18 years enrolled in seven participating Egyptian Haemophilia Treatment Centers (EHTCs) registered in the Data Collection System surveillance. Data on type and severity of haemophilia, bleeding spectrum, presence of inhibitors, precipitating risk factors and outcome of ICH was collected.

Results: 1247 children, 82% haemophilia A (HA) [55% severe, 25% mild] and 18% haemophilia B [25% severe, 40% mild] were assessed. Severe bleeding was reported in 35% and 80% bled during the first two years of life. Sixty-two [5%] episodes of ICH were reported in 54 [4.3%] children; 6 deliveries related, 4 spontaneous, 48 post-traumatic, and 4 unknown cause. None received primary or secondary prophylaxis. Inhibitors were detected in 30/240 HA tested [12.5%] children, and patients who experienced ICH had higher rates of inhibitors [18% vs 10%] respectively. The 2 peak ages for presentation of ICH in the studied cohort were in infancy and at the age of 10 years. 9 patients [16.6%] died, 9 recovered with motor and/

or cognitive deficit, and 44 children recovered without sequelae. Treatment was mostly conservative and included cryoprecipitate or solvent detergent cryoprecipitate with an increasing trend to use plasma or recombinant clotting factor concentrates in the recent years.

Conclusion: The prevalence of ICH is 1 in 1000 patient-year in severe haemophilia A in contrast to 2 in 1000 patient-year for mild haemophilia A. The risk factors for ICH included severe haemophilia A, pre-adolescence, presence of inhibitor, mild head trauma and no prophylaxis. High mortality and morbidity rates were reported.

W-P-041 (774) | Bone health screening and treatment in a complete cohort of patients with severe haemophilia in a single national comprehensive care centre

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Introduction and Objective: In people with haemophilia, life expectancy is now approaching that of the general population which has resulted in diseases of ageing, including osteoporosis, becoming increasingly prevalent. Haemophilia is associated with several disease specific risk factors for reduced bone mineral density including disease severity, present of inhibitors, viral co-infection and arthropathy. Screening and treatment in high risk populations reduces morbidity and disability as well as reducing the costs associated with surgical treatment of fractures.

Materials/Methods: Patient registered with a diagnosis of severe FVIII or FIX deficiency were identified from the National Haemophilia electronic health record (EHR). Initially a retrospective audit of laboratory or radiology testing for osteopenia/osteoporosis over a 5-year period (2011-2016) was undertaken. Subsequently, a formal Bone Health screening programme commenced in 2017 for all patients. Data on patient diagnosis, bleeding history, arthropathy, co-infection status, laboratory bone health screening (including Vitamin D levels, PTH, CRP, Testosterone levels) and Dual-energy X-ray absorptiometry (DXA) were collected from Electronic patient records (EPR) and the National Haemophilia EHR.

Results: A total of 109 eligible patients were identified. In the initial audit, only a small number of patients had had bone health screening including Vitamin D levels in 18 patients (16.5%) and DXA scanning in 8 patients (7.3%). Following rollout of a systematic bone health screening programme, 85 patients (78%) have undergone laboratory bone health screening and have been scheduled for DXA scanning. In the total cohort to date, Vitamin D deficiency has been identified in 39 patients (46% of those tested) while osteopenia has been detected in 7 patients (50% of those scanned to date) and osteoporosis has been diagnosed in 3 patients. Three patients have experienced low trauma fractures. Patients with Vitamin D deficiency or established osteopenia and osteoporosis have received appropriate treatment with Vitamin D/calcium replacement, bisphosphonate or an alternative agent which have been well tolerated.

Conclusions: With a targeted screening programmed, most patients with severe haemophilia have been offered bone health screening. Patient acceptance of screening and treatment is high. A coordinated approach between the medical and nursing team and individual patients increases screening uptake.

W-P-242 (620) | Bone markers in haemophilia

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Introduction and Objectives: A severe complication of haemophilia is arthropathy, bleed induced and associated with cartilage and bone degradation. Bone mineral density (BMD) is lower in haemophilia patients than control subjects. A direct association between specific biomarkers of bone formation and resorption and BMD has not been investigated. Our prospective study measured levels of seven selected bone markers in a large cohort of severe and moderate haemophilia patients (A and B) with normal or low BMD.

Materials and Methods: BMD was determined by dual energy X-ray absorptiometry (DXA scan). 33 patients had low bone density (24 SHA, 5 with osteoporosis, 4 moderate HA and 5 SHB). 40 patients had normal bone density (30 SHA, 7 SHB, 2 moderate and 1 mild HA). Serum levels of bone formation markers osteocalcin, RANKL, PINP and resorption markers osteoprotegerin, TRACP 5b, CTX-1, Dickkopf-1 and angiogenesis marker VEGF were quantitated using ELISA (NeoScientific, Cambridge Massachusetts, USA) where normal ranges were determined for each assay (n = 25).

Results: Students t-test (2-tailed) was performed for each biomarker comparing low and normal bone density groups. *P* values were: Osteocalcin, 0.73; RANKL, 0.06 (low BMD 3.7 ± 1.9 pg/mL, normal BMD 3.1 ± 0.9 pg/mL, normal 3.0 ± 0.9 pg/mL); PINP, 0.07 (low BMD 7.6 ± 5.8 pg/mL, normal BMD 5.8 ± 1.8 pg/mL, normal, 5.1 ± 1.5 pg/mL); osteoprotegerin, 0.20; TRACP 5b, 0.22; CTX-1, 0.14; Dickkopf-1, 0.96; and VEGF, 0.09. Dickkopf-1, an inhibitor of the Wnt signalling pathway known to impair bone regeneration, was increased 18% in low BMD patients (868 ± 952 pg/mL) and 22% in normal BMD patients (846 ± 772 pg/mL) (*P* = .96) compared to normal (506 ± 277 pg/mL). Excluding Dickkopf-1, 21% of patients with low BMD were positive for 2 or more of the markers

while only 12% of normal BMD patients were positive for 2 of more.

Conclusions: Two genes involved in the control of bone regeneration, RANKL and PINP show differences between normal and low bone densities approaching statistical significance while Dickkopf-1 appears to be elevated in haemophilia. Further study is needed to ascertain the association of bone markers, bone density and the severity of arthropathy in haemophilia.

13-MOLECULAR GENE THERAPY

T-FPMED01-001 (153) | Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvovec (BMN 270): Long-term efficacy and safety results in patients with severe hemophilia A

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Introduction and Objective: As a single gene disorder of Factor VIII (FVIII), hemophilia A (HA) is an ideal candidate for gene therapy. We present results from an ongoing Phase 1/2 study of valoctocogene roxaparvovec (BMN 270; AAV5-FVIII-SQ) gene transfer in patients with severe HA.

Methods: As of 14 September 2017, 13 subjects (6E13 vg/kg, *n* = 7; 4E13 vg/kg, *n* = 6) received a single intravenous dose of valoctocogene roxaparvovec, an AAV5 vector containing a B-domain-deleted FVIII gene. Safety, efficacy, immunogenicity, and other endpoints are being evaluated.

Results: FVIII activity is presented as median levels over 4-week intervals. In the 6E13 cohort, FVIII activity plateaued by Week 20 post-valoctocogene roxaparvovec, with median levels between Weeks 20-65 in the normal range (NR; 89-122 IU/dL); Week 65 median FVIII activity was 98 IU/dL ([range] 16-145 IU/dL). In the 4E13 cohort, median [range] FVIII activity continues to increase toward the NR (Week 20 [*n* = 6]: 34 [7-45] IU/dL; Week 32 [*n* = 3]: 51 [48-54] IU/dL; Week 36 [*n* = 3]: 45 [41-55]). Prior FVIII prophylaxis subjects had median [interquartile range, IQR] annualized FVIII infusions decline from 139 [122-157] (6E13) and 156 [126-183] (4E13) to 0 [0-0] 4 weeks post-infusion through last follow-up; median [IQR] annualized bleeding rates post-infusion were 0 [0-0] in both cohorts (no bleeding episodes in 5 subjects in each cohort). Mild, grade 1, asymptomatic alanine aminotransferase (ALT) increases were reported in six of seven 6E13 and four of six 4E13 subjects; one 4E13 subject had a grade 2 ALT increase. Peak ALT levels ranged from 44-141 U/L (upper limit of normal=43 U/L). All but 2 subjects (4E13) currently have a normal ALT level, and all but 1 subject (4E13) are off of corticosteroid therapy. Updated results will be presented at the meeting.

Conclusions: Gene transfer with valoctocogene roxaparvovec in subjects with severe HA resulted in sustained, clinically relevant FVIII activity that reduced self-reported bleeding and exogenous FVIII use >1.2 years post-infusion in the 6E13 cohort. FVIII activity in the 4E13 cohort continues to rise, reaching the lower end of the NR >0.5 years post-infusion. Both doses enabled achievement of long-term normalization of FVIII activity and prevention of hemophilia-related bleeding with a favorable safety profile.

W-P-051 (152) | Prednisolone treatment does not regulate FVIII expression in mice treated with valoctocogene roxaparvovec (BMN 270)

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Introduction and Objectives: Hemophilia A (HA) is a bleeding disorder caused by deficiency of factor VIII (FVIII). Valoctocogene roxaparvovec (BMN 270) is an AAV5-based gene therapy vector that expresses a B-domain-deleted human FVIII (hFVIII-SQ) under the control of a human liver-specific promoter. Recently, results from a phase 1/2 trial in severe HA patients treated with valoctocogene roxaparvovec were presented (Pasi et al., 2016). In this trial, patients dosed at 6E13 vg/kg were given prophylactic prednisolone treatment to minimize potential immune-mediated hepatocyte injury and decrease in hFVIII-SQ expression. For the majority of patients in this cohort, FVIII activity reached normal levels. One question arose from this study is whether prednisolone directly regulates FVIII expression produced from valoctocogene roxaparvovec. We undertook a study to determine if chronic prednisolone treatment following valoctocogene roxaparvovec administration affects hFVIII-SQ expression, and if elevation of liver enzymes in plasma occurs in mice treated with valoctocogene roxaparvovec with and without prednisolone.

Methods: C57BL/6 mice were treated with vehicle, 2E13 or 6E13 vg/kg of valoctocogene roxaparvovec. One week after valoctocogene roxaparvovec or vehicle injection, daily treatment with 2 mg/kg prednisolone or water was initiated. Mice were euthanized either 4 or 13 weeks after valoctocogene roxaparvovec or vehicle administration. Levels of *hFVIII-SQ* DNA and RNA, and hFVIII-SQ immunostaining in the liver, as well as levels of hFVIII-SQ protein and activity, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in terminal plasma samples were analyzed.

Results: Levels of liver *hFVIII-SQ* DNA and RNA as well as plasma FVIII protein and activity were dose-dependent with or without prednisolone treatment. Treatment with prednisolone for either 3 or 12 weeks did not modulate levels of liver *hFVIII-SQ* DNA, RNA, or the distribution of FVIII protein; nor did it regulate hFVIII-SQ protein and activity in the plasma. There were no statistically significant increases in the plasma level of AST and ALT in response to treatment with valoctocogene roxaparvovec.

Conclusion: Chronic prednisolone treatment did not affect hFVIII-SQ expression produced from valoctocogene roxaparvovec and no significant elevation of liver enzymes were observed in mice treated with valoctocogene roxaparvovec.

W-P-052 (548) | HemAcure: Application of combined gene and cell therapy within an implantable therapeutic device for the treatment of severe haemophilia A

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Introduction: Our consortium aims to develop a novel ex vivo cell-based therapy to treat haemophilia A (HA) that should ultimately lead to improved patient quality of life. Blood outgrowth endothelial cells (BOECs), a production source of factor VIII (FVIII) will be isolated from HA patients and genetically corrected with a lentiviral vector (LV) encoding for functional FVIII. Corrected cells will be expanded to guarantee a long-lasting therapy or cure. The cells will be tested for safety, efficacy and endothelial characteristics and transplanted into a subcutaneously implanted medical device for sustained secretion of FVIII in NOD/SCID γ-null (NSG) HA mice for preclinical studies. All processes will be performed under Good Manufacturing Practice (GMP) conditions, to ensure safety and quality according to the highest standards.

Material and Methods: BOECs were isolated from non-haemophilia donors' and patients' blood. Cells were efficiently transduced by LVs containing the B domain deleted form of human FVIII under control of the Vascular Endothelial Cadherin promoter (VEC). BOECs were characterized by FACS for endothelial phenotype and FVIII evaluated by APTT and ELISA. Ten million LV-VEC.hFVIII-BOECs were transplanted intraperitoneally on cytodex 3 microcarrier beads in NSG-HA mice ($n = 3$). In addition, corrected BOECS from HA patients will be transplanted into the medical device in NSG-HA mice for optimization of sustained FVIII secretion.

Results: The number of integrated LV copies/cell was ~3 for LV-VEC. hFVIII transduced cells, yielding in 67% of cells expressing FVIII determined by FACS. We confirmed endothelial phenotype of corrected cells by FACS detecting endothelial specific markers. BOECs survived and secreted FVIII at therapeutic levels (with a peak of 15% FVIII activity) for up to 13 weeks in mice.

Conclusion: With our strategy, we achieved secretion of functional FVIII at therapeutic levels up to 13 weeks in NSG-HA mice. Furthermore, we established a GMP compliant process for isolation of BOECs and currently establishing GMP compliance for the LV-transduction and expansion of BOECs as well. Based on the results we will accomplish GMP compliance for the whole process chain, we plan to transplant GMP produced, autologous gene corrected and safe BOECs for future clinical testing in HA patients.

14-ORAL HEALTH

T-FP-MTD-001 (181) | The PROBE Study – Global burden of bleeding from the mouth in Haemophilia – a call to action

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Introduction and Objectives: Severe periodontal disease is a major cause of tooth loss in adult populations worldwide alongside well-documented impacts on general health and well-being including heart disease, inflammatory joint disease and pulmonary infection. There is no global information as to the incidence and impacts of oral disease in people with haemophilia (PWH). Aims were to estimate oral hygiene practices using self-reported gingivitis among PWH and to estimate access to dental care among PWH using an episode of severe life-threatening bleed attributable to a dental cause as a proxy for unfavourable access.

Materials and Methods: Data gathered as part of the PROBE cross-sectional study included a self-reported assessment of gingival bleeding and enquired into life-threatening significant bleeds during the previous calendar year.

Results: Questionnaire responses from 1170 PWH and 525 participants without bleeding disorders (controls) across 21 countries were included in the analysis. Mean age was lower in PWH group (34.18 ± 17.84 vs 44.80 ± 13.77). Among PWH A & B (84.27%/15.73% respectively) 163 respondent reported life-threatening bleeds of

which 27% were either solely (n = 16) attributed to a dental cause or listed as one of a number of bleeding causes in those experiencing multiple episodes of bleeding (n = 28). The incidence of self-reported gingivitis in PWH (84.6%) was significantly higher than matched controls (15.4%) (P < 0.001).

Conclusions: Haemophilia has no inherent independent risk factors yet PWH were five times more likely to have gingivitis, which indicates poor adherence to appropriate oral hygiene measures. Well established protocols permit dental care for PWH to be carried out safely. However, the mouth was the single most common site generating self-reported life-threatening bleeds. This data suggests oral health is an important heath inequality with the potential to become more significant as PWH age and risk-factors for oral disease increase. Identification of factors generating this inequality and the facilitation of appropriate self-management of oral hygiene and access to dental care within an integrated care framework should be an imperative due to the significant impact of oral disease on general health, quality of life and the financial cost of treating advanced disease.

Conflict of Interest Disclosure Text: PROBE is an independent investigator led research project with grant/research support from: Baxalta, now part of Shire; Bayer; Bioverativ; CSL Behring; Novo Nordisk, Roche and Sobi with administrative support provided by the US National Hemophilia Foundation.

T-FP-DEN-001 (29) | Results of an oral health survey of people with von Willebrand Disease

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Introduction and Objectives: People with von Willebrand Disease (vWD) face unique challenges in maintaining good oral health and access to dental care. A survey, designed to identify key challenges, has been distributed to patients. Collection and interpretation of this data can inform policy, identify specific needs of this population, create educational programs for patients, families and health care providers.

Materials and Methods: A thirteen question survey was developed and approved by the IRB at A.T. Still University for distribution at a national conference for patients and families with vWD in the United States for four consecutive years (2014-17). The conference, organized by the Arizona Hemophilia Association, with funding by a grant from CSL Behring, is held annually in Phoenix, Arizona. Families from all over the United States who are affected by von Willebrand Disease are invited at no charge. It is a forum to learn about new medical advances, to gain tools that can help better manage von Willebrand Disease, and to share with others facing the same or similar challenges. The survey was distributed to all patients at the final session and asked to be returned anonymously. Parents were asked to complete surveys for minors.

Results: Key findings were that 56.8% of respondents reported bleeding on flossing, 62.3% of respondents reported that their dentist did not consult with their hemotologist prior to treatment, 13% of respondents reported being refused dental care because of their illness, and 42.0% reported serious bleeding after a dental visit. Total number of respondents was 162. Other questions focused on oral hygiene habits, number of people with extracted teeth, reason for last dental visit, age and gender.

Conclusions: People with vWD in the United States have limited access to care by trained providers, statistically significant post-operative hemostatic challenges and a lack of education about proper oral hygiene and the role of inflammation as a cause of bleeding in the oral cavity.

T-FP-DEN-002 (232) | The hidden impact of bleeding from the mouth – the lived experience of people with haemophilia

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Aim: to explore the lived experience of bleeding from the mouth for people with haemophilia (PWH).

Methods: In-depth interviews were undertaken with a purposive sample of women and men living with haemophilia in Ireland. The sample covered those from carrier status to severe bleeding phenotype. A topic guide was used and interviews were recorded, transcribed and analyzed via thematic analysis. Initial codes and preliminary themes were determined and agreed by two independent researchers.

Results: 60 interviews were conducted (52 men, 8 women) with an age range of 18-79. The mean time of interview was 57 minutes. Participants reported episodes of bleeding from the mouth as a result of trauma, tongue or cheek biting, gum disease, sports injuries and following dental surgery. Associated with these bleeds were experiences of fear, panic, nausea, choking, extended periods of hospitalisation, anaemia and blood loss sufficient to impact on consciousness. Self-management strategies included, application of packs to the mouth, and use of sports guards. For those with access to factor for home use, most reported prophylactic use of large amounts before allowing people to examine their mouths. In those without access to home treatment dental phobia and avoidance of dental care was common. Discussion. The majority of participants, regardless of severity, had experienced bleeding through their mouth. Many individuals with mild disease had been diagnosed following dental treatment and their own bleeding identity was tied to their mouths with their sole use of factor treatment related to bleeding from the mouth and associated with a significant fear of all dental treatment. At the severe end participants with gum disease reported living with the daily taste of blood in their mouth and waking up with blood on their pillowcases. Respondents also reported altering

their food choices in public or avoiding intimacy with their partners through fear of bleeding from the mouth. Conclusion. Bleeding from the mouth was common and impacted significantly on daily living. Dental fear and avoidance was a recurrent theme, mitigated by home access to factor in those with more severe haemophilia.

T-FP-DEN-003 (47) | North London Adult Haemophilia Network – Patient related outcomes with dental treatment

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Introduction and Objectives: Patients with bleeding disorders such as haemophilia are at an increased risk of post-operative bleeding following dental procedures. The North London Adult Haemophilia Network (NLAHN) connects the Royal London Dental Hospital with Haematology Departments and dental services in community. With the correct liaison between specialties the majority of dental procedures can safely be performed in the community and primary care setting. We aimed to assess levels of patient satisfaction, collect information on patient related outcomes and review current service provision.

Materials and Methods: Referrals to North London Adult Haemophilia Network (NLAHN) June 2015–June 2016, 69 Patients identified retrospective analysis of encounters patient telephone Survey.

Results: Wide variation in bleeding disorders, survey response rate 70%, high levels of patient satisfaction reported (>95%), report problems accessing primary care dentistry (46%), Patient related outcomes positive, Referral timeframes met, shared care demonstrated between hospital, community and general practice. Large variety in patient demographic and bleeding disorder, waiting times in line with national guidelines, provision made for urgent referrals.

Conclusions: Dental treatment in the hospital setting can be costly and patients often report difficulty accessing emergency treatment. This report has shown shared care is effective and can allow safe dental treatment for inherited bleeding disorder patients in community. Implementations for change include update of North London Adult Haemophilia Network patient information leaflet and reference to WFH guidelines in referral letters.

T-FP-DEN-004 (408) | Patient reported outcomes of post-operative bleeding following dental treatment

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Introduction and Objectives: Haemorrhage in patients with inherited bleeding disorders (IBD) following invasive dental procedures has been previously reported as adverse events when patients have re-presented to clinic. The routine post–operative bleeding experience of patients with IBD following routine dental treatment has been insufficiently documented. In this study, we evaluated the post-operative bleeding of patients who attended the Royal London Dental Hospital (RLDH) for dental treatment by analysing responses to a post-operative questionnaire.

Materials and Methods: Analysis of post-operative bleeding experience questionnaires was performed for all patient attendances having dental treatment in the restorative, oral surgery and paediatric departments at the RLDH. A post-operative bleeding experience questionnaire is routinely completed following dental treatment via a telephone call by specialist nursing staff the day after the procedure. If patients were not contacted they would be called again periodically until a response was received. Data was analysed for post-operative bleeding episodes, need for post-operative treatment and emergency follow up.

Results: Between 28/05/2015 and 12/10/2017, 166 patients attended for dental treatment. Eighty patients (48.2%) responded to the telephone questionnaire and were included in the analysis (n = 80).

Seventy-one out of 80 patients (88.75%) received routine, pre-procedure haemostatic cover (e.g Tranexamic acid and/or factor/platelet replacement). Sixty-four patients (80%) reported taking Tranexamic acid as tablets or mouthwash post-procedure. Only 4 patients (11.25%) sought emergency follow up with the haemophilia centre and required further haemostatic intervention. Thirty-seven patients experienced post-operative bleeding and tasted blood in their mouth, 26 of whom (70.3%) reported minor bleeding lasting either seconds, minutes or a few hours (maximum 5 hours); only 2 patients (5.4%) had prolonged bleeding lasting longer than 24 hours. The remaining 9 patients (24.3%) did not comment on their bleeding episode length.

Conclusion: This study illustrates the value of routine post-operative bleeding follow-up in the identification of patients experiencing post-operative oral bleeding following dental treatment. Limitations include incomplete documentation in several cases and lack of quantification of bleeding episodes. Improving compliance of documentation and follow up can help clinicians stratify risk and guide future need for haemostatic cover and early follow up.

T-FP-DEN-005 (131) | Clinical outcome of dental surgery in hemophilia patients: Treatment approach in a large referral center

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Introduction and Objective: Hemophilia A and B patients need highly maintained dental hygiene care to prevent dental decay. In the absence of factor concentrate replacement, post dental surgery bleeding can be critical in hemophilia patients. However, local hemostatic agents can reduce factor concentrate consumption which is essential in area where financial resources are limited. Our objective is to evaluate the clinical outcome of a low dose clotting factor concentrate along with local hemostatic agents on a large case series of hemophilia patients undergoing dental surgery.

Materials and Methods: In this quasi-experimental study, 71 severe hemophilia A and B patients registered at Hemophila Center in Southern Iran were evaluated within the past 3 years. All these patients were male and had factor activity less than 1%. None of them had inhibitor. The treatment regimen was one single pre-operative dose of 20 IU/kg and 30 IU/kg, one hour prior to surgery, for hemophilia A and B patients respectively. The same dose was scheduled 8 hours for hemophilia A and 12 hours for hemophilia B after the first infusion if patient had bleeds. Local dental cell, (oxidized cellulosic fabric, Chitotech company) which is a hemostatic tampon for dental bleeding and systemic hemostatic agent (tranexamic acid, orally for 3 days, immediately before dental surgery) were also given to reduce the need for replacement therapy during and following dental operation.

Results: A total of 71 patients (66 hemophilia A and 5 hemophilia B) with mean age of 31.4 ± 14.9 year (age range of 7-66 year) were included in this study. A dental extraction operation (# 53 patients) was the most common dental surgery followed by dental filling, root canal therapy, scaling and root planning. Post-operative factor concentrate was used for 52 patients. None of the patients developed hemostatic and non-hemostatic complications except one hemophilia A patient who developed dental fracture post dental extraction.

Conclusion: Low dose factor concentrate in conjunction with local and systemic hemostatic agents lead to stable hemostatic coverage in hemophilia patients undergoing dental surgery. This treatment strategy would be cost-effective in low socioeconomic areas with limited access to factors.

T-FP-DEN-006 (586) | Odontological management in patients with von Willebrand Disease

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Introduction and Objectives: Patients with bleeding disorders require special care while undergoing dental procedures, particularly during oral surgery, when post-operative complications might occur. Dentists need to be aware of bleeding management strategies in order to develop an appropriate treatment plan. To this end, a formal guideline addressing dental management for patients with haemophilia and von Willebrand disease (VWD) was developed in 2014 by a group of dentists from the Dentistry Program of Salta and specialists from the Haemophilia Foundation of Salta. Here we report on the utility of these guidelines during dental procedures performed in VWD patients.

Materials and Methods: The guideline was provided to dentists treating patients with VWD in and around Salta, Argentina. A haematologist assisted the dentists in planning a bleeding management strategy during minor surgeries, including providing recommendations for the factor dosing (FVIII/VWF) for each patient according to their VWD type. Local antifibrinolytics (epsilon-aminocaproic acid and tranexamic acid), anaesthesia (articaine hydrochloride 4%, subperiosteal injection) and a coagulation factor concentrate (pdFVIII/VWF, Octapharma AG) were used for tooth extractions and root canal treatments.

Results: Fifteen VWD patients undergoing dental procedures were followed for 2 years. The patients' age ranged from 12 to 58 years. Seven patients had VWD type 1 (unresponsive to desmopressin), 5 had type 2B, 1 had type 2N, and 2 had type 3. In total, 77 procedures were performed: 15 dental cleanings, 15 fluoride placements, 15 brushing technique demonstrations, 3 root canal treatments and 29 tooth extractions. Four of the 29 extractions were performed in patients with VWD type 1, 5 in patients with type 2N, 14 in patients with type 2B, 6 in patients with type 3. The guideline allowed the dentists to administer appropriate treatment and prevent excessive bleeding.

Conclusions: The guideline provided a formal and standardised summary of the basic knowledge on haemostatic management dentists need when treating patients with VWD. It is particularly important that dentists are aware of, and know how to manage, bleeding complications in patients with VWD since they are key health care providers in the detection of coagulation disorders.

Conflict of Interest: MSC and LF have no conflicts of interest to declare. Medical writing support was provided by nspm ltd, funded by Octapharma.

M-MP-086 (273) | Do dental students have sufficient knowledge and confidence to manage patients with inherited bleeding disorders? A comparison between students in the UK and Brazil

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Introduction and Objectives: Some health care professionals lack the confidence to treat patients with Inherited Bleeding Disorders (IBD) causing barriers to providing primary healthcare for this group of patients. This study used a prospective undergraduate student survey to evaluate the level of academic knowledge and confidence in managing patients with IBD in two different teaching hospitals. Improving the knowledge base and confidence of students may contribute to better delivery of healthcare from the profession after graduation.

Method: 73 final year dental students were surveyed in the UK (n = 41) and Brazil (n = 32) to compare their confidence and knowledge regarding treating patients with IBD.

Results: 34% of Brazilian undergraduates compared to 63% of UK undergraduates felt confident to provide periodontal treatment. 66% of students in Brazil would refer patients to hospital for periodontal treatment as opposed to 29% in the UK. 5% of all students were confident to provide extractions and 24% of all students were confident with procedures needing inferior dental blocks. 84% of students from Brazil and 93% from the UK were afraid to provide treatment due to fears of uncontrollable bleeding. More UK students feared litigation (49%), pressures from their practice managers (27%) and complaints (20%). 70% of all students would feel more confident with more discussion on current guidelines. Students in Brazil (84%) and the UK (95%) agreed that better communication with the patient's haematologist would improve their confidence to manage this group of patients.

Conclusion: Both cohorts included students who had a poor understanding of when to refer and treat. Most students are fearful of treating patients with IBD. Students in Brazil showed less confidence to treat for periodontal disease and were more likely to refer. Overall, more UK students expressed fears regarding provision of care within their healthcare system. All the students agreed that better communication with the patients' haematologist would improve their confidence. This study demonstrates a need to improve the experience and teaching of managing inherited bleeding disorders to undergraduates.

M-P-087 (772) | Audit of the use of oral anti-fibrinolytics with local haemostatic measures for patients with mild bleeding disorders undergoing dental extractions

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Introduction and Objective: The use of oral anti-fibrinolytics with local haemostatic measures after dental extraction in mild bleeding disorders may reduce bleeding and avoid the use of transfusion or other haemostatic agents. The National Coagulation Centre in Ireland offers integrated dental and medical care and is uniquely placed to evaluate a protocol using oral tranexamic acid and local haemostatic measures for dental extractions in a cohort of patients with mild bleeding disorders.

Materials and Methods: A retrospective audit was conducted of consecutive patients who had received dental extractions (maximum of two adjacent teeth) under local anaesthesia (LA) and anti-fibrinolytic cover at a single National Haemophilia Comprehensive Care Centre. Dental records and the National Haemophilia electronic health record were evaluated to determine use of standard local haemostatic measures within the socket, provision of specific verbal and written post-operative instructions and evidence of bleeding from post-operative patient contacts or treatment records.

Results: In total, 38 patients with Low Von Willebrand factor, platelet function defect or bleeding disorder of unknown aetiology were identified who had received a total of 54 dental extractions. All patients had received 1 g of tranexamic acid orally starting no later than the morning of the procedure and continued three times per day for five days post-operatively. 100% of patients had received local anaesthesia with adrenaline using a fine gauge needle and aspirating technique, oxidised cellulose in the socket, vicryl sutures and application of local pressure for up to 30 minutes. All patients received post-operative instructions to avoid smoking and vigorous rinsing and to take a soft diet. No patient reported bleeding or required further haemostatic support.

Conclusions: The use of standard haemostatic local measures with a five day course of oral tranexamic acid and stringent home care was sufficient to achieve good haemostasis in all patients with mild bleeding disorders in this cohort. Primary care pathways can now be designed using these techniques and future work will include development of personalized resources for patients and dentists together with algorithms to aid haematologists to identify suitable individuals to safely receive dental extractions in a primary care setting.

15-ORTHOPEDIC ISSUES

W-FPMSK-001 (679) | Prevention of late infection of prosthetic joints in patients with hemophilia

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Introduction: Many authors have reported an incidence on late prosthetic joint infection much higher in PWH than in other forms of arthritis. It was 17% in our series of knee replacements in PWH reported in 2005. While some authors speculated this was the result of immune suppression secondary to HIV infection, the incidence of late infection in our series was not significantly different between HIV+ and HIV– patients. Furthermore, series of joint replacements in PWH prior to HIV had similar high rates of late infection. We postulated that the primary risk factor was frequent intra-venous (IV) self-infusion.

Materials and Methods: In 2005, we began a comprehensive protocol driven program of patient education in meticulous sterile technique for IV self-infusion in all our PWH who had prosthetic joints. Since 2005, we have performed 49 primary joint replacements in 32 PWH (39 TKRs and 10 THRs), with a mean follow-up of 6 years. The data on these 32 patients was retrospectively reviewed with IRB approval and compared to our prior series. Primary infections were defined as a spontaneous infection of hematogenous origin without a known source. Secondary infections had a known source.

Results: In this present series, there have been no primary and two secondary infections (4.1%). One secondary infection occurred in a PWH after a pyarthrosis of the elbow infected his TKR with the same organism. The other occurred in a PWH who fell sustaining a deep laceration that communicated with his TKR. Each incident occurred five years following the index operation. One patient was HIV+ and the other HIV-.

Discussion: All infections in our previously reported group were primary. The reduction from 17% to 0% is highly significant (Fishers Exact test, two tailed $P < 0.007$. The demographics of the two groups are similar, but the incidence of HIV has decreased from 70% to 34%.

Conclusions: It seems probable that the primary source of late infection in PWH is frequent IV self infusion but immune suppression could be an aggravating factor. Thorough protocol driven patient education in sterile technique for IV self infusion and its relation to prosthetic joint infection seems clearly indicated.

W-FPMSK-004 (71) | Muscle function deterioration in patients with haemophilia: prospective experience from Costa Rica

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Introduction and Objectives: In haemophilia recurrent joint bleeds are responsible for the development of chronic joint damage. Structural damage is often preceded by joint dysfunction. This is mainly quantitative and qualitative changes in the contraction pattern of muscles around the joints. Muscle function in patients with haemophilia is still poorly investigated. The aim of this 2-year prospective study was to assess the changes in muscle function of lower limbs in a group of patients affected with hemophilia in San José, Costa Rica.

Materials and Methods: Muscle function of lower limbs was assessed by means of surface electromyography (sEMG) accomplished at study enrolment and after two years of follow-up. Gluteus medius, vastus medialis, biceps femoris, gastrocnemius and tibialis anterior were examined. All patients underwent concurrent clinical examination by using Haemophilia Joint Health Score (HJHS).

Results: Overall, out of 160 known haemophilic patients in Costa Rica, 60 (38%) underwent clinical and EMG evaluation between September 2009 and September 2011. Thirty-four patients (57%) were examined twice. Twenty-two patients (37%) were 2-11 years old. The oldest patient was 43 years old. The median age of patients treated on regular prophylaxis ($n = 32$, 53%) was 10.8 years (IQR: 6.9-15.8). Prophylaxis had been started at a median age of 4.5 years (IQR: 2.6-8.5). Of the 39 patients with target joints 31 (79%) had target joints in the lower limbs. A moderate correlation was found between total HJHS and the number of target joints ($r = 0.35$, $P = 0.007$), as well as between HJHS for lower limbs (i.e., excluding scores for elbows) and the number of target joints in lower limbs ($r = 0.33$, $P = 0.01$). sEMG parameters resulted altered in all patients and were not correlated to the presence of target joints and/or an abnormal HJHS. Muscle function deterioration was observed after 2 years of follow-up despite an unmodified HJHS.

Conclusions: Muscle function of lower limbs as detected by means of sEMG resulted impaired in patients with haemophilia irrespective of the presence of overt joint damage. sEMG is a simple and sensitive assessment tool able to detect muscle dysfunction and so favoring the implementation of early rehabilitation therapy.

W-FPMSK-005 (128) | 10 years follow-up of bone mineral density in patients with haemophilia

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Introduction and Objectives: Different studies report the correlation of haemophilia and reduction of bone mineral density: Ten years ago, Wallny et al. observed a high incidence of osteoporosis in patients with haemophilia (PWH) and identified haemophilic arthropathy, a typical complication in PWH, with chronic pain and loss of joint function and resulting inactivity, as a potential risk factor for the occurrence of osteoporosis. The aim of this study was to investigate the bone mineral density (BMD) of these patients after at least 10 years with a special focus on potential influencing factors such as joint status and comorbidities.

Material and Methods: Of the 62 PWH examined by Wallny et al. 33 were included in the present retrospective study: BMD, Vitamin-D, Calcium, joint status and medical history were assessed at a mean follow-up of 12.8 ± 1.7 years (range: 10.0-15.3).

Results: The mean BMD (t-value) of the lumbar spine and the femoral neck did not change significantly from −0.65 ± 1.49 (range: −3.60 to 2.79) and −1.43 ± 1.35 (range: −4.93 to 1.33) at the beginning of this study to −0.39 ± 1.68 (range: −3.30 to 3.30) and −1.37 ± 1.26 (range: −4.10 to 2.30) at the follow-up ($P = 0.29$ vs. $P = 0.979$). The average Vitamin-D level was 19.91 ± 10.39 (range: 6.4-49) at the time of follow-up. In total, 81.3% of the PWH suffered from a Vitamin-D deficiency. HIV and Hepatitis B or C had no influence on the BMD. Additionally, the use of osteoporosis medication vs. no osteoporosis medication did not show an effect on the BMD in the follow-up of 10 years.

Conclusions: PWH have a high prevalence of reduced BMD which doesn't seem to vary much over a long-term period of ten years. These patients should still be evaluated regularly – especially as PWH reach older age nowadays – in order to avoid the risk of osteoporosis associated complications like fractures. Additionally, the high percentage of low Vitamin-D levels makes frequent monitoring and substitution necessary. The long-term influence of joint status, comorbidities and osteoporosis therapy on the BMD needs to be investigated in further studies.

W-FPMSK-008 (150) | Handwriting analysis and elbow function evaluation in children with haemophilia

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Introduction and Objectives: Handwriting is a complex task that requires the integrity of different sensorimotor components to be performed successfully. Estimates of the incidence of poor performance during childhood in scholar age range from 10% to 30%. Children with haemophilia may suffer from joint bleeds including elbow bleeds. Subclinical bleeds may occur even during prophylaxis. The aim of this pilot study was to assess the presence of impaired handwriting in a group of children/adolescents with haemophilia and to evaluate elbow joint status.

Materials and Methods: Children/adolescents with hemophilia A or B able to write were eligible and underwent a handwriting test evaluated by means of the Moretti Handwriting Assessment. On the same day they underwent clinical examination of the elbows which included Haemophilia Joint Health Score (HJHS), tender points and pain assessment. Tender points were defined as reactive pressure points at specific anatomical sites as joint capsule, ligaments and tendons. Pain was assessed by using a pain mouse and the intensity of pain graded asking the patients to grip the mouse with a force proportional to the grade of pain they perceived. The force applied was measured in millibars (mbar).

Results: Overall, 19 children/adolescents with severe ($n = 17$) or moderate haemophilia A or B (median age: 12 years), regularly followed-up at the Milan Hemophilia Center were included. Six patients (32%) had overt dysgraphia and additional 9 (47%) had probable/possible dysgraphia. At time of enrolment 2 patients had current inhibitors and 17 were receiving prophylaxis. Seven patients had at least one elbow bleed in the previous year and all of them had disturbed handwriting, while none of those with normal handwriting had previous elbow bleeds. The HJHS calculated for each elbow was similar comparing patients with disturbed and normal handwriting while those with overt or possible dysgraphia had more tender points. All patients but 3 had pain in the elbow that could be graded as moderate with a median force on the pain mouse of 205 mbar (IQR: 159-257).

Conclusions: Overt dysgraphia was present in one third of study population who showed some silent symptoms of elbow joint function involvement.

T-P-050 (547) | Joint outcomes of the elbow, knee and ankles evaluated by Hemophilia Joint Health Score in patients with hemophilia: Trends by age and clinical predictors

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Introduction and Objective: Hemophilic arthropathy (HA) is a common complication in patients with hemophilia (PWH). Hemophilia Joint Health Score (HJHS) was a sensitive score to evaluate joint health of PWH. We aimed to investigate joint outcomes of PWH in Taiwan by HJHS and the clinical predictors.

Materials and Methods: Taiwan Society of Thrombosis and Hemostasis initiated a nationwide multicenter survey in Taiwan. From 2015 to 2016, 135 PWH (103 hemophilia A, 32 hemophilia B) were enrolled for joint evaluations with HJHS version 2.1. Among them, 89 PWH also had the roentgenograms of elbows, knees, and ankles for calculating Pettersson scores (PS).

Results: Mean HJHS total score was 5.7 ± 5.1 points for PWH aged <18 and 21.1 ± 14.9 for PWH aged ≥18. Ratio of HJHS total score > 6 points was 30.6% for PWH aged <18 and 86.7% for PWH aged ≥18. Mean HJHS total score and single joint score of the 3 index joints increased with age. PWH aged < 50 demonstrated maximum mean HJHS single joint score at the ankle followed by the elbow, and the least joint score at the knee. For mean total score, PS was lower than HJHS before age of 20 but exacerbated rapidly and exceeded HJHS after 20. For mean single joint score: Of knee, PS was lower than HJHS before 30 but exceeded HJHS after 30. Of elbow, PS was lower than HJHS before 20 but exacerbated rapidly and exceeded HJHS after 20. Of ankle, PS were always higher than HJHS for all age groups. By univariate analysis, subtype A or B, severity, HBV and HIV infections were not significantly associated with HJHS but age, PS, HCV infection, and high-titer inhibitor >5 BU (HTI), which were also proved as good predictors for HJHS by stepwise linear regression analyses, with the slopes of 0.3, 0.5, 4.8 and 11.9, respectively.

Conclusion: We demonstrated joint outcomes of PWH by HJHS. Ankles displayed the most susceptibility to arthropathy followed by elbows, and knees did the least. The clinical predictors of HJHS included age, PS, HCV infection and HTI. HCV infection and HTI had greater impact on HJHS.

Disclosure: The authors stated that they had no interests which might be perceived as posing a conflict or bias.

T-P-051 (308) | Risk of deep venous thrombosis after total knee arthroplasty in patients with haemophilia A

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Introduction and Objective: We previously reported that deep venous thrombosis (DVT) was not detected after total knee arthroplasty (TKA) in 36 Japanese patients with haemophilia between 2006 and 2013. In this report, we examined DVT by using ultrasonography (US) before and early postoperative day. It may be necessary to perform the examination with several procedures in patients with haemophilia on later day to obtain an accurate incidence of venous thromboembolism (VTE) after TKA. The objective of this study was to evaluate the prevalence of DVT after TKA with haemophilia A by using US and contrast-enhanced computed tomography (CT) prospectively.

Materials and Methods: 9 TKA in 9 Japanese patients with haemophilia A were enrolled in this study. A pneumatic compression device was used from the beginning of the operation until patients could perform standing exercises (day 2). No pharmacological thromboprophylaxis was used in this study. US of the lower extremities was performed before (between days -7 and -3) and after surgery (day 2 or 3) to detect DVT. Contrast-enhanced CT was performed after surgery (day 7) to detect VTE. D-dimer, fibrinogen degradation product (FDP), plasma coagulation factor VIII activities and fibrinolytic parameters were measured at 5 points that included 1 preoperative time point between days -7 and -3 and 4 postoperative time-points on days 0, 1, 7, 14 and 21.

Results: Patients were aged 49.6 (range 37-64) years, all patients were male. They didn't have histories of inhibitor and VTE. In addition, all patients were HCV positive. None was HIV positive. DVT by US was not found in either pre- or postoperative examinations, however contrast-enhanced CT detected DVT in 2 cases. All patients were hospitalized for more than 1 month, and no patients showed clinical signs for VTE during this period.

Conclusions: In this prospective 9 cases of TKA study, contrast-enhanced CT detected DVT in 22% in spite of not detecting by ultrasonography. As 2 cases of DVT by contrast- enhanced CT were subclinical, no additional treatments were needed. We will have to consider how to prevent and treat of VTE in patients with haemophilia underwent orthopaedic surgery.

Conflicts of Interest Disclosure: HT has received honoraria for speaking or participated in scientific advisory boards or symposia from Baxalta/Shire, Baxter, Biogen, Bioverativ, Chugai Pharmaceutical, CSL Behring, Bayer, Kaketsuken, Novo Nordisk and Pfizer, and grands from CSL Behring. MK has received honoraria for

speaking from Baxalta/Shire. The remaining authors state that they had no interests as posing a conflict or bias.

T-P-052 (418) | Muscle function of the upper limb in patients with hemophilia: results of surface electromyography (sEMG) analysis

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Introduction and Objectives: Persons with haemophilia (PwH) suffer from recurrent haemarthroses with subsequent joint damage. Biomechanical reactions of muscles and ligaments around the joint are the first that immediately occur after bleeding, with changes in contraction pattern. Hence, alterations in joint function usually precede structural changes but remain often undetected. Surface electromiography (sEMG) is a non-invasive tool useful to investigate muscle function in PwH and it has been already used to assess lower limb muscles around hip, knee and ankle joints. The aim of this pilot study was to assess the function of upper limb muscles through sEMG in a group of PwH.

Materials and Methods: sEMG was performed in a resting position, during isometric contraction and during isotonic repetitions. Supraspinatus, infraspinatus, biceps, triceps, forearm flexors and extensors were examined.

Results: Twenty PwH aged 6.6-18.2 years (median: 12) were included. Eighteen had severe haemophilia A, 2 had inhibitors and 18 were on regular prophylaxis. The right limb was dominant in 18 (90%). Seven patients had at least one elbow bleed in the previous year and the median HJHS calculated for elbows was 0 (IQR: 0-1) on both sides. Side differences over 15% were found in average in 62.5% of all patients (IQR: 50-85%). Side difference was more evident for the Biceps (85% of patients), and less evident for the Triceps (65%). The median side difference for the biceps was 37% (IQR: 25-47%). Quantity and quality of muscle function was consistently better at the dominant side. A relevant rise above 2.5 microVolts was observed in the resting tonus of supraspinatus and infraspinatus (80% and 95% of cases, respectively). The median number of tender points was 1 for both limbs (IQR: 0-4 and 0-3 on the right and left side).

Conclusions: In this series PwH showed side differences in muscle function of the upper limb that exceed limb dominance. Those differences can be shown with sEMG before relevant clinical symptoms occur. Stretching and strengthening exercise can help to regulate these side differences thus preventing the development of upper limb haemarthropathy.

T-P-053 (735) | Outcomes following total joint arthroplasty in persons with hemophilia: Analyses using the CDC's universal data collection surveillance project

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Introduction and Objectives: Total joint arthroplasty (TJA) is used to improve joint function in patients with hemophilia (Factor VIII and IX deficiency). For the hip, knee, and elbow, changes in range of motion (ROM) and the proportion of joints that met or exceeded the limits of ROM necessary for selected functional tasks (e.g. walking, sitting, etc.) pre- and post-TJA are reported.

Materials and Methods: Males with hemophilia enrolled in the Centers for Disease Control and Prevention's Universal Data Collection surveillance (UDC) who reported TJA on a hip, knee, or elbow during the study period 1999-2010 were included. Descriptive statistics were calculated using ROM data from the pre-TJA and post-TJA study visits. To measure the change in joint ROM, we first calculated the difference between the post- and pre-TJA ROM for each joint, then calculated the mean of these differences and associated 95% confidence intervals to assess statistical significance. We assessed changes in functional ability of each joint by comparing ROM limits for each joint to those needed to perform certain activities. The proportion of joints that met or exceeded the limits were calculated both pre- and post-TJA.

Results: 170 subjects with 212 TJAs (128 had 1 TJA; 42 had 2 TJAs): mean age 42.8 years (range=17-76); 80% FVIII; 75% severe hemophilia; 77% received episodic factor replacement; 5% had an inhibitor. Prevalence of hip TJAs was similar in patients with severe or moderate hemophilia; 80% of knee TJAs occurred in those with severe hemophilia. Knee and elbow TJAs were more common among younger while hip TJAs were more common among older patients. Post-TJA knee extension improved an average of 4.8 degrees ($P < 0.05$, 95% CI, [2.9, 6.8]); no other significant ROM changes were observed. In hips and knees with TJA, the proportion of joints with adequate ROM to perform selected functional tasks increased to a variable degree but no elbows improved post-TJA.

Conclusions: Potential for improved ability to perform selected functional skills in the hip and knee, but not in the elbow exist, despite lack of statistical significance in change in ROM post-TJA. Conflicts of interest disclosures

Two authors have acted as paid consultants for Bayer Pharmaceuticals, Inc., Baxter Healthcare, and Partners PRN. All other authors have no conflicts of interest.

T-P-054 (246) | Bilateral, simultaneous total knee replacement (TKR) surgery for hemophilia A with eloctate – A feasible and cost-effective approach

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Introduction and Objective: Older people with haemophilia often need total knee replacement. Protocols for hemostasis support during these procedures are variable. We report our experience with use of modest doses of Eloctate for bilateral simultaneous TKR surgeries for PWH.

Patients and Methods: Total 16 Severe Hemophilia A patients underwent 32 bilateral, simultaneous TKR. Age range was 28-51 years. Pre-operative 50iu/kg Eloctate was infused. Pre-operative FVIIIc Level was median 108iu/kg (86-126 iu/dl).). Post-operative Eloctate replacement was 40-50iu/kg once daily till day 5, then 30iu/kg once daily till Day15. FVIIIc assay was monitored at least once daily till day 10. Dose was tailored according to FVIIIc levels. Trough FVIIIc level was maintained above 60iu/dl for first 5 days. Average duration of surgery was 4 hours. Drains were removed after 48 hours. LMWH thrombo-prophylaxis & physiotherapy was started from post-operative Day 2. Clips were removed on Day 14. Eloctate was received through Humanitarian Aid Program of WFH.

Results: Total of 32 bilateral, simultaneous TKR were performed on 16 patients. 15 patients had no significant intra or post-operative bleeding & no transfusion support was needed. One patient underwent pseudo tumour excision and TKR in the same sitting & required extra 50iu/kg Eloctate+8 packed red cells + 8 FFP + 10 Cryoprecipitate intra operative during excision of Pseudo Tumour for total blood loss of 2200 ml as expected. He also experienced no post-operative bleeding till discharge. No wound or prosthesis infection was noted. Prosthesis survival was 100%. Total Eloctate used was 510-640 iu/kg over 14 days.

Conclusions: Bilateral simultaneous TKRs is feasible and cost effective and can be performed safely with modest doses of Eloctate. Thrombo -prophylaxis with LMWH can also be done safely in PWH undergoing TKR. At these doses, total Eloctate replacement was 40-50% lower than previously reported for TKR surgery for PWH.

T-P-055 (313) | Is it possible 'to forget the joint' after total knee replacements in hemophiliacs?

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Introduction and Objective: Success of total knee replacement (TKR) surgery could be subjectively evaluated with the ability of patient to perceive his knee "near normal," in other is this operation let the patient forget that if he ever had a surgery of that joint? Aim of this study was to evaluate the ability of hemophilic TKR patients to forget their knees.

Materials and Methods: In this cross-sectional study, 40 knees of 27 hemophiliacs (HA group) and 40 knees of 33 primary osteoarthritis patients (OA group) who had TKR between 2002 and 2017 (minimum six months follow-up) were included. Preoperative knee society and function scores (KSS), range of motion (ROM) values, primary complaints, walking aids were recorded. "Forgotten joint scores (FJS)," over the phone knee evaluations, visual analogue scales (VAS) for

TABLE 1. Preoperative and postoperative scores

	HA group N = 40		OA group N = 40		
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	P value
Age	41 ± 12.01		73 ± 6.59		**<.0001***
Preoperative scores					
Knee society score (KSS)	35.29 ± 16.85	40.50 (0-63)	42.65 ± 8.91	43 (25-64)	**.020***
KSS function score	52.89 ± 17.50	60 (5-80)	53.75 ± 10.79	50 (40-90)	.797
Preoperative VAS pain	6.97 ± 2.14	7 (3-10)	8 ± 1.68	8 (2-10)	**.036***
Range of motion	64°±31.15°	70° (5-115°)	105.40°±11.49°	106° (85-120°)	**<.0001***
Postoperative scores					
Forgotten joint score (FJS)	**79.78 ± 19.74**	**85.50 (31.25-100)**	**84.20 ± 11.08**	**86.95 (52.30-100)**	**.870**
Phone score (pain)	83.62 ± 19.15	92 (36-100)	85.80 ± 21.65	93 (6-100)	.288
Phone score (function)	82.62 ± 19.61	80 (40-100)	70.50 ± 17.35	75 (25-100)	**.004***
Postoperative VAS pain	1.40 ± 0.71	1 (1-3)	1.67 ± 1.12	1 (1-7)	.168

SD, standard deviation.
*Statistical significance.

pain were obtained at the latest follow-up. Statistical analyses were performed utilizing SPSS v18.

Results: Comparisons of scores were given in table 1. In HA group, preoperative KSS and ROM were significantly lower than OA group. Main preoperative complaint was disability in 60% of the patients in HA group; however preoperatively all patients in OA group suffered from pain (Fisher's exact test; $P < 0.0001$). Postoperative FJS was comparable between two groups. Preoperative VAS for pain was significantly higher in OA group; but postoperative decrease was significant in both groups ($P < 0.0001$). Necessity of walking aid was dropped from 56% to 12.5% in HA group and 52.5% to 30% in OA group.

Conclusions: Findings of this study showed that it is possible to "forget the joint" during daily life activities after TKR in HA. Patients in HA group have objectively "worse" knees; nevertheless their FJSs are as good as the ones in OA group. In hemophilic arthropathy, arthroplasty procedure seems to offer significant improvements by means of both pain and disability.

T-P-056 (574) | 18F-FDG PET/CT imaging of hemophilic arthropathy correlates with power doppler ultrasonography

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Introduction and Objectives: Repeated hemarthroses in patients with hemophilia may lead to hemophilic arthropathy with marked inflammation and synovial hypertrophy. Power Doppler ultrasonography is a useful tool in hemophilic arthropathy for assessment of disease activity and for monitoring response to treatment. Imaging inflammation with glucose analogue fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is based on that infiltrated granulocytes and tissue macrophages use glucose as an energy source. Metabolism and 18F-FDG uptake increase when inflammation occurring. The purpose of this study was to investigate the associations between ^{18}F-FDG PET/CT and Power Doppler assessment in patients with hemophilic arthropathy.

Patients and Methods: Four severe hemophilia A patients with 40 large joints (bilateral shoulders, elbows, hips, knees and ankles) were studied. All patients fasted except for water at least 6 hours prior to the PET examination. Sixty minutes after the intravenous injection of 10 mCi ^{18}F-FDG, imaging was performed using a spiral CT scan from the shoulder to the ankle with a 5 mm thickness per slice. The maximal standardized uptake (SUVmax) for each joint was measured. The Power Doppler assessment was also performed and the intensity of blood flow in the synovium was scored on a semi-quantitative scale from 0-3.

Results: The patients' median age was 27 years old with a range from 21 to 34 years. Two patients had factor VIII inhibitors. A strong correlation between the SUVmax and the Power Doppler ultrasonography scale was noted ($r = 0.775$, $P < 0.001$).

Conclusions: Our study demonstrates that ^{18}F-FDG PET/CT may detect the reactive inflammatory process of the hemophilic arthropathy and significantly correlate with Power Doppler assessment. Whole-body ^{18}F-FDG PET/CT could be a promising tool in determining the inflammatory activity of most large joints and quantifying of response to treatment of patients with hemophilic arthropathy and synovitis.

T-P-057 (364) | Medial patellofemoral ligament lesion in patients with hemophilia

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Introduction: In the patellar region, the medial patellofemoral ligament (LPFM) plays a fundamental role since its trajectory is comprised in layer 2 of the medial retinaculum. Hemophilic patients with recurrent episodes of hemarthrosis present a greater risk of ligament damage due to the underlying synovial/joint process.

Materials and methods: Retrospective study of a series of cases of 3 patients with severe hemophilia A. Average age of 25 years. All recurrent episodes of flexion dislocation. It was evaluated by the Kujala and Insall test. A minimal invasive surgery was performed with the placement of a semitendinous lining system and fixation with 2 interferential screws, a level of 2/3 higher than the patella and Nomura point respectively. In addition, the alteration of the femoral trochlea at the previous level is characteristic due to the generation of an osteophyte that alters and predisposes the patellar overtracking, favoring the increase in patellofemoral tension. Taking into account this alteration, the surgical resection gesture is fundamental. Minimum follow-up was 12 months.

Results: The 3 cases we had had an altered Q angle. A good patellofemoral balance was achieved with a conventional surgical technique, adding the plastic of the femoral trochlea which, in all cases, was altered by osteophytosis, predominantly anterior. Preoperative Kujala test was bad in all 3 cases (<50 pts), at 6 months postoperative average of 70 pts and at 12 months postoperative average of 91 pts. Insall test at 6 months postoperative all reported feeling better, 12 months after surgery 2 patients reported better improvement and 1 did not present changes compared to 6 months postoperatively.

Conclusion: Hemophilic arthropathy is an entity that increases the risk of tendon injury due to local structural alterations generated by the inflammatory process. With a standard surgical technique plus a plastic of the femoral trochlea, excellent results can be obtained.

T-P-058 (528) | Arthroscopic treatment of anterior ankle osteophyte in patients with haemophilia

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Introduction: Joints of patients with haemophilia is prone to bleeding. The diagnosis of anterior pinch syndrome is characterized by pain and limitation in dorsiflexion in the anterior region of the ankle.
Objective: Evaluate the arthroscopic treatment for painful ankle arthropathy with mobility restriction by an anterior osteophyte compared to open surgery.
Material and Method: Surgery were performed in 28 patients with 30 ankles presented anterior ankle osteophyte with pain and functional limitation of the joint. The preoperative AOFAS score was taken. The days of hospitalization, days of continuous infusion and the required bolus of factors for the surgery were evaluated. Complementary studies were performed where the lesion was evident. A group of 6 patients were operated between 2008 and 2010 with conventional open surgery and the remaining 22 patients underwent ankle arthroscopy, In all patients anterior osteophyte were resected. They were given 6 weeks of postoperative discharge. Six months postoperative AOFAS score was again taken to evaluate the evolution.
Results: According to the AOFAS score, there were significant differences between preoperative 43.9 and postoperative 74.4-. In all patients (open surgery and those who underwent arthroscopic surgery) pain decreased and they were able to return to their daily activities. Statistically significant differences were found between the group of patients operated through open and arthroscopic surgery with regard to days of continuous infusion and the requirements of continuous infusion of factors.
Conclusion: The arthroscopic treatment is a technique that allows a small approach and a shorter surgical time than open surgery with less requirement of factors, being this a benefit for the haemophilic patient.

T-P-059 (531) | Total bilateral knee replacement in severe haemophilia arthropathy with flexion contracture

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Introduction: Hemophilic arthropathy, causes pain, stiffness, joint deformity and is usually associated with severe flexion contracture with severe functional impairment. Anchylosis more than 90° flexion makes TKR procedure more complex. Among the main joints affected, the knee is related to the greatest disability problems.
Objective: The aim of this work will be focused on the surgical technique of releasing the extensor apparatus, used or knee joint replacement with severe flexion contracture.
Material and Method: We evaluated a 37 years old patient with 90° right knee, and 85° left knee of flexion anchylosis, 4 years of evolution. The patient use wheelchair for displacement. Patient received VIII factor bolus before performing the procedure.
Technical procedure: 1) Anterior approach centred on the knee, 2) Exposure of the extensor apparatus, 3) Osteotomy of anterior tibial tubercle, 4) Patellar osteotomy in the bone union with the articular surface. In this way the extensor apparatus is released and all adhesions can be removed from to the nearby tissues. 5) The osteotomy of the tibial plate is performed 0.5 cm from the articular surface. This osteotomy is performed without any guidance and the direction of the saw is parallel to the tibial surface. Then the knee can be flexed 120 °, 6) The fixation of the tibial plate is separated from the femoral by means of the electro scalpel and osteotomo. Once the tibial fragment is resected, the femoral condyle is exposed free to continue the usual technique with the femoral guides, 7) With the knee in flexion of 120 ° the tibia is carried forward and the osteotomy performed in tibia is exposed and the conventional guides can be used.
Results: Both knees were operated and TKR could be performed with this technique. Six weeks after the procedure, both knees reached 90° of flexion and 0° and −10° of extension, right and left respectively; the patient also can stand up and start walking rehabilitation plan. The patient evolved favorably walking with walker.
Conclusion: This surgical technique may facilitate the practice for surgeons that perform articular replacement in PWH.

T-P-060 (746) | Application of Botulinum toxin type A for the treatment of knee flexion contracture in PWH – Is it a useful treatment?

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Introduction: A flexed knee is a consequence of bleeding inside the joint. This produces an inhibition of the quadriceps, with a predominance of the hamstring muscles, which keep the knee in a persistent flexed condition. Because of this, there is an alteration of both posture and gait.
Objective: Evaluate the effectiveness of treatment of the knee flexion contracture (KFC) with botulinum toxin type A, with a larger sample than previous published.
Materials and Methods: 34 patients and 43 knees were included; 30 hemophilia A, 4 hemophilia B, 8 with inhibitor. Only one with moderate hemophilia, the others with severe. Average age 25 (9-52). The patients included had had a conservative treatment and retained an

KFC of less than 10°. The flexion and the KFC were measured pre-application and after 3, 6 and 12 months. We divided the knees into groups according with the KFC: Group I: −10° −30 ° (*n* = 18) Group II: −31 to 45° (*n* = 12) Group III: −46° or more (*n* = 13). Botulinum toxin type A was applied in hamstring and calf muscles, prior application of factor VIII, IX or factor VIIa in patients with inhibitor. The rehabilitation started after the application.

Results: The average improvement of the KFC was from −38° to −23°, the difference was 15 ° ° (*P* .001). The average improvement of the flexion was from 112° to 117 °, the difference was 5 °. Analysis of the improvement of the KFC by groups : GI : −22 ° to −13°, difference 9 ° (*P* .001), GII: −36° to −18° difference 18° (*P* .001), GIII: −73° to −51°, difference 22°. Not adverse effects were reported. Patients with inhibitor responded in the same way than patients without it.

Conclusion: This is a larger sample than previously presented and confirm our previous results. This is a low cost, useful procedure, easy of application with very good results.

T-P-061 (825) | Evaluation of the health status of the joints by ultrasound of patients with hemophilia through the protocol HEAD US in a reference center in Argentina

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Introduction and Objectives: Ultrasound is an economic and fast-performing method that has been shown to be useful for evaluating skeletal muscle system. We propose to carry out the ultrasound evaluation of the articulations of our patient population by certified professionals.

Materials and Methods: Observational study of volunteers with hemophilia aged between 2 and 65 years old. The joint health was performed using the Haemophilia Early Arthropathy Detection with ultrasound (HEAD-US) technique. Results was analyzed using SAS software.

Results: A total of 93 patients with hemophilia were analyzed; 18.4% were 0-5 years, 21.5% between 6-11 years, 20.4% were 12-17 years and 38.7% were adults. 9.0% of patients present hemophilia type B. 38.5% have a normal state in all joints. The state of each joint is analyzed considering the patients in severe state of the disease. It is noted that 25.0% of patients have a score greater than 4 points in the ankle, this being the most affected joint. There is association between the age group and the score of each articulation, through the Kruskal-Wallis test, was observed in all joints ($P < 0.001$); Adults were who presented higher scores. Cartilage is the most affected part, followed by synovitis and bone. Synovitis was greater in ankles than in elbows and knees. The distribution of ultrasound results is not the same for all treatments. In bone and cartilage, statistically significant differences were found between all the treatments except between secondary prophylaxis and demand treatment ($P = 0.981$ bone, $P = 0.789$ cartilage). In contrast, synovitis had statistically significant differences between tertiary prophylaxis and the rest of the treatments.

Conclusions: The HEAD-US allows us to detect early changes to the progression of advanced arthropathy, being a practice of easy availability and access to the evaluation of the main components of a hemophilia arthropathy without exposing the patient to irradiation or prolonged evaluation times. Knowing the joint state of our patients allows us to establish different therapeutic measures according to the degree of articular progression.

T-P-062 (771) | Experience on the utility of the "HEAD US" method in the assessment of patients with hemophilia in a University Hospital at Bogotá, Colombia in 2017

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Objective: Colombia is a developing country, in which great advances have been made in the management of high-cost pathologies. Our experience with hemophilic patients is described with undergo of skeletal muscle ultrasound using the HEAD US method (Haemophilia Early Arthropathy Detection with Ultrasound), apply on the joints with the greatest impact (elbow, knee and ankle). A reporting scheme describes and gives a score according to the degree of injury of the joint. This allows harmonizing and performing a better multidisciplinary work. Previous training on the HEAD-US method was made and we would like to describe our when putting it into practice.

Materials and methods: A descriptive study was carried out, including patients with hemophilia, who underwent joint ultrasound. A radiologist trained on HEAD US, performed ultrasound studies in each patient. A Toshiba-Xario with a high frequency transducer (18 MHz) was used, and a unified report according to the protocol was made. Nine patients were described in mild (2), moderate (3) and severe (4) hemophilia. Six ultrasounds were performed for each patient except one that had ankles covered, for a total of 52 ultrasounds. The protocol has a score depending on the bone, cartilage and synovial involvement of each joint studied.

Results: A group of 9 patients with a mean age of 25-year-old were diagnosed with hemophilia A. They were categorized as mild, moderate and severe disease. On the patients with mild hemophilia, the most affected joint was the knee and the less affected was the elbow, whereas on moderate and severe patients the ankle was the most affected and the elbow was the least.

Conclusions: The use of the HEAD-US method emerges as a non-invasive diagnostic tool with an affordable cost. A multidisciplinary work was made with valuable information about the state of the different joints to offer a treatment that allows preserving

them. A method of study and report is shown, where the findings are standardized with the less interobserver variability and a better communication with the multidisciplinary team that treat these patients.

16-OTHER TREATMENT MODALITIES

M-FPMED01-004 (384) | Pre-clinical studies demonstrate the efficacy and safety of SerpinPC, a specific inhibitor of the protein C pathway

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Introduction and Objectives: Hemophilia is caused by defect or deficiency in either factor (f) VIII (hemophilia A, HA) or fIX (hemophilia B, HB), and is usually treated by on-demand or prophylactic intravenous infusions. In about 30% of HA patients and 2% of HB patients the replacement factor is recognized as a foreign protein and inhibitory antibodies are generated. These "inhibitor patients" can only be treated on-demand with "bypassing" agents such as NovoSeven and several marketed clotting factor concentrates, such as FEIBA. All current treatments restore hemostasis by augmenting the concentrations of procoagulant factors. However, it is also possible to rebalance the hemostatic system by inhibiting natural anticoagulant pathways. Of particular interest is activated protein C (APC) which proteolytically inactivates the complex that produces thrombin (prothrombinase, composed of fVa and fXa). Coinheritence of partial APC resistance (fVLeiden) has been found to ameliorate bleeding frequency and severity in hemophilia patients, presumably by allowing prothrombinase more time to produce thrombin, the effector enzyme in blood coagulation.

Materials and Methods: We engineered a serpin (serine protease inhibitor) specific for APC over other coagulation proteases by making three mutations in α_1-antitrypsin. It was tested for efficacy and safety in mouse models.

Results: The variant, *SerpinPC*, rescued thrombin generation in vitro and fully restored hemostasis in HA and HB mice. The safety of *SerpinPC* was tested by treating wild-type mice with daily intravenous doses of 100 mg/kg for 7 days. *SerpinPC* was well tolerated, with no overt signs of toxicity, no increase in inflammatory markers or evidence of thrombosis. In addition, *SerpinPC* did not contribute to lethality in an LPS model.

Conclusions: *SerpinPC* is a safe and effective hemostatic agent that could potentially treat all forms of hemophilia, regardless of inhibitor status.

M-FPMED02-002 (414) | Eighteen years of experience with arterio-venous fistula (AVF) as venous access in children with congenital bleeding disorders.

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Introduction: Hemophilia treatment is based on regular intravenous injections of clotting factor concentrates to prevent or treat bleeds. Usually replacement therapy is started early in life and a stable and uncomplicated venous access is essential to perform therapy properly and long-term. In young children peripheral veins are often insufficient to bear the burden of frequent infusions and an alternative access is required. Central venous lines (CVL) are inserted at this aim, but their use can be complicated by infections or thrombosis. Since 1999, the creation of arterio-venous fistula (AVF) has been offered at our Center to Italian children with bleeding disorders and poor venous accesses. Here we report on the 20-year experience with AVF as alternative venous access in children with congenital bleeding disorders.

Materials and Methods: Children with congenital bleeding disorders with poor venous accesses and candidate to either prophylaxis or immune tolerance were eligible. The shunt was created at the elbow crease usually of the non-dominant limb using the brachial artery and a nearby vein under haemostatic coverage with either clotting factor concentrates or by-passing agents. The first access was allowed when proper arterialization of the vein was detected by Doppler ultrasound (US). Annual echocardiography and Doppler US of the shunt was recommended as follow-up. Surgical dismantling was recommended as soon as peripheral veins were adequate to be used regularly.

Results: Between August 1999 and November 2017 85 procedures in 75 children (66, 88% with hemophilia A) aged 0.8-14 years (median: 2.5) were performed. Sixteen children (21%) had a previous CVL. Fifty-two procedures (65%) were performed in children with inhibitors. The median caliber of vein, artery and shunt was 1.2, 1.5 and 1.8 mm, respectively. AVF did not mature in 11 cases (14%) and the median time to first access was 2.6 months (IQR: 1.5-3.9). Twenty-five shunts (34%) have been surgically dismantled after a median of 7.7 years (IQR: 6.3-12.8) of use and the reason for dismantling was transition to peripheral veins in 20 cases (80%).

Conclusions: AVF use allowed long-term uncomplicated prophylaxis and immune tolerance in children with congenital bleeding disorders.

W-P-054 (286) | The emerging role of virtual reality platforms in physiotherapy rehabilitation for hemophilia patients

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Hemophilia is a disease of recessive genetic origin and linked to the X chromosome in which are the genes that code for hemophilic factors VIII and IX. The Mexican Federation of Hemophilia has registered 6,022 patients with hemophilia and von Willebrand disease (until May 2017). Target joints for hemarthrosis are knee, ankle and elbow being more common in people with severe hemophilia. In patients with mild or moderate hemophilia the hemarthrosis may be secondary to trauma, as well as in the presence of high-response inhibitors. The primary objective of treatment is pain control, based on pharmacological treatment, and second recovery of the mobility arcs of the affected joint. In order to recover balance and postural stability, in addition to conventional treatment, there are now new treatment tools with the aim of reincorporating the hemophiliac patient to their activities, part of these innovations are balancing platforms and treatment with virtual reality platforms (Microsoft Kinect). It has been shown that promoting joint proprioception improves postural stability and decreases the risk of hemarthrosis and long-term functional sequelae.

Objective: Observe if a new rehabilitation based on virtual reality platforms favors the motor functionality of patients with hemophilia. Cohort-type study of hemophiliac patients from Hospital Infantil de México Federico Gómez from 6 to 18 years of age with grade I and II hemophilia arthropathy with prophylactic factor was carried out. They underwent a laboratory study of the march before the rehabilitation with virtual reality (15 days) and after this. A student t test was carried out for related sample.

Results: 10 patients were included, with middle age 9 (7-10) years. The relationship that was statistically significant was speed of right leg with a media relation −0.62, CI95% −0.114-0.010, and *P*: .024.

Conclusions: The rehabilitation with virtual reality includes a playful approach that involves patients and minimizes the degree of boredom, increasing their motivation and adherence to treatment. Another advantage in most virtual reality systems is the location of certain areas of the patient's body in real time, or even the location of their pressure center. This information allows the adjustment for each of the patients, of virtual reality systems in real time. Even, these data can be stored providing important information regarding the progression of patients. Although the data obtained have a good correlation between the variables of the march laboratory model, we still do not have a statistically significant relationship in all these variables, for which we will expand the sample of patients.

W-P-055 (537) | Radiosynovectomy provision in the UK: A single centre experience

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Introduction: Whilst the use of radiosynovectomy (RS) for bleeding and synovitis is a well-established treatment in parts of the world with limited availability of factor concentrate, it remains a rarely used technique in the UK. One possible reason for this is that such services have not developed due to an assumed lack of need for such intervention. It is clear however, that even with prophylaxis some patients develop synovitis, and those unable to use prophylaxis due to inhibitors are particularly at risk. Here we present a review of a RS service at a large comprehensive care centre.

Methods: A service review from 2006 to present was conducted. 30 patients (age range 13 to 86, median 23) had 49 interventions (RS) performed. 22 had SHA (2 with inhibitor), 3 had SHB (1 inhibitor), 4 moderate HA and 1 mild HA (with inhibitor). 21 ankles, 15 elbows, 11 knees and 2 shoulders were treated using Rhenium-186 or Yttrium-90 radio-colloids. Synovitis associated pain as well as bleeding was included in referral criteria for patents to the service.

Results: Outcomes data looked bleed number, factor concentrate usage and pain/function for the 12 months before and after the procedure for the affected joint. There was a 62% reduction in number of bleeds, 89% reduction in rFVIII usage and 75% reduction in rFVIIa usage. Most patients reported a moderate or significant improvement in their pain (85%). 1 patient had a reactive inflammatory reaction post procedure requiring joint aspiration. Those with inhibitors had multiple joint procedures. The elbow joint required most repeat procedures.

Discussion: This data demonstrates the clinical and financial value of a RS service, especially in those with inhibitors. Treatment for any bleeds post procedure also required less aggressive factor usage. Patients treated for synovitis pain showed no change in bleed number but did improve with pain symptoms. We propose that RS should be considered for such patients in the UK, given that in addition to improved function and reduced patient reported pain, the savings for health commissioning bodies may be considerable.

17-OUTCOME RESEARCH

T-FPMED02-005 (700) | coreHEM: A multi-stakeholder approach to developing a core outcome set for gene therapy in hemophilia

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Introduction and Objective: Gene therapy trials demonstrate a "cure" could be achievable changing the future landscape of hemophilia management. Multi-stakeholder consensus around a clearly defined, "core set" of outcomes (COS) will demonstrate and allow differentiation of the effectiveness and value of gene therapy relative to the current standard of care. A COS is a minimum set of outcomes that should be measured and reported in all clinical trials of a specific condition. When uniformly implemented, they increase the predictability and consistency of appraisals, coverage and reimbursement decisions by payers and Health Technology Assessment (HTA) agencies.

Materials and Methods: A COS was developed using a modified Delphi consensus process, which included online surveys and an in-person consensus meeting. A literature review and key informant interviews were used to create an initial list of outcomes for voting. Participants (patients, health care providers, payers, HTA agencies, regulators and industry representatives) condensed and prioritized the list by rating each outcome on a scale of 1 (not important to include in the COS) to 9 (essential to include). In early Delphi rounds participants could suggest outcomes to include. Outcomes were eliminated from consideration if <70% of voters rated the outcome from 7-9. To ensure patient-important outcomes were fully considered, outcomes were retained through the final round if the patient stakeholder group average rating was ≥7.

Results: After two Delphi rounds, there was consensus on three outcomes: frequency of bleeds, factor activity level and duration of expression. Additional outcomes in the domains of pain, physical functioning, emotional functioning, role functioning, resource use and perceived health status will be included. Adverse events of interest were evaluated and will be separately reported. Parameters of metrics to evaluate individual outcomes will be included.

Conclusions: Including the coreHEM COS in clinical development programs will ensure evidence required by post-regulatory decision makers exists, maximizing the likelihood that effective, high-value therapies will be rapidly available to appropriate patients. Additionally, patients and clinicians will have a comparable standard when making individual treatment decisions. Disclosures

coreHEM is funded by a grant from the National Hemophilia Foundation and with participation fees from Bayer AG, BioMarin Pharmaceutical Inc, Pfizer Inc, Shire Plc, Spark Therapeutics, St. Jude Children's Research Hospital, and uniQure B.V.

T-MP-078 (583) | Uptake of subsidised hepatitis C direct acting antiviral treatment among patients with bleeding disorders in Australia

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Introduction and Objective: Prior to routine screening of blood and blood products in 1993, Hepatitis C Virus (HCV) was the most susceptible among patients with bleeding disorders treated with plasma products. Epidemiological studies suggest that living with HCV without achieving a Sustained Virological Response (SVR) to treatment therapy is a higher risk for advanced liver disease and serious complications. The current prevalence of HCV among patients with bleeding disorders in Australia is unknown including treatment uptake and outcome. The main objective of this study is to obtain an overview of the burden of disease in Australia and evaluate the impact of subsidising HCV medication on treatment uptake and outcome. Methods Retrospective data was obtained from the Australian Bleeding Disorders Registry (ABDR) on all patients from Haemophilia Treatment Centres (HTCs) with appropriate ethics approval. Information was extracted on bleeding diagnosis, severity, HCV viral status, PCR test, treatment year and outcome. Patients that did not receive plasma products prior to 1993 were excluded from this study.

Results: A total of 2146 patients with bleeding disorders in Australia have been tested for HCV with antibody positive in 889 (41.42%); the majority have Haemophilia A or B or Von Willebrand Disease. 513/889 (57.71%) patients have cleared the virus (based on their PCR test) with or without treatment. One-third of patients (174/513) had received treatment in the last calendar year compared to the remainder who were treated in the 18 years prior. 20% (35/174) of successfully retreated patients had failed or could not tolerate previous interferon-based treatment. Of the 376 patients currently confirmed positive, more than half are still receiving treatment and their status will be updated following its completion.

Conclusions: The provision of Hepatitis C direct acting antiviral treatment on the Australian Pharmaceutical Benefits Scheme (PBS) has had a tremendous impact on treatment uptake and clearance of HCV. An ongoing challenge though is to identify all potential risk patients and maximising this opportunity to eradicate HCV.

T-P-079 (61) | Pain in adults with mild-to-severe hemophilia: Insights from the Hemophilia Experiences, Results and Opportunities (HERO), Pain, Functional Impairment, and Quality of Life (P-FiQ), and Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) studies

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Introduction and Objective: Pain associated with hemarthropathy is an important problem in people with hemophilia (PWH). This analysis describes the impact of mild-to-severe hemophilia on pain across 3 distinct studies incorporating self-reports and patient-reported outcome (PRO) instruments.

Materials and Methods: HERO surveyed adult male PWH from 10 countries by Internet, including EQ-5D-3L. P-FiQ enrolled US men with a history of joint pain/bleeding during hemophilia treatment center visits, including EQ-5D-5L, Brief Pain Inventory v2 Short Form (BPI), and SF-36v2. B-HERO-S surveyed US men/women with hemophilia B (PWH-B) by Internet, including EQ-5D-5L and BPI.

Results: HERO enrolled 675 PWH (median age, 36; 74% hemophilia A). Chronic pain was reported by 44%, 89% reported pain interference with daily life in the past 4 weeks, and 50% reported constant pain. Most (80%) indicated that pain had a negative impact on employment. On EQ-5D-3L, 75% reported moderate or extreme pain/discomfort "today." P-FiQ enrolled 381 PWH (median age, 34; 77% hemophilia A; 16%/13%/71% mild/moderate/severe). Over the past 6 months, 34% experienced chronic pain, 20% acute pain, and 32% both chronic/acute pain; most painful joints were ankles/knees (37%/24%). Acute pain was commonly described as "sharp"/"aching" (77%/65%) and chronic pain as "aching"/"nagging" (80%/50%). Acetaminophen/NSAIDs were used in the past 6 months by 62%/34% with acute pain and 55%/49% with chronic pain. On EQ-5D-5L, 76% reported pain/discomfort "today" (15% severe or extreme). On BPI, median pain severity/interference was 3.3/2.7 over the past week (range, 0-10). Median worst/least/average/current pain scores were 6/1/3/2; pain interference was greatest with general activity (74%) and mood (73%). On SF-36v2, 90%/75% reported bodily pain/pain interference in the past month. B-HERO-S enrolled 299 PWH-B (median age, 29; 29% female); 29%/13% reported acute/chronic pain. On EQ-5D-5L, 93% reported pain/discomfort "today," including 86%/96% of those with mild/moderate hemophilia. On BPI, median pain severity/interference scores over the past week were 5/5; most reported pain interference with mood (94%) and enjoyment of life (93%).

Conclusions: Cross-sectional studies with different methodologies and overlapping PRO instruments consistently indicate significant acute/chronic pain and pain interference affecting PWH. Greater use of validated pain assessments may help improve patient dialogue and individualization of pain management.

Conflicts of Interest: TW Buckner has served on advisory boards with CSL Behring, Genentech, Novo Nordisk, and Shire and as a consultant for Uniqure. D Quon has served on advisory boards for Shire, Bioverativ, Bayer, CSL Behring, and Novo Nordisk, and on the speakers bureau for Shire, Bioverativ, Grifols, and Novo Nordisk. M Witkop is currently Head of Research at the National Hemophilia Foundation. At the time of the research, M Witkop had received grant funding from Pfizer; served on advisory boards with Aptevo, Baxter Bioscience, Biogen Idec, Novo Nordisk, Octapharma, and Pfizer; and had served on the Novo Nordisk Speakers Bureau. M Recht has received grant/research support from Baxter, Biogen Idec, Pfizer, and Novo Nordisk and served as a consultant to Kedrion and Novo Nordisk. C Kessler has served on advisory boards for Baxalta, Bayer, Biogen, Genentech, Grifols, Novo Nordisk, Octapharma, and Pfizer and has received grant/research support from Bayer, Baxter, Novo Nordisk, and Octapharma. K Batt is a shareholder of Sanofi and Merck and has received grant/research support from Novo Nordisk. K Baumann has served as a consultant for Bayer and Novo Nordisk and as a speaker for Baxter, Bayer, and Novo Nordisk. CL Kempton has served as a consultant for Baxalta, Hoffmann La Roche, Biogen, CSL Behring, and Kedrion and has received grant/research support from Novo Nordisk. DL Cooper is an employee of Novo Nordisk Inc.

T-P-080 (62) | Anxiety and depression in adults with mild-to-severe hemophilia: Insights from the Hemophilia Experiences, Results and Opportunities (HERO), Pain, Functional Impairment, and Quality of Life (P-FiQ), and Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) studies

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Introduction and Objective: Anxiety/depression are increasingly recognized as problems in people with hemophilia (PWH) and

caregivers (CG) of children with hemophilia (CWH). This analysis describes the impact of mild-to-severe hemophilia on anxiety/depression across 3 studies incorporating patient-reported outcome (PRO) instruments.

Materials and Methods: HERO surveyed male PWH (aged ≥18) and parents of male CWH (aged <18) from 10 countries, including EQ-5D-3L for PWH. P-FiQ enrolled US male PWH aged ≥18 with a history of joint pain/bleeding, including EQ-5D-5L and SF-36v2. B-HERO-S enrolled US men/women with hemophilia B (PWH-B) and CG of children with hemophilia B (CWH-B), including EQ-5D-5L and PHQ-9 for PWH-B and PHQ-9 and GAD-7 for CG.

Results: HERO enrolled 675 PWH (median age, 36; 74% hemophilia A) and 561 parents (median age, 39; 75% with CWH-A). For PWH, 47% self-reported psychological/psychiatric conditions (stress/anxiety/depression/insomnia/fatigue) and 46% anxiety/depression "today" on EQ-5D-3L; 22% reported treatment for psychological conditions. For parents, 16% reported that their CWH received psychological treatment; 24% reported that they/their partners received psychotherapy/counseling related to their child's hemophilia. P-FiQ enrolled 381 PWH (median age, 34; 77% hemophilia A; 16%/13%/71% mild/moderate/severe); 14% had site-reported anxiety (26% received anxiolytics) and 19% site-reported depression (36% received antidepressants). On EQ-5D-5L, 43% reported anxiety/depression "today." On SF-36v2, 41% reported cutting down time spent on work/activities due to emotional problems in the past 4 weeks. B-HERO-S enrolled 299 PWH- B (median age, 29; 29% female; 25%/63%/11% mild/moderate/severe) and 150 CG (median age, 35; 77% mothers; 19% reported their oldest CWH-B as female; 18%/56%/22% mild/moderate/severe). For PWH-B, anxiety/depression were self-reported by 23%/22% and psychological treatment in the past 5 years self-reported by 50%. On EQ-5D-5L, 81% reported anxiety/depression "today"; 62% had PHQ-9 scores consistent with depression. Most CG indicated their CWH-B received psychological support (96%); 58% that they/their partner received support. Based on GAD-7/PHQ-9 scores, anxiety/depression were reported by 47%/53% of CG; those with children with moderate hemophilia B reported highest anxiety/depression scores.

Conclusions: Self-reported PRO data across studies with distinct patient populations consistently indicate anxiety/depression as significant problems in PWH and CG of CWH and highlight the value of validated PRO instruments for research/clinical purposes.

Conflicts of Interest: KB has participated on advisory boards for Bayer and Shire, has received grant/research support from Novo Nordisk, and serves as an independent consultant for Precision Health Economics. CG has served on or is serving on nursing advisory boards with Bayer, Genentech, Biogen Idec, Baxter/Baxalta, Grifols, Novo Nordisk, Pfizer, and Octapharma. MR has received grant/research support from Baxter, Biogen Idec, Pfizer, and Novo Nordisk, and served as a consultant to Kedrion and Novo Nordisk. RS has received grant support from Bioverativ and Shire and has participated in advisory boards with Shire, Biogen, CSL Behring, Aptevo, Bayer, Novo Nordisk, Octapharma, and Pfizer. DBC has nothing to disclose. DLC is an employee of Novo Nordisk Inc.

T-P-081 (63) | Functional impairment in adults with mild-to-severe hemophilia: insights from the Hemophilia Experiences, Results and Opportunities (HERO), Pain, Functional Impairment, and Quality of Life (P-FiQ), and Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) studies

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Introduction and Objective: Functional impairment is a frequent complication of hemarthrosis. This analysis describes the impact of mild-to-severe hemophilia on functional impairment in adult people with hemophilia (PWH) and children with hemophilia (CWH) across 3 studies incorporating patient-reported outcome (PRO) instruments.

Materials and Methods: HERO surveyed male PWH from 10 countries by Internet, including EQ-5D-3L. P-FiQ enrolled US adult male PWH with a history of joint pain/bleeding at HTC visits, including EQ-5D-5L, Hemophilia Activities List (HAL), SF-36v2, International Physical Activity Questionnaire (IPAQ), and the physiotherapist-administered Hemophilia Joint Health Score (HJHS). B-HERO-S surveyed US men/women with hemophilia B (PWH-B) by Internet, including EQ-5D-5L, HAL, and IPAQ, and caregivers of CWH-B.

Results: HERO enrolled 675 PWH (median age, 36; 74% hemophilia A), including 24% receiving disability-related benefits and 13% unable to work due to long-term disability. On EQ-5D-3L, 59%/47%/20% reported problems with mobility/usual activities/self-care "today." P-FiQ enrolled 381 PWH (median age, 34; 77% hemophilia A; 16%/13%/71% mild/moderate/severe; 66% self-reported functional disability in the past 6 months). On EQ-5D-5L, 61%/53%/19% reported problems with mobility/usual activities/self-care "today." On HAL, most frequent problems reported in the previous month were squatting (74%), kneeling (73%), and standing (72%) for a long time. On SF-36v2, 65% reported difficulty with work/activities due to physical problems in the past month. On IPAQ, 49% reported physical activity in the prior week. HJHS were worse for ankles than elbows and knees. B-HERO-S enrolled 299 PWH-B (median age, 29; 29% female; 25%/63% mild/moderate hemophilia) and 150 caregivers (median age, 35; 77% female; 19% reporting on female CWH-B; 18%/56% mild/moderate). On EQ-5D-5L, 78%/87%/75% reported problems with mobility/usual activities/self-care "today."

Median overall/complex lower extremity/basic lower extremity HAL scores (range, 0-100) were 65.2/62.5/66.7. On IPAQ, 94% reported activity during the past week (40% vigorous). Most PWH-B reported a negative impact of hemophilia on work/activity (95%/98%); most caregivers reported a negative impact on their CWH-B's engagement in activity (90%).

Conclusions: Cross-sectional studies using different methodologies and overlapping PROs consistently indicate functional limitations among adults and children with even mild-moderate hemophilia and suggest the importance of using validated functional assessments as part of comprehensive care across hemophilia severities.

Conflicts of Interest: GH has received grant/research support from Bayer and Novo Nordisk and has served on advisory boards for Biogen Idec and on the speakers bureau for Emergent BioSolutions. KB has served as a consultant for Bayer and Novo Nordisk and as a speaker for Baxter, Bayer, and Novo Nordisk. MW has served as a consultant for Novo Nordisk, Baxalta, CSL Behring, and Biogen. MR has received grant/research support from Baxter, Biogen Idec, Pfizer, and Novo Nordisk, and served as a consultant to Kedrion and Novo Nordisk. WO has nothing to disclose. CLK has served as a consultant for Baxalta, Hoffmann La Roche, Biogen, CSL Behring, and Kedrion, and received grant/research support from Novo Nordisk. DLC is an employee of Novo Nordisk Inc.

T-P-082 (584) | Cross-cultural adaptation of a Quality of Life measure (CHO-KLAT) for boys with haemophilia in the Ivory Coast

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Introduction and Objectives: In the Ivory Coast (IC), access to clotting factor concentrates is limited and the majority of persons with haemophilia (PWH) are treated with factor replacement on demand. This results in repeated bleeding episodes that may have a negative impact on Health-Related Quality of Life (HRQoL). HRQoL is an important outcome measure in PWH. However, few disease-specific measures of HRQoL are available in developing countries. The Canadian Haemophilia Outcomes-Kids Life Assessment tool (CHO-KLAT) is a child-centric disease-specific measure of HRQoL for boys with haemophilia (BWH) aged 4 to 18 years. This project aimed to adapt the CHO-KLAT$_{2.0}$ for use in BWH in the IC and to initiate collection of HRQoL data in this population. We choose to adapt the CHO-KLAT because of its strong measurement properties and the availability of a validated French version (the national language in IC).

Methods: Step 1: The French for France version of the CHO-KLAT was reviewed by local clinicians and minor changes were made, mainly to prepositions. Back-translation to the original English version and harmonization resulted in the initial Ivorian version of the CHO-KLAT. Step 2: Cognitive debriefing interviews were conducted with 5 BWH (mean age 13.4 years, 3 severe and 2 moderate haemophilia A, 1 case inhibitor positive), their parents and care-givers to ensure the initial Ivorian version of the CHO-KLAT was well understood. The information collected during the interviews was used to identify problems in understanding questions and to propose revisions to enhance accurate comprehension. The interviews were conducted by local clinicians, a partner from the Belgian HTC twinning team with guidance from a member from the Canadian CHO-KLAT development team.

Results: All CHO-KLAT items were well understood by the participants; however, 6 items were modified based on the interview results. The mean CHO-KLAT score was 56.7 (SD 6.1) for BWH and 47.7 (SD 15.6) for parents.

Conclusions: The Ivorian CHO-KLAT$_{2.0}$ was finalized in September 2017 and is available for larger scale use in BWH in the IC. Assessment of HRQoL in this population could be used to advocate for improved access to clotting factor concentrates in PWH in the IC.

T-P-086 (33) | Steps toward healthy coagulation

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Introduction and Objective: Hemophilia has undergone vast transformations over the past century, evolving from a condition associated with early death to one where afflicted individuals achieve nearly the same lifespan as their unaffected peers. Unlike other disorders (eg, metabolic disorders, immune deficiency), where the goal of therapy is to restore deficient enzymes or immunoglobulins to normal ranges, the goal of prophylaxis for hemophilia patients has been to achieve a minimum factor trough level of 1%, such that persons with severe hemophilia may achieve a mild/moderate phenotype but falls short of normal hemostasis. This minimal treatment mindset was largely driven by supply/storage issues with costly products. With imminent entry of new therapies (eg, enhanced half-life products and gene delivery), treatment goals are evolving from that of simply treating or preventing bleeds to one where cure, defined as normal hemostasis, is feasible in the foreseeable future. A new treatment paradigm is needed, both to accommodate the changing landscape of hemophilia care and to replace the irrelevant "minimal treatment" mindset. The

ultimate treatment goal, which, until recently, was aspirational only, is to achieve a lifestyle unhindered by the disorder.

Materials and Methods: A panel of hemophilia treaters, patient advocates, and industry representatives convened in a working group to develop a new treatment model in the context of the current and anticipated future treatment landscape. A new model was proposed that enables patients to achieve specific milestones in a stepwise fashion, culminating in a progressive definition of cure.

Results: Eight milestones were identified and are described in the table.

Conclusions: With the development of novel therapies for hemophilia, milestones for disease management have shifted such that cure is the final goal. This new treatment model lays the foundation for achieving the goal of normal hemostasis, using specific milestones on the path toward cure.

TABLE 1 8 Milestones Identified

Step	Milestone	Description
1	Sustain life	Prevent premature death
2	Minimal joint impairment	Improved quality of life; participation in activities of daily living
3	Freedom from spontaneous bleeds	Ability to engage in low-risk activities
4	Attainment of "normal" mobility	Participation in work, career, and family life without restriction
5	Freedom of mind not to fear minor trauma	More unrestricted lifestyle
6	Ability to sustain major surgery or trauma without additional intervention	Not dependent on specialized healthcare
7	Normal hemostasis	Optimal health and well-being
8	Cure	Health equality

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18-PEDIATRIC HEMOSTASIS

W-FPYR-001 (147) | Acquired von Willebrand syndrome – a complication of idiopathic pulmonary hypertension in children

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Introduction and Objectives: Acquired von Willebrand Syndrome (AVWS) is reported in high-flow high-shear congenital cardiac disorders including ventricular septal defects, aortic stenosis and persistent ductus arteriosus. Pulmonary hypertension (PH) is characterized by narrowed pulmonary vasculature. We hypothesized that the narrowed pulmonary vasculature in idiopathic PH also induces a high-flow high-shear state causing AVWS; this has not been previously reported.

Materials and Methods: We conducted a cross-sectional evaluation of children followed at SickKids with idiopathic PH. During scheduled clinic visits, patients underwent assessment for bleeding symptoms, using a standardized Bleeding Assessment Tool (ISTH-BAT), and baseline coagulation screening tests. Patients with bleeding symptoms and/or laboratory abnormalities in their screening tests were referred for more in-depth testing.

Results: 7 patients (5 females: 2 males; ages: 6-17 y) were identified. Five children exhibited bleeding symptoms with ISTH-BAT scores in the abnormal range (3 to 5). Main laboratory findings are shown in Table 1. Most patients demonstrated mild thrombocytopenia, von Willebrand factor levels in the low-normal range for blood type and reduced VWF activity/antigen ratios. All patients showed very prolonged platelet function analyzer (PFA)-100 closure times. Despite 5 of these 7 patients being on prostacyclin analog(s), none demonstrated abnormal platelet aggregation studies.

One patient underwent a double-lung transplant, with normalization of all hemostatic laboratory abnormalities post-surgery.

Conclusions: Many children with idiopathic PH presents mild to moderate bleeding symptoms, mild thrombocytopenia, markedly prolonged PFA-100 closure times and low-normal VWF levels – all of which are in keeping with AVWS. The complete normalization of the hemostatic defects with lung transplantation attests to the acquired nature of these defects. The recognition of this up until now unreported association of PH with AVWS demands further investigation to determine both, 1) the prevalence of this association in idiopathic PH and in other forms of PH, and 2) how best to manage it.

TABLE 1. Laboratory features: abnormal levels (for blood type in case of VWF and FVIII) are underlined and bolded. Similarly post lung transplant high levels are shown in ().

	1		2	3	4		5		6		7	
	Visit 1	Visit 2	Visit 1	Visit 1	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Pre DLT	Post DLT
Hemoglobin (g/L)	131	132	137	123	136	132	140	143	128	123	148	123
Platelets ($\times 10^9$/L)	**101**	**126**	**114**	**133**	**149**	169	230	283	170	180	**119**	273
PFA-100 CT Col/Epi (sec)	**>300**	**>300**	**220**	**>291**	**>300**	**>300**	**233**	**155**	**167**	**248**	**>300**	84
PFA-100 CT Col/ADP (sec)	**>300**	**193**	**286**	**>300**	**>300**	-	**168**	-	**152**	**222**	**>300**	-
FVIII[1] (%)	84	-	81	112	**59**	**57**	76	81	84	77	98	*(351)*
VWF:Ag (%)	71	75	76	91	**68**	**69**	-	62	**68**	**65**	**61**	*(418)*
VWF:Act[2] (%)	**63**	**66**	55	**50**	**62**	**56**	-	68	**58**	**60**	**34**	*(357)*
VWF:Act/Ag	0.89	0.88	0.72	**0.55**	0.91	0.81	-	1.10	0.85	0.92	**0.55**	0.85
VWF:CB (%)	65	-	123	**64**	**53**	-	-	**47**	-	**43**	**52**	*(471)*
VWF:CB/Ag	0.9	-	1.6	**0.7**	**0.8**	-	-	**0.8**	-	**0.7**	**0.8**	1.1
Multimers	N	-	N	N	N		N		N		N	-
Platelet aggregation	-		N	N	Deaggregation with low dose ADP, TRAP, collagen		N		N		N	
Platelet electron microscopy	N		N	N	Mild ↓ in dense granules		N		N		-	
Blood group	A		O	B	A		O		AB		A	

[1]INR and PTT were normal in all cases.
[2]Act: von Willebrand activity was measured using ristocetin cofactor assay (Patient 1) or GPIb-based assay (Patients 2 to 7).
LEGEND: Ag: antigen; Act: activity; CB: collagen binding assay; CT: Closure times; Col/ADP: Collagen/Adenosine diphosphate cartridge; Col/Epi: Collagen/Epinephrine cartridge; DLT: double lung transplant; FVIII: Factor VIII; INR: International Normalized Ratio; PTT: partial thromboplastin time; N: Normal.

W-P-058 (121) | Screening of bleeding disorders in school-age children by using Thai Pediatric Bleeding Questionnaire (TPBQ)

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Introduction and Objective: Mild bleeding disorders are underdiagnosis because the symptoms are usually inattentive. Recently, Thai Pediatric Bleeding Questionnaire (TPBQ) has been developed, and was first studied in patients with known bleeding disorders compared to healthy children. A score ≥3 was suggestive of bleeding disorders. TPBQ has not been used for screening bleeding disorders in children. Therefore, the objective of the study was to demonstrate the use of TPBQ as a screening tool in school-age children.

Materials and Methods: Grade 10 children from 2 high schools, with consents from their parents, were enrolled in the study. The TPBQ was introduced to the students in a small group of 5-6 facing each other with one facilitator, a pediatrician per group. The Pictorial Bleeding Assessment Tool was added for students reporting excessive menstruation. Students with the score ≥3 were given an appointment, with parents, to the Hematology Clinic. Then, the TPBQ was reapplied to verify the scores. Parents and patients were informed about the blood testing including CBC, bleeding time, PFA-100, coagulogram, vWF Ag, Ristocetin cofactor activity, factor VIII activity, platelet function test, and fibrinogen level.

Results: A total of 305 students, 59% female and mean (SD) for age was 15.1 (1.4) years were enrolled in the study. The median (range) of TPBQ scores, according to the PBQ and ISTH scoring keys, were 0 [(-2)-7] and 0 [0-6], respectively. A total of 8 students, 7 female and 1 male, had scores ≥ 3. The most common problem was bleeding in the oral cavity. At present, 6 students and their parents were seen at the clinic and had blood tested. Two out of 6 students diagnosed with type 1 vWD. The overall prevalence of bleeding disorders was 0.6%.

Conclusions: TPBQ can be used as a screening tool in normal children. Although children are able to provide most of the information of bleeding symptoms and may not aware of their bleeding problems during early childhood, the symptoms of bleeding in subjects with inherited bleeding disorders could persist through the older aged group. Further study to apply the TPBQ in larger population is recommended.

W-P-059 (193) | Effect of combination plasma derived and recombinant factor VIII on infusion volumes in children hemophilia A with and without inhibitors: an update of a single institution experience

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Introduction and Objective: The majority of pediatric patients in the US are treated with recombinant factor VIII (rfVIII). Plasma derived fVIII (pdfVIII) products that contain varying amounts of von Willebrand Factor (VWF) are also licensed for use. Patients with short FVIII half-lives and lower VWF levels may have improved pharmacokinetics with the addition of VWF. For a subset of inhibitor patients, the presence of VWF improves the kinetics of inhibition and may influence tolerance. However, the volume of infusion of pdfVIII product can be prohibitive to peripheral infusions. Here we update our single institution experience using combined therapy with rfVIII and pdfVIII mixed in a single syringe.

Materials and Methods: The electronic medical records of pediatric patients with hemophilia A treated at Children's Healthcare of Atlanta from 2012 to present were reviewed as part of an IRB approved study for patients with hemophilia A with or without inhibitors.

Results: A total of 7 patients have treated with combined therapy since 2012. One patient combines an extended half-life rfVIII product while the remaining 6 use a standard half-life concentrate. Three patients had inhibitors and 4 patients did not The indications for combination therapy included; three patients with low VWF levels and short fVIII half-lives and one patient with poor clinical response to rfVIII. An additional contributing factor was supratherapeutic VWF levels when treated with pdfVIII alone in one patient. All three patients with inhibitors chose combination therapy due to difficulty infusing the volume of pdfVIII peripherally. No adverse events including no thrombotic events have been seen with a median follow up time of 41 months.

Conclusion: All 7 patients tolerated combination therapy. Combination therapy resulted in lower infusion volumes which resulted in all patients giving all or most of their infusions peripherally when compared to pd-fVIII alone.

W-P-060 (452) | A tale of two cities – comparison of perioperative practices for placement of Central Venous Access Devices (CVAD) in paediatric haemophilia patients

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Introduction and Objective: CVADs are frequently placed in young children with haemophilia to aid in delivery of factor concentrates. We compared perioperative practices for CVAD placement in paediatric haemophilia patients to assess similarities and differences in practice across centres in 2 different cities.

Materials and Methods: Retrospective record reviews were conducted involving paediatric patients without inhibitors who underwent CVAD placement from January 2007 to September 2017 at 2 centres in Singapore (KK Women's and Children's Hospital and National University Hospital) and at 1 centre in Ontario, Canada (McMaster Children's Hospital). Information obtained included demographics, surgical details, pre-operative investigations, perioperative factor replacement, length of stay and perioperative complications.

Results: There were 11 CVADs placed in Singapore centres, and 7 placed in the Canadian centre. The mean age at first port insertion were similar – 31.8 months in Singapore and 32.7 months in Canada. There were differences in pre-operative investigations sent. In Singapore, 100% of patients had full blood counts, 83.3% had APTTs and 25% had factor assays and inhibitor screens. In

TABLE 1 (Continued)

Patient	Inhibitor	Current FVIII Dose (all SHF products)	Volume if given as pdfVIII	Volume of Combined pdfVIII + rfVIII	Infusing Peripheral IV or Central Line	Months on Combined Therapy
1	Yes	6000 IU	30 mL	15 mL	PIV	9
2	No	4700 IU	30 mL	14 mL	PIV	42*
3	No	2700 IU	15 mL	10 mL	PIV	31
4	Yes	5000 IU	30 mL	7 mL	Both	12*
5	Yes	7600 IU	40 mL	20 mL	PIV	41
6	No	3500 IU	20 mL	15 mL	PIV	50
7	No	8000 IU	80 mL	20 mL	PIV	50

*Number of total months on therapy while treated at our center.

**Volume calculations assume smallest number of vials; SHF: Standard half life products.

Canada, no patients had full blood counts or APTTs, but 100% of patients had factor assays and inhibitor screens. Excluding 4 cases from Singapore who underwent CVAD insertions at a time when they were being treated for other bleeds, there were also differences in perioperative factor replacement. The mean pre-operative factor dose just prior to surgery was 51 IU/kg in Singapore, and 72 IU/kg in Canada. The mean total factor use from the pre-operative dose to discharge was 8642.86 IU (424.98 IU/kg) in Singapore and 8924.14 IU (646.97 IU/kg) in Canada. Mean duration of clotting factor replacement was 5.0 days in Singapore and 6.9 days in Canada. Antifibrinolytics and perioperative antibiotics were administered in 83.3% and 41.6% respectively in Singapore. None were used in Canada. Average length of stay was 4.57 days in Singapore and 4.14 days in Canada. No perioperative bleeding complications within 30 days were recorded in any patient.

Conclusions: There are similarities and differences in perioperative practices around placement of CVADs in paediatric haemophilia patients across centres, with variations seen especially in preoperative investigations, perioperative factor replacement strategies and use of antifibrinolytics and antibiotics.

19-PHARMACOKINETICS

T-MP-087 (251) | Pharmacokinetic intervention to optimise FVIII prophylaxis: UKPK trial interim analysis

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Introduction and Objectives: The UKPK trial is a national study assessing the impact of implementing pharmacokinetic (PK) education and population PK guided prophylaxis discussions (intervention) in the clinic. The study aims to identify if this intervention influences prophylaxis prescribing (dosing and frequency), targeted troughs, factor concentrate usage and annualised bleed rates (ABR).

Material and Methods: Data was collected from the UKPK trial, a national, prospective, interventional, pragmatic clinical trial where patients had individual population PK prediction followed by PK education and a personalising prophylaxis discussion. Patients remained on trial for 12 months from consent. Additional data was collected on comorbidities, patient reported bleeds, adherence, physical activity and quality of life.

Results: 59 persons with severe haemophilia A (PWsHA) on Advate® prophylaxis were recruited from 16 UK centres. 42 patients have completed the intervention and 6-month follow-up data are included in the interim analysis. At study entry, 19% (8/42) were on optimal prophylaxis (ABR=0; Factor VIII trough (FVIII: C) >1 IU/dL). 67% (28/42) reported bleeds, with 43% (12/28) having a FVIII:C ≤ 1 IU/dL (ABR=6; 1-11) and 57% (16/28) a FVIII:C > 1 IU/dL (ABR=10; 1-44). Following the intervention, 38% (16/42) received optimal prophylaxis and 52% (22/42) continued to report bleeding. In patients with continued bleeds, 9/22 had FVIII:C < 1 (ABR=2; 1-10) and 13/22 a FVIII:C > 1 (ABR=6; 1-30). Although the overall ABR reduction did not reach statistical significance (10 vs. 5, $P = 0.197$), 20 patients were bleed free following the intervention. Weekly FVIII prophylaxis consumption was similar before (85.3 IU/kg/week) and after the intervention (86.9 IU/kg/week), excluding additional bleed-FVIII use.

Conclusions: This PK-guided intervention doubled the number of PWsHA with optimised prophylaxis with a trend toward statistical significance ($P = 0.08$) in this pilot study. However, 1 in 5 remain non-optimised and still bled and 1 in 3 bled despite predicted protective troughs of ≥1 IU/dL. Targeting trough levels of 1 IU/dL appears insufficient for this latter subgroup of PWsHA to achieve total bleed avoidance. This UKPK data will contribute unique insights to the challenges of successfully implementing personalised prophylaxis dosing.

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T-P-88 (182) | Management of major surgery in patients with haemophilia A with continuous infusion and bolus injections of FVIII pharmacokinetic approach to therapy

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Introduction: Management of major surgery represents one of the most challenging issue of replacement therapy in severe hemophilia.

Materials and methods: The aim of our prospective nonrandomized open label study was to evaluate continuous infusion (CI) of factor VIII (FVIII) and traditional bolus injections (BI) therapy in severe hemophilia A patients undergoing major surgical procedures requiring intensive replacement therapy during 13 postoperative days. We also evaluated a benefit of preoperative pharmacokinetic (PK) investigation in either CI or BI therapy.

Results: A total of 100 major surgeries (out of them 83 orthopedic, including 45 joint replacements) performed in 60 patients without inhibitors in a period between 1998 and 2016 were evaluated. CI and BI were employed in 49 and 51 surgeries, respectively. The 1st week median trough levels of FVIII were comparable in CI and BI groups [68% (IQR 59-90%) vs. 70% (57-77%)]. Using CI, we observed a lower,

albeit nonsignificant, blood loss, drop of hemoglobin and number of serious bleedings compared with BI. In the CI group significantly, lower number of patients required blood transfusions (16/33% vs. 28/55%, $P < 0.05$). FVIII clearance decreasing during CI resulted in a lower 1st week and total FVIII consumption in patients treated with CI compared to BI [357 (308-378) IU/kg vs. 426 (375-467) IU/kg and 520 (474-585) IU/kg vs. 612 (554-625) IU/kg, respectively, $P < 0.001$]. PK investigation was performed prior 60 surgeries (44 CI and 16 BI). We revealed a shorter T ½ <10 h in 17 (28%) patients tested, suggesting the potential of PK for individual tailoring of postoperative factor replacement. This was particularly important for BI regimen, while in CI maintenance dose of FVIII has been adjusted safely according to daily recalculation of actual FVIII clearance.

Conclusion: We observed higher efficacy and safety of replacement therapy in patients treated with CI compared to BI with significantly lower consumption of FVIII concentrates in patients undergoing total joint replacements. Preoperative PK evaluation allows to individualize and optimize factor replacement therapy and thus to increase the safety of major surgical procedures in hemophilia.

T-P-89 (745) | Limited sampling strategies for accurate determination of extended half-life factor VIII pharmacokinetics in severe hemophilia A patients

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Introduction and Objective: With the arrival of extended half-life products, hemophilia patients have the opportunity to adopt a less intensive prophylactic regimen. However, variability in pharmacokinetic (PK) response still precludes the development of a "one-size-fits-all" approach. Dose individualization can be burdensome when classical PK techniques, which require intensive sampling, are employed. A Bayesian PK approach combined with a limited sampling strategy (LSS) allows for easier uptake of dose tailoring in a clinical setting without compromising accuracy. We aimed to identify a LSS that allows for accurate determination of relevant PK parameters and results in the same clinical decisions as a densely sampled PK study.

Methods: Full individual pharmacokinetic profiles were simulated according to the PK parameters and demographic data from a published population PK model for recombinant factor VIII Fc fusion protein (rFVIIIFc) following a 50 IU/kg dose. Data points were systematically removed from the profile to create several LSSs for investigation. Strategies were evaluated by considering bias and accuracy of the PK parameters estimated using the LSS compared to those estimated using dense sampling and whether the same clinical decision would be reached for both sampling schedules. In this study, the individual's simulated FVIII activity at 72 and 96 hours post-infusion (corresponding to a twice weekly dosing schedule) drove clinical decision-making.

Results: One hundred individuals were simulated with data points at previous dose trough, 0.5, 1, 4, 12, 24, 48, and 72 hours post-infusion. Results are summarized in Table 1.

Conclusions: A LSS consisting of pre-infusion and 1-hour post-infusion samples produced estimates that were without bias, similarly accurate, and had nearly identical rates of inappropriate dose adjustment as compared to the dense sampling scheme. This suggests that samples collected from a single visit can accurately assess the appropriateness of a rFVIIIFc prophylaxis regimen.

TABLE 1 Data Points

Sampling Strategy	Half-Life Bias (mean ± SD)	Half-Life Accuracy (mean ± SD)	Inappropriate dose adjustment rate	
			At 72 hours	At 96 hours
Pre-1-24-48 h	−0.3 ± 5.2%	4.0 ± 3.4%	3%	6%
Pre-1-24 h	−0.2 ± 4.6%	5.5 ± 4.6%	7%	10%
Pre-1 h	1.6 ± 8.8%	7.2 ± 5.2%	9%	11%

T-P-092 (372) | Predictable and reliable individualized pharmacokinetic profiling with BAY 94-9027: Integrated population pharmacokinetics analysis

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Introduction and Objective: Patients with hemophilia A are currently treated by intravenous administration of factor VIII (FVIII) on demand or as prophylaxis. This study aims to characterize pharmacokinetics (PK) of BAY 94-9027, particularly regarding PK variability and its relationship to individual patient characteristics, using a population PK (popPK) approach.

Materials and Methods: A total of 2196 PK samples from 198 male patients aged 2 to 62 years obtained across different phase 1, 2, and 3 studies were used for analysis. The popPK analysis was conducted using NONMEM 7.2, and the M3 method was applied to consider samples below the limit of quantification in the analysis. Patient characteristics evaluated for their influence on FVIII kinetics were age, height, weight, body mass index, lean body weight (LBW), race, and von Willebrand factor (VWF) level. The developed popPK model was used to simulate PK endpoints of interest that were difficult to observe directly from measured FVIII levels, such as time spent above 1, 3, and 5 IU/dL following different single-dose administrations of BAY 94-9027.

Results: The FVIII kinetics were adequately described by a 1-compartment model with linear elimination parameterized by clearance (CL) and volume of distribution of the central compartment (V). The covariate analysis revealed that CL and V were statistically significantly associated with LBW, and CL was significantly correlated with VWF. Model qualifications indicated that the model adequately described the FVIII kinetics across different treatment schedules (dosing and frequencies) and age groups. Therefore, the model can be used for simulations (eg, to determine the percentage of patients who maintain FVIII levels above a certain threshold for different dosing regimens).

Conclusions: The popPK model revealed that the PK profile of BAY 94-9027 was monophasic; no second compartment could be identified compared with other FVIII products. For a drug with a monophasic profile and a good understanding of the sources of variability (LBW and VWF), individual kinetics can be successfully and reliably determined based on very few samples (even 2 measurable samples can be sufficient). Therefore, dense PK sampling is not necessary after administration of BAY 94-9027.

Conflicts of interest: Alexander Solms – Employment, Bayer; Maurice Ahsman – Compensated by Bayer for study participation; Peter Vis – Compensated by Bayer for study participation; Anita Shah – Employment, Bayer; Dirk German – Employment, Bayer.

T-P-093 (740) | Comparative assessment of the performance of pharmacokinetic tools for prophylactic dosing of anti-hemophilic factor recombinant plasma/albumin-free method (rAHF-PFM) concentrate in patients with Hemophilia A

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Introduction and Objective: Treatment of patients with moderate to severe hemophilia A (HA) entails factor VIII (FVIII) concentrate prophylaxis. Population pharmacokinetic (PopPK) dosing is an effective way to ensure that FVIII plasma activity levels remain above a desired target. Currently, two PK-based dosing tools are available to individualize FVIII prophylaxis with rAHF-PFM (Advate®). To compare the PK parameter outputs and dosing estimates of two PopPK-based dosing tools (Web Accessible Population Pharmacokinetics Service – Hemophilia (WAPPS) and myPKFiT) and to compare these outputs to a two-stage PK analysis.

Materials and Methods: Infusion and post-infusion measurements were extracted from the WAPPS database and analysed using WAPPS v3.0, the Advate® model, web-based myPKFiT v2.0, and compartmental analysis in WinNonLin. We reported: (1) success of fitting, (2) clearance (CL; dL/hr/kg), (3) volume at steady state (VdSS; dL/kg), (4) FVIII half-life (HL; hours), and (5) time to 0.01 above baseline IU/mL (hours). We also generated dosing estimates according to a 48-hour dosing schedule and a target trough of 0.03 IU/mL. A two-tailed t-test was used to assess for differences in dosing estimates. Data were anonymized as dictated by the WAPPS user DTA agreement.

Results: Of the 232 patients on Advate in the WAPPS database, 92 had post-infusion samples at 4 ± 2, 24 ± 4, and 48 ± 6 hours. Of the 42 cases dosed with 50 ± 5 IU/kg of FVIII, 29 allowed calculation of all required outcome measures. Six patients were moderate. The best-fit using a two-stage approach was a two-compartment model on 9 patients (CL 0.037, 0.026-0.043; HL 11.2, 11.1-14.4) and a one-compartment model on 16 patients (CL 0.019, 0.016-0.023; HL 9.9, 9.3-10.5). Dose estimates were produced for severe patients and were significantly lower for WAPPS as compared to myPKFIT ($t(23) = -3.302$, $P = 0.003$).

Conclusions: Differences in PopPK estimates between WAPPS and myPKFiT are small and non-directional. The lower dose estimates from WAPPS were similar to those determined using a NONMEM implementation of the Bjorkman model and similar patients [1939 IU (985-3824)]. Prospective studies are required to assess the clinical relevance of differences between PopPK tools.

20-PROPHYLAXIS

M-FPMED02-006 (41) | Impact of nonacog beta pegol on spontaneous bleeding events in children with haemophilia B: Up to 3.8-year data from the paradigm™5 clinical trial

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Introduction and Objective: Nonacog beta pegol (N9-GP) is a glycoPEGylated recombinant factor IX (rFIX) molecule with a prolonged half-life, developed for the treatment of haemophilia B. Here, we assess interim data from the extension phase of the paradigm™5 study to evaluate the impact of N9-GP prophylaxis on spontaneous bleeding in previously treated paediatric patients.

Materials and Methods: paradigm™5 is an ongoing, international, open-label, non-controlled trial that enrolled patients aged ≤12 years with haemophilia B (FIX ≤2%), stratified into two age groups (younger: 0-6 years; older: 7-12 years). The main study phase was 52 weeks, after which 22/25 patients entered the extension and continued to receive 40 IU/kg N9-GP once weekly. The following interim data include all relevant exposures in the main and extension phases (cut-off date: 1 April 2016).

Results: The mean N9-GP prophylaxis dose, annualised consumption, and exposure time were 43.2 IU/kg/patient, 2306 IU/kg/patient/yr, and 2.84 years/patient, respectively. Estimated mean FIX trough level was 0.171 IU/mL (95% confidence interval: 0.151; 0.193). Overall, 25 spontaneous bleeds were reported in 8 patients; 4 in 3 younger children and 21 in 5 older children. Ten spontaneous bleeds were reported in 6 patients during the main phase (mean treatment period: 0.97 years/patient) compared with 15 in 5 patients during the extension (mean treatment period: 2.13 years/patient). During the extension phase, 77% of patients (17/22) remained spontaneous bleed-free: 82% and 73% of younger and older children, respectively. The overall estimated mean annualised spontaneous bleeding rate (sABR) was 0.35 bleeds/patient/year (0.41 and 0.32 during the main and extension phases, respectively) and the median sABR was 0.00. No spontaneous bleeds were reported in target joints (present in 2 patients at baseline). No patients developed inhibitors and no unexpected safety concerns or serious adverse events related to study medication were reported.

Conclusions: Up to 3.8 years of data from the ongoing paradigm™5 extension trial confirms a low incidence of spontaneous bleeds in children with haemophilia B treated with N9-GP prophylaxis. Median sABR was low and generally decreased over time, with proportionally fewer bleeds throughout the extension phase versus the main phase. Most patients (77%) remained free of spontaneous bleeds during the extension phase.

Conflicts of interest: M Carcao: Grant/Research support from: Baxalta (Shire), Bayer, Biogen, Novo Nordisk and Pfizer; Consultant for: Baxalta (Shire), Biogen, CSL Behring, Novo Nordisk, Octapharma and Pfizer; Speaker Bureau of: Baxalta (Shire), Bayer, Biogen, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma and Pfizer.S Kearney: Grant/Research support from: Local PI research funding for Bayer, Bioverativ, Daiichi Sankyo, Grifols and Novo Nordisk; Speaker Bureau of: advisory board for Bayer, Bioverativ and Novo Nordisk.E Santagostino: Advisory board for: Shire, Bayer, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche and Sobi; Speaker Bureau of: Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Sobi.F Abdul Karim: None declared.M Taki: Consultant for: Bioverativ, Chugai, CSL Behring and Novo Nordisk; Research support from: CSL Behring; Investigator in clinical trials of: Baxalta (Shire), Bioverativ, Chugai, CSL Behring, Novo Nordisk and Octapharma; Speaker's fee from: Baxalta (Shire), Bayer, Bioverativ, Novo Nordisk and Pfizer.M Y Lu: None declared.M-L Garly and M Zak are employees of Novo Nordisk A/S, Søborg, Denmark.

W-FPYR-005 (135) | The effect of switching to rFVIIIFc on treatment patterns and annualised bleed rate before and after: A within-patient comparison from the UK National Haemophilia Database

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Introduction and Objective: Prophylaxis with rFVIIIFc may facilitate a reduction in infusion frequency (IF) and clotting factor consumption (CFC) relative to standard recombinant FVIII (rFVIII) in patients with Haemophilia A (HA). However, there are no direct comparisons of the two products. We compared IF, CFC and annualised bleed rate (ABR) in patients using FVIII prophylaxis before and after switching to rFVIIIFc.

Materials and Methods: rFVIIIFc was introduced in the UK from 1/9/16 using a restricted NHS England protocol that assumed rFVIIIFc prophylaxis would be provided using at least one fewer injection/week than required using rFVIII. We identified all non-trial patients switching from rFVIII to rFVIIIFc prophylaxis, 01/09/16-30/09/17, with ≥6-months compliant pre- and post-switch Haemtrack (HT) data. IF, CFC and ABR were calculated for both periods and comparisons made using summary statistics and Wilcoxon signed rank test.

Results: Sixty-one patients were eligible; 51 severe; 9 moderate (Median FVIII = 0.01 IU/ml) and one mild (FVIII = 0.11 IU/ml) HA. Median (IQR) age was 19 (9-41) years. The median (IQR) post-switch follow-up was 34 (31-38) weeks. Comparing pre- and post-switch periods, IF fell from a median (IQR) of 3.52 (3.10-3.96) to 2.38 (2.11-3.51) injections/week, (−32%; $P < 0.0001$), reducing in 91% of patients. CFC reduced from a median (IQR) of 5306 (3564-7610) to 4620 (3095-6166) IU/wk (−12%; $P < 0.0001$), reducing in 73% of patients. Median (IQR) ABR was 2 (0-6) pre-switch and 2 (0-4) post-switch (not statistically significant) with no significant change in the proportion bleed-free (44% pre and 45% post) or with an ABR >5/yr (32% pre and 21% post).

Conclusion: We observed a significant within patient reduction in IF and CFC following switching from rFVIII to rFVIIIFc. This reduction in treatment intensity was not accompanied by any significant change in bleed-rate, reflected by ABR. Median IF is consistent with previous trial reports. This provides further evidence that EHL rFVIII products can provide effective prophylaxis whilst reducing treatment burden.

Conflicts of interest: The study was supported by a project grant from Sobi; Author 1 is a Bayer haemophilia clinical research fellow and has received funding for travel, accommodation and meeting registration from Sobi.

Author 2: No conflicts;Author 3: Has worked as paid consultant for Sobi; Author 4: Has worked as a paid consultant for Sobi and is on the Sobi speakers bureau.

M-FPMED02-003 (469) | Safety and efficacy of multiple factor switches in a short time period in children with haemophilia A

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Introduction and Objectives: Tender processes in many countries result in the need to switch factor products when current products become unavailable. Recombinant factor products have enough differences that individual patients may react differently in terms of PK response or side effects. While the risk of inhibitor development in previously treated patients who switch factor products is extremely low, no data exists on the risks to those who subsequently switch products quickly again due to poor response or adverse effects. We report on 2 children with haemophilia A who switched products due to national tender changes and then required a second switch soon after due to adverse effects.

Methods: Patient records were reviewed, and demographic and clinical data collected. Both families consented to interviews and completion of the Canadian Haemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT). Baseline CHO-KLAT questionnaires completed prior to switching were reviewed. Pharmacokinetic (PK) data was also reviewed.

Results: Both children switched from 3rd generation full-length recombinant FVIII (FLrFVIII) to B-domain deleted recombinant FVIII (BDDrFVIII) due to a change in availability of FLrFVIII in Canada. One child then switched 10 months later to recombinant human B-domain deleted FVIII (rhFVIII) due to an increase in bleeding. Bleeding symptoms improved, are now rare, and PK showed better half-life with rhFVIII (9.5 h to 18 h). The second child developed chronic daily abdominal pain after switching to BDDrFVIII which resolved immediately after switching to rhFVIII 5 months later. PK assessment showed normal half-life of 12 hours. Neither child developed inhibitors. CHO-KLAT surveys showed improvement in energy, mood and control over life after the second switch. Both boys reported being more at ease and less worried about their health.

Conclusions: Multiple factor switches in quick succession, while not encouraged, appear safe in circumstances where a second switch may be necessary. The impact on both families was positive likely due to resolution of repeated bleeding and adverse effects. Close monitoring of inhibitor levels, pharmacokinetics, clinical bleeding and adverse effects is essential. More data on these rare patients should continue to be collected especially in jurisdictions where product tenders are of short duration.

M-MP-097 (43) | Simple and fixed N8-GP dosing regimen associated with measurable trough levels and low annualised bleed rates in children and adolescents/adults treated with N8-GP prophylaxis

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Introduction and Objective: N8-GP (turoctocog alfa pegol) is an extended half-life (EHL) glycoPEGylated recombinant factor VIII (rFVIII) being developed to offer prophylaxis with higher FVIII trough levels and with less frequent dosing compared with standard FVIII products. In phase 3 clinical trials, N8-GP provided effective prophylaxis, achieving low median annualised bleeding rates (ABRs) in paediatric and adolescent/adult patients with severe haemophilia A. We assessed the estimated mean pre-dose (trough) FVIII activity levels associated with low ABRs in patients who received simple N8-GP dosing regimens.

Materials and Methods: Male paediatric (0-11 years, pathfinder™5 trial) and adolescent/adult (≥12 years, pathfinder™2 trial) previously treated patients with haemophilia A (<1% FVIII) received N8-GP prophylaxis at 60 IU/kg twice weekly (TW) or 50 IU/kg every 4 days (Q4D), respectively. A subgroup of eligible patients in pathfinder™2 with ≤2 bleeds during the previous 6 months could elect to be randomised to receive either 75 IU/kg weekly (Q7D) or 50 IU/kg Q4D N8-GP. Pre-dose FVIII activity levels assessed at all visits from all patients measured using a chromogenic assay were analysed.

Results: A total of 68 paediatric patients (33 patient years of exposure [PYE]), 175 adolescent/adult (143 PYE) patients and a subgroup of 38 adolescent/adult (15 PYE) patients treated Q7D were included in the analysis. In these patients, the overall observed median (interquartile range) ABR for patients dosed TW, Q4D and Q7D was 1.95 (0.00-2.79), 1.18 (0.00-4.25) and 0.00 (0.00-2.23), respectively. For children dosed TW and adults dosed Q4D or Q7D, the estimated mean pre-dose FVIII activity levels were greater than 1% (ranging from 1.2-3.0 IU/dL).

Conclusions: In patients of all ages with severe haemophilia A, a simple dosing regimen of N8-GP (an EHL rFVIII), can improve FVIII pre-dose activity from undetectable into the range of moderate haemophilia (>1 IU/dL), which provides greater protection from bleeds. PK tailored dosing was not needed since fixed dosing achieved FVIII levels associated with moderate haemophilia which resulted in low ABRs.

Conflicts of interest: PC has received grants and/or research support from Novo Nordisk, Pfizer, CSL Behring Bayer and Swedish Orphan Biovitrum AB (publ) (Sobi), and has acted as a consultant for Novo Nordisk, Pfizer, CSL Behring, Baxter, Baxalta, Biogen

Idec, Shire, Roche, Freeline and Sobi. MC has grant/Research support from: Baxalta (Shire), Bayer, Biogen, Novo Nordisk and Pfizer; Consultant for: Baxalta (Shire), Biogen, CSL Behring, Novo Nordisk, Octapharma and Pfizer; Speaker Bureau of: Baxalta (Shire), Bayer, Biogen, CSL Behring, Novo Nordisk, Octapharma and Pfizer. WHOC is an employee of Novo Nordisk A/S. PAH has received research support from Bayer, Pfizer, Shire and Octapharma and has acted as a consultant for Bayer, Novo Nordisk, Pfizer, CSL Behring, Shire, Biogen Idec, and Sobi. JM is an employee of Novo Nordisk A/S. AT has participated in advisory board for: Roche, Novo Nordisk, Werfen; Speaker Bureau of: Bayer, Novo Nordisk, Roche, Wefen, Stago. AW has participated in advisory boards for Novo Nordisk, Baxalta (Shire), Octapharma and Bayer. ES has participated on advisory boards for: Shire, Bayer, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Bioverativ and Sobi; Speaker Bureau of: Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Sobi.

M-MP-098 (355) | Low dose (20 iu/kg/week), single infusion prophylaxis using long acting FVIIIc (ELOCTATE) in severe hemophilia A

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Introduction and Objectives: Intermediate to high dose prophylactic factor replacement protocols are well established in hemophilia. Compliance is a issue due to multiple infusions every week. IV Eloctate 20iu/kg weekly, single infusion prophylaxis for severe hemophilia A patients was used.

Patients and Methods: IV Eloctate 20iu/kg/weekly single infusion was done in hospital for 44 severe hemophilia A patients between age 5-11 years. All patients had more than 20 ED on episodic regimen and were negative for inhibitor. All patients were on regular physiotherapy schedule. All breakthrough bleeds were treated with extra infusions of IV Eloctate. Twelve weekly inhibitor tests were performed. ABR & Days missed at school were documented. Eloctate was received through Humanitarian Aid Program of WFH.

Results: In previous year median ABR was 14 (11-32), median number of target joints: 2 (1-4) with HJHS:10/116 (0-22).No single joint had HJHS more than 5.The median days missed previous year were 26 (20-61).All patients had more than12 months follow up showing 96% adherence to infusion schedule. The assessment at end of 12 months period showed reduction in ABR and days missed at school, with median ABR3 (2-9) & median days missed 9 (6-20). Median FVIIIc trough level:2.6 (2.4-3.2) iu/dl. The total number of break through bleeds were 102 and 127 extra doses of IV Eloctate used. A median 1100 (1040-1440) iu/kg/year of Eloctate was used . No patient developed Inhibitor.

Conclusions: There was marked reduction in ABR & days missed at school. No zero ABR was achieved. Baseline HJHS less than 10 had more reduction in ABR. Once a week low dose IV Eloctate is feasible & effective prophylaxis in resource constraint countries. Low dose prophylaxis is better than episodic factor replacement. Low dose prophylaxis initiated early in life may have additional benefit for PWH.

M-MP-099 (419) | Influence of age of prophylaxis initiation on hemophilia joint health scores in severe hemophilia A

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Introduction/Objectives: Prophylactic factor VIII (FVIII) administration is the standard of care for severe hemophilia A (HA), and early prophylaxis initiation is preferred to maintain joint health. We evaluated the influence of prophylaxis initiation age on Hemophilia Joint Health Scores (HJHS).

Methods: Participants in the University of Colorado's IRB-approved bleeding disorders cohort study with severe HA were included. HJHS, a physical exam score for hemophilic arthropathy, was performed at annual comprehensive clinic visits. Total HJHS was defined as the sum of ankle, knee, and elbow scores. Age of prophylaxis initiation was defined using the start of continuous prophylaxis with standard FVIII product at least 3x/week or extended half-life product at least 2x/week. Percentage of life on prophylaxis was defined starting at age 18 months. Data were analyzed using linear regression.

Results: Ninety-eight participants with severe HA were included, with only 6 patients treated exclusively with episodic FVIII therapy.

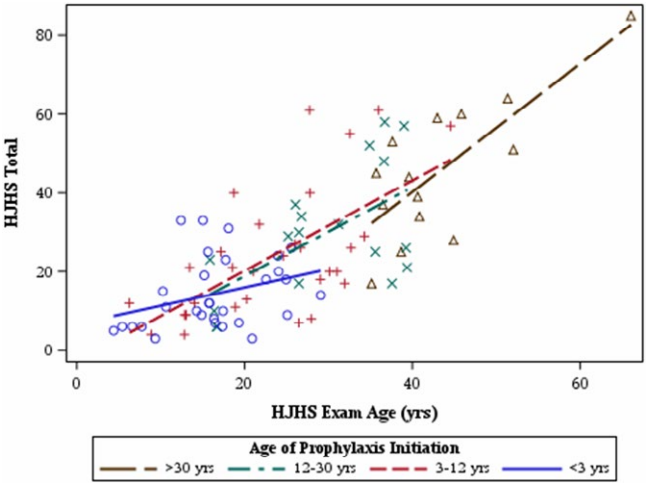


FIGURE 1 HJHS increase with age is attenuated with younger prophylaxis initiation.

Prophylaxis initiation age ranged from 0.7 to 60.5 (median 5.8) years. Total HJHS increased linearly with age, on average increasing by 1.075 points per year of age (95% CI 0.89, 1.26, $P < 0.0001$). This increase was attenuated in those starting prophylaxis prior to age 3 (figure). Total HJHS increased on average 0.46 points per year of age (95% CI −0.058, 0.98, $P = 0.08$) in those starting prophylaxis by age 3, whereas total HJHS increased on average 1.17 points per year of age (95% CI 0.89, 1.45, $P < 0.0001$) in those starting prophylaxis later. In the overall population, total HJHS decreased by 1.9 points for each 10% increase in proportion of life on prophylaxis (95% CI 0.96, 3.0, $P = 0.0002$).

Conclusion: Joint disease in hemophilia increases with age. Previous studies have shown that prophylaxis slows arthropathy progression. This study suggests that the progression of arthropathy, as detected by HJHS exam, is slowed most when prophylaxis is begun prior to age 3 years.

M-P-100 (95) | Low-dose prophylaxis versus on-demand treatment in Indonesian children with severe hemophilia A: An interim report

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Introduction and Objective: Repeated joint bleeds leading to irreversible progressive joint damage (hemophilic arthropathy) is the main problem in children with hemophilia. Current standard prophylacytic treatment in developed countries is beyond our capability as Indonesia has constraint resources. This study was aimed to investigate the efficacy and safety of low dose secondary prophylaxis compare to on-demand treatment in children with severe hemophilia A.

Materials and Methods: An open, randomized controlled trial was conducted on severe hemophilia A children aged 4-18 years in Pediatric Hematology-Oncology Division Dr. Cipto Mangunkusumo Hospital for 12 months. Eligible subjects were randomized into 2 groups: prophylaxis and on-demand group. All subjects were evaluated at month-0, 6 and 12 for inhibitor factor VIII (Bethesda Assay), ultrasonography (HEAD-US scores) of six index joints (bilateral knees, ankles and elbows), and HJHS (version 2.1, 2011). Subjects in prophylaxis group received factor VIII (Koate-DVI®, Grifols) 10 IU/kgBW 2 times per week for 12 months. Any bleeding episode in both groups were treated according to standard treatment (on-demand).

Results: During February–August 2017 there were 50 subjects enrolled in the study. Our interim analysis showed mean age in prophylaxis and on-demand group were 11.8 ± 3 years and 12.1 ± 3 years, respectively. Median number of joint bleeds in prophylaxis group was 2 (0-17) while in on-demand group was 5 (0-24), (95% CI -6 to 1; $P = 0.004$). Median number of total bleeding episodes in prophylaxis group was 5 (0-21) while in on-demand group was 10 (1-29), (95% CI −10 to −3; $P < 0.001$). The HJHS difference at month-0 and 6 between two groups was better in prophylaxis group (95% CI −3 to 0; $P = 0.009$), as well as the HEAD-US scores (95% CI −4.2 to 0.1; $P = 0.063$). No subjects in both groups showed inhibitor factor VIII.

Conclusion: Low dose prophylaxis was effective to reduce joint bleeding episodes and improved HJHS and HEAD-US scores, compared to on-demand treatment.

Disclosure: This study was funded by Research Grant from Grifols including study drug (Koate-DVI®) used for prophylaxis.

M-P-101 (305) | Results from a prospective, dose escalating, prophylaxis study in young boys with severe hemophilia a in China: The China Hemophilia Individualized Prophylaxis Study (CHIPS)

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Background: In China, 90% of boys with severe hemophilia A (SHA) manifest significant arthropathy by age 6 years (Wu R et al Haemophilia, 2014). Short-term pilot studies demonstrated that low-dose prophylaxis (10-15 IU/kg x2 /week) reduced joint bleeds by 80% but was ineffective in eliminating joint damage (Wu R et al Haemophilia, 2011, Tang L et al Haemophilia, 2013). Optimizing prophylaxis in China for boys with SHA is an urgent priority.

Aims: To investigate the efficacy of an individualized, dose escalating prophylaxis protocol in young boys with SHA in China.

Methods: This is a prospective, ethics approved clinical trial conducted at 2 major Hemophilia Treatment centers in China. Boys with SHA (baseline FVIII < 2%), ages 1-7 years, inhibitor negative, >50 Exposure Days and a history of index joint (elbows, knees, ankles) bleeds were eligible. The design included 4 dose escalation steps; Step 1: 10-15 IU/kg x2/week; Step 2: 10-15 IU/Kg, x3/week; Step 3: 15-20 IU/Kg x3/week; and Step 4: 20-25 IU/Kg every other day. A priori escalation criteria were based on the frequency of index joint bleeds, scores from the Hemophilia Joint Health Score (HJHS) and Ultrasound (US) examinations of index joints.

Results: 41patients were consented and enrolled, with 8 drop-out. The mean age was 4.8 yrs. (range: 2.1-7.9 yrs.) and the median follow up observation period was 12 months (range: 4-12 months). In total, the patients have completed 93% of the required number of months on study (335/360 patient months). Musculoskeletal (MSK) assessment showed a total of 19 boys with target joints (65%). In addition, a total of 25 patients completed 40 dose escalations. Of these patients currently on prophylaxis, 7 patients are on step 1 (24%); 9 on step 2 (31%), 11 on step 3 (38%); and 2 on step 4 (7%). The criterion for escalations are summarized in Table 2.

Conclusions: This is the first prospective, individualized, dose escalating prophylaxis study for boys with SHA in China with the goal of minimizing

bleeding and joint damage. Findings from the HJHS and US examinations to guide dose escalation, in conjunction with index joint bleeds, is a unique feature of this clinical trial. Our results indicate a promising reduction in joint bleeds by using the 4-step escalation low dose regimens with equal utilization of Steps 1, 2 and 3 by the patients. Low dose prophylaxis may be ineffective in some cases and assessments of bleeding patterns and joint structure/function is important to inform modification of prophylactic regimens. These observations will be useful in the design of cost effective prophylaxis regimens for boys with SHA in China. Keywords: Dose Escalation, Hemophilia A, Prophylaxis

TABLE 1 criterion for escalations

Study period	ABR	AJBR
3M Pre-study	12.2	8.5
12M observation	4.9	4.9
% of bleed reduction	59.8%	42.3%

	Number of patients		
Criteria for escalation	Step 1 to 2.	Step 2 to 3	Step 3 to 4
Joint bleeds	15	5	2
Joint bleed.+HJHS	4	4	0
Joint bleed +U/S	1	2	0
Joint bleed.+HJHS+U/S	0	1	0
HJHS+U/S	2	0	0
HJHS	2	1	0
U/S	1	0	0

M-P-102 (729) | Evaluation of factor VIII pharmacokinetic parameters using myPKFiT™ device for hemophilia A patients in Brazil – initial data from ProPK-Brazil study

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Introduction and Objective: Tailored prophylaxis based on factor(F) VIII pharmacokinetic (PK) is an attractive cost-effective strategy for hemophilia A (HA) patients. However, multiple blood sampling with washout period is usually required for it. Recently, a web-based population PK Bayesian tool (myPKFiT™) was designed to predict the PK parameters of FVIII recombinant concentrate, Advate®. Here, we evaluate prospectively the FVIII-PK among HA patients using Advate®, comparing two PK protocols derived from 6 or 2 samples, and possible factors that may influence FVIII-PK results in this group.

Materials and Methods: FVIII-PK evaluation was performed in severe HA patients (FVIII<1 IU/dl) using Advate® through the analysis of 6 sampling (pre, 30 min, 1 h, 4 h, 6 h and 24 h after FVIII infusion, with 72 h washout) and/or 2 points collected from a single visit to the center (3 h and 24 h after, without washout).The FVIII half-life results were analyzed regarding age, body weight/body mass index (BMI), von Willebrand factor antigen (VWF:Ag), blood group, *F8* genotyping and history of inhibitor using independent T test or one-way ANOVA, when suitable. The Chronbach's alpha and the intraclass correlation coefficient (ICC) evaluate the reliability of FVIII half-life results between both methods.

Results: 45/48 patients enrolled performed a 6-point FVIII-PK. 16/45 (35.5%) fulfilled 2-point FVIII-PK with minimum interval of 6mo. 3 patients accomplished only 2-point FVIII-PK. Table 1 summarizes the results. For FVIII half-life for 6 and 2-point methods, there was a high level of reliability as showed by a Chronbach's alpha of 0.8 and a ICC of 0.78 (95% CI 0.38-0.92). None of the evaluated variables influenced the FVIII-PK parameters in this group.

Continuous variables are expressed as mean ± standard deviation, unless otherwise stated. Categorical variables are expressed as number and percentage. *No statistically significant difference in FVIII half-life was observed between different categories of these groups.

Conclusions: We observed a good agreement between both FVIII-PK protocols, assuring the results obtained with the 2-points PK protocol with a single visit to the center. These results are part of the ongoing project ProPK-Brazil.

M-P-103 (708) | Four-year bleeding frequency in haemophilia A patients on prophylaxis: data from the AHEAD study in 22 countries

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Introduction and Objective: As new products become available, there is an increased need to compare their effectiveness in prophylaxis with standard products. We aimed to establish an

TABLE 1. Clinical and laboratory data from included patients.

	6-point PK, *N* = 45	FVIII half-life (h)	2-point PK, *N* = 19	FVIII half-life (h)
Age at PK (years)	15.9 ± 8.7		15.9 ± 9.4	
Body weight at PK (kg)	56.8 ± 24.8		58.1 ± 24.4	
BMI at PK (kg/m^2)*				
Healthy weight	20 (44.3%)	11.9 ± 3.2	8 (42.1%)	9.8 ± 2.7
Underweight	6 (13.3%)	9.9 ± 2.5	3 (25.8%)	8.7 ± 1.6
Overweight	6 (13.3%)	12.3 ± 3.1	6 (36.6%)	10.8 ± 2.6
Obese	13 (28.9%)	11.8 ± 2	2 (10.5%)	10.2 ± 0.2
F8 genotyping*				
Inversion 22	24 (53.3%)	10 ± 2.9	10 (52.8%)	11.6 ± 2.7
Missense	5 (11.1%)	9.5 ± 1.7	3 (15.8%)	10.8 ± 1.3
Nonsense	2 (4.4%)	9.4 ± 0.3	–	–
Frameshift	1 (2.2%)	14.4	1 (5.3%)	14.9
Splice	1 (2.2%)	6.7	1 (5.3%)	11.9
Unavailable	12 (26.7%)	12.5 ± 3.3	4 (21.1%)	10.6 ± 1.2
FVW:Ag	130.6 ± 44.3		132.2 ± 51.9	
Blood group type*				
O	26 (57.8%)	10.6 ± 2.6	12 (63.2%)	9.1 ± 2.2
Non-O	19 (42.2%)	13.1 ± 2.5	7 (36.8%)	11.6 ± 1.7
History of inhibitor*				
Positive	10 (22.2%)	11.6 ± 2.7	2 (10.5%)	9.9 ± 2.1
Negative	35 (77.8%)	11.7 ± 2.9	17 (89.5%)	10.6 ± 5

effectiveness benchmark by assessing bleeding frequency in the AHEAD studies.

Materials and Methods: These non-interventional, prospective, long-term cohort studies span 22 countries and include patients with severe or moderate (factor VIII <1-5%) haemophilia A (HA) treated with Antihemophilic Factor (Recombinant). Preliminary data from prophylaxis patients with calculated annualised bleeding rates (ABR) at each time point were analysed in the International (INT, NCT02078427) and German (GER) arms.

Results: 1,117 patients (715 INT, 402 GER) have been enrolled. The numbers of prophylaxis patients with ABR data for analysis were 611, 478, 371, and 251 in years 1, 2, 3, and 4, respectively. Over the 4-year period, prophylaxis patients had a median ABR of 1.7/2.4 (INT/GER) in year 1, 1.3/2.2 in year 2, 1.5/1.9 in year 3, and 1.0/2.1 in year 4. Median annualised joint bleeding rates (AJBR) were 0.9/0.8 (INT/GER) in year 1, 1.0/0.0 in year 2, 1.0/0.7 in year 3, and 0.0/0.9 in year 4. Over the 4-year period in the INT and GER arms combined, a median of 38.0% of prophylaxis patients had an ABR of <1, 13.9% an ABR of 1-<2, and 10.2% an ABR of 2-<3. The corresponding AJBR results were 54.9%, 14.5%, and 7.4%. Results are shown by year in the table.

TABLE 1 Percentage of Prophylaxis Patients Achieving ABR/AJBR Levels By Year: Combined INT And GER Arms

	Year 1	Year 2	Year 3	Year 4
ABR	*n* = 611	*n* = 478	*n* = 371	*n* = 251
<1	37.0%	37.6%	38.3%	39.0%
1-<2	14.4%	13.4%	14.3%	13.6%
2-<3	11.1%	8.4%	9.7%	10.8%
≥3	37.5%	40.6%	37.7%	36.7%
AJBR	*n* = 523	*n* = 417	*n* = 339	*n* = 228
<1	54.6%	55.1%	54.8%	56.2%
1-<2	14.3%	14.6%	12.7%	14.9%
2-<3	7.2%	6.1%	10.5%	7.7%
≥3	23.9%	24.2%	22.0%	21.1%

Conclusions: These data show that ~40% of patients on prophylaxis had an ABR of <1 and ~55% had an AJBR of <1 in routine clinical practice. About half of patients had an ABR of <2 and ~70% an AJBR of <2. The AHEAD studies jointly represent one of the largest long-term prospective HA cohorts, providing a reliable benchmark for new products or therapeutic approaches. KKh: shareholder (Baxalta, Novo Nordisk, Octapharma, Roche, Pfizer, Shire); grant/research support (Novo Nordisk); speaker bureau (Bayer, Novo Nordisk, Octapharma, Roche, Pfizer, Shire, Sobi). JO: grant/

research support (Shire, Bayer, Biotest, CSL-Behring, Novo Nordisk, Octapharma, Pfizer); consultant (Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum); speaker bureau (Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum).EB: consultant (Bayer, Shire, Novartis); speaker bureau (Pfizer, Bioviiix).

KKu: grant/research support (Bayer, Biotest, CSL Behring), consultant (CSL Behring, Shire).

RP: grant/research support (Pfizer, Bayer, Shire); consultant (Pfizer, Sobi, Shire).AH-K: consultant (Shire).

RK: grant/research support (Shire, Bayer, CSL-Behring, Novo Nordisk, Octapharma, Pfizer); consultant (Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum); speaker bureau (Shire, Bayer, Biogen Idec, Biotest, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum).GC, KNS-T, HB, and PP are employees of Shire.

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[Correction added on 31 October 2018, after first online publication: Name of the author Gretchen Chiu has been corrected to Gretchen R. Chiu and affiliations 5, 8 and 10 of this abstract have been corrected in this current version.]

M-P-104 (692) | Pharmacokinetic guided prophylaxis in children with severe hemophilia A and its potential impact on factor concentrates requirements

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Introduction: Today, prophylaxis is a standard approach to the management of children with severe hemophilia. Interindividual differences in FVIII pharmacokinetics (PK) explain individual differences in the maintenance of FVIII minimum levels and/or clinical efficacy of standard prophylactic regimes. The effect of prophylaxis may be improved by PK guided regimes. Objectives

To evaluate the efficacy of standard prophylaxis in severe hemophilia A children and to estimate the potential impact of PK guided prophylaxis on FVIII requirements.

Material and Methods: Treatment regime, joints annual bleeding rate (ABRJ) and yearly FVIII consumption were evaluated in children on standard prophylaxis. FVIII pharmacokinetics was investigated and the computer program was employed to model prophylaxis regime to maintain FVIII troughs ≥1%.

Results: Twelve children aged between 2.5 and 16 yrs with a median body weight 38 (range: 14-64) kg, starting prophylaxis at the age of 18 mths (range 10-24 mths) were evaluated. Median (IQR) FVIII dose 27 (21-31) IU/kg was administered 3 (2,8-3) times per week with yearly FVIII consumption of 4386 (3276-4524) IU/kg. Three boys have one target joint, however, the last year median ABRJ in the whole group was 0 (IQR: 0-1; range 1-5). PK investigation showed a clearance of 4.1 (2.96-5.9) mL/kg/h, MRT 10.7 (10.4-14.1) h; Vd 54.0 (38.1-60.0) mL/kg; AUC 650 (541-800) U h/mL, T1/2 10.1 (7.6-10.5) h and time to FVIII trough ≤1% 48 (range 35-76) hrs. FVIII median dose according to PK guided regimen was 30 (26-40) IU/kg, however, in all but one patient a 2 days interval was recommended. Estimated yearly requirement of FVIII was higher (M:5532, IQR 4732-7280 IU/kg) compared to standard prophylaxis ($P < 0.01$). In PK guided prophylaxis suggested time period with FVIII levels <1% was 0-7 hrs/week. Using standard prophylaxis this time was 16-37 hrs/week, yet ABRJ was zero in 8/12 (67%) of patients.

Conclusions: PK guided prophylaxis can ensure the maintenance of FVIII levels above the required minimum. However, when planning this approach, the probability of higher factor requirements must be taken into account. We believe it is advisable to decide on the use of mathematically modeled prophylaxis also according to the patient's bleeding phenotype.

21-RARE BLEEDING DISORDERS

M-FPMED01-003 (233) | Clinical correlation with a multidisciplinary approach facilitates the diagnosis of patients with a suspected inherited platelet disorder using next generation sequencing

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Introduction and Objective: The diagnosis of inherited platelet disorders (IPDs) is challenging and often requires multimodality laboratory evaluation. Next Generation Sequencing (NGS) has allowed lower cost molecular analysis that is more widely accessible and affordable for clinicians. The utility of the test results in clinical practice depends on the interpretation of the sequencing results in light of clinical data. This process is difficult given the low incidence of these disorders and limited expertise outside of reference centers. We report the diagnostic yield of NGS panels using a multidisciplinary approach that includes correlation with history and laboratory findings.

Materials and Methods: 40 consecutive patients were evaluated by our reference laboratory using one of three available IPD panels: thrombocytopenia, platelet function or comprehensive platelet disorder between 7/2017 and 11/2017. Detailed clinical and laboratory information was obtained and used to interpret the variants

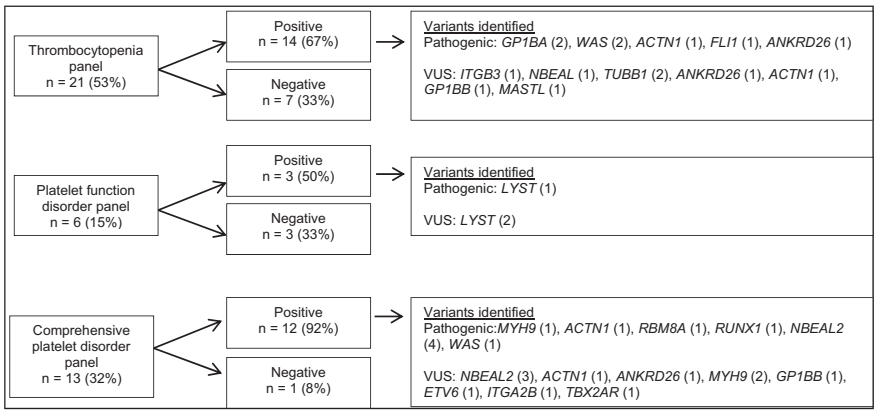


FIGURE 1. Proportion of positive cases (pathogenic and VUS) and type of variants identified according to NGS panel test order in patients with a suspected inherited platelet disorder.

following ACMG standards by a multidisciplinary team (scientists, physicians and genetic counselors).

Results: Tests ordered, and results are presented in Figure 1. 38 variants were identified in 29 patients (73%). 21 (55%) were variants of uncertain significance (VUS) and 17 (45%) were pathogenic. A definitive diagnosis of an IPD was reached in 14 cases (35%). Eight of the identified variants were considered unlikely to explain the clinical phenotype.

Conclusions: Despite a high proportion of cases having variants identified, an IPD was confirmed in only half of the positive cases. A high proportion of the non-diagnostic cases had novel variants that fit the phenotype but require segregation studies and/or functional data to confirm their pathogenicity. In a significant proportion of cases, the identified variant did not correlate with the phenotype and additional testing was recommended. The multidisciplinary approach is successful at providing clinically meaningful and actionable recommendations that enhance the scope of practice of the general practitioner.

T-P-097 (45) | From thrombasthenia to thrombocytopenia, alloimmune thrombocytopenia in newborns of Glanzmann thrombasthenia patients

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Introduction: Glanzmann's thrombasthenia (GT) is a rare bleeding disorder characterized by a defect of glycoprotein IIbIIIa on the platelet membrane. Previous case -reports described bleeding manifestations in newborns to mothers with GT. The objective of this study was to examine the occurrence of thrombocytopenia in newborns of mothers with GT; relation to the presence of maternal antibodies directed against the glycoprotein IIbIIIa was examined.

Materials and Methods: Our tertiary referral center is a comprehensive national hemophilia center. Data base search was conducted for all female GT patients since 1999 to 2017 who underwent pregnancy and delivery. Medical files of the offspring were examined for post-natal course including platelets count and bleeding manifestations.

Results: During the period between January 1999 to October 2017, 6 neonates were born to 3 GT patients at our center (Table 1). Newborns' demographical and clinical data is presented in table 1. Three of the 6 newborns had severe thrombocytopenia –with platelets count under 20,000. Two of the thrombocytopenic newborns were twins of a primigravida GT patient who underwent in vitro fertilization (IVF). This GT patient had a second pregnancy two years later during which she was treated with immunoglobulins. The newborn delivered afterwards had a normal platelet count. The other thrombocytopenic newborn was the second child of a GT woman whose previous newborn did not have thrombocytopenia. All newborns that had thrombocytopenia, were born to GT mother who tested positive for platelets antibodies. All children are alive and well without further complications.

Conclusions: Pregnant GT patients should be examined for the presence anti-platelets antibodies. Should platelets antibodies be detected in the maternal blood treatment with IV immunoglobulins is recommended. As most antibodies are directed against IIBIIIa protocols applied NAIT may be applied. Severely thrombocytopenic newborns of mothers with GT should be treated by platelets transfusion and immunoglobulins.

TABLE 1 Patient demographic and clinical data

Patient	Maternal origin and Genotype	Sex	Gestation Age (weeks)	Birth weight (grams)	Apgar	Platelet Count at birth	Platelet nadir	Newborn treatment	Newborn outcome
Twin 1	Iraqi Jewish Homozygote for ITGB3, 11 bp del	f	37 + 6	2550	8/9	18,000	18,000	Immunoglobulins 2gr/kgplatelets transfusion	Alive and well, thrombocytopenia resolved by day 7
Twin 2		f	37 + 6	2005	9/10	16,000	16,000	Immunoglobulins 2gr/kg1 platelets transfusion	Alive and well, thrombocytopenia resolved by day 5
3		m	38	3530	6/9	282,000	N/A	Mother treated with immunoglobulins during pregnancy	Alive and well
4	Iraqi Jewish Compound heterozygote for ITGB3 11 bp DEL and 11.2Kb del	m	40 + 3	3025	9/10	214,000	N/A	Null	Alive and well
5		f	39 + 3	2945	9/10	53,000	10,000	d-4 platelets transfusion + immunoglobulins 1gr/kgd-6 platelets transfusion + immunoglobulins 1gr/kg	Alive and well-thrombocytopenia resolved by day 9
6	Arab Homozygote ITGA2B, 13-bp del	m	38 + 4	3,605	9/10	234,000	N/A	null	Alive and well

T-P-098 (377) | Recombinant factor VIIa for treatment of patients with Glanzmann thrombasthenia – a thrombin generation-based study

Tamara Levy[1]; Ivan Budnik[2]; Assaf Arie Barg[1]; Nurit Rosenberg[3]; Uri Seligsohn[1]; Gili Kenet[1]; Tami Livnat[1]; Sarina Levy-Mendelovich[1]

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Introduction: Glanzmann thrombasthenia (GT) is a rare bleeding disorder. The disease is caused by the lack or dysfunction of platelet membrane GPIIb/IIIa (integrin αIIbβ3) that normally serves as a fibrinogen and von Willebrand factor receptor and is essential for platelet aggregation. Bleeding episodes in GT patients are most commonly managed with platelet transfusions. However, patients who have developed antiplatelet antibodies or have experienced clinical refractoriness to platelet transfusions are in need of an alternative treatment. Recombinant factor VIIa (rFVIIa) is a common alternative treatment option.

Objective: To evaluate ex vivo the ability of rFVIIa to improve thrombin generation in GT patients in order to tailor individual treatment regimen.

Methods: A total of 22 GT patients were enrolled to the study in a non-bleeding state. Thrombin generation was measured in platelet-rich plasma and initiated by recalcification in the absence or presence of increasing concentrations of rFVIIa (0.7-14.0 μg/ml). Clinical and laboratory follow up of patients was documented.

Results: Among the GT population, 14 patients were homozygous for an 11-bp deletion in β3, 6 were homozygous for a 13-bp deletion in αIIb, one was homozygous for a deletion/insertion in αIIb, and one was homozygous for an 11.2-kb deletion in β3. In the GT patients, mean thrombin peak height and endogenous thrombin potential was reduced by 25% and 26%, respectively, and lag time was prolonged by 53% compared to controls. Although spiking of patients' plasma with rFVIIa induced a statistically significant increase in thrombin generation, an individual response was noted. In most of the patients, a marked improvement of thrombin generation was achieved even with low concentrations of rFVIIa (equivalent to 25-50 μg/kg), whereas in other patients there was a low or even no response. Treatment of patients with rFVIIa during bleeding episodes or as preoperative management induced adequate hemostasis as expected based on thrombin generation results.

Conclusion: These observations suggest that the hemostatic efficacy of rFVIIa in patients with GT is individual and may be predicted and perhaps be monitored by thrombin generation assay. We suggest that low dose of rFVIIa may be sufficient for treatment of active bleeding and as perioperative treatment.

T-P-099 (552) | Comparison of platelet nucleotide assays and lumiaggregometry in the diagnosis of storage pool disorder

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Introduction and Objective: Electron microscopy is the gold standard of investigation for diagnosis of Storage Pool Disorder (SPD) but availability of equipment means it is not easy to routinely use. Currently in the UK the laboratory diagnosis of hereditary platelet SPD is commonly made by quantifying total ATP and ADP content of platelet rich plasma (PRP) and assessing the ratio of ADP to ATP using a luminescent assay. Lumiaggregometry using PRP or whole blood to assess platelet function and the release of ATP from the dense granules during aggregation may also be used to diagnose SPD. In this study we compare the use of PRP Lumiaggregometry to platelet nucleotide assays in the diagnosis of SPD.

Methods: We reviewed results from 108 patients previously diagnosed with SPD registered at our Haemophilia Comprehensive Care Centre between 1994-2017. PRP Light transmission aggregometry, PRP lumiaggregometry and platelet nucleotide assay results were evaluated. PRP Lumiaggregometry reference ranges were evaluated on 20 healthy controls and ATP release with ADP agonist concentration of 10uM ranged from 0.11-1.8 nM and with 2 µg/mL collagen ranged from 0.46-2.5 nM. The manufacturers ATP release reference ranges were 0.5-1.06 nM and 0.74-1.92 nM respectively. For evaluation of our results the manufacturer's reference ranges were chosen as this allowed a larger cohort to be evaluated.

Results: 14/108 (13%) patients had no recorded platelet nucleotide testing and so were excluded from analysis. 83/94 (88%) of the remaining patients had ADP platelet nucleotide levels ≤ 0.22amol/platelet 10^{12}/L (lower limit of reference range) and were included in the final analysis. 39/62 (63%) of the patients had ADP 10 µM ATP release levels ≤0.5 nM and would have been classified as having SPD based on PRP lumiaggregometry alone. 34/61 (56%) of the patients had ATP release levels ≤0.74 nM using collagen agonist at a concentration of 2ug/mL and would have been diagnosed with SPD.

Conclusion: If PRP lumiaggregometry is used alone for diagnosis of SPD, agreed reference ranges need to be established as our data suggests that stand-alone PRP Lumiaggregometry with the manufacturer's reference ranges is not sensitive for diagnosing SPD.

T-P-100 (223) | Determination of effective vitamin K concentrations to reverse the coagulation phenotype in VKCFD1 patients

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Introduction and Objectives: Vitamin K Dependent Coagulation Factor Deficiency type 1 (VKCFD1) is a rare hereditary bleeding disorder caused by mutations in *ɣ-glutamyl carboxylase* (GGCX). GGCX ɣ-carboxylates glutamate residues of vitamin K dependent (VKD) proteins, including blood clotting factors (e.g. FII, FX). This modification is essential for the activity of VKD coagulation factors, thus for maintaining hemostasis. Until now there are 30 GGCX mutations reported to cause VKCFD1. These patients are treated with vitamin K (K) which reverses the coagulation defect in most cases. The aim of this study is to characterize the effect of GGCX mutations on VKD coagulation factors and thus to evaluate the effective dose of K needed for treatment.

Materials and Methods: A *GGCX* knockout (KO) HEK293T cell line was generated by CRISPR/Cas9 technology. cDNAs of *GGCX* together with *F2*, *F10* or *protein C* were cloned into bicistronic vector. KO cells were transfected with GGCX wt and mutants and treated with different K concentrations to determine ɣ-carboxylation of the respective co-transfected clotting factor by ELISA. Statistical analyses were performed using GraphPad Prism 5.01 software to impose dose-response curves in order to identify half maximal effective concentrations (EC50).

Results: Elevated K concentrations increased ɣ-carboxylation of FII, FX, and Protein C similar to wt when co-transfected with GGCX mutations W157R, V255M, or S284P. Other mutations as R83P and H404P revealed increased ɣ-carboxylation of the coagulation factors but did not reach ɣ-carboxylation level as high as detected for wt. Moreover, mutations S300F and R485P did not show recovery at all even at high doses of K.

Conclusions: Our data suggests that patients harboring W157R, V255M or S284P will show a reversible coagulation phenotype where therapy with K will lead to normal coagulation. Increased but subnormal clotting factor activities can be achieved for R83P and H404P by K treatment. Patients with mutation S300F or R485P will never reach physiological coagulation even with high dosages of K. Since our data are in accordance with the reported patient's phenotype, calculated EC50 concentrations will help to determine patient-specific K doses to successfully rescue the coagulation defect in VKCFD1 patients.

T-P-101 (146) | A novel FGG missense mutation possibly leading to fibrinogen storage disease

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Introduction and Objectives: Fibrinogen storage disorders (FSD) are rare disorders characterized by accumulation of mutant fibrinogen in hepatocytes, leading to hypofibrinogenemia and liver injury. We discovered a new mutation at a locus classically associated with FSD. We aimed to describe the clinical and laboratory features of affected individuals, and to compare them with non-affected members of the family.

Materials and Methods: Following ethics board approval, we collected clinical information for all consenting family members. Fibrinogen activity and antigen were evaluated by the Clauss method and immunological assay. Genotyping was done for all participants. Group comparisons used Wilcoxon sum rank, χ^2 or Fisher exact tests, as appropriate.

Results: 29 individuals over four generations participated to the study. 12 were found to be heterozygous for the c.1012T>A (p.Phe338Ile) mutation in exon 8 of the *FGG* gene (see Table 1). Hypofibrinogenemia was found in 11/12. Mean fibrinogen level was 1.11 (antigen) and 1.20 g/L (activity). The oldest subject had repeatedly normal level of fibrinogen, without evidence of inflammatory state. The mean Bleeding Assessment Tool (ISTH-BAT) score was 2.00 (Range: 0-6). No patient sustained a thrombotic event. The index case (No 1) presented persistent elevation of liver enzymes with no obvious cause. Alanine aminotransferase levels were elevated in 4/5 children but normal in all adults. No subject has undergone liver biopsy so far. As in other reported cases of FSD, the phenotype is transmitted in an autosomal dominant manner. No hypofibrinogenemia was found amongst family members without

TABLE 1 Mutation in exon 8 of the FGG gene

No	Age	Sex	BAT	Bleeding symptoms	Thrombosis	Hepatic abnormalities	Fibrinogen antigen (g/L)	Fibrinogen activity (g/L)
1	3.0	M	1	Epistaxis	None	Elevated LFT (ALT up to 572 U/L; most recent ALT 92 U/L)	0.7	<0.6
2	5.2	M	2	Epistaxis, prolonged bleeding from minor wounds	None	Mildly elevated LFT (most recent ALT: 40 U/L)	0.61	0.50
3	6.5	M	0	None	None	Elevated LFT (ALT up to 93 U/L)	0.57	0.60
4	8.9	M	0	None	None	Mildly elevated LFT (most recent ALT: 24 U/L)	0.78	0.60
5	10.4	M	6	Epistaxis, post-procedural bleeding	None	None	0.78	0.60
6	31.1	F	5	Menorrhagia, PPH, post-procedural bleeding	None	None	0.99	1.00
7	34.3	F	2	Ecchymosis, PPH	None	Occasional abdominal pain, normal LFT	0.96	1.00
8	55.2	F	3	PPH	None	None	1.61	1.60
9	57.5	F	5	PPH, post-procedural bleeding	None	None	1.24	1.30
10	62.9	M	0	None	None	None	1.07	0.90
11	66.2	F	0	None	Transient cerebral ischemia	None	1.26	1.50
12	91.8	M	0	None	None	None	3.88	3.00

FSD is associated with constant hypofibrinogenemia. Our observation of variable liver phenotype has yet to be explained.

ALT, alanine aminotransferase, normal values < 19 U/L; BAT, ISTH/SSC-Bleeding Assessment Tool; LFT, liver function tests; PPH, post-partum hemorrhage.

the mutation. Affected members tended to have higher ISTH-BAT scores than unaffected members (2.00 vs 0.56, $P = 0.03$).

Conclusions: This is the largest study describing a family affected by a mutation at a classical locus for FSD. Our study confirms that

T-P-102 (596) | Novel approaches to the diagnosis and classification of anti-FXIII allo-, and autoantibodies

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Introduction and Objectives: Factor XIII (FXIII) consists of two catalytic A subunits and two inhibitory/protective B subunits. Alloantibodies against FXIII subunits rarely develop in inherited FXIII deficiency but make its management very difficult. Acquired FXIII deficiency due to anti-FXIII autoantibodies is also a rare bleeding diathesis usually with severe, sometimes life-threatening soft tissue bleedings. Neutralizing anti-FXIII-A antibodies may interfere with FXIII activation and/or inhibit activated FXIII (FXIIIa), while non-neutralizing antibodies form complex with either of the FXIII subunit and accelerate their clearance. The traditional method for detecting neutralizing antibodies is the mixing study and its semi-quantitative variant, the Bethesda-Nijmegen assay. There is no established method for the diagnosis of non-neutralizing antibodies. Our aim was to introduce new methods in the diagnosis and classification of anti-FXIII antibodies.

Methods: For quantitatively assessing the inhibitory capacity of an antibody we determined the 50% inhibitory concentration (IC50). For the determination of the antibody's binding affinity to FXIII and its subunits surface plasmon resonance measurement was introduced. For targeting the effect of neutralizing antibody a three-step assay system was designed. The cleavage of FXIII-A by thrombin was investigated by Western blotting, the effect on Ca^{2+} induced activation and FXIIIa was investigated by modified FXIII activity assays. The clearance of FXIII was assessed by activity measurement following the administration of FXIII concentrate.

Results: Anti-FXIII-A antibodies from three patients were characterized using the above methods. The IC50 for IgGs varied between 0.05 and 0.34 mg/mL. The antibodies bound with the same high affinity (Ka: in the range of 10^{-8}–10^{-9}) to FXIII-A_2 and FXIII-A_2B_2, but not to FXIII-B_2. The three-step activity assay and the clearance study revealed different types of anti-FXIII-A antibodies: the alloantibody and one autoantibody exerted a combined effect; they inhibited FXIII activation and FXIIIa activity and accelerated the clearance of FXIII. The main effect of one autoantibody was the inhibition of FXIIIa.

Conclusion: Introduction of new methods in assessing anti-FXIII antibodies improved their functional characterization and allowed us to design a new classification, which could contribute to novel therapeutic approaches.

T-P-103 (612) | Retrospective evaluation of phenotype and management of A-Hypo-Fibrinogenemia in a cohort of Italian patients

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Background: A-Hypo-Fibrinogenemia (AF, HF) patients experience hemorrhages or thromboses, and the clinical management can be difficult. Aim of this study is to obtain information on AF/HF clinical phenotype and management.

Methods: This is a spontaneous, retrospective, multicenter national study. Data are collected from clinical records.

Results: Three AF and 12 HF patients have been enrolled (7M, 8F). Median follow up: 61 months (1-616). Median fibrinogen activity, antigen level: 52 mg/dL (0-150), 73 mg/dL (0-140), respectively. Six patients experienced epistaxis, hematomas, ecchymoses, menometrorrhagia, intra-abdominal bleeding, gum bleeding, hemarthrosis, intracranial hemorrhage. Fresh Frozen Plasma (FFP), Fibrinogen Concentrate (FC), cryoprecipitate, whole blood, tranexamic acid was administered in the majority of these events. 2 AF patients are on long term prophylaxis, 1 with FFP, the other with FC. Reasons for prophylaxis are: anti platelet agents and LMWH administration and intracranial hemorrhage. One ischemic stroke, 1 lower limb arterial thrombosis, 1 cerebral sinus thrombosis, 1 aortic thrombosis and contemporary ischemic lesion of 4th toe of right foot, 1 concomitant aortic and inferior vena cava thrombosis occurred: 3 events during FC therapy, 1 during puerperium, 2 without apparent trigger. Heparin, LMWH, antiplatelet agents, fibrinolytic agents, warfarin and fondaparinux were then administered. One gastrectomy, 1 lower limb amputation, 5 gynecological, 1 otorhinolaryngological, 1 plastic surgery and 1 dental extraction were performed in 2AF and 3 HF patients: in AF patients, FC or FFP prophylaxis was always administered during surgery. In HF patients, just tranexamic acid was administered in case of 1 dental extraction. Bleeding was observed after 2 surgeries performed without prophylaxis in 2 HF patients. Eight pregnancies started in 3 HF women. Two spontaneous deliveries (SD) and 2 cesarian sections (CS) were performed; 4 spontaneous

abortions occurred. In 3 cases, FC prophylaxis and in 4 LMWH was administered during pregnancy. One venous thrombosis, 2 hemorrhages, 1 DIC, complicated 4 pregnancies. FC was administered at delivery and LMWH during puerperium, for the 2 CS. No complications at delivery occurred.

Conclusions: AF/severe HF patients experience the worst hemorrhagic/thrombotic events. The need exists to collect more data, to provide useful information to better characterize and manage these rare diseases.

T-P-104 (616) | Retrospective evaluation of phenotype and management of Dysfibrinogenemia and Hypodysfibrinogenemia in a cohort of Italian patients

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Background: Dysfibrinogenemia (DF) and Hypodysfibrinogenemia (HDF) patients (pts) can be asymptomatic, or can experience hemorrhages/thromboses, and the management can be difficult. Aim of this study is to obtain information on DF/HDF clinical phenotype and management.

Methods: This is a spontaneous, retrospective, multicenter national study. Data are collected from clinical records.

Results: Forty-four pts have been enrolled in 4 centers: 36 DF (82%), 8 HDF (18%); 19M, 25F. Median follow-up: 7.2 months (1-203). Median age at diagnosis: 36 years (range 3-81). Median fibrinogen activity/antigen level: 54.5 mg/dL (0-156) and 250 mg/dL (66-380), respectively. Fourteen pts experienced hemorrhages: epistaxis, hematuria (presence of kidney stones), hematomas, ecchymoses, menometrorrhagia, and gastro-intestinal (presence of esophageal varices); no specific therapy was administered. In one DF patient, affected also by Intermediate Thalassemia, a portal venous thrombosis occurred after splenectomy, carried out without replacement therapy and antithrombotic prophylaxis. He was treated for a long period with warfarin, then switched to Low Molecular Weight Heparin (LMWH) without anti-hemorrhagic prophylaxis. He never experienced hemorrhages. Twenty-five years after the first thrombosis, he suffered from an acute myocardial infarction, while he was still on LMWH. After this event, anti-platelet therapy was added to LMWH, without replacement therapy. This patient is also heterozygous for FIIG20210A. Sixty-six minor/major surgeries and dental extractions were performed in 26 pts. In 22/66 (33%) cases, anti-hemorrhagic prophylaxis was administered [Fresh Frozen Plasma in 3, Fibrinogen Concentrate (FC) in 2, Tranexamic Acid in 17]; in 5/66 (7.5%) cases, LMWH was administered; no hemorrhage occurred. Fifteen pregnancies occurred in 10 women. In 1 case, LMWH prophylaxis was administered during pregnancy and in 3 others during puerperium. In 2 cases, FC was administered at time of spontaneous delivery (SD). Nine SD and 6 cesarian sections were performed without complications.

Conclusions: Patients from this case series experienced few hemorrhagic/thrombotic events. The majority was asymptomatic, and the most severe events were related to associated disorders. Nonetheless this study has the potential to collect data from a numerous population of pts who live in the same country, and therefore to provide useful information to better characterize and manage these rare diseases.

T-P-105 (720) | Collaborative crowd advocacy for families with rare diseases for molecular diagnostic services

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Patients with rare factor deficiencies have created forums where they can access knowledgeable providers, educational and diagnostic services not currently available in most hospitals or medical centers across the country. An example of this model of patient empowerment is the Factor VII Retreat organized by Comprehensive Health and Education Services (CHES) held this year in Scottsdale Arizona celebrating their 7th annual conference. In addition to educational updates, they offered molecular evaluation of each patient and all other family members in collaboration with Center for Inherited Blood Disorders (CIBD) and the Hematology Advanced Diagnostic Laboratory (HADL). Factor VII deficiency is a challenging syndrome as the factor activity assays do not always correlate with the bleeding phenotype.

Materials and Methods: During the 2-day FVII Retreat, consent forms, bleeding questionnaires and blood samples were obtained from those in attendance. A total of 154 individuals were evaluated comprising : 58 patients, 48 families with index patients, 41 related siblings or offspring, 48 parents, and 4 grandparents. Factor levels were obtained through each patient's primary physician at the time of diagnosis, and whole gene sequencing was performed at HADL, using their validated Next Generation Sequencing (NGS) clotting protein panel which contains FVII along with 21 additional clotting genes.

Results: Among the 154 individuals sequenced, variants were identified in 55 patients and 67 relatives. Only 3 patients had no Factor VII variants identified. Among all 154 individuals, 48 different variants

were detected in the Factor VII gene. Of those variants, 15 were not listed with the NCBI databank. This data was provided to each primary physician along with any informative variants found in the other 21 genes evaluated.

Conclusion: It is critical to evaluate the patient AND family members to determine which molecular variants are pathogenic in any inherited disorder . In addition, these efforts add critically important information on the function of FVII and the linkages between molecular variants and bleeding phenotype. Synergizing with programs such as CHES, HADL and CIBD is key to find resources for meetings and infrastructure to create these educational opportunities for all patients and families with rare bleeding disorders.

T-P-106 (748) | Genotypical abnormalities in patient with phenotypically confirmed rare bleeding disorders

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Introduction and Objective: Patients with a Rare Bleeding Disorder (RBD) may experience haemorrhages not related to the classical diseases, haemophilia or von Willebrand Disease. In most cases the disease is diagnosed by standard phenotypic approaches in combination with the clinical symptoms. The objective of this study is to confirm the phenotypic based diagnosis with a targeted gene approach.

Materials and Methods: Two hundred eleven patients with hemostatic abnormalities were sequenced with a classical targeted approach by Sanger sequencing or by ion semiconductor next generation sequencing technology (IonTorrent PGM™). All coding regions including intron-exon boundaries were sequenced. Two different classes of hemostatic genes were analysed: procoagulant genes (*F2*, *F5*, *F7*, *F10*, *F11*, *F12*, *F13A1*, *F13B*, *FGA*, *FGB*, *FGG*) and platelet specific genes (*GATA1*, *GFI1B*, *GP1BA*, *ITGA2B*, *ITGB3*, *MYH9*, *NBEAL2*).

Results: Of the 161 patients tested for abnormalities in the procoagulant genes, 41 carried a (likely) pathogenic mutation, and 13 carried variants of unknown pathogenicity (VUS). For the more heterogeneous platelet abnormalities only 3 out of 50 patients had (likely) pathogenic mutations and 4 patients a VUS.

Conclusions: The patients' phenotype was an important parameter for targeted single gene approach to detect genotypic abnormalities in RBD patients. The overall yield to detect pathogenic mutations was 28%. The targeted single gene approach resulted in a yield of 14% in case of abnormalities in primary hemostasis. The success rate in secondary haemostatic abnormalities was higher (32%) but still relatively low. To increase the yield, we recently implemented whole exome sequencing (WES) as a diagnostic test. WES allows analysis of a large panel of genes in one single test making it a time and cost efficient approach. The hemostatic gene panel we designed contains 132 genes at this moment proven to be involved in hemostatic disorders including genes involved in primary hemostasis (platelet and vessel wall), secondary hemostasis and fibrinolysis. If the diagnostic panel reveals a negative result, exome wide analysis will be performed.

T-P-120 (502) | Treatment of acute bleeding in adolescent patients with congenital afibrinogenemia: Pharmacokinetics and efficacy of a new fibrinogen concentrate

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Introduction and Objectives: Individuals with congenital afibrinogenemia may experience severe/frequent bleeding episodes (BE). Human fibrinogen concentrate (HFC) can arrest bleeding by correcting the hemostatic defect. Objectives were to study the pharmacokinetics (PK) and efficacy of a new highly purified, double virus-inactivated HFC (Octapharma) in adolescents.

Materials and Methods: Data were analyzed from two multinational, prospective, open-label studies. FORMA-01 studied PK of new HFC vs. comparator (CSL Behring), surrogate efficacy (thromboelastometric maximum clot firmness [MCF] in plasma), and safety, after single infusion of 70 mg/kg. FORMA-02 assessed hemostatic efficacy on a 4-point objective scale, MCF, and safety, for on-demand treatment of BEs.

Results: Data were available for 8 patients with afibrinogenemia aged 12-17 years. PK data from adolescents in FORMA-01 for new HFC vs. comparator are shown in Table 1; in adults, AUC_{norm} was also larger and clearance slower for new HFC vs. comparator (both $P = 0.0027$). One hour after infusion of new HFC or comparator, mean±SD MCF ($n = 6$) increased from 0 mm to 9.0 ± 2.0 and 8.8 ± 2.6 mm, respectively (9.9 ± 3.3 and 10.4 ± 4.9 mm in adults). In FORMA-02, two adolescent patients received new HFC dosed individually for treatment of BEs. Mean MCF increased by 5.5 ± 0.7 mm 1 h after first infusion (6.6 ± 3.0 mm in adults). Treatment efficacy was rated excellent in both patients. There were no related serious adverse events, severe allergic or hypersensitivity reactions, or thromboembolic events, and no anti-fibrinogen antibodies were detected.

Conclusions: Data from two prospective studies demonstrate the favorable PK, safety, and efficacy profile of new HFC in adolescents with congenital fibrinogen deficiency. PK parameters were broadly comparable vs. comparator HFC in this small group of adolescents, and there were no marked differences with new HFC in adolescents vs. adults. MCF increased significantly after infusion of new HFC, and hemostatic efficacy was rated excellent. No safety concerns were identified.

TABLE 1 Pharmacokinetic parameters of new HFC and comparator in adolescent patients with afibrinogenemia (n = 5*) in the FORMA-01 study. Data is shown as mean ± SD.

	New HFC	Comparator
AUC_{norm} (h·kg·g/L/mg)	1.57 ± 0.44	1.29 ± 0.67
Clearance (mL/h/kg)	0.68 ± 0.18	0.91 ± 0.33
C_{max} (g/L)	1.53 ± 0.32	1.15 ± 0.29
Incremental *in vivo* recovery (mg/dL/(mg/kg))	1.95 ± 0.41	1.52 ± 0.21
Mean residence time (h)	100.7 ± 20.1	94.8 ± 18.0
$T_{½}$ (h)	72.8 ± 16.5	64.8 ± 11.9
T_{max} (h)	2.61 ± 1.37	1.70 ± 2.68

*One subject was excluded from the PK analysis due to a protocol deviation.

AUC_{norm}, area under the curve divided by dose per kilogram of body weight; C_{max}, maximum plasma concentration; HFC, human fibrinogen concentrate; SD, standard deviation; $T_{½}$, half-life; T_{max}, time taken to reach the maximum concentration.

T-P-121 (140) | Effect of antithrombin lowering on thrombin generation in rare bleeding disorder patient plasma

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Introduction and Objectives: Analogous to hemophilia A or B, many rare bleeding disorders (RBDs) are characterized by ineffective clot formation due to insufficient thrombin generation arising from deficiencies in clotting factors. In phase 1/2 clinical trials, fitusiran, an investigational RNAi therapeutic targeting antithrombin (AT), has demonstrated dose dependent AT lowering, improved thrombin generation and decreased bleeding frequency with monthly dosing in patients with hemophilia A or B with and without inhibitors. By improving thrombin generation, fitusiran may also be applicable for the treatment of some RBDs. Here we investigated the effect of AT lowering on thrombin generation in RBD patient plasma.

Material and Methods: AT activity was inhibited by adding an anti-AT antibody to platelet poor plasma from patients with severe congenital deficiencies of FV, FVII or FX. Thrombin generation potential was evaluated by Calibrated Automated Thrombogram (CAT) with 1 or 5 pM TF and 4 μM phospholipid. CAT was also performed for different levels of replacement factor added to deficient plasma specimen.

Results: In severely deficient (<1% factor activity), FV, FVII or FX plasma, there was no detectable thrombin generation by CAT assay. AT activity lowering (to ~20% of baseline) alone provided negligible thrombin generation improvement in plasma with severe FV, FVII or FX deficiency. However, the combination of AT activity lowering together with replacement of the deficient factor to 1 to 10% of normal boosted thrombin generation significantly, often into the normal range.

Conclusions: The ex vivo thrombin generation in RBD patient plasmas support the hypothesis that lowering AT can improve thrombin generation in FV, FVII and FX deficiency. Preliminary results suggest that a minimum amount of FV, FVII or FX activity may be necessary for this response. These data provide preliminary evidence to support the potential application of fitusiran in certain RBDs.

T-P-122 (172) | Rare bleeding disorders; Improvement on the amount of collected data as a result of increasing awareness

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Introduction and Objective: The rare bleeding disorders (RBDs) are usually transmitted in an autosomal recessive manner and have a diverse clinical presentation, varying bleeding scores and bleeding episodes. The precise incidence of RBDs in Turkey is not clear due to lack of a national registration system. Here, we report the improvement on the amount of data at Ege Adult Haemophilia Centre that has established 4 years ago.

Materials and Methods: We retrospectively collected data of adult patients with known RBDs, registered in Ege Adult Hemophilia Centre between 2014-2017.

Results: The distribution of the factor deficiencies according to the years was summarized in table 1. Among the current number of the RBDs (n = 84), FVII deficiency is the most common factor deficiency and mucocutaneous bleeding is the most common symptom. The median age was 39.3 years (mean 31; range: 19-77 years) and number of female/male patients were 38/46 respectively. Thirty nine (46%) patients were asymptomatic and diagnosed by preoperative/routine laboratory analysis or family histories. Prolonged bleeding history after dental or surgical operations was seen in 25 patients and circumcision in 15 patients. Intracranial haemorrhage was seen in 3 patients with FXIII deficiency and also had a history of umbilical cord bleeding. Five patients; two have FVII deficiency, one has FXIII deficiency and one has vit-K dependent factor deficiency were on prophylactic factor replacement treatment by rFVIIa, FXIII concentrate and PCC respectively.

Conclusion: Rarity of RBDs limits in-depth analysis of their clinical and laboratory features and limits their knowledge. Therefore, the establishment of new treatment centres is mandatory to improve the amount of collected data in order to strengthen the power of the analysis. Multinational multicentre data collection for long-term postregistration surveillance remains an important milestone in the study of RBDs.

TABLE 1 Number of distribution of the factor deficiencies according to the years

	2014	2015	2016	2017
Total number of patients	25	38	50	84
FV deficiency	1	3	4	5
FVII deficiency	13	17	21	36
FX deficiency	1	2	2	4
FXI deficiency	5	7	9	16
FXII deficiency	1	2	3	5
FXIII deficiency	1	2	3	4
Combined FV-VIII deficiency	-	-	-	2
Vit.K-dep. Factors deficiency	-	1	2	5
Afib./Dysfib.	3	4	6	7

22-VWD

M-FPMED02-001 (503) | A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with VWF/FVIII concentrates in patients with severe inherited von Willebrand disease and frequent bleeding episodes

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Introduction and Objective: In the last 20 years lots of important progresses have been done for treatment of von Willebrand Disease (VWD). However, prospective randomized clinical trials specifically designed to evaluate the benefits of prophylaxis with VWF/FVIII concentrates are lacking. The aim of this study was to assess the efficacy of secondary long-term prophylaxis with VWF/FVIII in the prevention of bleeding in severe VWD patients compared to on-demand treatment.

Material and Methods: In a 12-month, phase III, open-label study, patients (aged ≥6 years) with severe inherited VWD with frequent bleedings were randomized to receive prophylactic or on-demand treatment with VWF/FVIII (Fanhdi®/Alphanate®, Grifols) according to current licensing status for use in VWD in each participating country. The primary efficacy endpoint was the proportion of patients who did not present any spontaneous bleeding episode during the study period. Secondary efficacy endpoints included: incidence rate and mean duration of bleedings, interval between randomization and the first bleeding, the mean number of infusions and the mean doses of VWF/FVIII per bleeding. Safety endpoints included monitoring adverse events (AEs) and thrombotic events.

Results: Twenty-two patients were screened and 19 were randomized (9 on-demand, 10 prophylaxis). Twelve patients (7 on-demand, 5 prophylaxis) completed the study. All on-demand patients had VWD type 2 or 3 vs. 70% of prophylaxis patients. All on-demand patients and 60% prophylaxis patients experienced bleedings during the study. The number of bleeding episodes was significantly lower in prophylaxis group (n = 32 vs. n = 172; P < 0.0001), although a single on-demand patient experienced 112 episodes. The risk of bleeding was lower in the prophylaxis group (relative AR estimate: −0.667 [95%CI: −2.374, −0.107; P < 0.001]). Epistaxis was more frequent in on-demand (n = 52 vs. n = 15) while gastrointestinal bleeding was more frequent in prophylaxis (n = 13 vs. n = 1) although a single prophylaxis patient experienced 80% of the episodes. All AEs resolved; none of them was considered to be due to study medication.

Conclusions: The randomized clinical study, even with a small sample size and its associated heterogeneity in the baseline characteristics of the patients, confirmed a low number of bleeding episodes in patients on VWF/FVIII prophylaxis compared to those on on-demand treatment.

Disclosures: FP received honoraria or consultation fees from Kedrion Biopharma, Octapharma. Speaker fee for participating at educational meetings organized by Ablynx, Shire; member of Ablynx and F. Hoffmann-La Roche Advisory Board. ABF has been involved in advisory boards of Baxalta-Shire, CSL-Behring, Grifols, Kedrion, LFB, and Octapharma with honoraria related to VWD. VJY has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Shire, Bayer, CSL-Behring, Grifols, Novo Nordisk, Sobi, Octapharma and Pfizer. GC received research funding (directly to institution from Pfizer, CSL Behring); membership on an entity's board of directors, speakers bureau, or its advisory committee (CSL Behring, Shire, Bayer, Sobi, Novo Nordisk, Kedrion, Genzyme, Pfizer). The other authors declare no conflicts of interest.

W-FPYR-004 (530) | Impaired thrombus formation of von Willebrand Disease under high shear flow condition is improved by Factor VIIIa mimetic bispecific antibody (emicizumab)

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Background: Von Willebrand Disease (VWD) is the most prevalent bleeding disorder characterized by qualitative or quantitative defect of VWF which mediates platelet adhesion and aggregation under high shear. Additionally, reduction of FVIII observed in VWD could be associated with impaired thrombus formation under high shear. We hypothesized that the bispecific antibody (emicizumab) which substitutes for activated FVIII (FVIIIa) can be effective for VWD.

Aims: To analyze the hemostatic effect of emicizumab on VWD patients using flow chamber system.

Methods: Whole blood obtained from VWD patients (mild (VWF:RCo>10%) type1 (n = 6), severe (VWF:RCo<10%) type 1 (n = 3), 2A (n = 6), 2N (n = 6) and 3 (n = 4)) was perfused into the collagen-coated flow chamber with or without emicizumab under high shear ($2500s^{-1}$). Formed thrombus was immunostained and analyzed with confocal laser scanning microscopy. Relative increase of thrombus with emicizumab was calculated as improvement ratio. 100% and 0% of improvement ratio was set to thrombus formed by the addition of FVIII/VWF and PBS, respectively.

Results: Surface coverage (SC) and thrombus height (TH) was decreased in VWD (SC:9.0 ± 9.2%, TH:0.96 ± 0.97 μm) compared to normal (SC:32.7 ± 5.5%, TH: 3.7 ± 0.98 μm). SC was correlated with TH in VWD (r^2=0.83) and, therefore, thrombus size of VWD can be estimated either by SC or TH. Addition of FVIII barely improved SC and TH in all types except type 2N. By contrast, emicizumab improved thrombus formation in all types. Improvement ratio of SC was better in mild type 1 (56.4 ± 35.8%), type 2A (47.8 ± 42.5%) and 2N (54.7 ± 26.6%) than in severe type 1 (24.8 ± 13.4%) and type 3 (18.1 ± 15.8%). Improvement ratio of TH was better in type 2N (39.6 ± 23.9%) than in mild type 1 (23.8 ± 14.0%), 2A (26.8 ± 18.3%), severe type 1 (16.8 ± 9.7%) and 3 (16.8 ± 14.1%). The larger the non-spiked SC, the better the improvement of SC by emicizumab in all types. Furthermore, the larger the non-spiked SC, the better the improvement of TH by emicizumab in mild type 1 and 2N. It is speculated that emicizumab works supportively in the presence of minimum thrombus under high shear.

Conclusion(s): Emicizumab improves impaired thrombus formation of VWD even under high shear and, therefore, could be used as a novel therapeutics for VWD.

Keywords: von Willebrand disease1, shear stress2, emicizumab3, von Willebrand factor4 H.Y. and Y.S.

Name of organization: Chugai Pharmaceutical Co., Ltd. Type of relationship: Receipt of grants/research support. T.K. and K.H. :

Name of organization: Chugai Pharmaceutical Co., Ltd. Type of relationship: Patents and Employment.

M.S.: Name of organization: Chugai Pharmaceutical Co., Ltd. Type of relationship: Receipt of grants/research support, Receipt of honoraria or consultation fees, Membership on an entity's Board of Directors or advisory committees and Consultancy Includes expert testimony.

Name of organization: Roche, Type of relationship: Receipt of honoraria or consultation fees, Membership on an entity's Board of Directors or advisory committees and Consultancy Includes expert testimony.

K.N.: Name of organization: Chugai Pharmaceutical Co., Ltd. Type of relationship: Receipt of grants/research support, Receipt of honoraria or consultation fees and Membership on an entity's Board of Directors or advisory committees.

Name of organization: Roche, Type of relationship: Receipt of honoraria or consultation fees, Membership on an entity's Board of Directors or advisory committees.

W-MP-63 (749) | Evaluation of the effect on endogenous factor VIII activity (FVIII:C) after recombinant von Willebrand factor (rVWF) administration during the elective surgery study in patients with severe von Willebrand disease (VWD)

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Introduction and Objective: rVWF was well tolerated and has demonstrated on-demand and surgical hemostatic efficacy in patients with severe VWD. We report data from the elective surgery study (NCT02283268) to demonstrate the rapid rise (mean rate, 7.7 IU/dL per hour [range: 1.0-17.2]) and stabilization of endogenous FVIII upon rVWF administration alone.

Materials and Methods: Patients with severe VWD received rVWF 40-60 IU/kg VWF:RCo intravenously 12-24 hours before surgery to allow endogenous FVIII:C to increase to ≥30 IU/dL (minor/oral surgery) or ≥60 IU/dL (major surgery) within 3 hours before surgery. If levels were not achieved, rVWF was to be coadministered

TABLE 1 Patient-Level Data For Those Who Received rVWF+rFVIII

	FVIII:C at Screening (IU/dL)	12-24 h rVWF Dose (IU/kg)	FVIII:C Within 3 h Before Surgery (IU/dL)	1 h Pre-op rVWF/rFVIII Dose* (IU/kg)	Total Post-op rVWF/rFVIII Dose (IU/kg)
Major surgery					
Total hip replacement	3	57.1	88	32.6/14.5	244.7/NA
Molar extraction	4	51.4	107	50.8/22.8	237.1/60.7[†]
Prosthesis left ankle	1	47.2	36	82.7/42.3	236.2/NA
Minor surgery					
Radioisotope synovectomy	2[‡]	58.5	55	44.5/NA	42.8/17.4
Colonoscopy	21	59.9	99	34.2/NA	NA/NA
Nasopharyngoscopy-laryngoscopy	2	55.8	130	8.0/NA	NA/NA
Oral surgery					
Tooth extraction[§]	13	36.1	62	18.1/NA	36.1/NA

NA, not applicable. *Dosing occurred within 1-2 h before surgery. [†]Patient received a total of 6 doses (7.6 IU/kg x 4, 15.2 IU/kg x 2). [‡]Two screening assessments: first result of 29 IU/dL (inadequate wash-out period); second result of 2 IU/dL. [§]Only patient to receive intraoperative dosing (18.1 IU/kg rVWF + 8.1 IU/kg rFVIII).

with rFVIII within 1-2 hours before surgery; if levels were achieved, rVWF was to be administered alone. Patients were monitored for 14 days postsurgery.

Results: All 15 patients had overall/intraoperative hemostatic efficacy ratings of excellent or good and most rVWF infusions (93/104) were administered alone. Five patients received 11 concomitant rVWF+rFVIII infusions. Three received a coadministration 1 hour before major surgery (total hip replacement, molar extraction, prosthesis left ankle), although 2 met the protocol-defined trough FVIII:C (table). The patient undergoing molar extraction also received 6 coadministrations postoperatively (FVIII:C, 110-152 IU/dL in 5 cases; 23 IU/dL in 1 case). One patient received a coadministration intraoperatively for tooth extraction (FVIII:C, 72 IU/dL). Lastly, 1 patient received a coadministration postoperatively for radioisotope synovectomy (FVIII:C, 73 IU/dL). This patient also received a postoperative dose of rVWF alone. Notably, 2 patients received no additional rVWF postoperatively.

Table. Patient-Level Data For Those Who Received rVWF+rFVIII

Conclusions: Most rVWF infusions (90%) were administered alone. Five patients received 11 infusions of rVWF+rFVIII, but only 2 of these infusions occurred when FVIII:C was below the protocol-defined trough level. rVWF alone substantially increases endogenous FVIII:C levels and may be sufficient during major surgeries in patients with adequate baseline FVIII:C, thus offering greater treatment flexibility.

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[Correction added on 31 October 2018, after first online publication: Affiliations 3 and 11 of this abstract have been corrected in this current version.]

M-P-011 (383) | Pigs with Von Willebrand disease show altered expression of VEGF and VEGFR-2 in the gastrointestinal tract

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Introduction: Symptoms of patients affected by Von Willebrand disease (VWD) predominantly arise from reduced blood coagulation. Additionally, up to 20% of those patients show gastrointestinal (GI) bleeding from angiodysplastic lesions. Angiodysplasia is also described in other organs e.g. skin or nailfold, while the pathogenesis of those aberrations still remains elusive. In this study, distribution and expression of VEGF and its receptor VEGFR-2 were investigated in the GI tract of pigs affected by VWD.

Material and Methods: The colony of pigs examined segregates for a natural mutation of the Von Willebrand factor (VWF) gene causal for VWD type 3. We harvested tissue samples of the small intestine (SI) and caecum of two heterozygous carriers (HC), one homozygous affected animal (HA) and two wildtype animals (WT). Phenotype and

genotype were confirmed by blood VWF levels (VWF:Ag) and molecular genetic analysis. Distribution of the proteins was investigated by immunohistochemistry (IHC) and expression of the corresponding genes was compared by qPCR using two endothelial specific housekeepers *PROCR* and *CD31*.

Results: VWF:Ag for the HA was <3%, those for HC were 20% and 34%, respectively, and thus comparable to VWD type 1. The VWF:Ag of both WT was >100%. The expression of *VEGF* was increased in the SI (361%) and the caecum (320%) of the HA, respectively. Similar observations were made for *VEGFR2* in both, SI (172%) and caecum (465%). The HC showed increased expression of *VEGF* in the SI (130%) and of *VEGFR2* in the caecum (218%), but decreased expression of *VEGFR2* in the SI (75%) and of *VEGF* in the caecum (31%). Those observations were partially reflected by IHC stainings, especially concerning blood vessels.

Conclusions: Our results strongly indicate an influence of VWF on *VEGF* and *VEGFR2* expression in the GI tract. In the case of complete absence of VWF, we observed increased expression of both genes. For moderately reduced VWF:Ag varying effects occurred. This impact on these highly potent regulators of angiogenesis might play an important role in the pathogenesis of angiodysplasia. Our pig colony seems to be a suitable *in vivo* model to further investigate the pathogenesis of VWD.

W-P-64 (410) | Diagnosis of von Willebrand disease in population of Western Mexico

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Introduction and Objectives: von Willebrand disease (VWD) is highly sub-diagnosed in Mexico because the required tests are complex and mostly unavailable across the country. This study aims to diagnose VWD patients from Western Mexico by screening, confirmatory tests and only in VWD 2A and 2B patients by Sanger sequencing.

Materials and methods: 215 unrelated were recruited and signed the informed consent. They were referred because of mucocutaneous bleeding. Hematologists made a general physical examination and applied a standardized clinical questionnaire to assess the bleeding tendency (Tosseto, 2006). Plasma samples were obtained for screening (CBC, blood group, PT, aPTT, fibrinogen, Ivy BT), initial confirmation tests (VWF:Ag, VWF:RCo, FVIII:C) and VWF multimers analysis. DNA samples were obtained from peripheral blood for sequencing exon 28 of the *VWF* gene by the Sanger method and ulterior analysis by NGS.

Results: Patients' age ranged from 1 to 74 years; among them, 63% had affected relatives and 37% sporadic cases. Out of 215 index patients (140 pediatric, 75 adults); 166 (77%) had O blood group compared to the rate of 63% in general Mexican population ($P = 0.024$). 33% of patients were classified as VWD type 1 (VWD1): 30% mild VWD1 (20-50% VWF:Ag) and 3% severe VWD1 (<20% VWF:Ag). 1% were VWD type 3 and 20% VWD type 2 (23% 2A, 21% 2B, 7% 2N and 49% showed a complete VWF multimers pattern). Three VWD 2B patients were heterozygous for mutations detected by Sanger sequencing: R1308C (two cases) and V1316M. The remaining patients were diagnosed as thrombocytopenia (9%), thrombocytopathy (8%), coagulopathy (11%) or having hemorrhagic symptoms but normal tests (26%). 13 patients were excluded.

Conclusions: The excess of VWD patients with O blood group confirms a higher bleeding risk related to this hemotype that is predominant in Mexican population. A sizeable proportion of patients must be screened by complementary tests to verify their VWD subtyping. Genetic analysis by Sanger is very useful in the diagnosis of specific-domain variants as VWD 2B and 2A, while exomic sequencing will allow to classify the rest of cases and VWF interactions with their physiological ligands.

W-P-65 (630) | Data collected at USA National Type 3 Von Willebrand Disease Conference

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Introduction and Objectives: The use of an audience response system (ARS) is an effective way to collect data for future use. The first USA National Type 3 Von Willebrand Disease (VWD) Conference was held in Florida, USA, May 2017. It is estimated there are approximately four hundred Type 3 VWD patients in the United States with approximately 250 identified within the ATHN dataset. Eighty Type 3 VWD patients representing over 30 states in the U.S. attended the Conference, with ages ranging from 1-75 years old.

Materials and Methods: Thirty-two ARS questions were introduced to the audience using handheld keypad units (clickers). The clickers were distributed to Type 3 VWD patients 16 years or older or a caregiver responding for a patient under 16. A clicker distribution method was developed to ensure anonymity and continuity of individual patient response. First, three questions established demographics (age, gender, HTC usage) to link to the unique clickers. The remaining questions addressed topics such as prophylaxis, inhibitors, and bleeding/family history. Additionally, patients were queried about the Conference, engagement with medical care teams and planned future actions.

Results: Active participation ranged between 56 to 65 responses per question. Of the respondents, thirty-five percent were male and eighty-nine percent stated they received their care at a Hemophilia Treatment Center (HTC). Thirty-eight percent of the respondents

represented patients under the age of eighteen. Eighty-three percent of the respondents were the first person diagnosed with any type of VWD in their family. Joint issues were the most challenging symptom for forty-two percent of the respondents. Thirty-four percent reported adherence to prophylaxis while twenty-seven percent stated prophylaxis was never discussed/recommended to them. One hundred percent felt safe at the conference and that their privacy was respected. Ninety-eight percent would be both willing to attend the conference again next year and participate in research if this conference was repeated.

Conclusions: The high response rate indicated the attendees' willingness to participate in this conference's research. Patients would like to participate in future Type 3 VWD conferences and research. E.K. provides educational consulting and programs for Bayer and National Hemophilia Foundation.

W-P-66 (651) | The management of menorrhagia in Von Willebrand Disease: Single center experience

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Introduction and Objectives: Menorrhagia is a common clinical problem in Von Willebrand Disease (VWD) and management of this condition has traditionally been the domain of the hematologists. Women with VWD frequently have menorrhagia and report impaired quality of life and increased absence from school or work during menstruation. In this report we evaluated the ratio of menorrhagia and management of this condition in VWD.

Materials and Methods: Our center is among the biggest centers in Turkey which serves all regions in Country. There are 165 patients with VWD registered to our center (91 females, 74 males; mean age: 16.1 years; range: 1.6-28.6 years). 116 of these patients are type-1 (70%), 30 type-2 (18%) and 19 type-3 (12%). Among 91 female VWD patients, 66 are type-1 (73%), 14 are type-2 (15%) and 11 are type-3 (12%). Bleeding severity was measured using the Tosetto Bleeding Score.

Results: Among the 91 female patients, 64 have menstrual cycles (70%). 35 of 64 patients have menorrhagia (55%). Of these patients, 24 are type-1 (69%), 6 are type-2 (17%) and 5 are type-3 (14%). When the ratio of menorrhagia was evaluated according to VWD types, it was 49% in type-1 (24/49), 60% in type-2 (6/10) and 100% in type-3 (5/5).

Based on the severity of menorrhagia, most frequent treatment options were tranexamic acid, desmopressin and VWF-containing factor VIII concentrates. Additionally, oral contraceptives were used in 11 girls (17%) with menstrual cycle disorders. Treatment modalities according to VWD types are indicated in the table below.

Conclusion: Women with VWD frequently have menorrhagia in need of treatment. Severe bleeding episodes can be controlled with VWF concentrates; depending on the VWD type, mild bleeding episodes usually respond to treatment with desmopressin. Other treatments that can reduce symptoms include fibrinolytic inhibitors and hormones for menorrhagia. In conclusion, the successful management of VWD with menorrhagia requires the combined expertise of gynecologist and hematologist, most likely in specialized centers such as hemophilia treatment centers.

TABLE 1 Treatment of menorrhagia in VWD.

	Treatment		
VWD	Tranexamic acid (+oral contraceptive)	Desmopressin + tranexamic acid (+oral contraceptive)	VWF concentrates + tranexamic acid (+oral contraceptive)
Type 1	11 (5)	11 (2)	2 (1)
Type 2	–	4 (1)	2 (1)
Type 3	–	–	5 (1)

W-P-67 (754) | Genotypic analysis of patients with von Willebrand Disease

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Introduction and Objective: Von Willebrand disease (vWD) is a bleeding disorder caused by inherited defects in the concentration, structure or function of Von Willebrand Factor (vWF). The classification of vWD remains difficult, cumbersome, expensive and not always conclusive . The various vWD types warrants specific treatment, leading to the requirement for better diagnostic measurements. The objective is to improve vWD classification by performing VWF direct sequencing for diagnostic purposes.

Materials and Methods: Targeted gene analysis was performed on 596 patients suspected to have vWD, either by classical Sanger sequencing or by ion semiconductor next generation sequencing technology (IonTorrent PGM™). All coding regions including intron-exon boundaries were sequenced. Large deletions and duplications in the *VWF* gene were detected by MLPA.

Results: 596 patients were analysed and 368 patients had a *VWF* genetic abnormality. The mutations found were 13 nonsense, 342 missense and 16 splice-site mutations, 27 small deletions, 8 duplications, 2 deletions-insertions and 17 large deletions detected by MLPA. In 228 patients no mutations were detected in the *VWF* gene. Of all mutations detected 366 were reported previously and 59 were novel. The novel mutations found were 3 nonsense, 34 missense and

5 splice-site mutations, 4 duplications, 12 small deletions and 1 large deletion detected by MLPA. 93 patients were carrying the D1472H polymorphism affecting the von Willebrand Factor Ristocetin cofactor activity.

Conclusions: Our systematic targeted genotypic approach resulted in 62% of the cases in vWD confirmation. Furthermore, we were able to confirm in 90% of the cases a specific vWD classification. Since the overall yield to detect (likely) pathogenic mutations was only approximately 60% with the conventional targeted gene analysis approach and bleeding scores do not always match, whole exome sequencing (WES) was recently implemented. The first results showed combinations of VWF genetic abnormalities with autosomal recessive abnormalities in genes involved in other primary hemostasis disorders like Hermansky-Pudlak Syndrome. More results are expected to become available within 6 months and will be presented.

W-P-74 (535) | An automated chemiluminescent assay is able to detect VWF collagen binding variants

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Introduction and Objectives: von Willebrand factor (VWF) collagen binding (CB) variants located within the A3 domain of VWF are commonly diagnosed by the measurement of VWF binding to type I and/or type III collagens using Enzyme Linked Immunosorbent Assays (ELISAs). More recently VWF A1 domain CB variants have been studied using type IV and VI VWF CB ELISAs. Recently a type III VWF:CB assay has been fully automated using chemiluminescent technology. The objective of this study was to determine whether patients with VWF CB variants in the A3 domain could be detected by an automated chemiluminescent assay.

Materials and Methods: Plasma samples from four patients that had been previously diagnosed with VWF collagen binding defects (S1731T, S1783A and M1761K) by an in-house VWF:CB ELISA using type III human placenta collagen (Southern Biotech, USA) were evaluated. All samples were previously assayed using the following laboratory assays: one stage clotting (C) factor (F) VIII assay on an ACL TOP (Instrumentation Laboratory (IL), USA) an in-house VWF:Ag ELISA, a lyophilised platelet based VWF:RCo assay on a CS2100i (Sysmex, Japan) and by an SDS agarose gel VWF multimer assay (all samples had a normal VWF multimer pattern). All samples were then tested using the HemosIL® VWF:CB chemiluminescent assay that contains type III collagen-triple-helical peptides coated to magnetic particles on an ACL AcuStar (both IL, USA).

Results: All the patient samples with previously diagnosed VWF:CB variants showed reduced values in the VWF:CB chemiluminescent assay (Table 1).

Conclusion: We have shown that the HemosIL® AcuStar VWF:CB activity chemiluminescent assay is a suitable assay for the detection of VWF collagen binding variants found in the A3 domain of *VWF*.

23-ADHERENCE

M-MP-117 (479) | A Canadian perspective: Use of the self-report VERITAS-Pro to document adherence levels in individuals with hemophilia on prophylaxis

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Introduction and Objective: Adherence to prescribed treatment regimens is an important and much debated area of hemophilia care (Khair, 2014). In Canada, current measurements of patient adherence to prophylaxis treatments include a variety of informal strategies such as reviewing patient infusion records, assessing variance between prescribed and utilized factor and/ or discussing patient treatment decision making. The focus of this nurse led study was to utilize a validated tool for adherence, the VERITAS-Pro (Duncan et. al, 2010) to document levels of adherence and supplement this data with an infusion record rating method as per Ho et al (2014) in a sample of Canadian patients.

TABLE 1 VWF:CB activity

ID	FVIII:C (IU/dL)	VWF:Ag Assay (IU/dL)	VWF:RCo Assay (IU/dL)	VWF:CB (Type III) ELISA(IU/dL)	VWF:CB (Type I) ELISA (IU/dL)	HemosIL® AcuStar VWF:CB Activity (IU/dL)	Variant
1	123	78	72	13	22	6.1	Het.c.5347 T>G, p.S1783A
2	126	122	112	24	ND	8.2	Het.c.5282T>A, p.M1761K
3	63	43	44	40	18	18.1	Het.c. 5441 T>A, p.S1731T
4	63	59	55	49	39	19.4	Het.c. 5441 T>A, p.S1731T

Materials and Methods: Individuals with severe or moderate Hemophilia A or B, age 14-44, currently on prescribed prophylaxis were approached for inclusion in the study. Those consenting to participate completed the VERITAS-Pro and a general adherence rating scale. Clinicians involved in that patient's care, also completed the same general adherence scale. Where available infusion records for a 24-week period prior to enrollment were extracted and adherence rated as per Ho, et al 2014.

Results: 61 subjects were recruited from eight hemophilia treatment centers across Canada. Most participants were diagnosed with hemophilia A (51 of 61) subjects and 5 participants had moderate disease (2 FIX; 3 FVIII). The total VERITAS-Pro score mean was 43 (range 24-70). Subscale mean scores ranged from 4.5 to 9 demonstrating participants overall reported greatest adherence in communicating and the least in dosing. Variance in general adherence between patient self-report and provider ratings will be reported. Adherence to prescribed dose and frequency will be reported for those participants with detailed infusion records (n = 44).

Conclusions: This multicenter, nurse-led project documents adherence to prescribed prophylaxis regimens in a sample of Canadian individuals with Hemophilia A or B. This evaluation was done utilizing the VERITAS-Pro, a patient and clinician general adherence tool and in a subset of patients' infusion record surveillance assessing for both dosing and frequency concordance with prescription.

M-P-118 (77) | Adherence rate among severe hemophilia patients in a Brazilian city

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Introduction and Objective: Although the prophylactic treatment (prophylaxis) in hemophiliac children has been shown to prevent repeated joint bleeding, the attention of the multi professional team (MT) should be focused on the treatment adherence. This study's aim was to evaluate the adherence rate of severe hemophilia patients to prophylaxis.

Materials and Methods: We evaluated 103 severe hemophilia A and B patients in prophylaxis in one-year time. The variables evaluated were: age, prescribed dose, number of vials used in each infusion, number of days the patient took to return to haemophilia treatment center to seek a new medical prescription.

Results: Participants were classified as: good, medium and low adherence respectively, when the mean delay was less than 7 days; between 7 and 14 days and greater than 14 days. The mean delay was 20 days. The highest adherence rate, by age, was in the group less than 10 years old (81%), and the lowest, in the group over 40 years old (36%), P = 0.021. In our community, the group with lower adherence may reflect that, they are accustomed to chronic pain, do not value prophylaxis and do not believe that it can bring benefits to their health status. This fact warns us that the MT attention must be redoubled in this group of patients. After adjusting in a multiple regression model, it was observed that the non-adherence rate was 3.16 times greater in patients aged 40 or older when compared to those younger than 10 years old. Also, the non-adherence rate was 2.06 times greater in subjects with a prescribed dose greater than 2000 IU when compared to those with a dose of less than 1500 IU, reflecting that the number of vials required for infusion contributes with the non-adherence process.

Conclusions: The group of patients over the age of 40 was shown to have low adherence to prophylaxis. This group deserves special attention from the MT in need of innovative strategies to guarantee adherence to the treatment. The number of vials in the prescription should be object of attention for the greater than 40 years old.

M-P-119 (229) | Adherence in adolescents with haemophilia: Concurrently feeling safe and doing what you prefer.

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Introduction: Adherence to prophylaxis in haemophilia is the lowest in adolescents. To support adherence and to explore the reason for non-adherence, it is important to understand motivators, facilitators and barriers. The aim was to clarify the underlying reason for non-adherence to prophylaxis from an adolescent with haemophilia perspective.

Methods: A qualitative study in Dutch adolescents (14-25 years) with haemophilia using prophylaxis was executed. Data was collected using three focus group interviews and 12 individual interviews. The interviews were transcribed, coded and analysed in an iterative process, leading towards the description of different adherence phases. Member checking in three respondents was used to increase the accuracy, credibility, validity, and transferability of the description of adherence patterns.

Results: In total, 21 interviews were performed. Respondents described that taking over prophylactic treatment and subsequent self-management behaviour was divided in three consecutive phases. In the first phase, adolescents relied mostly on their parents (e.g. parents administering prophylaxis). Due to high parental role, most young adolescents had a high adherence. In the second phase, when adolescents were older, they were concurrently aiming in their adherence behaviour between "feeling safe" and "doing what you prefer." Patient explored if

the prescribed prophylactic dose was necessary. Experiencing in bleeds in past influenced the fact the adolescent wants to "feel safe," which resulted in higher motivation to adhere to prophylaxis. Concurrently, the adolescent wants to do what he prefers in his life, e.g. joining healthy peers with sport activities and drinking alcohol. In the third phase, when the adolescents were becoming young adults, they developed a personal prophylaxis standard based on previous experiences. Feeling safe and doing what you prefer was still important, yet they learned previous experiences which contributed to a personal treatment standard which fits in their daily life. This led to varying adherence levels.

Conclusion: In conclusion, adolescents are concurrently aiming feeling safe vs. doing what they prefer concerning their adherence to prophylactic treatment. For health care workers, it's important to be aware of it and to discuss this in a non-judgemental atmosphere. Open conversations about adherence and personal preferences, could lead towards a higher adherence.

M-P-120 (302) | The effectiveness of the education interventions to enhance adherence to prophylactic treatment in Korean hemophilia patients

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Introduction and Objective: Regarding a quality of life and the cost-effectiveness, a patient's adherence to prophylactic treatment is one of the most important factors to achieve desired outcomes. The aim of this study is to know the effectiveness of the education interventions to enhance adherence to prophylactic treatment in Korean hemophilia patients.

Materials and Methods: We used the VERITAS-Pro as a measuring method for adherence to prophylactic treatment. We had two groups in study design, one group had not educated with education card for presentation of importance of morning administration of clotting factor concentrates and guidance of education program of skill for self-infusion and the other group had educated with the card. We compared the scores of each subscale in two groups and concentrated to subscale "Timing" in two groups.

Results: Ninety-five eligible patients were recruited to uneducated group and 123 patients to educated group for participation from five hemophilia treatment centers. The mean total score was 40.4 (range: 24-75) and 39.9 (range: 24-77), respectively. The subscale means scores of the uneducated group and educated group were 8.43 and 7.90 (Timing), 6.12 and 5.88 (Dosing), 6.43 and 6.33 (Planning), 5.99 and 6.35 (Remembering), 6.22 and 6.25 (Skipping), and 7.23 and 7.24 (Communicating), respectively. The mean scores of 2 items in subscale "Timing" showed difference between two groups statistically significant ($P < 0.001$).

Conclusions: In this study we learned the education programmes for the patients with prophylactic treatment should be designed with delicate and concrete contents. With the result of the previous study we recognized the need of education programmes focused on the proper time of the regular administration of clotting factor concentrates so we made the education card with focusing the morning infusion and self-infusion. Although we could not improve the total scores of VERITAS-Pro, we enhanced the proper timing of injection with the education intervention. We convinced this whole process can enhance adherence in patients with hemophilia in Korea.

M-P-121 (386) | Mapping the provision of psychological care for haemophilia patients in the United Kingdom and Ireland

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Introduction and Objectives: The national guidelines of both the United Kingdom (UK) and Ireland, for the provision of haemophilia care, state that patients should have access to comprehensive care which includes counselling services, preferably to a named counsellor, who has experience of patients with haemophilia and inherited bleeding disorders The aim of the survey was to identify the provision of psychological care currently provided and was conducted by the Haemophilia Psychological Association (HPA) UK & Ireland.

Materials and Methods: A link to an online survey was posted to clinical nurse specialists by Haemnet, an organisation that supports health and social care professionals in haemophilia, and to members of the HPA. The survey included 34 multiple choice questions. Responses were received from 20 individuals (13 haemophilia nurses, 7 psychologists/psychotherapists) which included responses from 11 out of the 28 Comprehensive Care Centres and 9 additional Haemophilia Treatment Centres. Ninety-five percent ($n = 19/20$) had witnessed patients or their families demonstrating haemophilia-related psychological needs. Forty-five percent ($n = 9/20$) had a named psychological professional in their department, 25% ($n = 5/20$) commonly referred to another centre/department and 30% ($n = 6/20$) had neither of these facilities. Of this last group 67% ($n = 4/6$) believed that patients at their centre had unmet psychological needs. Of the 14 centres that had some psychological provision 50% ($n = 7/14$) of the respondents believed that the psychological professional had specialist knowledge of haemophilia whereas 29% ($n = 4/14$) believed that they did not and 21% ($n = 3/14$) did not know. Only 36% of the respondents ($n = 5/14$)

said that the psychological professional had an identified number of hours dedicated to the haemophilia service and those hours ranged per week from 5-10 to 37.5.

Conclusion: Patients, within the UK and Ireland, do not have equitable access to services for haemophilia-related psychological care, as recommended by both national guidelines, and some centres have no provision at all clearly this situation needs to be addressed.

M-P-122 (393) | Benefit of a multidisciplinary team approach to switching from standard to extended half-life products for prophylaxis in Haemophilia A and B patients

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Introduction and Objectives: Funding for extended half-life (EHL) products in the treatment of Haemophilia and B in England is linked to patient selection criteria, pharmacokinetic monitoring and for ongoing use the improvement in outcome criteria. Patient adherence to their prophylaxis regime and accurate self reporting of treatment and bleeds was a prerequisite to considering patients for change along with an agreed "need for change." The approach developed by our multidisciplinary team and the impact of this will be described.

Materials and Methods: Treatment records were reviewed of all adults and children >12 yrs to identify patients who may benefit from either reduced frequency of injections and or reduced breakthrough bleeds. A patient information sheet was created with health psychologist, haemophilia nurse specialist and medical input outlining information on the steps required before and after switching to EHL and the patient commitment required in recording treatment used. Patients identified were seen in clinic in a multi-professional visit and the information discussed on the sheet and the patients' own treatment priorities established and their understanding of prophylaxis confirmed and any barriers to their adherence with prophylaxis identified discussed.

Results: Of 20 patients approached from December 2016 to October 2017 13 have switched. Reasons for not switching included concern over the additional PK visits and patient satisfaction with their current regime. Switching in 7 patients with Haemophilia A required 3-7 visits with 2 patients requiring dose adjustments (1-3). In the 6 patients with Haemophilia B switched 3-13 visits with 2 patients requiring 1 dose adjustment. All patients at the end of the initial 3-month monitoring have achieved clinical benefit aimed for and continue on EHL and are continuing to adhere to their schedule and record treatment use on Haemtrack.

Conclusion: Discussing patient's understanding of prophylaxis and the ways this can be optimized using a PK approach in an integrated manner with multi-professional involvement can support adherence.

M-P-123 (485) | How to become a high recruitment site for clinical studies

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Introduction: The Israel National Hemophilia Center treats over 670 patients in hemophilia by a comprehensive team, including 5 study coordinators. The center is a high recruitment site and went through many audits and 2 FDA inspections in the last 5 years with great results (NAI inspection classification). Comprehensive treatment starts from the point of diagnosis-usually at a very young age (in most cases following circumcision) and continues the rest of their lives. We hereby describe our experience with study recruitment and patients' adherence to studies. Method: Once the site is notified to be selected for a new clinical trial the Centre's Data Base is immediately scanned for relevant complaint candidates that can benefit from the new study. Once the protocol and the inform consent is approved by the ethic committee the investigator and the study coordinator approach the relevant candidates to provide more details and send the ICF for patient's review. For studies of babies (PUP) carrier mothers are approached at pregnancy prior to delivery of a child with hemophilia. During study period, use of "WhatsApp" application allows the study team to immediately communicate with the patient and provide real time solutions to any issue raised.

Results: We currently run 17 sponsored clinical trials (with study medication) and 13 additional investigator initiated /registry studies. About 15% of the severe Hemophilia patients in Israel participate in clinical trials aimed at improved care and use of new longer acting concentrates or non-replacement agents. In more than half of the sponsored trials with study medication our site is considered to be one of the largest recruiting sites including PUP (previously untreated patients) trials, which are quite challenging due to early exposure enforcement at circumcision on Day8. The percentage of dropouts is 0% and all patients are satisfied with study team "WhatsApp" groups, promoting adherence and compliance to study protocols.

Conclusion: Comprehensive team work with constant data base search to identify best study candidates, early study presentation to candidates, continued team support and collaboration via use of "WhatsApp" groups set the ground for Excellency and high recruitment and adherence to clinical studies.

M-P-124 (551) | Family-based multidisciplinary educational program: A pilot of 10 children and families

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Introduction: Children with moderate and severe hemophilia (4-18 years old) are assessed annually during a multidisciplinary outpatient's clinic at the Creveldkliniek, the Netherlands. Besides an optimal, medical strategy to prevent bleeding episodes, information given to families from a multidisciplinary approach should not only be structured and complete, but also preventive. Aim: To evaluate and improve our outpatient's clinic, a pilot study was started as a combined effort from our team together with and children and their parents\families.

Materials and methods: Randomly included were 10 children (and families) without functional deficits (HJHS<3) or recent bleeding, divided into age groups 6-11 years (n = 5) and 12-16 years (n = 5). A control group consists of the same number and age groups. In 2016 patients and families were offered a structured program consisting of: 1) An app- as an aid for physiotherapist to instruct families on: Inspection of peripheral healthy joints; Characteristics of intra articular bleeds and functional consequences; Full functional recovery after each bleed, based on functional milestones: preventive measurements, recognition of onset and stopping of a bleed, functional recovery after a bleed has stopped, evaluation. 2) Purchase of crutches, slings and cold-packs, including using instructions are part of the program, as well as contact with local physiotherapists, and setting up a National Hemophilia Physiotherapist Network. E-learning- nurses evaluation on home treatment and instruction of self-infusion; A topic list of our social worker to cover the impact of hemophilia on all aspects of personal and social development of patients and parents, including acceptance.

Results: To assess impact of this program, measurements from 2016 were evaluated in 2017, so after one year. Both quantitative data (Hemophilia Joint Health Score, PedHAL, Hemophilia Self-Efficacy Scale, ABR) and qualitative data (questioning onset of a bleed, stopping of acute bleeds, aids used during functional recovery and contact phone numbers) were evaluated, including an interview asking for general comments and specific input to improve the app into a second version. Results will be presented as well as the application and future strategies.

M-P-125 (568) | A qualitative study of transition from paediatric to adult services within the South West Haemophilia Clinical Network: Patient and family experiences

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Introduction and Objectives: The South West (SW) clinical network covers six paediatric centres and has developed transition services to five adult centres. Owing to the geographical scale of the SW region of the UK, Bristol Comprehensive Care Centre was commissioned in 2012 to provide multidisciplinary outreach clinics with consultant, nurse and physiotherapist alongside regional hospitals to provide local care and support to children and their families with bleeding disorders. Chronic diseases in teenagers can impact on physical, cognitive, social, and emotional areas of development for teenagers. Research shows chronic childhood condition such as haemophilia can disrupt transition and create major challenges for both the young person and their family. Consequently, teenager's concordance to treatment regimens is impacted. Teenagers with haemophilia are undergoing multiple transitions including their level of independence, living arrangements, education, relationships, and transition to adult services. Additionally, research has outlined keys factors that affect treatment concordance in teenagers with cancer which include patient emotional functioning (depression and self-esteem), patient health beliefs (severity and vulnerability), and family environment (parental support and parent-child concordance). This study aimed to explore patient and family's experiences of the transition process. The identified themes are hoped to suggest changes to service provision and suggestions of how to improve teenagers' concordance with UKHCDO quality standards, which are currently not met by the SW clinical network. Method: Details of potential participants in a transition aged range (13-25-year olds) were extracted from hospital records. All potential participants were invited opt in to the study via a postal letter or email. Each young person who consented had a telephone interview using a standardised interview schedule. Thematic analysis was carried out on the results.

Results: Findings from the thematic analysis will be discussed.

Conclusions: Recommendations for services changes in SW clinical network to support improved support for families and teenagers through transition will be outlined. The impact of transition on how the clinical network meets the UKHCDO quality standards will be summarised.

M-P-126 (781) | Impact of the clinical social worker's intervention in the attendance at a hemophilia treatment center

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Introduction and Objectives: The care of patients with hemophilia requires a biopsychosocial approach. The purpose of this study is to demonstrate that the clinical social worker within the multidisciplinary team in the care of patients with hemophilia and their families plays an important role in the attendance rate at the Hemophilia Treatment Center.

Materials and Methods: Cross-sectional descriptive study of patients diagnosed with hemophilia treated at the Hemophilia Clinic of the University Hospital "Dr. José E. González" in a period from February 2013 to November 2017. There were included 36 male patients with federal health coverage. A total of 58 monthly academic sessions were given by the multidisciplinary team, which topic was previously chosen by attendees, and coordinated by the Clinical Social Work Professional. Statistical correction was performed through the SPSS program, version 22.

Results: The study reported an attendance of 79.26% in patients with federal health coverage. However, our medical center extends attention to other 15 patients without the coverage (those don't include the replacement therapy in our hospital, but receive an educational training), who's attendance rate reports 51.18%. The global adherence percentage for both groups corresponds to 70.8%.

Conclusions: The clinical social worker helps our patients to feel comfortable and calm by knowing there's a specific program integrated just for their illness. Furthermore, coordinates the fundraising for patients needs leading to a high rate of adherence to the program. By receiving training, the patients become self-sufficient.

M-P-127 (795) | Role of ultrasound as a tool to improve the adherence of patients in the treatment of prophylaxis with coagulation replacement factors

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Introduction and Objectives: Hemorrhagic complications in patients with hemophilia have decreased substantially with treatment of prophylaxis with replacement factors. Good adherence to treatment is important to avoid such complications. Ultrasound is a low-cost method that can be performed in the practice, with adequate training. We intend to analyze the role of ultrasound in relation to the adherence of our patients.

Materials and Methods: Patients with hemophilia A and B severe in prophylaxis treatment were studied. These patients or their guardians after signing informed consent were polled with the VERITAS-PRO survey to assess the degree of adherence. During the clinical consultation, ultrasound was performed according to the HEAD-US protocol, and the patients were divided into 2 groups: those who had increased joint injuries and those who did not. All patients were newly surveyed with VERITAS-PRO after ultrasound. The results obtained were analyzed using SAS software.

Results: We analyzed a total of 35 patients diagnosed with hemophilia in the province of Santa Fe. 62.9% are under 18 years of age (children/adolescents) and the remaining are 18 or more years old (adults). 37.1% were treated with primary prophylaxis, 42.9% with secondary prophylaxis and the remaining with tertiary prophylaxis. The median adherence score in patients' pre-ultrasound were 25.5 (RIQ 3.0) in pediatric and 37.0 (RIQ 20.0) in adults The comparison of surveys prior to ultrasound with those performed later did not present significant differences in any of the sections ($P = 0.093$), in patients without changes in ultrasound. On the contrary, the comparison of the surveys of patients with ultrasound changes showed a significant increase in the score of the VERITAS-PRO post-ultrasound ($P = 0.035$). The area where more failures were found was in the questions related to time and doses both in adults and in children.

Conclusions: Ultrasound is an instrument of usefulness in the usual clinical consultation, because it allows to detect feigned response, and by means of facts to sensitize the patient of the importance of the adherence to the treatment.

M-P-128 (801) | Evaluation of adherence to treatment of primary, secondary and tertiary prophylaxis in patients with hemophilia in five specialized centers in Argentina

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Introduction and Objectives: The prophylaxis treatment in patients with hemophilia in the right way has been shown to prevent the development of hemophilic arthropathy. Our aims were: to assess the level of adherence to prophylaxis treatment. and to analyze the reasons for non-adherence.

Materials and Methods: Observational study of patients aged between 1 and 65 years old with hemophilia A and B, severe and moderate, who are in primary, secondary or tertiary prophylaxis that concur with our care centers, prior signature of informed consent. The measurement instrument for adherence was the Spanish version of the VERITAS-PRO survey. The surveys were performed by patients and/or parents/guardians.

Results: A total of 92 patients from 6 different provinces in Argentina were analyzed. 39.1% of patients are treated with primary prophylaxis, 50.0% with secondary and 10.9% with tertiary. The average age was 17.7 years old. The total scores obtained differ significantly between pediatric and adult patients ($P = 0.003$) with a median value of 37.0 (IQR 18.0) for the first group and 30.0 (IQR 10.0) for the second group. No significant differences were found in the total scores with respect to the type of hemophilia ($P = 0.761$) and the type of prophylaxis ($P = 0.552$). According to the results of the survey, only 10.9% of patients were "more adherent," 82.6% had a questionable adherence and 6.5% were not adherents. No patient analyzed was non-adherent with health risk. The questions related to the time and the planning area were those that had higher values in patients with questionable and non-adherent adherence. Major failures were observed at the time of day that patients were given injections.

Conclusions: Knowing the degree of adherence of our patients will allow us to optimize resources in terms of their treatments, as it will help us to differentiate the lack of response from inadequate treatment performance. Identifying the facts that cause the bad adherence will allow us to improve the adherence of our patients and thus avoid complications in patients with hemophilia.

24-ADVOCACY AND OUTREACH

T-FPMTD-005 (381) | Ready, set, go: An interactive webinar series for Twinning partnerships

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Introduction: Canada has a long history of involvement with the WFH Twinning Program, with 8 treatment centre and 13 organizational twinning partnerships since 2000. The International Committee of the Canadian Hemophilia Society (CHS) provides support for Canadian programs involved in twinning. In 2017, the committee created an educational webinar series to encourage and enable interested volunteers to engage in twinning.

Methods: The three-part series was announced at the CHS Annual Meeting in May 2017 as "Ready, Set, Go." It was intended to introduce prospective twins to the fundamental considerations of twinning, from evaluating your readiness to twin (Ready), through the process of establishing a formal twinning (Set), to the pearls and pitfalls of the twinning partnership (Go). The webinars were advertised on the CHS website, social media feeds, news bulletins, and national magazine, with a registration link available. They were scheduled to correspond to the WFH timelines for twinning assessment visits and applications. The hour-long sessions were intended to be interactive and were recorded for future viewing. Presenters were members of the International Committee who had been involved in previous twinning partnerships and could share their personal experiences.

Results: The first webinar had 18 registrants and 16 attendees, and the recording has since been viewed 56 times. Because of technical issues, the webinar hosting platform was changed for the second webinar to encourage better interaction between participants. Unfortunately, because of summer scheduling, there were only 13 registrants and 4 attendees for that webinar, but there have already been 30 views of the recording. The third webinar is scheduled for the end of November.

Conclusions: The increased availability of webinar capabilities provides a convenient way to deliver novel educational outreach. Twinning is a particularly rewarding experience, but also represents a serious commitment and effort. This series should help to clarify the steps involved and help to continue Canada's long and effective involvement in twinning. Based on feedback from other regions, the recordings are also available as open-access for other centers and patient organizations, both established and emerging, to use as they prepare their own twinning efforts.

M-MP-136 (481) | Culturally responsive practices: Interacting with indigenous communities through Piritoto

Te Whainoa Te Wiata

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The bleeding community has seen great changes take place over the past few decades, but treating haemophilia is not only scientific, it is also holistic. Ultimately, trust between the western world and that of the indigenous is fragile at best, this has caused a lack of engagement and resulted in poor access to treatment for indigenous people with haemophilia. Therefore, establishing avenues to strengthen relationships between two worlds is paramount to outreach and improving basic treatment needs. Over the last 18 months "Piritoto" a Culturally Responsive Practices (CRP) workshop has been running with the outreach workers of Aotearoa/New Zealand. Piritoto translates to "connecting and binding bloodlines" which is the overarching principle of the CRP workshops. Integrated societies often produce a dominant culture with a monocultural view that struggles to acknowledge cultural practices, thus creating conflict. Due to the frayed relationship between the two cultures of Aotearoa/New Zealand, Piritoto was designed initially to bridge the two worlds. These workshops are discussions around the Māori (Indigenous of

Aotearoa) world, Māori view and contemporary Māori attitudes. Although, these are confronting discussions the outcomes and feedback have been positive. This presentation will introduce a brief background of the indigenous culture of Aotearoa/New Zealand, including the relationship between Māori and non-Māori. This will also identify the steps taken to improve relationships between two peoples. In doing so, acknowledging simple cultural differences with issues such as blood and its significance to indigenous people. In this lies an example of a common misunderstanding between the western world and indigenous people. In conclusion it is believed that the cultural identity of a person cannot be acknowledged until it enters the mind of the practitioner. Treating symptoms is short term but treating the person can produce positive long-term outcomes for all. Therefore, the purpose of Piritoto is to bring the values of the indigenous world and bind them to current practices of haemophilia care.

M-P-137 (68) | Patient assessment by use of the International Classification of Functioning (ICF) in Indonesian patients with hemophilia

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Introduction and Objectives: Most patients with hemophilia are assessed focusing on body level. However joint function gives little information on activity and participation. In a country where clotting factor is scarce and social support by the government lacking, it is important to get information on participation.

Methods: We assessed a total of 59 patients form Yogyakarta, Solo and Semarang (Indonesia) using the ICF model. Joint function was not measured, we asked for bleedings and limitations and how patients were functioning (activity), visited school or had a job (participation). Environmental factors were prophylaxis, on demand, on demand with limited amounts of clotting factor or no treatment at all.

Results: A total of 59 patients were assed (49 hemophilia A, 8 hemophilia B, 1 von Willebrand, 1 unknown (prolonged APTT); 27 adults and 32 children between 3 and 18 years, (mean 22.7). 11 patients had had a documented intracranial bleed, 4 neurological problems. 11 patients were once per week prophylaxis, 5 had no treatment at all and 43 on demand with low dose. 7 children and none of the adults were without joint limitations, 1 adult and 4 children had one, 26 adults and 21 children had 2 to 7 affected joints. 24 patients walked normal (16 children and 8 adults), 24 with a contracture (10 children, 14 adults), 11 were using crutches or in a wheel chair (5 adults, 6 children). 5 of 27 children between 6 and 18 years did not go to school (2 got home education). 3 lost 1-3 days per month from school, 6 one or more days per week, from 4 no information was obtained. 6 of 27 adults had no income, 11 had unskilled labour and 10 skilled work.

Conclusion: Without measuring the exact joint function we got a good impression of activity and participation. This is important as in countries with limited resources the need of proper rehabilitation and supportive measures after each bleed is very important. Good information of parents, children and school can help to improve education which is appropriate for people with limitations in functioning.

M-P-138 (470) | Out reach program and advocacy of hemophilia care in Kenya

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Background: At AMPATH Oncology Institute, Hemophilia care Center was formed in 2011, with the support from Indiana Hemophilia and Thrombosis Centre (IHTC) and the Novo Nordisk Hemophilia Foundation (NNHF). It embarked on conducting hemophilia care and educational outreach programs in health institutions as well as communities to create awareness on hemophilia.

Objectives: Provision of high quality hemophilia diagnostic services. Provision of high quality hemophilia care and treatment through initiation of comprehensive clinics. Provide support to blood transfusion centers through enhancing their capacity to manufacture therapeutic blood components. Provide a comprehensive register of patients with hemophilia and other blood disorders. Educate and train patients, caregivers and healthcare professionals throughout Kenya.

Methodology: Clinical care program, at AMPATH Oncology, providing high quality hemophilia diagnostic services to people with bleeding disorders. Workshops and trainings – Organizing theoretical and skill building workshops and trainings on hemophilia and other blood disorders, which targets multidisciplinary teams of health workers. Home visits – Conducting home visits to our patients at various centers, creating awareness of hemophilia and bleeding disorders. School visits – Visiting hemophiliacs in schools, educating teachers on hemophilia and its management.

Results: More than 30 health facilities have been trained. 20 Schools have been visited and trained, 20 patient home visits have been done. During the visits and trainings emphasis is made on ensuring proper understanding of hemophilia and other bleeding disorders and its management thereby debunking myths about the condition. A good referral system has been developed for hemophilia and other bleeding disorders with a robust patient registry. Health professional, nurses, doctors from all over the country have been educated by experts in the care of bleeding disorders.

Conclusion: Awareness has been created on hemophilia in Kenya. Both morbidity and mortality from hemophilia has been reduced through this program.

M-P-139 (494) | Development of diagnostic algorithm for von Willebrand disease within WFH the Twinning Tallinn-Helsinki program

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Introduction and Objectives: It was not possible to make a definite diagnosis of von Willebrand disease (VWD) subtypes or severe forms of haemophilia A in Estonia until 2016. To close these diagnostic gaps, a specific goal of the World Federation of Hemophilia (WFH) centre twinning link between Tallinn (Estonia) and Helsinki (Finland) Haemophilia Treatment Centre (HTC) was to update the protocols for laboratory diagnosis of bleeding disorders in Estonia.
Materials and Methods: Adult and paediatric ISTH-BAT (International Society on Thrombosis and Haemostasis – Bleeding Assessment Tool) were translated into Estonian and incorporated into routine practice to identify individuals with clinically relevant bleeding tendency/symptoms. New fully automated assay protocols were implemented in STA-R Evolution analyzer (Stago, France) and their analytical performance was evaluated: Von Willebrand factor (VWF) activity assay (Innovance® VWF Ac, Siemens, Germany) – part of the VWD screening panel; FVIII low-range assay – for the correct classification of severe haemophilia A and of type 3 VWD (available 24/7). A new VWF multimer electrophoresis assay (Sebia, France) was evaluated preclinically, including the main VWD types and 2B, 2A and 2N subtypes. Regular meetings and discussions focusing on clinical cases were established between clinicians and laboratory.
Results: Coagulation tests were verified and accredited according to ISO 15189:2012. Based on available laboratory assays in Estonia, diagnostic algorithms for VWD and acquired von Willebrand syndrome were created. The response to desmopressin was evaluated in Tallinn Children`s Hospital. The assessment of desmopressin response will also be addressed among adults.
Conclusion: The Tallinn-Helsinki WFH Twinning Program has played a pivotal role in developing coagulation test methods in the North Estonia Medical Centre laboratory and in promoting interdisciplinary meetings and international cooperation in the Baltic region. The authors have no conflicts of interest.

M-P-140 (683) | Hemophilia in Brazilian courts

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Introduction: Brazil is not a self-sufficient country in factor replacement therapy production for its hemophiliac citizens, which leads to the need to import the medication. The dispensation of this product suffers from its own conflicts that elucidate the phenomenon of the Judicialization of Health as it will be demonstrated.
Objective: The aim is to inform about the violation of the hemophiliac citizens' Constitutional Health Right and to demonstrate that Protocol established by the Ministry of Health is not adequate to treat hemophilia in its entirety.
Methods: Is was used bibliography review and revision of documents. Discussion: In 2016, the Brazilian Supreme Court suspended the injunctions that determined that the Federal District Government had to supply Recombinant Factor IX Concentrates or, failing that, Recombinant Long-Term Factor IX for Type B hemophiliacs and Concentrates of Recombinant Factor VIII for type A hemophiliacs. The patients were felt obliged to enter the Courts because the Brazilian Protocol, established by the Ministry of Health, does not contemplate supplying the Recombinant Factor IX, only plasma-derived factor, a situation that puts Brazilian hemophilic patients at risk. The scenario has its own peculiar conflicts, since it puts in check the needs of hemophiliac citizens and the distribution of public resources. It is worth pointing it out that the Brazilian Federal Constitution, in its 196 article, determines that Health is a Right that should be enjoyed by all citizen and the Government has the duty to provide it. The Government pledges to prioritize preventive activities (article 198). In this sense, it is necessary to consider prophylaxis therapy as the most effective treatment, since it prevents joint injuries and subcutaneous tissue bleeding, as well as promotes patients' quality of life and should, therefore, be adopted as the standard treatment. In the same way, it is also the most economical, since it diminishes the long-term impact on the health budget.
Conclusions: The study demonstrates that the Brazilian health managers do not promote the quality of life of hemophiliacs, which leads patients to seek the Judiciary to implement their Right to Health.

M-P-141 (685) | NHF's state-based advocacy coalition program

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Introduction and Objective: The National Hemophilia Foundation (NHF) consistently prioritizes the need for consumers to engage with their legislative and administrative officials regarding access to care needs/issues affecting those with bleeding disorders. This

is true at the national level, but also locally. The NHF State Based Advocacy Coalition (SBAC) program began in 2012 with 5 key states to respond to various advocacy challenges affecting access to care for the bleeding disorders community. Now in its sixth year, the NHF SBAC program is providing support to 18 states that include 28 NHF chapters, representing thousands of families with bleeding disorders across the USA.

Materials and Methods: The SBAC program requires the following elements. Year One: Host a Strategic Advocacy Strategy Session with NHF. Identify state advocacy priorities for the year. Establish an Advocacy Committee with appropriate leadership positions filled (chair, vice chair, secretary etc.) that meets monthly. Develop a 3-year Strategic Advocacy Plan. Host an Advocacy Day at the state capital with training for volunteer advocates. Year Two: Demonstrate year 'round advocacy through chapter programming. Define a mechanism for advocacy communications (newsletter, social media, web). Adhere to a regularly scheduled advocacy committee meeting (monthly and quarterly). Host a stakeholder meeting in preparation for the upcoming legislative season (fall). Update the coalition's Strategic Advocacy Plan yearly. Demonstrate success in growing grassroots advocates (grasped concepts of Advocacy 101, functioning in a leadership capacity for chapter's advocacy efforts, etc.).

Results: One measure of success of the SBAC program is the increased interest in advocacy by NHF chapters and an expressed desire to be part of the program. Our collective presence at state capitals around the country and relationship building with agency officials has substantially increased awareness and improved access to care. An important byproduct of the program is record breaking participation from grassroots advocates at both state and federal levels Conclusions

We have found the greatest success has come from the technical expertise that is offered to chapters along with the opportunity for ongoing education and networking. Another key area of success stems from the accountability to objectives required to participate in the program.

M-P-142 (741) | 7 sessions in 2 days: Description of a comprehensive training workshop for AFH volunteers

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Introduction and Objective: French Hemophilia Association (AFH) volunteers have expressed the need for training to effectively carry out fieldwork and better support people living with rare bleeding disorders. Since 2016, the AFH has systematically implemented a training model for its volunteers.

Materials and Method: Training is offered to volunteers involved in regional chapters, working groups and committees. On a weekend, seven interactive workshops are built to: To learn AFH's history, to define the values, the visions, the advocacy, the position of the AFH and to diffuse them. Define the different types of possible and existing ways of involvement within the AFH. Identify the skills that a volunteer can bring to their role, identify the skills needed and learn how to get involved in a local chapter and/or at the national level Relay the needs of the chapter members, determine the actions most consistent with the needs of the chapter members, define a methodology to prepare and fund these actions, how to complete chapter's new memberships application, integrate and improve national level file management. Find funding for local chapter actions and funding for the Hemophilia Research Endowment Fund. Learn to measure and evaluate each action with precise objective criteria. Learn how to set up an interactive General Assembly.

Results: In 2 sessions, 52 participants have been trained. Main results : Reinforcement of motivations through the interactive format of the workshops; Awareness of the importance of the work already done thanks to the chronological timeline of the history of the AFH, the political importance of public health advocacy; Recognition of the volunteer role and support to fulfill their responsibility; Definition of the chapter's representative role at the different territorial levels; Strengthen the motivation of the volunteers involved at both the regional and national levels; Cohesiveness of the work of all volunteers; Knowledge enrichment of each participant. The lack of training of the participants in group animation.

Conclusion: The AFH, by training those who constitute it, feeds its creativity and its influence.

M-P-143 (815) | Afath: The AFH international action program to serve the WFH vision in African French speaking countries

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Introduction and Objective: In 2012, the African French speaking countries (AFSC) were less represented among the WFH NMO's members. That meant those countries couldn't have real support from the WFH. The French hemophilia association (AFH) decided in 2012 to give all its revenue coming from the 2012 WFH congress in Paris, to serve the WFH vision "treatment for all." In collaboration with WFH and the French National Blood Institute (INTS), AFH developed a specific program for AFSC to increase diagnosis, care and access to treatment and help patients' organization and leaders emerge.

Materials and Method: Based on a network created by the INTS, AFH identified in 2012, in 18 AFCS, hematologists and transfusion specialists ready to improve diagnosis and care for patient living with

hemophilia in their country. Thanks to the help from Ph. De Moerloose (University Hospital of Geneva), AFH identified also French hematologists who were ready to give such medical support. AFH identified among its members some volunteers able to train their African peers and recruited 1 staff member. Thanks to the WFH methodological support, the Alliance franco-africaine pour le traitement de l'hémophilie (Afath) program had been put into place. The Afath program is a 2 years program (sometimes 3 years) for each country. Afath is based on 2 joint medical and volunteer visits in situ per year. The objective is to train and increase knowledge for diagnosis, appropriate care and treatment. Within the 2 years action plan, AFH provides basic trainings on advocacy, education for patient and capacity building.

Results: 6 different countries: Burkina-Faso, Madagascar, Togo, Mauritania, Benin and Congo have been receiving support respectively from HTC's from Saint-Etienne, Clermont-Ferrand, Toulouse, Nîmes, Tours and Bordeaux and from AFH and its chapters of Brittany, Midi Pyrénées and Centre-Val de Loire. In 2016, Madagascar and Burkina-Faso became WFH associated members and joined the WFH program. Those 2 countries will have in 2018 two joint medical and HOT Twinning.

Conclusion: More than 100 patients have been diagnosed since the end of 2014. They have appropriate treatment and sometimes prophylaxis thanks to the WFH Humanitarian Aid program.

25-CAPACITY BUILDING

T-FPMTD-006 (789) | Building the AFH strategic plan 2017-2019: 1 year of work for a 3 years plan – the art of democracy

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Introduction and Objective: In 2015, the French hemophila Association (AFH) didn't have a multi-year strategic plan (SP). AFH built a SP for 5 reasons: Build the future actions on strong orientations shared and approved by all the members; Define an orientation plan for a 3 years period; Assure continuity of actions beyond leaders who can change anytime; Imagine the AFH answer to the future challenges has to face; Get a tool to advocate towards our community and stakeholders on what AFH wants to do.

Materials and Method: Creation of a working group (WG) to elaborate and analyze a questionnaire and to ensure effective follow-up. The purpose of the questionnaire: To have a feedback from key opinion leaders and volunteers on what we did in the last 3 years. The items: assessment of AFH's commitment in research, education, public health, digital communication; AFH involvement in psychosocial support, schooling, physical activities; Diversification of funding. 1 question added on what our next priorities should be. It was an on-line questionnaire (30 days dead-line with two reminders) with 13 questions, free remarks were always possible. Questionnaire sent to 133 persons working with AFH: industry, health care providers, ministry of health/agencies, other patient's organizations, EHC and WFH and main volunteers and staff.

Results: An average response rate of 60% (75% among the volunteers) and a total amount of 178 free remarks. The WG synthesized the results, first in 9 main topics: (1) public health (2) access, quality and safety of care (3) Education for patients (4) Support and information to the community (5) multi-faceted community with multiple challenges (6) volunteering (7) Research (8) International action (9) Human resources and funding, summarized in 5 strategic directions. 3 of the 5 strategic directions were discussed with a board during an ambassador exercise session in order to precise the SP.

Conclusion: Build a SP is building associative democracy: each step must be approved by the board and the final document must be approved by the patients' community. Long process but facilitate the understanding of the NMO willingness. Final approbation by the members at 99.7%.

M-P-146 (192) | Building capacity to advocate for comprehensive care centres in Canada

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Introduction and Objective: Following a cross-Canada assessment of Hemophilia Treatment Centres (HTCs) in 2014-2015, the Canadian Hemophilia Society (CHS) published a national report on standards of care and the capacity of (HTCs) to respect those standards. It also submitted individual assessments of service delivery to 24 of the 25 HTCs. The study confirmed what had been previously reported: shortcomings in the level of human resources, notably nursing, physiotherapy and psycho-social, leading to problems in respecting certain standards of care, for example, annual patient assessments and close monitoring of coagulation therapy, as well as sub-optimal physical resources, for example, inadequate space for the clinic. Given that health care delivery is a responsibility of each of the 10 provinces in Canada, it was clear that CHS' 10 provincial chapters would need to take a leading role in advocating with health authorities to obtain increased resources. As few of the current chapter leaders had experience in government relations, it was decided to offer provincial workshops to build capacity.

Materials and Methods: The CHS designed a day-and-a-half workshop to offer to chapters. Before the actual workshop, a survey was administered to gauge knowledge and needs. Participants were also asked to read key studies and be ready to present them at the workshop, and to consult with HTCs to validate key issues. During the workshop itself, experienced patient leaders gave lectures on best practices in advocacy. Participants developed a case for support on a priority request relevant to their province and role-played a meeting with mock health officials. A follow-up survey was administered to measure the outcomes.

Results: Chapter advocacy meetings have been held in two provinces with 10 participants at each. A national advocacy meeting brought together 35 provincial representatives from all 10 chapters. Satisfaction with the workshops was high. More chapter workshops are planned.
Conclusion: While CHS volunteers had extensive experience in advocacy in the 1970 to 1990s, those skills need to be developed in the latest generation of leaders.

M-P-147 (652) | Establishment of oral care for Caribbean patients with congenital blood coagulation deficiency

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Introduction and Objective: The University Hospital of Martinique plays a major role in the multidisciplinary management of patients with constitutional deficits of hemostasis in the Caribbean region. The development of an oral checklist has been an indispensable tool for clinical follow-up of patients. This booklet coordinates the multidisciplinary care and represents essential traceability for patient's individual care and ensures a relay of the care with the dentists exercising in network of city. This TheraPeutic Education (TPE) program is complementary to the routine conventionally practiced, as part of odontological surgeries.
Material and Methods: Clinical, biological, and socio-demographic data were collected. The data recorded in these oral health records are transferred to national databases, providing a relay in the remote care of these patients. The improvement of the quality of life will be evaluated by the establishment of a survey and satisfaction questionnaire, backed up by a registry of blood diseases.
Results and Discussion: This oral health monitoring program has avoided many tooth extractions in many patients with coagulation deficits. The systematic visit of all patients and the prescription of medical checkups have been included in a clinical monitoring and therapeutic education program. In this multidisciplinary field, the nurse of the Regional Center of Hemophilia Treatment (RCHT) was implicated for the accompaniment of home treatments, including auto-treatments. Severe hemophilia A patients were treated under plasmatic products, moderate and minor forms benefited from recombinant treatments. Some patients were good responders to Minirin®. This TPE program at the Martinique RCHT could be used to treat other rare diseases of Afro-Caribbean populations, such as sickle cell disease.
Conclusion: The establishment of an E-learning/E-health program will be an essential tool that will ensure the relaying of clotting factor deficiencies oral care in the Caribbean island region, thus ensuring equal access to care, compared to that proposed in Europe.

T-P-190 (15) | From our roots to the treetops, the Advanced Youth Leadership Training Workshop: Building for the future

Karl Archibald

Haemophilia Foundation of New Zealand INC., Christchurch, New Zealand

The Haemophilia Foundation of New Zealand Inc. (HFNZ) has a proud history of developing young leaders and advocates who work together to deliver the best outcomes for our members. Over Waitangi weekend, 03-06 February 2017, HFNZ held its first ever Advanced Leadership Training (ALT) weekend in the central North Island.
ALT followed on from the HFNZ Youth Leadership Training weekend run in August 2014, and was targeted at specially selected young people from around New Zealand. Also included was a member from the Cambodian Hemophilia Association, which has twinned with HFNZ. These 18-30 year olds have stepped up into leadership roles in their organisations and have grown their involvement in their bleeding disorder communities. The ALT programme was designed specifically to enhance their leadership skills. The challenges started the moment they landed in Auckland on day one. Split into two teams the groups had to problem-solve their way to the first night's base, 192 km south. Here the leaders learnt about HFNZ's roots, history, sacrifices, shared personal stories, learned what it is like in a developing country, about not for profit leadership for tomorrow, social enterprise, and about building on the foundations set down before them. On day two the teams had to make their way 150 km east to Rotorua, where executive members of the HFNZ National Council discussed risk management, what the foundation is doing today and what could happen tomorrow. On day three the participants learned some higher-level advocacy strategies, and discovered ways to manage group conflict. The final day covered the global youth scene, some planning for tomorrow, and setting SMART goals. There have been some great outcomes from the ALT. There is a higher level of engagement, with 13 foundation related goals or projects planned or completed. These include running local events and workshops, becoming a committee member, further leadership development, and greater advocacy through increased board involvement. Overall, ALT has provided greater knowledge, increased confidence, and a better understanding of the impact that each person has on the future of the bleeding disorder community.

26-CARE DELIVERY

S-NURWK-003 (581) | Introduction of nurse-led telephone review service for mild inherited bleeding disorders improves attendance rates, frees hospital resources and is highly rated by patients

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Introduction and Objectives: In the United Kingdom, the National Service Specification for haemophilia advises all patients with mild inherited bleeding disorders (IBD's) must be reviewed annually by their haemophilia centre. Patients, who rarely experience problems relating to their bleeding disorder, often view attending annual hospital-based appointments as unnecessary. This results in a failure to attend appointments and a disconnection from their haemophilia centre. This leads to a poor understanding of how to manage their condition and how to advocate for themselves with non-specialist clinicians in emergencies, or when surgical or other invasive procedures may be necessary. The introduction of structured, nurse led telephone clinics, across the North London Adult Haemophilia Network (NLAHN), offers an alternative method for patients to be reviewed. This innovative strategy was evaluated to assess whether the needs of the patients were being met.

Method: The Clinical Nurse Specialists (CNS) from the NLAHN devised a short service evaluation questionnaire using simple Likert scale ratings and a free comment section. All patients across the NLAHN sites that had received a telephone review in 2016 were posted an anonymised questionnaire, with a freepost return envelope.

Results: 514 questionnaires were distributed. 174 were returned, 18 were excluded as incomplete, giving a return rate of 28%. Overall 89% (139/156) rated the new service between excellent and very good, 89% (139/156) were very satisfied with the information received in the review and 95% (149/156) were happy to continue to receive telephone reviews. Negative comments concerned perceived need for regular blood tests.

Conclusion: Patients with mild IBD's found nurse-led telephone reviews an acceptable alternative to hospital appointments. Telephone clinics are more convenient for patients in terms of time and resources and allow continued engagement with their haemophilia centre, ensuring regular education about their condition and the services offered. Overall attendance rates for follow up of patients with mild IBD's have improved, with an associated reduction in routine hospital appointments. The introduction of this service has been popular with patients and has had a positive impact on hospital-based resources, including reducing the financial waste of missed attendances without negatively impacting patient care.

S-NURWK-004 (467) | Welly-Vest the tailored solution to protecting indwelling port-needle in an accessed CVAD

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Introduction and Objective: Venous access within the paediatric severe haemophilia population can be difficult and can require insertion of central venous access devices to facilitate prophylaxis or Immune Tolerance. Management of ports rightly often focuses on issues relating to the accessing and infection avoidance in maintaining patient safety and port functionality. Following a bleed around a port, caused by the rubbing of a car-seat seatbelt, in a paediatric patient. The Wellington Haemophilia Centre had to consider options to protect the port area when patients have a Long-term accessed port.

Materials and Methods: This has led to the design and development of the "Welly-Vest." The Welly-Vest is a tailor-made waistcoat with a see-through protective dome that allows staff to see the needle and "port" site. Whilst preventing small hands from easily "playing" with the gripper needle and providing a level of protection against knocking the accessed port.

Results: Learning from patients and their family's experience of using and wearing has seen the Welly-Vest evolve and now has a pocket that allows easy access to the Microclave bung at the end of the gripper needle cannula. The material used in construction has also changed to be lighter weight, less bulky and more user-friendly.

Conclusions: Whilst the Welly-Vest involves the cost of manufacture we believe that the cost is greatly outweighed by the protection and security it provides to patients/families and in the prevention of port damage and bleeding in the surrounding tissues. As such it has been freely embraced by the small number of patients whom have required one so far.

M-P-132 (99) | Improving care and treatment options for women and girls with bleeding disorders

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Women and girls may experience increased bleeding symptoms as carriers of haemophilia. They can also be affected by other hereditary bleeding diatheses such as Von Willebrand disease, platelet dysfunction defects or deficiencies of coagulation factors (F) such as FI, FII, FV, FVII, FX, FXI, and FXIII. Women and adolescent girls with undiagnosed bleeding disorders frequently experience heavy menstrual bleeding (HMB; menorrhagia), leading to impairment of daily activities.

Methods: A variety of hormonal measures are available for the treatment of menorrhagia. Mechanical means of treating menorrhagia include endometrial balloon tamponade, endometrial ablation, and hysterectomy. Pregnancy and childbirth can present hemostatic challenges to women with bleeding disorders, and management should be instigated accordingly. Precautions with regard to PPH are particularly important in women with bleeding disorders.

Results: Under-recognition of bleeding disorders in females may lead to inappropriate, or lack of, treatment. This may be avoided by increased disease awareness, prompt and accurate diagnosis, and a multidisciplinary approach to patient care. This review considers the range of hereditary bleeding disorders that may affect women and adolescent girls, and their evaluation and management. Bleeding disorders in women are a public health concern. In many developing countries, women are caregivers for their children, and maternal morbidity or mortality can have a major health and economic impact on their families. The World Health Organization has reported that, worldwide, 18 million women between 30 and 55 yrs. of age perceive their menstrual bleeding to be excessive, with 10% of these women experiencing blood loss severe enough to be clinically defined as menorrhagia; 10-15% of women may experience this at some point during their lifetimes. Evaluation of a suspected bleeding disorder in a woman should involve consideration of personal and family history of bleeding signs and symptoms, with the clinical and gynecological assessment.

Conclusion: Bleeding disorders have a disproportionate effect on women and girls as a consequence of menstruation and obstetric events. Increased disease awareness, together with prompt and accurate diagnosis, will help to educate affected individuals and prevent gynecological and obstetric comorbidity. Many treatment options are now available.

M-P-133 (318) | Turkey's model for the formation of the hemophilic arthropathy council

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Introduction: The treatment and follow-up of hemophilia needs to be evaluate in multidisciplinary team which includes a hematologist, hemophilia nurse, orthopedist, physiotherapist, psychologist, nuclear medicine specialist, dentist and social workers. The difficulty of forming an experienced team in hemophilia in our country has led to the formation of hemophilia councils in certain regions. Hemophilic Arthropathy Council was first established in 1996 under the leadership of TrHD in the Department of Orthopaedics and Traumatology of the Istanbul Medical Faculty and this medical team formed. In this study, Hemophilic Arthropathy Councils were evaluated since 1996.

Materials and Methods: Hemophilic Arthropathy Council's data was evaluated between 1996-2016. The number of councils held, the number of patients and the decisions that were implemented were recorded. From the available data, the council and patient numbers between 1996-2016 were evaluated and in terms of the decisions implemented, these were evaluated from 2013 onwards.

Results: The councils were organised 409 times between 1996 and 2016 and 2238 patients were evaluated. The decisions of radioactive synovectomy (RAS), total endoprosthesis (TEP), arthroscopy, osteotomy and surgical procedures were taken and performed. In many patients, joint problems were resolved by taking physiotherapy. From 2013, a total of 60 councils were held and 380 patients were evaluated and 154 viscosupplementation, 86 RAS, 72 TEP, 23 radial head resection, 6 osteotomy, 9 arthrodesis and 1 achilloplasty decisions were taken.

Conclusion: The Turkish Haemophilia Society Model is the most suitable model for the Hemophilic Arthropathy Council which is the most important decision-making body in order to be able to provide equal hemophilia care in countries with wide and different geographical regions and to increase the quality of life of patients by allowing access to multidisciplinary treatment for joint problems and for preventive measures. Within twenty-one years, 10 different hemophilic arthropathy councils have been established in different regions of our country. For this reason, we believe that the hemophilic arthropathy council, which is available in our country, may be an example for developing countries in relation to the multidisciplinary evaluation of hemophiliacs.

W-P-077 (347) | Comprehensive haemophilia care through a dedicated Haemophilia Treatment Centre (HTC) – An experience from South India

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Introduction: HTCs are specialized centres for providing comprehensive haemophilia care. Comprehensive care signifies the preventive and rehabilitative components in addition to current illness management. Uptake of services and over all wellbeing of patients depends on the efficacy of the HTC. Aim: To describe the spectrum of patients with Haemophilia (PWH) under HTC. Methodology: The HTC was started in 2013. Anthropometric measurements and demographic data were collected by a social worker from all enrolled patients. Children were assessed by a senior paediatrician and adults by a family physician. Factor assay was done in the HTC for all patients. HTC staff nurse oversaw factor infusion. Periodical examination of joints was done by

physiotherapist and patient/care taker counselling by clinical psychologist. Low dose prophylaxis (PT) was started initially for ten children in 2015. The treatment response was promising and the same was extended to adults in 2016. All patients under PT were screened for inhibitors at baseline and at completion of 12 months of follow up. All health professionals were trained in comprehensive haemophilia care. Regular camps for case detection, workshops, awareness classes and rehabilitation were conducted in the centre. Home therapy was introduced in 2016.

Results: A total of 640 PWH were enrolled (A 523/B 117). There was 446 severe haemophilia patients (A 374/ B 72). In the total of severe PWH, 247 were adults (A 203/B 44) and 199 (A 171/B 28) were children. Fifty severe haemophilia children (A 43/B 7) were getting continuous prophylaxis and 34 children in this group were under regular PT. In adults with severe haemophilia 34 (A 31/B 3) were in PT and 27 (A 25/B 2) among them were in regular PT. Only 3 individuals (2 children, 1 adult) discontinued PT. Currently 27 (A 23/B 4) children and 23 (A 21, B2) adults are under home therapy.

Conclusion: Comprehensive care for PWH is feasible in a low resource setting through a dedicated HTC. This setting provides good patient compliance and proper utility of resources.

W-P-078 (348) | Patient reported outcomes on ways to improve haemophilia care: Results from the CHESS Study

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Introduction and Objectives: Haemophilia care has improved significantly in the last 2 decades, and patient reported outcomes are becoming increasingly important in its overall evaluation. Our aim was to explore how people with haemophilia (PwH) viewed that haemophilia care could be further improved, based on the Cost of Haemophilia across Europe: A Socioeconomic Survey (CHESS).

Materials and Methods: The present analyses focused on the variable "Ways to Improve Care," for which PwH could select one or several from 11 available options including "more effective products (e.g. longer acting treatments)," "better availability of new products," etc. In total 523 PwH were analysed and divided in two groups: PwH selecting more effective products (Group A) and PwH selecting other options (Group B). Descriptive analyses focused on treatment strategy (prophylaxis vs. on-demand), target joints (TJs), bleed episodes, and quality of life (QoL) as reported in EQ-5D, a generic health status measure. Results are presented as means (SD).

Results: Group A included 339 (65%) PwH, with a mean age of 36.2 (14.4), while Group B included 184 (35%) PwH, with a mean age of 40.1 (15.9). PwH in Group A were generally younger (70% in the 18-30 years vs. 48% in the >60 group), and on primary prophylaxis (72% vs. 58% on primary on-demand). Additionally, PwH in Group A represented 72% of PwH with >2 TJs (vs. 59% of PwH with 0 TJs) and had a mean of 5.2 (7.4) bleeds in the last 12 months (vs. 3.8 (5.3) for PwH in Group B). The EQ-5D score was similar for both groups (0.77 (0.3) and 0.78 (0.3)), however PwH on prophylaxis treatment reported lower QoL in Group A versus Group B across age groups.

Conclusions: A high proportion of adult PwH requested more effective products, and especially PwH on primary prophylaxis; showing there is a need to further improve haemophilia care. The results indicate that perceptions around ways to improve care are associated with age, joint health, and the overall burden of the disease. Further assessment is needed to understand the contribution of these aspects to haemophilia-specific QoL.

Author Disclosures: JOH and DN are employees of HCD Economics, which received funding from Sobi for the research. K-JM, AW, and PK are employees of Sobi, a company involved in the development and commercialization of Elocta®. Sobi was involved in the development and review of the poster. The authors had full editorial control of the poster and provided their final approval of all content. The original data collection in CHESS was funded by Sobi, Bioverativ, and Novo Nordisk.

W-P-079 (369) | Knowledge Transfer of Musculoskeletal (MSK) Outcome Measures (OMs) to Improve Assessment of MSK disease in Persons with Hemophilia (PWH)

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Introduction and Objectives: Musculoskeletal (MSK) bleeding causes pain and disability in persons with hemophilia (PWH). MSK outcome measures (OMs) facilitate detection of early MSK disease and thus provide the opportunity for early introduction of prophylaxis aimed to delay the progression of arthropathy. Most OMs are in English and require local training of health care professionals (HCPs) to ensure competency in their administration. The objective of this project was to train Thai HCPs to competently administer and become local trainers utilizing two Thai translated validated OMs.

Materials and Methods: HCPs from 7 hemophilia treatment centers (HTCs) in Thailand, including 5 from northern Thailand and 2 from Bangkok attended a 3-day training workshop in 2016 and a 1-day

follow-up training course in 2017 led by international physiotherapists. An additional training by Thai experienced trainers was held in 2017 for new HCPs from the northern HTCs who did not attend the 2016 workshop. Key MSK-OMs, the Hemophilia Joint Health Score (HJHS) plus its instruction manual and training video and the Functional Independence Score in Hemophilia (FISH) were formally translated into Thai with content verification before use.

Results: Thirty Thai HCPs including hematologists, physiatrists, hemophilia nurses, physiotherapists and an occupational therapist were trained. Only three participants had some previous experience with the selected MSK-OMs. Seventeen PWH volunteered as subjects in the training sessions. The instructors and content were evaluated with mean scores of 98% and 96% respectively, indicating a high level of satisfaction. Most participants indicated a wish to have follow-up training courses to further enhance their competency with use of the selected MSK-OMs in their clinical practice.

Conclusion: Knowledge transfer of MSK-OMs is critical to improve MSK assessment of PWH in Thailand where resources are limited. The combination of external experts with selected local experts from one major HTC proved very effective in the training of inexperienced HCPs in HTCs located in Northern Thailand. Initial detailed training followed by a practical training workshop was a key to the success of the program and should facilitate this "train the trainer" approach to other HTCs in Thailand using local trainers alone.

W-P-080 (212) | The establishment of a managed clinical network to enhance collaborative provision of service for haemophilia in Scotland

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Haemophilia services in Scotland have a track record of working on a collaborative basis for the benefit of patients and to provide high quality and equitable health care for people with inherited bleeding disorders. Following years of informal collaboration between all professional groups a National Managed Clinical Network (NMCN) for inherited bleeding disorders was commissioned in 2016. The Scottish Inherited Bleeding Disorders Network (SIBDN) includes two comprehensive care centres (Glasgow and Edinburgh) and three Haemophilia Centres (Aberdeen, Inverness and Dundee). The new network is part of a group of over 20 other NMCNs in Scotland. Each network brings together everyone involved in providing specialist care for particular groups of patients with the rarest and/or complex healthcare needs. All NMCNs also have a remit to include patients and third sector groups. SIBDN encompasses a variety of personnel from multidisciplinary teams within the haemophilia centres in Scotland (medical staff, nurses, data managers, allied health professionals etc) as well as colleagues from NHS National Services Scotland who manage and fund recombinant and commercial concentrates for people with inherited bleeding disorders. It also includes representatives from patient groups as well as individual patient and carer representatives. Overall network strategy is set by a steering committee made up of a clinical lead, multidisciplinary staff from treatments centres across Scotland, with representatives from the network's work streams which also include patient group representatives. The network activities fall into three broad areas or work streams: Communication and Patient Engagement, Best Practice Policies and Protocols, and Quality Improvement, Data and Audit. Overall, the activities over the last 2 years of the MNCNs designation have proven to be valuable and inclusive though not without challenges. Moving forward the experience gained in this time can only ensure ongoing improvements in provision of quality haemophilia care in Scotland.

W-P-081 (220) | A single centre study to investigate the impact of autism on the management of severe haemophilia in children

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Introduction and Objective: Major advances in Haemophilia treatment have dramatically improved the quality of life for children with the condition, however for the small subset who also have Autism, management is anything but straightforward. The characteristics of Autism such as behaviour, communication and social interaction difficulties have a significant impact on their daily lives. This study aims to explore the impact Autism has on the management of Severe Haemophilia and to explore what specific challenges are faced from the caregiver's perspective.

Materials and Methods: Four boys with a diagnosis of Severe Haemophilia and Autism were included in the study. A mixed method approach was utilised to gather both quantitative and qualitative data. A simple questionnaire was devised incorporating both open and closed questions. The caregivers were asked specific questions about the challenges they faced in managing their child's Haemophilia and then given the opportunity to expand their answers. An analysis of "Haemtrack" data was also carried out in order to identify missed doses and explore the reasons treatment couldn't be given. The data was also used to determine whether a link between sub therapeutic treatment and Autism exists and what measures can be implemented to improve adherence.

Results: The preliminary findings suggest that Autism causes significant difficulties both psychologically and practically in the management of Haemophilia. The major challenges identified are around medication administration and ability to cope with unexpected events such as bleeds and hospital admissions. A review of "Haemtrack" data corresponds to the caregiver's perception that doses have frequently been missed due to the prohibitive

behaviours of the child. The information provided by the caregivers indicates that adherence has improved as the child has got older.

Conclusion: There is currently very limited research into the challenges associated with having both Haemophilia and Autism. The caregiver's feedback clearly demonstrates a need for further research and support. This study highlights some of the predominant issues associated with having both conditions and explores possible future improvements in caring for this specific patient group.

W-P-082 (250) | Delivering clinical trial opportunities at haemophilia treatment centre

Sarah Johns

Royal Cornwall Hospitals Trust, Truro, UK

Introduction and Objectives: Clinical Trials are a vital component of modern medical care and the NHS has a duty to promote research and innovation – "every patient should be offered the opportunity to take part in Research and Clinical Trials." The Truro Haemophilia Centre is located in the far South West of the UK. There are currently about 250 patients – adults and children – registered with inherited bleeding disorders of varying severity. The nearest Comprehensive Care Centre is located 170 miles away. Patients registered at the Truro Centre found it difficult to access Clinical Trials due to the distances that they had to travel. The Haemostasis Team in collaboration with the local Haematology Trials team, set up systems of work which enabled patients to take part in Clinical Trials which may have otherwise not been available or difficult to access.

Materials and Methods: The centre does not employ a dedicated Haemophilia trials team, but the Haemophilia Clinical team and the Haematology Trials team were keen to work together to make Haemophilia Trials available to locally registered patients. This development in practice involved education and collaboration at all levels. The first Haemophilia medicinal trial in Cornwall was in 2009 and was a Phase 1 recombinant VW Factor. Since then there has been a further Phase 1 trial, Phase 2 trials, Pharmacokinetic studies and several observational studies.

Results: Haemophilia Clinical Trials can safely be managed in a DGH without dedicated facilities. However, it does require the dedication and enthusiasm of the whole team. Collaboration and a good working relationship with respect for each other's roles have been essential. We have not found it difficult to recruit patients, although understandably some of the trials were too time consuming for some of our busier patients.

Conclusion: Development of an innovative way of delivering care has enabled patients to access Clinical Trials and has had the following benefits: Inclusion of greater numbers of patients in Clinical Trials; Access to new treatments that may not have otherwise been available to patients living in more remote areas; Raising awareness of Clinical Trials for patients with inherited bleeding disorders.

W-P-083 (340) | London 2020: Understanding patients and carers: Views of London haemophilia services and pathways

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Introduction: The UK health service has a reputation for high quality haemophilia services and pathways for patients. Around one-third of haemophilia patients are treated in London centres. As the range of treatment options grows and services respond to these changes, it is important to understand patients and their families' perspectives on what those changes may mean for them.

Methods: Haemnet set out to better understand the views of patients and their families about current services and the changes they would like to see. An online survey was promoted through posters in haemophilia centres, supported with a series of short videos hosted on Haemnet's YouTube channel and promoted through social media in an 8-week campaign. Survey completion was incentivised by donations to the Haemophilia Society.

Results: Of the 51 respondents, >50% were patients aged 20-79 years, 56% were aged <39. Most lived in Greater London (43%) or South East England (39%) with those furthest afield coming from the South West, North West and Yorkshire and Humber. Responses were received from patients attending all London Centres. Families and carers appreciated the responsive and high-quality services and facilities of the London centres, particularly the support and care they received from their nurses and physiotherapists. Access to clinicians with expert knowledge of haemophilia and their relationships with the teams was highly valued. Two-thirds of respondents expressed frustrations related to appointment inflexibility and information recording systems, particularly other hospitals' access to their information in emergencies. Lack of local specialist care and support was a further frustration, because of the resulting cost to families and carers in time and money. >70% of patients offered suggestions that would make a real difference to their care. These included updates on personnel changes in centres, more information on advances in treatment and access to new products, greater flexibility in appointments, and less variation in access to physiotherapy. A common theme was the desire that local health services and emergency services should have greater understanding of haemophilia.

Conclusion: Patients' views should inform the future shape of services as they respond to the changing haemophilia treatment landscape.

W-P-084 (349) | London 2020: Clinicians – perspectives on the future shape of London haemophilia services and pathways

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Introduction: The UK's National Health Service (NHS) has a reputation for high quality haemophilia services and patient pathways. These services currently face opportunities and challenges on three fronts: the growing range of haemophilia treatment options; greater engagement of patients in self-management; and the continuing goal of clinicians to improve clinical practice while the NHS is tasked with delivering efficiency savings. Around one-third of UK haemophilia patients are treated in London. We set out to better understand the current and future shape of London services and pathways.

Methods: We undertook a series of qualitative interviews with clinicians from across multidisciplinary teams in the London haemophilia centres and conducted a thematic analysis of these interviews.

Results: There is much that works well and impacts positively on the quality of life of people with haemophilia. For example, the excellent care provided through established formal pathways that enable patients from one hospital to access specialist services in others, most notably with respect to dental care. Informal pathways are being developed (e.g., for radiosynovectomy) that will further enhance the quality of care provided. The positive outcomes resulting from intensive treatment, effective MDT working, and the high levels and range of experience as well as access to clinical trials were further themes highlighted by interviewees. Looking to the future, recurring themes included the need to share experience of new treatments (such as, dosing strategies, the role of laboratories) and developing knowledge and understanding among patients and families/carers, particularly around access to new therapies. The importance of MDT involvement, the potential for greater and different nurse roles and the need for more physiotherapy and psychosocial support were also raised. Questions were put forward about the balance of outreach provision closer to home alongside evolving hospital provision to meet individual patient needs.

Conclusion: Working collaboratively in responding proactively to these changes was recognised as a central theme, as was the challenge of creating opportunities to do so while maintaining day-to-day delivery of care.

W-P-085 (391) | Use of ultrasound for assessment of musculoskeletal disease in persons with hemophilia: Results of an International Prophylaxis Study Group (IPSG) survey

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Introduction and Objective: Plain radiography (X-ray), magnetic resonance imaging (MRI) and ultrasound are important tools for the assessment of musculoskeletal (MSK) disease in persons with hemophilia (PWH). However, the role of ultrasound, especially point of care ultrasound (POCUS), remains to be defined. The objective of this survey was to evaluate the current use of ultrasound, including POCUS, for the assessment of MSK disease in PWH.

Materials and Methods: A web-based survey was sent to Medical Directors of a number of international hemophilia treatment centres (HTCs).

Results: Responses to the first invitation to participate were obtained from 99/302 (32.8%) of individuals with representation from 23/24 (96%) countries surveyed; subsequent invitations are planned. Responding centres included North America (44 respondents/184 submitted centres, 23.9%), Europe (40/89, 44.9%), Australasia (9/17, 52.9%), and South America (6/12, 50%). Of responses received, 65% were from centres that treat both adults and children, 21% solely pediatric, and 14% solely adult. Based on the number of patients with severe hemophilia A registered in the HTCs, 23% are considered small (up to 40 patients), 43%, medium (41-100 patients), and 33%, large (>100 patients). Regular use of X-ray, MRI and ultrasound were reported by 90%, 86% and 86% of respondents respectively. Reported use of POCUS varied markedly (0-53%) between countries. POCUS is most often performed by a physiotherapist (26/49, 53%) or a hematologist (21/49, 43%). The majority of centres who reported use of POCUS (42/49, 86%) had at least one staff-member formally trained in POCUS. POCUS is perceived as most useful to confirm an acute joint bleed (86.9%) and to confirm the presence of synovial hypertrophy (83.3%). The greatest perceived barriers to the implementation of POCUS are the lack of trained health care

professionals (68.2%) and the overall time commitment required to perform POCUS (64.8%).

Conclusion: Globally, there is variability in the use of POCUS. As more HTCs implement this relatively accessible technology, it is increasingly important to ensure that operator training is made available. Standardized and validated acquisition and interpretation protocols for POCUS should be implemented for use in the assessment of MSK disease in PWH.

W-P-086 (387) | Girdlestone procedure in a 50-year-old woman with Type 3 von Willebrand Disease (VWD) – reducing pain, restoring function and maintaining independence: the value of patient-centred care by the Multidisciplinary Team (MDT)

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Introduction and Objectives: Type 3 VWD is a severe, rare inherited bleeding disorder treated with prophylaxis factor replacement. Complications include pathological joint changes similar to those seen in severe haemophilia. A Girdlestone procedure, whereby the femoral head is removed, can be employed where infection leads to failure of total hip replacement (THR), frequently as a last resort in orthopaedic surgery. Anticipated outcomes are poor in terms of mobility, personal independence and the increased use of walking aids caused by a significant leg length discrepancy to the affected limb. This is the first time that this procedure has been performed in a person with Type 3 VWD further complicated by other lower limb joint replacements. Following a period of physiotherapy rehabilitation and podiatry input, pain was reduced, functional ability increased, and independence maintained.

Materials and Methods: A 50-year-old woman with Type 3 VWD underwent a Girdlestone procedure, due to failure of THR. Early interventions using a combined approach of physiotherapy techniques and podiatry, modified footwear and in-shoe foot orthoses in conjunction with orthopaedics follow-up were undertaken. The aim was to stabilise the joint, maintain muscle alignment and restore function with the expectation of increased wheelchair use.

Results: A Girdlestone procedure reduced pain to minimal levels facilitating intensive physiotherapy rehabilitation combined with podiatry modified footwear and foot orthoses. Collaboration with the patient's goals, function was restored to pre-morbid levels in terms of walking and independence was maintained.

Conclusion: A patient centred holistic approach to post-operative recovery may lead to an improvement in patient reported pain and disability. The value of the MDT in collaborating with patients should not be overlooked. Rehabilitation within the MDT may present an opportunity to improve function and outcomes measures in the older bleeding disorder patient group.

W-P-087 (464) | Impact of a nursing home support program for prophylactic factor administration in children with severe haemophilia

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Introduction and Objectives: Home therapy is a mainstay of haemophilia management. In certain situations, additional support may be needed to ensure safe and timely administration of factor prophylaxis in the home. While the majority of home support programs have been designed for aging or disabled men with haemophilia, there has been little data on their role in providing support for families of children with haemophilia. We report on the experiences of 3 families with complicated home situations who successfully transitioned to stable home prophylaxis with the assistance of a home support program provided by the factor manufacturer.

Materials and Methods: Three families of children with severe haemophilia A and complex home situations were reviewed. All children were switched to an extended half-life factor as a result of a change in national tender. Two of the 3 families had multiple boys with severe haemophilia A (4 in one family, 2 in another) in addition to other unaffected children. The third family consisted of an only child with difficult venous access issues that made transition to home therapy from regular hospital visits challenging. Nurse support in the home was managed through an independent company contracted out by the factor manufacturer. Clinical outcomes and impact on family quality of life were examined before and after home nursing assistance started.

Results: All three families had successful transitions to home nursing support. The family with 4 boys with haemophilia went from frequent to no hospital admissions for central line bacteremia once home support was provided. The other families saw an increase in quality of life due to the elimination of regular hospital visits for factor prophylaxis. One family reported more engagement of their boys in school activities as a result of decreased time away from school, more freedom with infusions at home, and more control over their lives.

Conclusions: Nursing home support programs have significant benefits for children and families of young children living with haemophilia. Their use should continue to be encouraged and supported.

W-P-088 (507) | How "good" a healthcare professional should be? An empirical study on the acquired and required psychosocial competences for comprehensive haemophilia care

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Introduction and Objective: The comprehensive care (CC) model promoted by the WFH is nowadays widely acknowledged, although its actual implementation is subject to considerable variations among Countries and/or Centres, due to socio-cultural aspects and resources availability. In this framework, healthcare professionals (HCPs) are asked to acquire psychosocial competences, which are transversal to various professions, but are also expressed and contextualised depending on the professional specificities and circumstances. This study, which is part of a two-year research project, aims to identify and describe such non-technical competences in relation to five major domains that a previous study recognised as representative of HCPs' experiences in working with haemophilia: dealing with policies, resources and stakeholders in the local care system; challenges when caring for impaired adult PWHs; diagnosis and counselling about reproductive choices; challenges when coping with adolescent PWHs; considering the impact of family dynamics.

Materials and Methods: Structured interviews with haemophilia HCPs, people with haemophilia (PWHs) and their family members, from seven different countries, were content analysed. Technical and non-technical competences and needs associated with different actors (i.e. HCPs, PWHs, family members) in the five domains were coded. Details about the interviewee (i.e. role, Country) were also considered to reflect on cultural and organisational specificities.

Results: The triangulation between the perspectives of the main actors involved in haemophilia care led to the identification of relevant needs and cross-professional and non-technical competences supporting the CC model. The representation of the HCPs' work will be described through the identification of the challenges to be addressed and the competences to be developed in each domain, introducing some reflections about how professional and cultural specificities may affect the CC model.

Conclusions: Overall, this research project contributes to improve knowledge and awareness of the different psychosocial aspects that the CC model requires to be fully achieved. Such knowledge can be integrated in research designs and can become the basis for further developments in interventions (e.g. training paths, work organisation in haemophilia CC centres). It can also be used for constructing a cross-professional and cross-national "core curriculum" in order to promote CC in haemophilia.

W-P-089 (696) | Paediatric early warning system in haemophilia patients: A consideration

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Introduction and Objectives: The Paediatric Early Warning System (PEWS) was implemented nationally two years ago in Ireland in 2015. It provides a framework for care and empowers staff to escalate care for children who show signs of deterioration or for whom there are concerns. The first doctor on call is notified at a PEWS score of 3, and senior medical staff are alerted at a score of 6. The objective of this study was to determine if haemophiliac patients were triggering on PEWS when presenting with a bleed.

Materials and Methods : A retrospective analysis of the PEWS charts of six patients who attended Our Lady's Children's Hospital, Crumlin over the period 2015-2017 was undertaken. Their PEWS score, which is based on the patient's vital signs, was examined. Each patient may 'score' between 0 and 3 on each vital sign based on deviation from the normal range for their age group. The information from each PEWS chart was collated to obtain the final results. Patient X had his blood pressure excluded from this study due to a known history of hypertension.

Results: Six patients were identified, all male, age range 4 to 15 years (mean 9.67 years). Patients were admitted with a variety of bleeds including head injuries, joint bleeds, muscle bleeds and haematemesis. Three patients had severe factor 8 deficiency, two had severe factor 9 deficiency and one had von Willibrand disease. All patients were admitted requiring treatment and observation for their bleed. The PEWS score for patients on admission to the ward were in the range 0-1 (mean 0.17). The PEWS score throughout their inpatient stay remained in the range 0-2 (mean 0.28). One patient had a subsequent bleed to another site while as an inpatient which PEWS did not detect; their PEWS score remained 0.

Conclusions: Care would not have been escalated to medical staff due to the PEWS score remaining lower than 3. Therefore, clinical knowledge and skill, and patient insight remain the best indicators of a bleed in a haemophiliac patient, consequently leading to appropriate management.

27-DATA AND DEMOGRAPHICS

T-MP-124 (424) | The World Federation of Hemophilia Annual Global Survey: Low dose prophylaxis

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Introduction and Objective: Through the Annual Global Survey (AGS), the World Federation of Hemophilia (WFH) has been

TABLE 1 Prophylaxis Regimes for Factor XIII, by GNI of countries.

	Total	High income	Upper middle income	Lower middle income	Lower income
High: 25-40 IU/kg every 2 days	13 (23%)	12 (92%)	0	1 (8%)	0
Intermediate: 15-25 IU/kg 3× per week	20 (36%)	4 (20%)	13 (65%)	3 (15%)	0
Low: 10 IU/kg, 2× per week	23 (41%)	0	8 (35%)	9 (39%)	6 (26%)

collecting national aggregate data on people with bleeding disorders since 1999. It is well established that prophylaxis is the gold standard for preventing bleeds and subsequent joint damage in persons with hemophilia. However, standard dose prophylaxis requires more clotting factor concentrate than on-demand therapy and is not economically feasible in many countries. Such countries have started using lower doses of prophylaxis, to gain the benefits of prophylaxis treatment while keeping costs down.

Materials and Methods: The Report on the AGS 2016 includes demographic and treatment-related data from 113 countries, representing 90% of the world population. The AGS began collecting data on prophylaxis in 2010. In 2015 a new question was added: "What is the most common dose (IU/kg) of factor administered and frequency?" Responses to this question have never been published in the AGS Report.

Results: Fifty-six countries provided data in the AGS 2016 on the most common dose of factor VIII and IX administered. Responses for factor VIII were classified according to intensity, as defined by the WFH Guidelines for the Management of Hemophilia (Table 1) The breakdown of the 23 low dose prophylaxis countries, by gross national income (GNI) per capita is: lower income (26%), lower middle income (39%), upper middle income (35%), and high income (0%). The regions with the most frequent use of low dose prophylaxis were Africa (39%), South-East Asia (17%), and Eastern Mediterranean (17%).

Conclusions: Data from the AGS illustrates that low dose prophylaxis is a treatment option being used in low to lower middle-income countries across the world. The WFH AGS data is available to the bleeding disorder community as an advocacy tool.

T-P-125 (670) | Single centre experience comparing Factor VIII half-life to von Willebrand factor levels and blood group in a cohort of severe haemophilia A patients

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Introduction: The role of von Willebrand factor (vWF) in primary haemostasis, and in the extension of Factor VIII (FVIII) half-life ($t_{½}$) by protection from catabolic degradation is well established in the literature. Furthermore, in recent publications FVIII concentrates containing vWF have been demonstrated to reduce the risk of inhibitor development in Haemophilia A (HA) patients, and to reduce the neutralisation effect of those inhibitors on FVIII replacement. Additionally, it is well understood that Blood Group O is associated with low endogenous levels of vWF in both the normal and HA populations. Case studies of patients with co-existing HA and von Willebrand Disease (vWD) demonstrate significant reductions in FVIII $t_{½}$. Less well explored is the impact of HA patients' baseline vWF levels, due to factors such as ABO Blood Group or other baseline variables, on the in-vivo $t_{½}$ of FVIII concentrates infused during HA treatment.

Material and Method: In this audit retrospective data were collected from medical records of HA patients treated with a vWF containing FVIII concentrate to explore links between baseline vWF (RCoF) levels, ABO Blood Group, prior inhibitor status and FVIII $t_{½}$ measured in a cohort of 28 patients. Data collection was completed between January and August 2017. Subsequent collection of missing datapoints was undertaken with the goal of achieving a complete data-set for this cohort.

Results: Baseline data showed inconsistency with $t_{½}$ data ranging from 4 to 11-time points. 66% (n = 18) patients were blood group A with 57% (n = 16) being A+. This is significantly higher than the national average (34%) and is unexplained. Baseline von Willebrand levels were not reported on most patients and led to further testing to complete the Audit.

Conclusion: These data provide interesting insights into the baseline characteristics of a relatively small cohort of HA patients. Further work is needed to investigate possible correlations between ABO blood group and HA and the influence of baseline vWF on in-vivo $t_{½}$ of FVIII concentrates in HA patients.

T-P-126 (797) | Severe hemophilia A in Colombia: Cost according to the therapeutic needs of patients

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Introduction: Hemophilia in Colombia is a disease that represents a high social and economic burden. However, the health system guarantees the access to all treatment for patients with this condition according to their needs.

Objective: To evaluate costs of treatment among patients with severe hemophilia A in Colombia.

Methods: This study identified the patients with severe hemophilia A using the data reported by the health insurance companies to Colombian High-Cost Disease Fund. We included patients without inhibitors (<0.6 BU/mL), patients with low-response inhibitors (0.6-4.9 BU/mL) and patients with high-response inhibitors (≥5.0 BU/mL), additionally, patients in prophylaxis, Immune Tolerance Induction (ITI) and patients with both treatments. The total costs for the patient attention in the last year were used. A comparison between the groups according to the presence of inhibitors and by the treatment was made.

Results: 970 severe hemophilia A patients were identified. 99 patients of them were excluded because were treated on demand depending on each bleeding episode and 15 didn't have costs information. Finally, were include 681 patients: 97.2% were in prophylaxis, 1.9% in ITI and 0.9% in ITI and Prophylaxis. The total costs paid for patients was US$ 65.933.252 in the last year. The average cost paid for a patient without inhibitors was US$71.060 far below that paid by the patients with low response (US$ 115.738) and high-response (US$336.571) inhibitors. According to the treatment, the average cost paid for patients in prophylaxis with clotting factor was US$ 71.211, less than the average cost when the prophylaxis was with a bypassing agent (bypassing agent 1 = US$ 334.037 and bypassing agent 2 US$ 238.315). An insurance company paid for a patient in ITI an average of US$ 461.186.

Conclusion: The need for a special treatment for this complication increases the cost for the healthcare attention around 3 times comparing patients without it. It is important to analyze the impact of policies into the health system related to the hemophilia including the pharmaceutical policy with the aim to make the changes required to achieve the best benefits for the health system and the patients.

T-P-127 (810) | Inhibitors incidence in the Colombian population with hemophilia

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Introduction and Objectives: The development of inhibitors in the population with hemophilia, is a situation that conditions the patients' clinical outcomes and the costs derived from their healthcare. The aim was to identify the presence of inhibitors and the use of immune tolerance induction (ITI) in the Colombian population with hemophilia.

Materials and Methods: a retrospective descriptive observational analysis was performed with information from the national registry of hemophilia and other coagulopathies of the Colombian High-Cost Diseases Fund. The information reported in 2016 and 2017 was used. Men with hemophilia of all ages were included. The statistical analysis was performed with Stata v.12 software.

Results: 2076 men with hemophilia were included, 84.3% (n = 1752) were type A and 15.6% (n = 362) were type B. 52.6% (n = 1.167) had severe hemophilia, 22.7% (n = 471) moderate and 21.1% (n = 438) mild, with a median age for each group of 21, 19 and 31 years old respectively. During the period, 27.3% (n = 319) of the severe patients had inhibitors. At the end the last year 14.2% (n = 165) had low-response inhibitors and 8.2% (n = 96) had high-response inhibitors. 19.4% (n = 62) of them had access to ITI at least once in their lives. The ITI doses ranged between 24 and 200 IU/kg. 3.7% (n = 12) of the patients with inhibitors received only ITI, 2.5% had ITI and prophylaxis with a bypassing agent, and 10% required on-demand therapy. During the last year the overall incidence of all inhibitors in the population was 9.0% (n = 188), 8.4% (n = 174) of low-response and 0.6% (n = 14) of high-response. 9.1% (n = 161) in hemophilia A and 7.4% (n = 27) in hemophilia B. In patients with severe hemophilia the incidence of all inhibitors was 11.9% (n = 140), 6.8% (n = 32) in moderate hemophilia and 3.1% (n = 14) in mild hemophilia. At the end of the year, 61.2% patients who developed inhibitors had a high-response inhibitor and 4.8% had low-response inhibitor.

Conclusions: The annual incidence of inhibitors (15%) is lower than the reported in other populations and the documented by the World Federation of Hemophilia (20-30%); the reason is not clear yet. It is necessary to continue gathering data to have more information about the true incidence of inhibitors in Colombia.

28-EDUCATIONAL AND COMMUNICATION MODELS

W-MP-098 (442) | Utilization of a virtual reality based tool in hemophilia education

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Introduction and Objectives: Virtual reality (VR) based platforms are increasingly utilized in medical education, primarily for training skills/training in surgical settings. This study compared use of VR based hemostasis education to conventional educational methods.

Materials and Methods: In 2016, a power point (PP) and VR module were developed to communicate FVIII production, structure, activation, function and inactivation. These modules were used during an educational workshop in 2016 and 2017; targeting

hematology fellows, physician assistants and nurse clinicians caring for persons with hemophilia and inhibitors. Learners were randomly assigned to one of two groups: VR or instructor-led-PP. Both groups completed a short, detail-oriented post-test. After the test, learners crossed over to the other educational modality. Between 2016 and 2017, the PP presentation and presenter were identical. The VR module was updated for 2017, based upon the testing results of 2016.

Results: We collected 42 responses, with scores summarized in Table 1. Group specific average correct responses were not significantly different between the two groups (PP group: 2016 average = 50% vs. 50.5% in 2017; VR group: 2016 average = 40% vs. 49.5% in 2017). Correct responses varied across different questions, without a similarity trend over the two years. Higher median scores were achieved in 2017 after revision of the VR module, but this difference did not reach statistical significance ($P = .26$).

Conclusions: Disappointingly, both VR and PP were modestly successful tools to promote hemostasis related education but by year 2, our VR based tool was comparable to the established methodology of teaching with PP/instructor led sessions. Learner feedback can be incorporated to enhance efficacy of VR tools. Future studies will be needed to better compare educational utility of VR and its effect on retention of material for clinician education. We plan to incorporate additional revisions to the VR module to enhance outcomes.

Table 1. Individual scores of learners – overall, and per comparison groups.

Comparison groups	Median score (%)	Range (%)	Comparison
All Individual Responses (n = 42)	45.5	18.2-100.0	N/A
Virtual Reality 2016 (n = 11)	36.3	18.2-72.7	$P = .39$
Powerpoint 2016 (n = 13)	36.3	18.2-100.0	
Virtual Reality 2017 (n = 9)	54.5	18.2-90.9	$P = .82$
Powerpoint 2017 (n = 9)	54.5	27.3-63.6	
All VR Responses (2016 & 2017)	40.9	18.2-90.9	$P = .44$
All PP Responses (2016 & 2017)	50.0	18.2-100.0	

P, *P* -value from Wilcoxon rank sum test with continuity correction; VR, virtual reality, PP, powerpoint.

W-MP-099 (723) | A novel patient educational strategy for families with children with hemophilia

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Introduction and Objective: Education in hemophilia is facing challenges in developed countries like Canada. The possible explanation for this is the improvement and access to treatment. When treatment was less available, both experiential learning from bleeding events, and more commonality in patient concerns synergized the patients and their family members to seek learning opportunities by actively discussing their disease with healthcare professionals and patient organizations. However, as treatment improved, disease morbidity decreased, leading to key issues in the education of hemophilia patients seeming less pertinent to families present day lives and knowledge fading more rapidly as the child ages without encountering disease complications. Scientific development has provided shield for the patients to live safer lives with minimal complications and the families' focus has drifted away from their child's medical condition. With this focus diverted, past health education strategies need to be adapted.

Materials and Methods: To increase interest and effectiveness of our hemophilia treatment center (HTC) hemophilia education, we set out to create a parent educational strategy driven by a family affected by hemophilia and fit better to today's learning environment. A partnership was struck with nursing and the parent to provide key content and user viewpoints. This team then went forward to create teaching vehicles formatted for commonly used social media platforms.

Results: Previous teaching strategies at our HTC were clustered at diagnosis and home treatment initiation time points. Education material had good content, but the format was deemed outdated. Key content from original materials were reformatted and represented in easily accessible videos and static information pages. These new teaching tools were then circulated to a small group of parents with children with hemophilia and usage and satisfaction results reported. Ease of use and accessibility characteristics were also examined.

Conclusion: Both updated information and delivering methods of the information are the key to the success of education in hemophilia. Our novel educational strategy was designed to tackle both. With the success of the pilot program, it would open new doors for education in hemophilia.

W-MP-100 (832) | Newly diagnosed family weekends

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Introduction and Objectives: Newly Diagnosed Family weekends are designed to reduce isolation and provide information and support for parents with a child who has recently been diagnosed with a bleeding disorder.

Methods: Weekends are designed to provide a safe and relaxed opportunity for parents to gain information from specialist nurses, physiotherapists and psychologists, as well as meet other families, youth ambassadors and local group representatives. This provides an opportunity to understand more about the bleeding disorder their child has, the impact it may have on family life, where they can find information and support as well as practical sessions with a physio on supporting joint good health. Often it is also possible to observe someone have treatment, either via a port or intravenously for the first time. The weekends are held in family friendly Centre Parcs resorts to bring about a sense of normal family life, and provide a creche for children; often providing an opportunity for the parents to leave their child with a stranger for the very first time. For many families, this is the first opportunity to meet other parents who have a child with a bleeding disorder.

Results: Families report 100% satisfaction rates with the weekends and report leaving with increased confidence. Many feel empowered to have more informed conversation a with their health professionals, and to enable their children to become more active and less restricted in their everyday activity. Families connect with The Society at an early point, build lifelong relationships with each other and the charity.

W-MP-101 (188) | Evaluation of a program to improve identification of new hemophilic patients in Mali: Lessons and challenges

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Introduction: Hemophilia is a rare bleeding disorder which is lest diagnosed trough the world. Around 90% of the 70% of undiagnosed patients live in developing countries such as African black countries. In Mali around 95% of potentials hemophilia patients were not identified and cannot accessed to any treatment. To improve hemophilia care in Mali by identification of new patients, and increase access to treatment, we have initiated a training program which involved health care providers, patients and their families and traditional practitioners. Here, we report our lessons from this program which could help others team.

Methods: A prospective training program concerning 5 regions and the district of Bamako in Mali was initiated during two (2) years. The study included three health professional from different districts and hospital: medicine doctor, nurse and lab technician. To improve the identification of new case, we associated the traditional practitioners strongly involved strongly in health system in developing countries. The training session for patients concerned presentation of hemophilia, symptoms, diagnosis treatment and complications. During these sessions, both oral presentation and video projection about hemophilia in Mali were given.

Results: The overall program included 408 participants: 179 health care providers, 24 patients, 79 members of hemophilia family and 126 traditional practitioners. A first important direct impact was the development of relation between these two groups (patients and family and traditional practitioners). Another direct impact was the transfer of some patients from traditional office to the hospital for diagnosis and treatment. More we initiated the development of a direct relation between traditional practitioners and the teams in charge of hemophilia treatment. Finally the program led to increase the number of identified patients through 42 in 2016 to 103 patients in 2017.

Conclusion: The integrate hemophilia care program which included patients, patients families members and traditional practitioners seems a good strategy to improve identification of news hemophilia patients in developing countries.

Keywords: bleeding disorder, hemophilia, development country, Mali

W-MP-102 (498) | Patient perspectives on and preferences for future treatments for haemophilia

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Introduction: Treatment options for haemophilia have advanced rapidly in the past decades and new products such as gene therapy and extended half-life coagulation factor products are currently under development.

Objective: To gain insight into the perspectives and preferences of persons with haemophilia (PWH) for future treatment options. A better understanding of their perspectives will help tailor information provision about new treatments.

Materials/Methods: A qualitative study was performed in PWH recruited through the Dutch Haemophilia patients' association, the haemophilia clinic at the Academic Medical Center in Amsterdam,

the Netherlands and by a call in a haemophilia Facebook group. Semi-structured interviews were held with 14 persons (including 2 mothers of children aged 7 and 10 years) with moderate-severe (n = 3) or severe (n = 11) haemophilia A or B. Ages in the adults ranged from 21 to 74 years old. We aimed to include PWH with varying engagement in the haemophilia community and therefore possibly different levels of familiarity with new treatment options. Interviews were transcribed verbatim. A thematic content analysis was used with the help of MAXQDA (version 12).

Results: Participants experienced no great difficulties with their current treatment. Some mentioned non-adherence to their treatment schedule and enjoyed taking the freedom to adjust their schedule to their needs. Therefore, they did not feel the need for new treatments in the near future for themselves but believed that new products might benefit others for whom injecting was more difficult or for those who struggle with haemophilia. Reasons to switch to new products would be fewer injections, alternatives for injecting, faster administration modes and lower costs. Respondents also mentioned knowledge of side effects to be important in their decision to switch. Participants had limited knowledge about future treatments and assumed they would be informed about them by their treating physician. When PWH searched for information on new therapies on the Internet, this information was often difficult to find or to understand.

Conclusions: PWH are not familiar with future treatments and existing information is too difficult or hard to find. There is an opportunity for clinicians and patient associations to provide information about new treatment options in a patient-friendly format.

W-P-103 (48) | Bleeding disorders education day for school nurses

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Introduction and Objective: As a nursing quality improvement project, the Hemophilia Treatment Center of Valley Children's Hospital found an unmet need to educate school nurses regarding their responsibilities caring for children with bleeding disorders. Coordinated effort was developed and implemented for an eight county and 29 school district to address the needs in elementary to secondary schools. School nurses are often the first medical professionals to see children in our service area. At Valley Children's, 25,000 of 146,000 unique patients in 2016 did not have primary care physicians. By surveying school districts, a half-day conference was organized for school nurses at Valley Children's Hospital campus on Saturday August 27, 2016 from 8:00 am to 12:30 pm. Invitations were sent to school districts in eight counties served by our clinic. Valley Children's funded the event at no cost to participants.

Materials and Methods: To announce the conference, each VCH, HTC patient was given a flyer to return to their schools. Additionally, school districts within the eight-county service area were sent email, FAXs, mailed formal invitations or reached by phone.

Results: There were 29 school districts within the eight-county area represented. The 86 participants represented the following disciplines; 2 Nurse Administrators, 69 School Nurses; 7 Acute Care Nurses; 5 LVN's; 1 Medical Assistant; 1 Teacher and 1 Health Aide. One participant traveled 130 miles. Physicians, pediatric nurse practitioners, registered nurses, and social workers gave presentations about hemophilia A/B, and von Willebrand Disease. Reviews of physiology and case data illustrated various issues school nurses encounter. Nurses were encouraged to question hospital staff and explain their unique needs. Particular attention focused on services clinic staff could offer. Pre-test and post-test analysis showed improvement from 63% to 98% correct knowledge, indicating a significant increase in nurses' knowledge. Participants expressed the need to learn more about Hemophilia A/B, von Willebrand's disease, including Women and girls with bleeding disorders.

Conclusion: This format received high marks from school officials and met expectations of school nurses at the conference. Conference evaluation showed increased confidence to care for students with bleeding disorders.

W-P-104 (35) | A training program for self infusion

David Hopper

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Introduction and Objectives: Self-infusion of prophylaxis for children can be quite a difficult time in the transition period in haemophilia. Children have to overcome barriers such as fear and a lack of confidence when learning to self-infuse. A program to help educate children about the importance of correct use of prophylaxis currently does not exist. The long term benefits compliance with prophylaxis provides may help overcome these barriers to self-infusion and help patients take ownership of the condition at the earliest possible opportunity.

Materials and Methods: Infusion, confusion education day is aimed at children with severe haemophilia, taking regular prophylaxis and is led by the paediatric nurse and physiotherapist. All children in this cohort between the age of 9 and 16 years old linked to Newcastle Upon Tyne Hospitals where invited to attend the course. Five children with severe haemophilia agreed to attend. The content on the course included a section on understanding haemophilia with an interactive part in which the children talked about their own diagnosis. The importance of prophylaxis and regular exercise was detailed in a short presentation. A practical element which allowed the children to practice self-infusion using an artificial vein, with the possibility of practice on the nurse was used to help overcome fear and a lack of confidence.

Results: The children were asked to fill in a short questionnaire about how they found the self-infusion workshop.

TABLE 1 Questionnaire

Question	Response
Do you enjoy the workshop?	Yes (×5)
What was the best aspect of the workshop?	Practicing self-infusion ×5
Are you ready to learn to self-infuse?	Yes (×5)

Conclusions: All children who attended the course reported the session was very educational and they enjoyed practicing self-infusion. Leaving the session they all agreed to continue the process of learning to self-infuse and follow up appointments were made with the family to help achieve this outcome. This course seemed a success and we hope to discuss rolling it out across the UK.

W-P-105 (145) | Educational puppets for hemophilia: The old versus the new

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Health Sciences North, Sudbury, Canada

Introduction and Objectives: An event was held for families affected by hemophilia and other bleeding disorders. During an educational session we compared 2 puppets representing boys with hemophilia. Are the improvements on the new puppet beneficial in making the puppets a useful tool for education on hemophilia?

Materials and Methods: We supplied and explained both the puppets and their accompanied resource story book. Individuals were given time to interact with each puppet. We gave each individual an evaluation form with 3 questions. 1) What do you like/dislike about the new version of the puppet? 2) What do you like/dislike about the old version of the puppet? 3) Is there anything missing on the puppet to improve teaching?

Results: The old puppet's colour wasn't realistic and didn't look like a boy. They found that it was light weight and would be easy to travel with. It was easily undressed and most commented that they liked the fact that a tooth could easily be removed and was a good teaching point. The new puppet had a more realistic look resembling a boy. He had a new style of clothes but had too many layers and was more difficult to undress. He was too big and didn't sit as well on a person's lap. The knee joints looked more realistic and he had a medic-alert bracelet on.

Conclusions: At the end of the session the families stated that there were some flaws in both puppets but they were both good teaching tools and it helped making learning about hemophilia fun for children. The adults admitted that they also had fun with this learning opportunity. The children found that the new book was very interactive.

W-P-106 (185) | Development, evaluation and updates of HIRT? (Hemophilia Injury Recognition Tool)

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Background and Objective: Young men with mild hemophilia (YMWMH) do not bleed frequently, and thus can experience delays in recognizing when a musculoskeletal injury requires medical attention. To overcome this challenge, and with the longer term goal of preventing significant health consequences, our team of clinicians, researchers and young men with mild hemophilia developed a mobile app that YMWMH can use for self-assessment of musculoskeletal injuries. We have conducted an evaluation of this mobile app, ***HIRT?*** (Hemophilia Injury Recognition Tool) on perceived injury self-management in YMWMH in Canada. We present the process of the app development, outcome data from the evaluation and forthcoming app updates.

Methods: Qualitative research to understand the experience of living with mild hemophilia. Development of a self-care-pathway which on request from YMWMH was created into an app. Evaluation of perceived injury self-management strategies and participant confidence levels. Non-parametric: Wilcoxon and McNemar tests were used to determine association between perceived self-management strategies when using and not using the app with significant levels set at $P < .05$. Qualitative data was created using Interpretive Description analysis of recorded and transcribed interviews. Recommended improvements are being implemented.

Results: Eighteen YMWMH were engaged during the development process. Twelve young men aged 18-35 years participated in the evaluation. Perceived confidence levels significantly increased ($P = .004$) with the use of the app. Five qualitative themes were identified: accessibility, credibility, the benefit of alarms, confidence and usefulness. Improvement ideas were also identified relating to the app utility.

Conclusion: This study provides promising evidence to support the feasibility and use of ***HIRT?*** as an injury self-management tool for YMWMH. Future research could investigate the effect of the app on injury self-management and the potential use of the app internationally.

Keywords: Mobile app, injury self-management, mild hemophilia.

W-P-107 (215) | Experience of basic course of physical therapy in haemophilia in South America

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Introduction: In South America the major health policy in haemophilia is not only the access to medical treatment, but also the physical treatment to prevent and give solution for acute and chronic musculoskeletal disease for haemophilia. However, there is not a consensus of which topics are necessary for a curricular for basic course in physical therapy and haemophilia care. The principal aim of this study was reporting the general knowledge before and after basic training and satisfaction of participants.

Method: Twenty-eight-physical therapists and two medical doctors were recruited. The participants were from Chile, Uruguay and Paraguay. The structure of the training and exam were designed by three physical therapists with more than ten years of experience and one expert in health science education. The training course consisted in sixteen hours in two consecutive days. It was divided in four aspects: 1) Primary issue of physiopathology in haemophilia; 2) Physical assessment; 3) Basic element in medical treatment and physical therapy; and 4) Clinical examination in real patients (six patients). An evaluation exam was done [scale 0-10] before and post-course, also applied a satisfaction questionary based a Likert scale [1-5]. The non-parametric statistic was applied to know knowledge improvement before and after course.

Results: The initial experience in haemophilia participants was a median of 0 year [min: 0 max: 30]. The initial qualification was 6.5 [min: 3.9 max: 8.7], the final qualification was 8.9 [min: 7.6 max: 10], with significant difference between both ($P < .001$). The satisfaction of course based a Likert scale by participant was 4.8 ± 1.

Conclusion: The results showed a significant knowledge improvement about basic topics in haemophilia and with excellent satisfaction of participants. In this course we proposed sixteen hours to give basic aspects in treatment for physical therapist related with haemophilia patients.

W-P-108 (227) | eLearning of pharmacokinetic monitoring in hemophilia with application in the clinical practice

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Introduction: Individual pharmacokinetics profiling (iPK) in hemophilia has become a useful tool to individualize prophylaxis in each patient. Exploiting the potential of iPK requires education of physicians to the use of PK population models in their routine clinical practice. The aim of this initiative is to provide theoretical bases to introduce hematologists in the use of WAPPS-Hemo platform in the personalization of hemophilia therapy.

Methods: We performed an online theoretical and practical course, in which each participant could access to the virtual content of four of the modules. The virtual academic platform included interactive video classes, scientific bibliography and real practical cases. Each teaching module was composed of a masterclass talk by one of the teachers along with scientific articles complementing each presentation. Furthermore, a permanent forum was provided for interactive consultations, comments and suggestions from participants. The Bayesian PK tool employed was WAPPS-Hemo, a Web-Accessible Population PK Service for all existing factor concentrates. The 4 modules were: 1-Introduction to PK analysis and population PK models. 2-Presentation of the WAPPS-Hemo, applications and clinical utility. 3-Independent exploration of the platform by working on their own patient data. 4-Interactive questions and answers regarding the use of the platform.

The expected duration of the course is 22 hours. The course material is available in English and Spanish. The course realization was made possible by an educational contribution from Bayer Healthcare.

Results: The course was piloted in Colombia. One hundred and seventy health professionals' and experts in the management of hemophilia participated in the course: 85 adult hematologists, 40 pediatric hematologists, 17 general doctors/other specialties, 14 pharmacists, 6 nurses and 8 other health professionals. Experts in PK monitoring from McMaster University and Hospital La Fe thought the course. Participants received a certification of the training course issued by McMaster University in Canada once the course had finished and passed the written test.

Discussion/Conclusion: Bayesian estimate allowed to know the individual PK profile and could be a useful tool to individualize prophylaxis. The positive feedback provided by participants to the first edition of the course makes us consider performing further editions in Colombia and in other countries.

W-P-109 (275) | The marketing of your NMO

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Introduction and Objectives: When we talk about marketing, people immediately think that we are talking about a large and global company. But marketing is something so normal in our lives that we do not realize how important it is. The personal image that we project can affect or improve your marketing before other people. During my experience with hemophilia I have noticed the misuse of the image that maybe we can project to others. When someone hears the word hemophilia without knowing the meaning, we can receive already a rejection. I have discovered that the same thing happens when NMOs go to the radio, to television or to an interview with a health authority to discuss benefits. In the same way, I have seen that the NMOs maintain problems of participation and lack of volunteers, their relations with the pharmaceutical companies are not the best and in some NMOs the board does not know how to improve their relationship with other organisms or societies. My objectives are to transfer the knowledge and result that I have based on the experience in improving the marketing in my NMO and my personal business in Panama. Educate and help the participants to find feasible tools in order to reach the loyalty of volunteers or patients to their NMO. Educate the leaders to see their NMO transformed into a large company where economic, social and participatory benefits can be obtained. Everything is possible in the adaptation of good marketing for NMOs.

Methods : Induction, analysis of examples and presentation of completed projects.

Results: We have achieved the recognition of private companies in which we have been able to collect money for our foundation, the percentage of participation in the activities increase, also the number of activities and projects, a corporative vision within an NMO.

Conclusions: Many times, we do not achieve our goals because we do not know how to use the tools that help us to achieve it. Marketing is a tool that is used every day in every place on the planet.

W-P-110 (324) | Von Willebrand in pictures

Sue Ann Hawes

Canadian Association Nurse in Hemophilia Care, Halifax, Canada

Introduction and Objectives: A nursing group recognized the need for a visual and portable tool for teaching about Von Willebrand Disease (VWD). Currently, there is a well utilized resource for hemophilia published by the World Federation of Hemophilia (WFH) called Hemophilia in Pictures. It is available in binder format along with a CD power point presentation. This resource is visually appealing with illustrations that allow for easy interpretation by all learners regardless of language spoken, level of literacy or learning limitations. A new resource tool for VWD has been developed using the same concept as Hemophilia in Pictures however to keep up with advancing technology an iPad version was developed. This format allows for greater flexibility when presenting the information and can be used in a variety of settings including summer camps, small clinic spaces, school classrooms and any other area where computer access is limited.

Materials and Methods: Appropriate pictures were designed to narrate each section of the presentation and to clearly explain VWD using limited text. This initiative received funding for a pilot project involving 10 Hemophilia Treatment Centres (HTC). An iPad was provided to each clinic for trial over a 3 month time frame to evaluate its effectiveness. During the initial pilot project this presentation was only available in English. A measurable survey in the form of a questionnaire was designed and distributed to all the pilot sites.

Results: The results from the survey were extracted and collated. An evaluation was completed and this tool was proven to be effective.

Conclusion: It is important that health care professionals have clear concise tools for teaching. The desired outcome for this project was to have a teaching tool that would provide up to date, clear, simple and valuable information about VWD for all learners.

W-P-111 (796) | Bringing families affected by Factor XIII deficiency together for a novel educational program

Dawn Rotellini; Kate Nammacher; Meagan Richards; Sarah Waite-Ardini

National Hemophilia Foundation, New York, USA

Introduction and Objectives: Factor XIII (FXIII) deficiency is an extremely rare factor deficiency, with an estimated incidence of 1 in 3 million births. Living with or supporting someone with a serious, extremely rare bleeding disorder can be stressful, especially when they don't have a comprehensive understanding of their condition. There is little consumer education for people living with Factor XIII deficiency in the United States leaving this community with minimal support or education. As a result, the National Hemophilia Foundation (NHF) created the *Strength in Numbers: F13 Family Conference*, a live educational conference. The program has been held annually since 2015.

Materials and Methods: Families were recruited through word of mouth and attended an on-site reception with other FXIII program participants, as well as two educational sessions in 2017. The first educational session focused on the basics of FXIII deficiency from a medical standpoint, while the second focused on the psychosocial aspects of living with FXIII deficiency.

Results: Since 2015, the number of families in attendance increased by 33%. In 2017, a total of 16 families attended (46 individuals, 19 of which are affected). Not all families had previously attended—37.5% of families were new to the program in 2017 and 50% were new in 2016. Overall, participants find value in the program for two reasons: meeting and bonding with people affected by FXIII deficiency and learning

alongside of them. In 2017, overall participants said they strongly agreed with the value in meeting other people affected by FXIII deficiency. They also strongly agreed that the educational sessions were relevant to them. One participant's comments sum up both of these sentiments: "Finding the patients and what symptoms they have had and just the information on FXIII helps when going back home."

Conclusions: The growth of this program alone demonstrates the need for consumer education for those living with FXIII deficiency. The program has not only brought people affected with FXIII deficiency together, but it has helped build ongoing networks of social support.

W-P-112 (800) | Factor X deficiency consumer education program's inaugural year

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National Hemophilia Foundation, New York, USA

Introduction and Objectives: Factor X (FX) deficiency is an extremely rare factor deficiency, with an estimated incidence of 1 in 1 million births. Living with or supporting someone with a serious, extremely rare bleeding disorder can be stressful, especially when they don't have a comprehensive understanding of their condition. There is little consumer education for people living with FX deficiency in the United States leaving this community with minimal support or education. As a result, the National Hemophilia Foundation (NHF) created *The Power of Ten*, a live educational conference.

Materials and Methods: Families were recruited starting with outreach to local chapters, NHF's social media channels and local HTCs. From there, initial families were recruited and then awareness of the program spread by word of mouth. A physician and a nurse were recruited to lead two separate educational sessions. One session focused on the medical aspects of FX deficiency (genetics, diagnosis and treatment). The other session, led by a nurse, focused on the psychosocial aspects of living with FX deficiency. Participants were asked to fill out an evaluation form at the end of the conference.

Results: A total of 11 families attended the inaugural conference, which was a total of 43 individuals. Of those, 30 participants that completed an evaluation, on a 5 point Likert Scale, participants said they "agreed" to "strongly agree" (4.76) with the following statement: "I found value in meeting with other people affected by FX deficiency." From a qualitative perspective, 15 comments related to meeting other people affected by FX deficiency were found the participant evaluations. For example, one of these comments reflected the sentiment of the response: "It was amazing to meet others with FX deficiency for the first time. I'm finally not the only one!"

Conclusions: The inaugural year of this program has allowed people affected with FX deficiency to meet and build a community of those affected by this rare and serious bleeding disorder.

W-P-113 (806) | Inhibitor teams: building stronger connections and deeper learning

Dawn Rotellini; Kate Nammacher; Meagan Richards; Sarah Waite-Ardini

National Hemophilia Foundation, New York, USA

Introduction and Objectives: The National Hemophilia Foundation (NHF) has offered the Inhibitor Education Summits (also known as the summits), a live consumer education conference, annually for more than ten years. The summits are for people with hemophilia A or B with an active or tolerized inhibitor and their support network. In 2017, NHF introduced a new component to the conference: Inhibitor Teams.

Materials and Methods: NHF met with the National Inhibitor Summit Steering Committee in 2016 and developed the idea of Inhibitor Teams as a way to better engage participants by connecting them with other members of the inhibitor community that they might not otherwise meet. Inhibitor Teams are small groups of randomly assigned participants that meet three times throughout the conference. Some Inhibitor Summit faculty and NHF staff moderated their pre-assigned group's discussions as Inhibitor Team Leaders. Inhibitor Team Leaders were trained prior to each summit. Each participant's badge included their Inhibitor Team name on it as a way for participants to easily identify their team members. The conference app was adapted to foster team member connection.

Results: A total of 214 families (727 individuals) attended the summits in 2017. Of these families, 11.21% had never attended summit before, so connecting with fellow participants was particularly meaningful. Likewise, active inhibitors were represented in 56% of the families; through their Inhibitor Teams they could connect with others that have been or are going through the challenge of an active inhibitor. Participants on average agreed (4.19 on a 5 point Likert Scale) that they found value in meeting with their Inhibitor Team. Qualitative evaluation data collected also supports this. For example, one participant said, "teams were a great way to meet folks I otherwise may or may not have met or got [the] chance to talk to. Like meeting others that share same life experiences as myself and my family."

Conclusions: Inhibitor Teams were a welcomed addition to the Inhibitor Summit program in 2017 with participants finding value in the time spent with their team.

W-P-114 (562) | The age of technology: skype vs. face to face teaching

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Background: NHS England is under increasing pressure to deliver high standards of care whilst optimising service efficiencies. It is essential for clinicians to adopt innovative ways to deliver gold standard healthcare.

Teaching is a key aspect of the physiotherapy and nursing roles to educate those involved in the care of children with haemophilia (CWH). At our centre we conducted a pilot study to evaluate the effectiveness of teaching and to establish Skype based sessions.

Method: Over a 3 month period we introduced skype as an alternative method of teaching. All sessions were conducted by a physiotherapist and nurse. The aim was to increase confidence of those caring for a CWH and their knowledge of recognising/managing bleeds. Questionnaires were designed using a combination of Likert scores and qualitative questions and sent to evaluate the session, assessing knowledge of Haemophilia pre/post teaching, comparing them to the initial learning objectives. In addition a cost analysis was carried out.

Results: Three face to face and skype sessions were conducted, the response rate for the questionnaire was 100% and 14% respectively. Initial analysis showed an overall increase in confidence in managing a CWH post teaching from 1/ 2 on the Likert scale to 4/5, for both delivery methods. 100% of teachers felt they would still contact the parents and the first aiders but would additionally contact the Haemophilia centre after the session. Post teaching all were able to recognise and manage a bleed appropriately.

Conclusion: This pilot study has shown that both methods result in increased confidence with the management of CWH. Skype based teaching sessions considerably reduce the cost to departments and NHS Hospitals. One limitation is the availability of the appropriate IT equipment within the school to deliver skype based teaching. The intention in the future would be to extend this to those caring for mild and moderate CWH.

W-P-115 (743) | Hemophilia at school: Training education professionals for the assistance to students with hemophilia

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Introduction and Objectives: Hemophilia is poorly known by most education professionals, giving rise to the exclusion of students with hemophilia from regular activities, and jeopardizing their learning and development. This work aimed to evaluate the impact of a project (Hemophilia at School) consisting of school visits for providing reliable information to education professionals in charge of students with hemophilia.

Materials and Methods: We visited hemophilia patients' schools and performed lectures consisting of basic concepts about hemophilia, identification of bleeds, Dos and Don'ts in case of bleeds and necessary adaptations for hemophilia patients. Thoughts of education professionals and hemophilia patients relatives regarding the training were assessed using specific questionnaires.

Results: Schools of seven unrelated hemophilia patients were visited between february and november 2017, with the participation of 62 education professionals. 32/62 (52%) of professionals answered the post-training questionnaire. Among them, 26/32 (81%) felt more confident in working with hemophilia patients at school, 25/32 (78%) reported a higher level of communication between the school and the families of hemophilia patients, and 32/32 (100%) considered the training important for their work. 18/32 (56%) transmitted the acquired information to relatives, friends or other professionals, and 23/32 (72%) were able to properly describe actions to be done in case a student with hemophilia has a bleed. Regarding parents, 6/7 (86%) answered the questionnaire. 1/6 (17%), and 6/6 (100%) rated as positive the attitude of education professionals with respect to hemophilia before and after the training, respectively. In comparison to 1/6 (17%) before the training, 6/6 (100%) reported to feel comfortable in leaving their children in school after the training. With respect to school dynamics, parents perceived education professionals more confident regarding hemophilia and how to act in case of bleeds, and reported increased participation of their children in school activities after training.

Conclusion: Providing training for education professional through school visits is efficacious to increase participation of hemophilia patients in school activities, and is also a strategy to ensure good care for them in case of bleeds, and to reduce parents concerns.

W-P-116 (603) | 'My Haemophilia Centre' App – Immediately available essential information for patients with haemophilia and IBD

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Introduction and Objectives: The optimal management of patients with inherited bleeding disorder (IBD) requires clear communication, education and information between both patients and their haemophilia Centres. Information and knowledge tends to get fragmented in memory and not updated. This can result in patients attending A&E 'out of hours' at their local DGH (District General Hospitals) with little

or no knowledge of who to contact and similarly, for surgical/dental procedures or precautions for travelling abroad. The 'My Haemophilia Centre' app allows patients to quickly and simply access trusted quick-reference information, online or offline, at any time of the day or night. This empowers patients to advocate for themselves/family members when needed. It is easily branded to patients own centres.

Materials and Methods: After preliminary work to understand online sources of haemophilia specific information, an initial patient focus group established 'what would be useful' to patients via an app. Key insights were: Can be long periods where patients have limited connection to their Haemophilia Centre; patients require information at certain times, i.e. travel, dentist appt; in an emergency patients need to have the correct contact number in hand; communicating via e-mail or post only reaches some patients. In July 2017 a pilot App was launch at The Royal London and a project plan for over 50 patient downloads. The app is free to download from iTunes or Google play but requires a centre specific code to activate.

Results: A Patient and Public Engagement meeting was held in October 2017 whereby patient feedback included 'how useful' this app had been for him– "you tend to forget what you know" – "the contact my centre direct link was really useful when you are experiencing a bleed and fumbling to try to get the correct number as your mind goes blank". We have had over 200 downloads in the 3 months of pilot and feedback so far is very positive.

Conclusions: A generic haemophilia centre app that can be "adopted and branded" by any haemophilia centre offers great potential to share important emergency and educational information between centre staff and their patients and families. Disclosures: My Haemophilia Centre App - developed in collaboration with Pfizer.

W-P-117 (585) | The role of pharmacy in education and training in hemophilia care in Kenya

Samuel Mbunya

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Background: At AMPATH Hematology, the Hemophilia education and training program was initiated in 2012, with support from the Indiana Hemophilia and Thrombosis Centre (IHTC). In 2017, after 5 years of education and training it was noted that there were challenges in managing acute and chronic bleeds in patients with hemophilia and that the pharmacy had an important role to play in improving patient outcomes through a multiformat educational initiative for pharmacists.

Objectives: 1- Promote the involvement of Pharmacists and pharmaceutical technologists in the education and training forums. 2- Examine the various pharmacologic approaches to the treatment of patients with hemophilia, including patient-specific factors to consider. 3- Discuss selected treatment strategies for patients requiring hemostatic agents. 4- Identify patient counseling strategies that can help pharmacists enhance treatment adherence and reinforce physician-prescribed hemophilia care. 5- Identify elements of a systems approach in which pharmacists utilize their knowledge of hemophilia to work with patients and other healthcare professions and develop appropriate, effective treatment strategies that optimize outcomes through treatment monitoring, patient education, and utilization management.

Discussion: Patients with hemophilia who present with acute or chronic bleeds, or have to undergo surgery are a challenge in the Kenya hospital setting, and pharmacists can provide assistance in initiating therapy with hemostatic agents and play a key role in dosing, and monitoring. These educational trainings will provide an overview of the epidemiology and pathophysiology of hemophilia and will outline various strategies for treatment of patients with hemophilia, specifically those with acute and chronic bleeds or planned surgeries. Factors to consider when making formulary decisions regarding hemostatic agents will be presented during the trainings.

Conclusion: The care of hemophilia patients is challenging and the role of pharmacists in the care of hemophilia patients in Kenya is slowly evolving. These education and training initiatives will focus on the efficacy, safety, and role of newly approved therapies for hemophilia A or B for the prophylaxis in the prevention of long-term complications of hemophilia. How pharmacists can enhance treatment adherence and reinforce treatment outcomes will be determined through these educational initiatives.

W-P-118 (623) | Knowledge and improvement of health literacy and numeracy in adolescent patients with hemophilia A and B

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Introduction and Objectives: Prophylactic treatment with factor concentrate improves life expectancy and quality of life by minimizing bleeding in Hemophilia A and B patients, but adherence to treatment is essential. Several barriers to adherence exist. Health literacy (HL) and numeracy (HN) are likely underestimated barriers, especially in adolescents, but may influence how health-related information should be presented to help their readiness for transition to adult care. This longitudinal pilot study was designed to assess cognition, HL and HN of hemophilia patients, age 12-21 years, as it relates to number of joint bleeds, understanding of their factor product, and their treatment adherence over 6-12 months, while using visual aids and personal education to simplify difficult health and numeracy concepts related to hemophilia management, including drug pharmacokinetics.

Material and Methods: There were 2 study visits for each subject. Visit 1: Initial assessment including demographics, prior hemophilia management, MoCa cognitive testing, baseline HL using REALM-teen and our own HN tool, and an educational intervention regarding PK terminology and justification for prescribed treatment regimens.

Visit 2: Repeat assessment of HL and HN and re-evaluation of hemophilia management 6-12 months later. Adherence to prescribed factor dosing, number of ER visits, number of joint bleeds and joint scores were collected.

Results: 34 subjects are enrolled to date. On initial assessment, 94% of subjects had normal cognition, however 31% (11/34) were reading at or below 7th grade level and 38% (13/34) were not health numerate. Only 50% knew their estimated infusion dose of factor. Visit 2 data has been collected for 12 subjects (35% of 34) to date. There was a 50% improvement in knowledge of factor dose, 25% improvement in numeracy, and 25% improvement in adherence to prophylaxis. Three subjects had increased joint bleeding and worsening joint scores, all related to trauma during busy summer months.

Conclusions: This interim data suggests a deficiency in HL and HN in adolescent patients, where personal educational intervention may improve knowledge about managing their hemophilia which may ultimately improve adherence and joint health.

W-P-119 (622) | Hemophilia eLearning modules: A resource to improve care

Georgina Floros; Sarah Crymble; Colleen McNamee; Orla Smith; Pavandeep Dhillon

St. Michael's Hospital, Toronto, Canada

Introduction and Objective: Hemophilia and other inherited bleeding disorders are rare. With the majority of patients treating their bleeding disorder in the home and comprehensive care centres, hospital staff rarely encounter these patients. Hospital staff need a resource that will allow them to learn about hemophilia and other inherited bleeding disorders, quickly and efficiently, at times when they encounter these patients. The objective of creating an e-Learning module is to provide staff with enough information, in a short amount of time, to have preliminary understanding of the management of hemophilia and inherited bleeding disorders. An additional objective is to educate hospital staff that patients with bleeding disorders are active participants in their health care who typically are highly knowledgeable about their disease and treatment needs. The goal was to have hospital staff feel more competent when caring for this patient population, including knowing how and when to seek expertise from the Hemophilia Comprehensive Care Team.

Materials and Methods: With support from the education department, an e-Learning module was created with three main areas of focus (1) Blood Disorders 101 (2) Prevention and Early Assessment and (3) Treatment. The e-Learning module can be accessed by any staff at St. Michael's Hospital and will be promoted by the Hemophilia Comprehensive Care Team.

Results and Conclusion: In a busy hospital inpatient setting, education needs to be easily accessible. E-Learning is an excellent way to educate staff quickly and at a time that is relevant to their practice.

W-P-120 (727) | Enhancing postpartum care of women with bleeding disorders through awareness and self-empowerment

Georgina Floros; Michelle Sholzberg; Filomena Meffe; Jessica Petrucci; Justin Pham

St. Michael's Hospital, Toronto, Canada

Introduction and Objectives: Women with inherited bleeding disorders are more likely to suffer from post-partum bleeding than the general population. In the St. Michael's Hospital multidisciplinary clinic for women with bleeding disorders, a primary goal is to provide perinatal care to mothers and babies. Expecting mothers of our clinic are seen by an adult hematologist, an obstetrician, an anesthesiologist and pediatric hematologist. Following their antenatal assessment a summary plan is developed that outlines the care of mother and baby at the time of labour and delivery and in the post-partum period. Our practice is to use tranexamic acid for a minimum of 10 days post-partum to minimize immediate and delayed post-partum hemorrhage. New mothers are preoccupied with caring for their new baby and they often forget to take care of themselves. Therefore, many experience unnecessary post-partum bleeding and do not connect with our team to adjust care.

Materials and Methods: In response, we created a resource to educate new mothers with inherited bleeding disorders about the importance of managing postpartum bleeding by encouraging appropriate use of tranexamic acid and to provide prompts for reconnecting with our clinic. An additional goal is to ensure that our patients feel supported, self-aware and empowered once discharged from hospital. Specifically, the pamphlet outlines what kind of bleeding is to be expected after childbirth and helps guide new mothers to recognize when bleeding is worrisome, reminding them to contact the clinic for care and/or present to immediate medical attention.

Results and Conclusions: We have anecdotally observed that taking tranexamic acid appropriately and for as long as is clinically indicated improves post-partum quality of life. This education pamphlet represents the main intervention of a quality improvement project that is assisting our team to achieve a reduction in post-partum bleeding in women with bleeding disorders followed in our multidisciplinary clinic. We have completed the first Plan-Do-Study-Act (PDSA) cycle of this project and are moving into the next phase where will we integrate directed feedback from patients to further positively impact their care. In future PDSA cycles, we plan to formally assess post-partum health-related QOL and iron stores.

W-P-121 (631) | First National USA Type 3 Von Willebrand Disease (VWD) Conference

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Introduction and Objectives: It is estimated there are approximately four hundred Type 3 Von Willebrand Disease patients in the United States. Patients often experience severe bleeding episodes and many psychosocial challenges. Being a rare disease state, both experienced medical and psychosocial support is not always readily available to patients. Patients are often isolated from other Type 3 VWD patients, resulting in a lack of peer support. In response, the First National Type 3 Von Willebrand Disease Conference was held in May 2017 in Florida, USA. The goal of the conference was to connect patients with each other, medical professionals and the bleeding disorder community in a safe and supportive environment.

Materials and Methods: Eighty Type 3 VWD patients, along with a companion(s), were provided an all-expense paid four-day conference to connect, learn and share experiences. Patients came from over 30 different states and ranged in age from one to seventy-five years old. A twenty-two member faculty and a staff of fifteen presented educational programs and facilitated social activities throughout the conference, resulting in a total attendance of 240. The conference faculty included doctors, nurses, social workers, physical therapists and bleeding disorder educators and represented a variety of medical specialties including hematology, gynecology, dentistry, genetics, pain management and psychology. To guide the educational content, patients were asked at registration what medical and psychosocial issues they find the most challenging. The conference consisted of ten full-assembly sessions and a choice of seven breakout sessions offering nineteen different topics. An electronic audience response system (ARS) monitored the attendees' comprehension and material's effectiveness along with collecting patient data.

Results: Sixty-five patients participated in the ARS. When asked if their pre-questions were answered, 93% responded with either "yes" (81%) or "no, but know how to get it now" (12%). Additionally, 47% stated they have never met another Type 3 VWD patient outside of their own family. Ninety-eight percent would attend this event again.

Conclusions: Assessment of the patients' responses indicate an increase in medical knowledge and community resources and intention to act on information received. Disclosure: E.K. provides educational consulting and programs for Bayer and National Hemophilia Foundation.

W-P-122 (640) | Preparing for a child with a bleeding disorder to start school: A combined team approach

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Division of Hematology/Oncology, IWK Health Centre, Halifax, Canada

Introduction and Objective: School participation is essential for a child's physical, mental, and social development, however for children with bleeding disorders safety is a main concern and finding the right balance of school activities can be challenging and intimidating for school personnel. Education around the management of bleeding disorders in school has traditionally been provided through the family and/or nursing. A combined role offered by nursing and physiotherapy may prove to enhance education and alleviate stress associated with physical activity participation and management. The effect of a combined education session is expected to result in high levels of staff and family satisfaction in feeling prepared for the child starting school, as well as improve school participation.

Materials and Methods: 12 in-person school visits were performed by either the nurse coordinator alone or through a combined session with the team physiotherapist for children with severe bleeding disorders that were starting school. Education was provided by the nurse coordinator on general bleeding disorder topics, while physiotherapy provided more in-depth information about activity considerations. General feedback was collected after the session.

Results: Feedback was compared between the two visit types. General themes indicate staff and families favored the combined nurse and physiotherapy combined sessions. Additional information around activity participation and safety was thought to be beneficial. All parties reported feeling better prepared for the child to start school in a safe manner in comparison to if no activity teaching took place. It was felt that students were better integrated into regular programming with activity teaching.

Conclusions: Combined school visits with both nursing and physiotherapy resources resulted in high parent and staff satisfaction around the child with a bleeding disorder starting school, and lead to levels of school participation that was similar to their peers. Formal evaluation is planned to be collected via survey. Future studies are indicated to explore how combined visits may best support school transition. Additional school educational resources around activity are being developed as an aid for visits.

W-P-123 (661) | International Hemophilia Knowledge Translation Program (HemoKT): A community-driven peer-to-peer international education project

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Introduction and Objectives: In the realm of bleeding disorders (BD), knowledge translation (KT) is a constant challenge. Patients without an adequate understanding of their disease are not aware of the mechanisms of the pathology, treatment options, and the importance of treatment. A good use of Information and communication technologies (ICT) could help remedy this problem. This project intends to facilitate KT pertaining to the molecular mechanisms involved in the development of BD, prognosis, treatment options and the importance of treatment for patients with coagulopathies; and to give patients from NMOs around the world the opportunity to further develop their understanding of their pathology, making them patient experts who will be able to help educate their peers.

Materials and Methods: After a survey of the most important concepts relating to BD, a series of 5 minute YouTube videos will be developed. These videos will be hosted on a website named the International Hemophilia Knowledge Translation Program (HemoKT). It will contain a community-driven wiki, a forum, useful links and a FAQ page. This material will be developed by two hemophilia patients (both authors). The website will be translated into multiple languages by collaborating hemophilia patients in different regions of the world. All video content in each different language will be reviewed by qualified hematologists who will be identified on the website.

Results: This is an ongoing project. Two videos on hemophilia and three on von Willebrand disease have already been produced and have been published on YouTube. The videos total 3,719 views; 57% of the views were by males; the age group that most viewed included between 35 and 44 years, followed by the population aged 25 to 34 years, and the population aged 45 to 54 years.

Conclusion: The high number of views obtained for the first videos demonstrate that there is a need for KT in the BD community, and that engaged and informed patients are well positioned to accomplish this task using ICT. During the 2018 World Congress, the project team will present the first version of the HemoKT website (in Portuguese and English) and current statistics.

W-P-124 (690) | Parents empowering parents (PEP): It's a small world after all

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Introduction: Parents Empowering Parents (PEP) was introduced at the 1996 WFH Congress while PEP was rapidly spreading across the hemophilia community in the USA. It is a global program, offering parents of children with inherited bleeding disorders an educational and psychosocial opportunity to gain parenting insight, to build parenting skills, and to encourage parents to raise their children to become independent and productive adults. The goal of PEP is to empower parents to overcome feelings of hopelessness, helplessness, and isolation that prevent them from raising their child to be a productive adult. PEP was written and introduced in 1996 by the HTC at Children's Hospital of Michigan USA. Since that time, PEP has proven to be a viable global psychosocial intervention for parents focusing on the emotional impact of raising and empowering children with an inherited life-long, complicated medical condition. This presentation features a panel of professionals who have brought PEP to their countries, highlighting the role professional collaboration has played in empowering parents through PEP in their various countries.

Method: A trained team of professionals and parent-peers teaches PEP to parents. The 2 ½ day PEP program operates in fourteen countries around the world. To date, PEP has been translated to other languages. Notably, the program has been adapted for use with parents of children with sickle cell anemia and autism. PEP's growth and development would not have been possible without the sustained sponsorship of Bayer Pharmaceutical, along with support by other global companies.

Outcomes: PEP currently serves parents in 14 countries in collaboration with the USA PEP team. The result: over 2,300 parents across the globe have been educated, supported, and empowered through PEP. Reducing isolation, increasing parental education, and increasing improved medical treatment and care have been the outcome.

Conclusions: Through global collaboration efforts, families living with inherited bleeding disorders have the increased possibility of receiving education through PEP to empower them to gain parenting skill and better cope with their child's medical condition as well as empowering their children to become a productive, capable, and contributing adult.

W-P-125 (722) | Questions and answers on gene therapy for persons living with a rare bleeding disorder: Methodology and results to build knowledge in our community

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Introduction and Objective: Gene therapy (GT) is one of the promising treatments to cure hemophilia. More and more French hemophilia society (AFH) members are asking for information about it and want to understand it. On May 20th, 2017, AFH built a one-day national meeting on GT opened to people living with a rare bleeding disorders (PRBD), their parents, doctors, pharmaceutical companies,

researchers, and journalists. Since the concept of GT is still not well understood in our community, we had to help the community build a common understanding and a questioning that facilitate the acquisition of knowledge.

Materials and Methods: The First session allows all PRBD to familiarize themselves with the concept of gene therapy (3 basic schemes were given to the audience) in an interactive workshop (3 workshop co-animated by a PRBD and researcher/caregiver) and to formulate questions so that during the second session, which involved two experts of the gene therapy, answers would be given or debated.

Results: 75 registrants, 4 themes and 14 questions emerged: GT in general: 1) When does GT trial start in France and when is it available? 2) Is GT applicable to all rare bleeding disorders? 3) Is GT a personalized treatment or a standard one? 4) What are the principal vectors associated with GT? Risks and follow up: 5) Are there any risks such as cancer, thrombosis, immunogenicity, toxicity? 6) is it possible to terminate the GT (switch off)? 7) What is the follow-up/monitoring during the trial and after? 8) Is it a sole or multiple injections? 9) Can the injection(s) be combined with current standard treatment? Cure or not: 10) is GT a real cure? 11) Can the disease still be transmitted during the treatment? Economics and ethics: 12) Cost per treatment and pharmaceutical companies, social responsibility? 13) Access across the world to this innovation? 14) Can all patient have access to GT?

Conclusion: At the end of the day, 94% of the participants found that the program had met their expectations. A brochure outlining the work done will be published in 2018.

W-P-126 (724) | Empowering French people concerned or affected by Von Willebrand disease (VWd) to live with their condition

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Introduction and Objective: Currently, most people living with VWD in France still don't have access to therapeutic programs as people living with Hemophilia. The Von Willebrand (WD) Committee within the French Hemophilia Association (AFH) worked together with the healthcare and patient community to implement changes to improve VWD patients care and quality of life.

Materials and Methods: The VW Committee conducted an analysis of over 500 emails from a secure internet forum made available to the VW community. Twelve themes emerged from this study, one being therapeutic education. The Committee then reached out to a interdisciplinary team made of hematologists, nurses, physical therapists, pharmacists and parents-patients resources (PPR); recognized in the community as experts in this field. With the forum analysis and interviews of VW support group members the team elaborated five therapeutic education workshops tailored to VW patients: 1 I bleed, what do I do; 2 Communicate, how to say, to explain; 3 Physical activities/Sports; 4 Women questions; 5 Autonomies, how to take care of myself. Also created was a weekend therapeutic education workshop for patients above ten years old and their family members; this allowed long-distance commuters to participate serenely in the workshops.

Results: AFH organized in 2016 and 2017 a national weekend VW therapeutic education workshops for 50 participants about 25 families. In two sessions conducted and co-animated by four hematologists, four nurses, two physical therapists and two PPRs. The first year's workshop was filmed to promote Therapeutic Education via social media and the AFH website. The target audiences are patients, immediate family members, and health professionals. Testimonies from participants and workshop facilitators were used to explain purpose and benefits of such event with a particular emphasis on what participants have learned and what had changed in their relationship with VWd.

Conclusions: The numerous positives feedback from participants of weekend VW therapeutic education attests to the VW committee's action. The Committee will continue to create workshops on new subjects.

W-P-127 (728) | Factors and obstacles to peers' involvement (parents-patients resources) in educational actions

G. Duport; P. Guillon; T. Sannié; S. Ayçaguer

Association française des hémophiles (AFH), Paris, France

Introduction and Objectives: Since 2008, the community grouping of rare bleeding disorders (RBD) in France is involved in the Parents-Patients Resource Program (PPR) initiated by the French Hemophiliacs Association (AFH). This program aims to integrate parents or patients trained in Therapeutic Education (TE) into the design and implementation of educational sessions in collaboration with caregivers. In 2017, PPRs were invited to meet and to give account of their actions.

Materials and Methods: A 2-day seminar brought together 13 PPRs (ie 1/3 of the PPR) from 11 Hemophilia treatment centers (HTC's) as well as a caregiver from an educational team. Each PPR presented their achievements in cross-exchanges. 15 types of difficulties emerged from a Metaplan®. Solutions were developed (envelop games). The solutions were challenged by the caregiver.

Results: It has become apparent that the function of PPR goes beyond the simple role of educator to their peers: personal valorization, self-confidence, taking initiatives, positive impact on professional

life. 4 areas of improvement have emerged: Better integration into the HTC team by taking into account the constraints of each; Finding time to make yourself available as a PPR; Strengthening your animation skills during educational programs; Develop a common culture in TE with all actors.

Conclusions: The commitment of caregivers and PPRs in collaborative educational work requires the efforts of everyone. The AFH must not only train PPR (10 pairs PPR-carers will be formed in 2018) but also be more responsive to the difficulties of PPR and more present in accompanying actions in the field.

W-P-128 (809) | Giving men with VWD a voice

Corinne Koenig; Kate Nammacher; Felix Olaya

National Hemophilia Foundation, New York, USA

Introduction and Objectives: Von Willebrand disease (VWD) is the most common bleeding disorder, affecting men and women equally. Despite this, awareness surrounding VWD is low. Outreach efforts often only target women, leaving many to assume VWD does not affect men. To begin changing this perception, the National Hemophilia Foundation (NHF) conducted a needs assessment to understand men's awareness of VWD and experience getting a diagnosis for future programming.

Materials and Methods: On behalf of NHF, Harris Poll conducted a nationally representative online survey. In 2016 1,002 adult men were interviewed to learn about their health behaviors and awareness of VWD. A second online survey was conducted targeting men who were diagnosed with VWD to learn about their path to diagnosis and the impact of VWD on their lives. This survey was given to adult men in the US from 2016 to 2017 and 49 responses were included in the analysis.

Results: The Harris Poll found that only 28% of men say they are aware of VWD and 68% are not sure of the symptoms. Medical providers (69%) are the main sources the men turned to for information about their health, followed by internet sources (40%). The second survey found almost 60% of respondents diagnosed at 18 years of age and older. When asked what motivated them to seek medical care, 45% cited a significant bleeding incident. Over half reported limitations to work, physical and social activity. Medical providers were one of the most common sources of information and support for men with VWD and the first place men went for information. NHF created a website where men can take an online self-BAT (bleeding assessment tool) to see if they are at risk for VWD and next steps to follow. NHF developed a webinar on VWD in men for medical providers outside of hematology.

Conclusion: More awareness of VWD is needed and outreach focused online and to medical providers. Diagnosed men need more education and support surrounding their disorder. NHF will continue to pursue outreach efforts and creation of resources for men with VWD.

W-P-129 (827) | Ageing with a bleeding disorder

Elizabeth Carroll

The Haemophilia Society, London, UK

Introduction and Objectives: The Societies services are designed to reduce isolation and provide information and support for our community as they get older, they aim to reduce isolation, and provide information, support and the opportunity to meet others who may be living with co-morbidities.

Methods: We filmed several members of our ageing community to understand more about their everyday life. This film included those from age 30 as many of this community did not receive prophylaxis as a child and have had joint damage as well as being infected with HIV and Hep C, so have different experiences than those younger than this. We also filmed interviews with a specialist nurse and physio. The interviews and a member survey helped us begin to develop new services and resources. Several unexpected outcomes arose from the filming and member survey including huge concerns over needing to move to a nursing or care home with multiple conditions and how high quality care would be maintained and suitable placements identified. We are developing a care home resource pack that will be available for members but will also provide information for care home staff and commissioners who pay for care.

Results: A new care home resource pack will be developed and available at Congress to meet the needs of the ageing community who have complex and multiple health needs as they get older.

W-P-130 (828) | Inhibitor support

Elizabeth Carroll

The Haemophilia Society, London, UK

Introduction and Objectives: The Societies Inhibitor conferences and activity are designed to reduce isolation and provide information and support for anyone living with or caring for someone with an inhibitor, they aim to reduce isolation, and provide information, support and the opportunity to meet others living with an inhibitor.

Methods: We filmed several members of our community living with an inhibitor to understand more about their everyday life. This film included those with an inhibitor, their family and carers. We also filmed interviews with a specialist nurse and physio and are about to undertake a member survey to fully understand the community's needs. We have developed conferences and events to bring the inhibitor community together to provide a safe and relaxed opportunity for parents and adults to gain information from specialist nurses, physiotherapists and psychologists, as well as meet other families living with an inhibitor as well as informing members about new treatment developments. We are developing an inhibitor resource for the affected community that will address the needs highlighted

in the film project and member survey. This pack will be described further in the post and will be available at Congress.

Results: Members have informed us they feel empowered to have more informed conversation a with their health professionals, and to enable their children to become more active and less restricted in their everyday activity following our inhibitor conferences. Members with long standing inhibitors feel more informed and less isolated following the conference. We aim to present the results of the inhibitor survey in the poster, with outcomes and impact.

W-P-131 (829) | Local heamophilia groups around the United Kingdom

Elizabeth Carroll

The Haemophilia Society, London, UK

Introduction and Objectives: Families and individuals affected by a bleeding disorder can often feel a sense of uncertainty and isolation. Local groups provide a vital network of mutual support for the people with bleeding disorders around the United Kingdom enabling members to meet others in their local community. Potential members are currently recommended by The Haemophilia Society UK or given information by their local Haemophilia Centres.

Materials and Methods: Local groups organise social events within their area to provide an environment in which families and the bleeding disorder community can come together. This creates the opportunity for families to share their experiences, which in turn increases each other's knowledge around the disorders and increases awareness into new treatments and other support available. One example of a local group is the Lincolnshire Haemophilia Group (LHG) which within the past few years have hosted events including Christmas lunch, Strawberry Tea, ten pin bowling, as well as walking, cycling and swimming activities.

Results: Each event hosted by LHG welcomed between 10 and 20 members. Through these events a local support network has been established, creating invaluable friendships between each of the families and the Heamophilia nurses. Wendy, a current member of the LHG and said, "The information provided by the Heamophilia centres are useful however the most helpful information came from speaking to other parents who have gone through the exact same thing." As well as providing support between individuals, the local groups contribute by fundraising and campaigning for the Heamophilia Society UK. The local groups are increasing public awareness of bleeding disorders through fundraising events as well as previously providing funding for travel and accommodation to national and international haemophilia events for their members.

Conclusion: Local groups create a community which can reduce the feeling of isolation in people affected by a bleeding disorder in their local area.

W-P-233 (160) | Addressing teacher's fears of haemophilia – 10 years of a successful model

Julia Ekert; Chris Barnes; Janine Furmedge; Nicola Hamilton

The Royal Children's Hospital, Melbourne, Australia

Introduction and Objectives: The Royal Children's Hospital, Melbourne has held an annual haemophilia teachers' seminar with the support of the local Haemophilia Foundation since 2006. The goal of the seminar was to address a perceived lack of information available to schools in assisting families dealing with the stress of a child with a bleeding disorder starting pre-school or school. In addition there remains significant uncertainty amongst educators regarding haemophilia management and expectations of having to deal with a child with a life threatening bleeding disorder.

Materials and Methods: The seminar program includes a formal series of lectures from the multidisciplinary team and an interactive session where boys with haemophilia share their experiences of having haemophilia in the home and school environment. Formal evaluation has occurred over a ten-year period via written questionnaire completed at the end of each seminar. A combination of question types was used, including a five-point rating scale to evaluate the overall value of the seminar and whether teacher expectations were met. In addition, focused and open-ended qualitative questions were used to explore what teachers considered to be key messages and to invite positive and negative feedback to guide future seminar content.

Results: Feedback from participants has been overwhelmingly positive. Ninety-eight percent of respondents felt their expectations had been well met (rank 4-5) and that the seminar was very valuable (rank 4-5). Themes identified from comments include reduced teacher anxiety, confidence to manage injury/bleeds, the importance of normalisation and an appreciation of parental anxiety. The interactive session with the boys and their parents has proved to be the most popular part of the seminar.

Conclusion: Modification of the haemophilia teachers' seminar based on feedback has resulted in a program designed to meet the needs of educators in providing information and support about children with bleeding disorders. The success of the seminar highlights the potential for this type of education format to be incorporated into a comprehensive haemophilia treatment centre. This model may also be appropriate for other medical conditions.

29-FAMILY ISSUES

T-FPMTD-002 (545) | Burden of bleeds and other determinants on caregivers of children with moderate or severe haemophilia – Results of the BBC Study

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Introduction and Objectives: Caring for a child with haemophilia can cause a great burden to the caregivers reaching from personal sacrifice, financial impact on the family to emotional stress of the caregiver. Data on caregivers' burden in haemophilia are scarce. Recently a haemophilia-specific caregiver burden questionnaire was developed in the US (HEMOCAB™), the situation in Europe is still not known. The aim of the study was to assess caregivers' burden and to evaluate the impact of bleeding on caregivers in 7 European counties (France, Germany, Italy, Poland, Sweden, Turkey and UK).

Methods: The 'HEMOphilia associated CAregiver Burden scale' (HEMOCAB™) was distributed to caregivers for completion. Socio-demographic data were collected in addition to clinical data of their child, which was retrieved from medical records.

Results: So far, data from 88 caregivers (mean age 38.07 ± 6.7) and their children with haemophilia (mean age 8.47 ± 5.4 years; range 0.55-17.73) from 5 countries (Germany, Poland, Sweden, Turkey, UK) have been collected. Caregivers were caring for children with mainly haemophilia A (86.4%), severely affected (86.4%) and who were receiving prophylaxis (83%). Children had on average 3.58 ± 4.9 total bleeds and 1.56 ± 3.1 joint bleeds. 27.3% reported chronic pain with intensity (VAS) of 5.86 ± 2.4 (range 1-10). Most caregivers were female (85.2%), married (77.3%), living with a partner (83%), had a higher educational level (61.3%), and 64.7% were working, mainly full time (38.6%). 20.7% had a long-term condition themselves; 64.8% reported that haemophilia affected the family life and 34.5% said that haemophilia had an economic impact on the family. The HEMOCAB™ showed good psychometric characteristics in terms of internal consistency (Total Score α =.970). Caregivers reported highest burden in the domains 'Perception of your Child' (M = 43.94 ± 25.3), 'Emotional Stress' (M = 41.0 ± 22.5) and 'Impact on You' (M = 33.24 ± 28.4) of the HEMOCAB™. Caregivers burden was significantly higher when joint bleeds occurred (P < .0001).

Conclusion: HEMOCAB™ was demonstrated to be a good instrument to assess caregivers' burden in Europe. Caregivers felt mainly impacted in the perception of their child and their emotional stress related to caring for a child with haemophilia. Counselling and/or support programmes should be implemented to reduce the burden for caregivers of children with haemophilia.

Keywords: caregiver burden, haemophilia, Europe, HEMOCAB, assessment.

M-MP-148 (516) | The family attention program: Evolution and settlement after 40 years

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Introduction and Objective: The family attention program (FAP) began 40 years ago when the Catalan Association of Haemophilia was founded and, since then, it has been a priority for the entity. Throughout these years, the FAP has evolved, adding new activities according to the possibilities and needs of each historical moment. This work has two objectives: 1. the study of the FAP evolution and; 2. The definition of its current characteristics.

Materials and Methods: To develop the study, we had diverse meetings with: Different Board members of the organization (5); Families with haemophiliacs of different ages (10 children, 10 adolescents and 10 adults) that represent 13.5% of the community with severe coagulopathy; Professionals that have worked in the association: 1 psychologist, 1 social worker, 1 masseuse, 1 yoga instructor and 1 administrative; Volunteers that have collaborated with the entity: 1 male nurse, 1 pedagogue. We also reviewed materials, reports and magazines done throughout the history of the organization.

Results: We realize that some of the needs of the families throughout history are the same, while others are different. The critical moments are: diagnosis, start of the domiciliary treatment, HIV and HVC coinfection, and secondary effects of the antiretroviral and/or hepatitis C treatments, chronic pain due to arthropathy, hospital admissions, family loss and grief process, migration fact when it is the case. These needs have been faced through diverse ways and specific programs from volunteers to professionalized services. The example of other families or people with haemophilia is valued as the best reference.

Conclusions: The current FAP is characterized by being an integral program focused on the person and his/her family with the objective of improving the quality of life through activities framed in different areas: social, educative and psychological. Some activities are focused exclusively on the carers more than the haemophiliacs. Some of the activities go beyond the specific organization and serve as a model to other community entities with which we work in network or through twinning programs.

M-P-149 (230) | Psychological burden of hemophilia on family's functioning: Which place for siblings?

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Introduction and Objectives: Living with a child affected by a bleeding disorder such as hemophilia has consequences on family's functioning. The daily life is usually centered on the care management and has to be adapted to the special needs of the child who suffers from hemophilia. Each member has to define his own role on this particular family functioning, especially siblings. In fact, parental, social and medical attention are oriented on an eventual hemorrhagic event and set up rules to prevent it. The sibling's relationship is carefully observed to protect the child affected which may lead to forget sibling's special needs as normal children. The main objective is to understand the psychological consequences of hemophilia on the family functioning, especially on siblings. We aim to set up a specific therapeutic support dedicated to siblings of children with bleeding disorder.

Materials and Methods: 23 families participated to a psychosocial study. Sibling's relationship, psychological well-being and quality of life of siblings and parents of a child with bleeding disorder were assessed by quantitative methods. A qualitative study is actually under process to understand the parent's subjective perceptions on the hemophiliac burden on the family functioning. Two trained psychologist will conduct non-directive and taped-recorded interviews with parents. The data collected will be entirely transcribed and analyzed with the Interpretative Phenomenological Analysis (IPA) method. Themes will be extracted from the speech to highlight specific issues from the parent's experiences.

Results: We attend to include half of the participants from the quantitative study in the qualitative one. The non-directive interview permits to highlight if the sibling's issues are evocated by parents spontaneously or not and which place they have on the family functioning. As caregivers, we need to allow for a special place for each member of a family affected by a chronic disease, especially for siblings as human being.

M-P-150 (285) | How to prepare for a good school start for children with bleeding disorders?

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Introduction and Objectives: When children with bleeding disorders start school adaptations are needed – first and foremost, informed personnel and an action plan is necessary. Some cases also require that the school is extra equipped. The presented study maps the perceived needs of parents and school principals in Sweden. The study results were used as the foundation for an action plan.

Materials and Methods: A company specializing in surveys conducted interviews with 20 parents of children with various bleeding disorders and 7 principals (and 1 teacher) of schools in different parts of Sweden. Interview results were anonymized and compiled by the company.

Results: Parents and school agreed on some parts of the needs prior to school start, i.e. that parents should be initiating the contact. Both parts stressed the important role of the hemophilia treatment centers, and it became obvious that needs vary between families: some families wanted the school to first contact the treatment center if something happened whereas other families wanted to be informed before the treatment center was contacted. Parents would like the school to be more proactive with information about whom at the school to contact, and they see the need for involving all school personnel. Schools referred to the importance of planning ahead and the need of a step-by-step action plan. Schools and parents disagreed on informing classmates and their parents, where schools generally wanted to be more open and families more closed, with some families preferring to just tell a selected few.

Conclusions: Expectations and needs vary for each child starting school. However, basic demands remain the same and some of them may be catered for with an action plan. Besides creating a well-founded action plan, we also found areas to examine further like the relationship between parents, school and health care.

M-P-151 (783) | Bringing together 24 children to the French Hemophilia Association (AFH) summer camp: A balance between educational and recreational

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Introduction and Objective: Young people living with a rare bleeding disorder often have difficulty going on vacation. For two weeks, ones every two years, the French hemophilia association (AFH) offers to children from 9 to 14 years old a secure environment to meet, exchange and learn. The main objectives are: to strengthen the link

between the AFH and families, to give them a break in the daily management of the disease, to offer therapeutic education sessions (TE), to organize and secure a first departure, to acquire autonomy.

Materials and Method: Organization of this type of event must be validated by the French administrative authorities. The AFH has an official authorization. The supervision of 24 children consists of a director, 4 animators, 2 nurses, 1 physiotherapist, 1 representative of the AFH, patient resource and health professionals to co-animate the TE workshops. A special communication is set up between the nearest hemophilia treatment center and the AFH. Summer camp's activities: 2 half-days of nautical activities (sailing or paddle), 1 day of tree top forest adventure, 3 days of cultural visit, 3 half-days TE sessions: how to get ready for a long stay trip; sport practice; to say or not to say about my illness, 3 half-days health education physiotherapy, 3 half-days education health nurse, 1 half-day of yoga, evaluation at the end of the stay.

Results: The children enjoyed leisure activities very much, but the care related activities and therapeutic education were not heavy for them but felt like activities necessary and beneficial to acquire autonomy. This action of the AFH aims to acquire knowledge and know-how to better live the disease in a recreational setting. Summer camp is one of the rare opportunities to meet other young people with the same pathology, and to compare their experiences. It is a moment of emancipation from parents; it is also an opportunity to remove children from their sometimes-heavy anxiety.

Conclusion: Sharing experience helps children overcome their own prejudices, share tips, and find solace. It becomes a motivating factor to gain autonomy. For the AFH is a good way to establish strong link with the youngest among the community.

M-P-152 (791) | How to help family to deal with diagnostic of a rare bleeding disorder: A original methodology proposed by the French Hemophilia Association (AFH)

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Association française des hémophiles [AFH], Paris, France

Introduction and Objective: Parents of young children diagnosed with Hemophilia or von Willebrand disease most of time feel distraught when the disease is announced. Even if they are supported by healthcare providers, being able to exchange with other parents and get out of their solitude can help them gain real autonomy. In June and November 2017, the French Hemophilia Association (AFH) organized 2 weekend regionals workshops.

Materials and Method: The AFH proposed a meeting to an audience of 12 parents (workshop 1 in the north of France) and 8 parents (workshop 2 in the south) of children from 3 months to 3 years old in the format of 8 interactive workshops around 5 educational objectives: Work on the questions that parents ask themselves following the announcement of the diagnosis and give them the opportunity to express their feelings. Develop autonomy, an ability to cope with the diagnosis. Ability to be able to project oneself into the future; Improve quality of life; Identify a support network (AFH, caregivers). The workshops were co-animated by 2 nurses, 1 physiotherapist, 1 psychologist, 3 AFH patient resources, 2 volunteers and 1 staff member.

Results: After establishing a framework of trust, and non-judgment, the families presented themselves cross-culturally. To allow the parents to share their own experience, their feelings since the diagnosis, a session was worked through an exercise built on Photolanguage®. In order to identify health professionals, a session answered the questions: when to contact them? Which professionals for which situations? Another session was devoted to the children needs for motor development without the apprehension of hemorrhagic accidents. Preparation for entering in community institutions (nursery or school) was also discussed. A session allowed parents to imagine the future of their children through the intervention of a young adult, an AFH patient resource. A presentation of the AFH and actions of the regional chapters was then proposed.

Conclusion: The assessment and the very positive feedback from the families have confirmed our approach. These workshops made families actors in their care management. In 2018, 2 new workshops will be organized.

M-P-153 (759) | Family intervention: An education day for parents of newly diagnosed children with Haemophilia in Northern Ireland

Susie Willis; Fionnuala Sayers

RBHSC, Belfast, UK

Introduction and Objectives: Families have described their child receiving a diagnosis of haemophilia as a traumatic and lonely time, and many family members talk of isolation and fear. The Paediatric Haemophilia Multi-Disciplinary Team (MDT) at Royal Belfast Hospital for Sick Children (RBHSC) wanted to provide better support for the newly diagnosed families within their service. They wanted to provide a forum for families to meet together and gain insight from 'experienced' parents and children. We hoped this type of support would increase knowledge and understanding, and that parents would gain benefit from meeting other families.

Materials and Method: On 20th October 2017, RBHSC held their first education day for parents of preschool children with a diagnosis of haemophilia. Eight sets of parents attended, accompanied by eleven children. Short talks were given by different members of the MDT. There were also presentations from children who had been living with haemophilia for several years already, and from a parent whose child was now 15 but had been newly diagnosed as a young infant. The children who attended were looked after by members of the team in a separate room to the parents.

Results: Feedback questionnaires were completed anonymously by seven sets of the parents following their attendance. All parents stated that they found the day 'very useful' and that the topics covered were those they found most important. They described that the most beneficial parts of the day were meeting other families and listening to the experiences of parents and children. One parent stated "We have the most amazing support from the team. Anything we ask for, support or advice, we get. We are very supported, which gives us so much confidence in caring for our son."

Conclusions: It would be of benefit for future events to assess anxiety levels of participants, pre and post the intervention. Assessment of knowledge gained as a result of the intervention would also be of interest.

30-HEALTH AND SOCIAL ECONOMICS

W-P-134 (624) | Importance of a legal assistance service in the Haemophilia Foundation

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Introduction and Objective: According to Argentine law, a court ruling in a patient's favour can be achieved through a legal procedure referred to as 'protective action' or *amparo de salud*, stipulating that the *obra social*, health insurance or healthcare system must provide the required medication and treatment. Sometimes, however, despite a favourable judicial ruling, the *obra social*, health insurance or healthcare system does not adhere to the judicial order, or follows it only for a limited time before ceasing to comply further. In such cases, there is the option to resort to further legal action citing '*non-compliance with a court order*' to force the non-compliant party follow the order, or continue to do so. A penalty may also be requested to achieve the same goal. Penalties are imposed, according to an amount fixed by the judge, as daily fines for each day of non-compliance with the judicial order. The primary objective of our analysis was to determine whether access to medication could be attained for the patients of the Haemophilia Foundation of Salta. A secondary objective was to assess whether court orders were being continuously followed over time.

Materials and Methods: We analysed protective actions, legal suits and requests for penalties in favour of children, adolescents and adults associated with the Haemophilia Foundation of Salta between 2010 and 2017.

Results: A total of 22 protective actions were taken in favour of 22 patients, with the aim of securing access to medication and treatment. In all 22 cases, a favourable ruling was achieved. Subsequent legal action due to non-compliance of the *obra social* was taken in 7 cases and penalties requested. These measures resulted in continued provision of medication and treatment in all cases, without necessitating the imposition of fines. The planned actions were therefore effective in 100% of the cases.

Conclusion: Our observations show that the existence of a legal assistance service for haemophilia patients within the foundation is important. Studying each individual case with its particularities and its history is essential, as legal solutions differ on a case-to-case basis.

Conflicts of Interests: DAL has no conflicts of interest to declare.

W-P-135 (637) | Relationship between treatment strategy and impairment in severe hemophilia

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Introduction and Objective: To describe the relationship between treatment strategy and productivity loss in severe haemophilia using real world observational data.

Materials and Methods: Data were drawn from the 'Cost of Haemophilia across Europe – a Socioeconomic Survey' (CHESS), a cost-of-illness assessment in severe haemophilia A and B across five European countries (France, Germany, Italy, Spain, and the UK) conducted in 2015. Physicians provided clinical and sociodemographic information for 1,285 adult patients, 552 of whom completed corresponding questionnaires covering out-of-pocket expenditure and psychosocial impact. Percentage overall work impairment (WI) and activity impairment (AI) due to health was calculated for each respondent using the General Health Work Productivity and Activity Impairment (WPAI: GH) questionnaire.

The relationship between WI/AI and treatment strategy at the time of the study (prophylaxis (PX) or on-demand (OD)) was assessed. Treatment was further stratified based on those who had received the strategy consistently since initiation ('primary' regimens) versus those who had switched strategies at a later date ('secondary' regimens) (PPX/SPX and POD/SOD). Impairment levels were contrasted with population norms derived from a US-based study.

Results: AI was derived from 541 patients; WI from 239 employed patients. Mean WI was lowest among the PX cohort, with 23% of actual work impaired due to health problems (POD: 21%; SOD: 30%), though WI remains higher than normative levels (15%) across all regimens. Similarly, mean AI was lowest in PX, with 34% of daily activities impaired due to health problems (POD: 38%; SOD: 38%), though nevertheless greater than normative levels (22%). AI and WI in PX patients was influenced by primary versus secondary regimen status, with PPX WI of 18% versus 24% in SPX, and PPX AI of 21% versus 37% in SPX.

Conclusions: The results are suggestive of differential productivity loss between treatment strategies in severe haemophilia. Levels of impairment are influenced by the demographic

characteristics of each treatment group, including a substantially younger average age in the PPX cohort. Further research into the driving factors of impairment will assist in qualifying the relationship between treatment strategy and productivity loss for persons with haemophilia.

W-P-136 (549) | Unmet need in gold standard primary prophylaxis treatment in severe haemophilia in terms of chronic pain

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Introduction and Objectives: Prophylactic treatment with factor concentrate is now considered the gold standard from childhood and adolescence (primary prophylaxis), with later use more contentious due to high per patient cost. While the efficacy of primary prophylaxis in minimising the frequency of spontaneous and recurrent bleeds is well documented, the aim of this research is to evaluate unmet need in best practise treatment of severe haemophilia in terms of chronic pain.

Materials and Methods: Data were taken from the 'Cost of Haemophilia across Europe – a Socioeconomic Study' (CHESS), a 'bottom-up' cost-of-illness study in adult severe haemophilia across France, Germany, Italy, Spain, and the UK. Physicians provided clinical and sociodemographic information for 1,285 adult patients including bleeds, target joints, level of pain, comorbidities and resource use information. 552 patients completed corresponding questionnaires covering out-of-pocket expenditure and psychosocial impact. The level of haemophilia-related pain currently experienced was captured on a 4-point scale of increasing pain and impairment: 'no pain', 'mild pain', moderate pain' and 'severe pain'. 'Moderate pain' and 'severe pain' included some degree of impairment on activities on daily living.

Results: Of 217 primary prophylaxis patients, 103 (47%) experienced some degree of physician-reported chronic pain relating to their haemophilia at the time of last consultation. Of those recording pain, 81 (79%) reported 'mild' pain with occasional use of non-narcotic analgesic medication, and 22 (21%) reported 'moderate pain' requiring use of non-narcotic medications and causing interference in the occupation of the patient or in activities of daily living.

Conclusions: The results of this analysis suggest that while the benefits of primary prophylaxis factor therapy are well established, there remains a level of unmet clinical need in terms of ongoing level of chronic pain experienced. There is a group of primary prophylaxis patients that are experiencing 'moderate pain' relating to their haemophilia that is having an impact of their ability to work and perform activity of daily living.

W-P-137 (598) | Impact of reimbursement process on annual per patient cost in severe haemophilia in the EU5

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Introduction and Objectives: Treatment in haemophilia is often a contentious area due to high per patient costs, with little information publicly available around pricing levels across countries. This research aims to provide insight in to the impact of differential EU5 reimbursement mechanisms, with emphasis on German and UK markets.

Materials and Methods: Data were taken from the 'Cost of Haemophilia across Europe – a Socioeconomic Study' (CHESS), a 'bottom-up' cost-of-illness study in severe haemophilia A and B (HA & HB)across France, Germany, Italy, Spain, and the UK (EU5). The study captured detailed annual treatment information on 1,285 patients. Average patient cost and annual factor consumption in international units (IU) was calculated based on prophylaxis regimen and dose per bleed information from CHESS data, excluding inhibitor treatment.

Results: Annual mean treatment cost was nearly €162k (HA) and €230k (HB) per respective patient. Mean annual factor cost per country is inconsistent, despite IU levels remaining comparatively more stable. Disproportionately high factor use in HB in Spain was largely due to a high dose prophylaxis policy in place at the time this research was conducted. Germany and the UK see very similar patient IU usage per annum, and prevalence of severe haemophilia (approximately 2,000 HA and 3-400 HB patients). However, the two countries have contrasting reimbursement systems; Germany take a decentralized approach to haemophilia commissioning, the UK administers cost minimisation via a centralised tender system. The UK sees significantly lower per patient costs (€105k vs. €298k (HA); €137k vs. €315k (HB)).

Conclusions: The results support the premise that cost minimization is optimal in a market for homogenous products (as the factor product market was until recently). However, it is important to consider current paradigm activity moving forward as the principles that underpin this reimbursement approach no longer hold with heterogeneity in the product market.

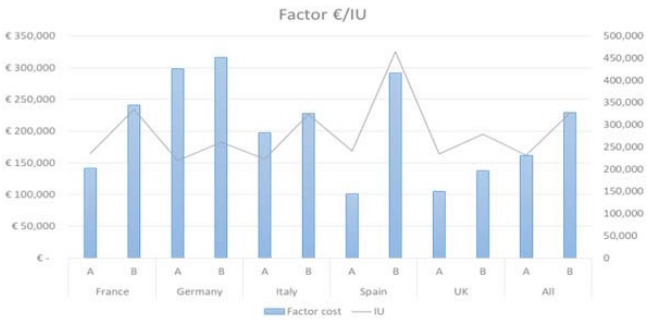


FIGURE 1 Factor Cost/ IU

W-P-138 (614) | Effect of poverty levels on the management of hemophilia in Uganda

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Introduction: Uganda is a country trying to attain a middle-income economy, whilst the majority of people live below the poverty line. This has a negative impact on the management of hemophilia. Poverty impacts access to hemophilia services, resources and skills, and leads to an increased vulnerability in the hemophilia population. Poverty also impacts upon determining health risks, health-seeking behavior and health outcomes.

Materials and Methods: In a population of 40 million people, Uganda has just 152 people diagnosed with hemophilia and receiving factor (primarily on-demand). As Uganda has no national health care insurance, health care is a family responsibility. A survey was conducted among affected households to find out the effects of poverty on the management of hemophilia.

Results: Our survey found that 92% of families live in remote areas, and hemophilia treatment was still being accessed only at the national referral hospital (MULAGO) in the capital (Kampala). In the case of a bleed, a trip to the hospital to receive factor costs up to $30. This is the average monthly income for 70% of family households in Uganda. Due to these costs, some families choose not to seek treatment, or are unable to afford the travel, resulting in prolonged bleeding, permanent disability and loss of life in some severe situations. Family life suffers due to limited income being used to access health care.

Conclusions: With the current improved treatment of hemophilia in Uganda, there is a great need to extend diagnosis and factor access to patients in remote areas. Nationally, there is also a need to involve the ministry of health in hemophilia care and management and to raise hemophilia awareness in order to identify undiagnosed hemophilia patients in rural communities. This could be achieved through more capacity building camps and sessions, and practical help for hemophilia affected households to manage health and wealth to sustain the family.

31-HEMOPHILIA PROGRAMS AND ORGANIZATIONS

M-MP-154 (53) | Haemophilia makes hero "Hero summer camp" in China

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Hero summer Camp for haemophilia boys has been held for 5 years in Beijing. Since 2013, more and more haemophilia boys came to the camps. They gain respect, love, friendship and confidence here. Hero summer camp is organized by Beijing children's hospital and China haemophilia family which is a haemophilia patients organization in China. It also supported by Novo Nordic haemophilia fund. In Hero summer camp, nearly 50 haemophilia families gather and share their experiences and stories. It is also a good chance for haemophilia home treatment and self infusion training. Haemophilia doctors and nurses give speech on haemophilia care and teach parents and boys to do injection hand by hand. A chorus is established for the haemophilia boys in the summer camp. The chorus is named "red apple". They performed in the summer camp at the very beginning. Then professional singer heard about their stories, and so moved to be their teacher and impresario voluntarily. "Red apple" becomes so popular now, and many charity activities invite them to perform. On 2017 haemophilia day, Beijing children's hospital and China haemophilia family schemed a "Flash show" in the hospital. The video was transmitted by CCTV, the Chinese national TV station. Through all the efforts, hero summer camps become a brand image. The boys become "hero" and are not afraid haemophilia anymore. Parents learn haemophilia knowledge in the camps. Also, it is an "advertisement" for haemophilia and more and more care and attention from society are given to the rare disease.

M-MP-155 (830) | The UK Haemophilia Parental Support Study – Are families with children with bleeding disorders being supported appropriately? A single site pilot study using the Parental Needs Scale for Rare Diseases (PNS-RD)

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Introduction and Objective: Parents of children with bleeding disorders face years of challenges and personal sacrifice. The level of support given to families differs; some centres have dedicated psychosocial support available for all families, others offer support only when it is identified as being needed, and some centres offer no support at all. The purpose of the current study was to investigate whether the support currently being offered to families at Great Ormond Street Hospital for Children (GOSH) is appropriate in meeting parent's support needs.

Material and Methods: The validated 14-item Parental Needs Scale for Rare Diseases (PNS-RD) were mailed out to each family (mothers and fathers) with a cover letter explaining the study and a pre-paid stamped addressed envelope for return. The survey asked parents to rate their perceived level of support need across four domains: Understanding the disease (four items); Working with health professionals (four items); Emotional issues (three items); and Financial needs (three items) and combines these domains to give a total needs score/100.

Results: 1070 questionnaires were posted; 231 completed and returned; 43% (n = 99/231) were by fathers. 15 distinct bleeding

disorders responded, the majority of parents said they were confident in their knowledge of their child's disease, felt satisfied with the overall support they received and were coping emotionally. Financial costs appeared to be the greatest need with almost half of parents reporting struggling financially with the medical costs associated with their child's disease (43%, n = 86/202) and 47% (n = 92/197) stating they could not afford to pay for respite services. The highest total needs score reported was 56/100.

Conclusions: This is the first time parents of children have been surveyed about their support needs. The support being offered at GOSH appears to meet the needs of many parents. While parents appear a homogenous group with regards to their support needs financial difficulties were the greatest reported need. Access to financial/budget advice would be of particular benefit to families struggling financially. Further research is needed comparing differences in needs for families at different stages of diagnosis, and between mothers and fathers.

Conflict of Interest Disclosure: The authors declare that they have no significant conflicts of interest. Research funded by Haemophilia centre Great Ormond Street Hospital.

M-P-156 (608) | Utilization of extended half-life recombinant of Fc-Fusion protein concentrate from WFH donation in Indonesia

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Introduction and Objective: Availability of factor replacement therapy is important to manage bleeding or surgery in hemophilia patients in developing country with limited coverage of anti-hemophilia factor (AHF). This study was aimed to report utilization of extended half-life recombinant of FVIII or FIX Fc-fusion protein (EHL-rFVIIIFc or EHL-rFIXFc) concentrates from WFH donation.

Materials and Methods: Observational study was conducted in Dr. Cipto Mangunkusumo General Hospital in Indonesia from March 2016 until October 2017. All patients who received EHL-rFVIIIFc or EHL-rFIXFc concentrate in outpatient clinic, emergency department, and inward were included in this study. Indication for using EHL concentrates are inadequate supply/unavailability of AHF, surgery, or life-threatening bleeding. Donation from WFH was coordinated by Indonesian Hemophilia Society, collaborated with Hemophilia Treatment Center (HTC). Data were collected from each HTC who request for EHL concentrates for their patient. Age, bleeding, surgery, type of concentrate, and outcome were recorded.

Results: Three hundred fifty-five patients, aged 1- 43 years old from 18 HTCs used EHL concentrates, 79% of them were hemophilia A. Majority of factors were used in outpatient clinic. Eighty nine percent concentrates were used for acute bleeding i.e. joint (75%), muscle (15%), emergency (5%), others (5%). Others were osteonecrosis, pseudo tumor, and gingival bleeding. The most common life threatening cases in emergency setting were intracranial (51%) and iliopsoas (24%) bleeding, others were abdominal, ENT, and genitourinary tract bleeding. The EHL concentrates were also used for surgery in 11% patients, circumcision was the most frequent surgery done (75%). Orthopedics surgery were total knee replacement, CTEV correction, synovectomy, arthrodesis, while others type of surgery were neurosurgery (hematoma evacuation, cranioplasty, lymphhemangioma removal), ENT (coin lesion extraction), abdominal (laparotomy and endoscopy), and dental extraction. Most of patients showed good outcome, except 1 patient died due to uncontrolled massive bleeding.

Conclusion: Extended half-life recombinant of Fc-fusion protein concentrate from WFH donation in Indonesia was used to treat acute bleeding. Support from WFH is very beneficial for patients with limited coverage of AHF from government.

M-P-157 (505) | Global alliance for progress (Gap) program in Vietnam: Primary results

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Introduction: Vietnam is a developing country with limited resources. In order to promote the development of hemophilia care in Vietnam to a higher level, in 2016 the Ministry of Health and the World Federation of Hemophilia (WFH) had authorized the National Institute of Hematology and Blood Transfusion (NIHBT) and Vietnam Hemophilia Association joined the GAP program of the WFH in four years 2016-2019.

Objectives: 1. Ensure continuation of government support for a national hemophilia care program; 2. Improve care delivery in the country by strengthening the existing network of seven hemophilia treatment centers (HTCs) and by creating satellite centers; 3. Support the development of medical expertise of healthcare professionals in selected HTCs and in general throughout the country; 4. Increase the supply of factor concentrates and increase patients' access to factor concentrates; 5. Strengthen the patient organization; 6. Develop and implement a national registry.

Method/Activities: Outreach to other regions of the country to identify new patients with hemophilia and other inherited bleeding

disorders; Maintain cooperative relationship with government health authorities (the MoH, Insurance Department…) to ensure continuing support for a national hemophilia care program; Educate and train the healthcare professionals and medical community on hemophilia care, expand hemophilia care delivery system in nationwide; Carry out activities to strengthen the association's ability such as peer group meetings, NMO registry, educational services, fundraising, volunteer recruitment, advocacy, budgeting and international cooperation.

Results: 400 new patients with hemophilia and other bleeding disorders were diagnosed; two international training courses organized for 300 members of comprehensive care team including hematologist, orthopedist, physiotherapist, rheumatologist, odontostomatologist. Parallel with that, patients and families were trained about organizational skills and preventative self-care and were encouraged to be more actively involved in organizational activities as well. NIHBT participated in pilot study to evaluate effectiveness of World Bleeding Disorder Registry supported by the WFH that was the premise for implementing the national registration program in Vietnam.

Conclusion: Implemented activities in the GAP program have contributed to improving the quality of hemophilia care in Vietnam in 2016 and 2017.

M-P-158 (522) | One solidarity crowdfunding initiative linked to our twinning program with the Haemophilia Cuba Society

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Introduction and Objective: The Catalan Association of Haemophilia and the Haemophilia Cuba Society have been linked through a twinning program since 2016. During this time, we have developed different actions and programs. In one of our trips to Cuba we realized that lots of haemophiliacs have severe joint damage and they did not have resources that could help their mobility. When we returned to Barcelona we set an objective of getting orthopaedical materials to palliate this need.

Materials and Methods: We needed to look for funds to buy crutches and wheelchairs and for this reason we used a crowdfunding platform called "Do my part". We designed a challenge: "Help us to improve the mobility of Cuban haemophiliacs" and we made it coincide with the 2016 #GivingTuesday. A global movement that wants to stimulate and multiply the good actions of the people, its goal is to dedicate a worldwide day to celebrate the act of giving. In parallel we did a media campaign through our community and twitter. Finally, we have to resolve the problem of the orthopaedic material delivery because it has a huge complexity due to the situation of the country.

Results: We collected 695 euros and we were able to buy 78 crutches units for adults and 22 for children. In addition, we got 4 wheelchairs for adults and one for a child thanks to the altruistic collaboration of our community. The delivery could be done thanks to the collaboration with Sant Juan de Dios Hospital. This hospital order has three centres in Cuba and they sent them some shipments during the year. Our crutches and wheelchairs were added to one of their shipments with the commitment that the Haemophilia Cuba Society would go to pick the material up once it was there.

Conclusions: The crowdfunding platforms could be useful to get funds to specific projects, in our case, it allowed us to make our twinning program with the Haemophilia Cuba Society bigger and today 55 Cuban haemophiliacs have orthopaedic resources to help their mobility.

M-P-159 (648) | The health's French network of rare diseases for inherited bleeding disorders

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The first national rare disease disorder plan (PNMR1) 2005-2008 allowed the creation in France of reference centers for rare diseases. In the field of hemostasis disorders, 3 reference centers were set up: the reference center for hemophilia and other rare diseases (CRMH), the reference center for Willebrand disease (CRMW) and the reference center for platelet disorders (CRPP). A second plan scheme (PNMR2) 2011-2016 has gathered close reference centers leading to the creation of 23 rare diseases health's networks overlaying a broad and coherent field of rare diseases. From this PNMR2, the rare diseases health's network for inherited bleeding diseases (MHEMO) was created in December 2014. The objective of the MHEMO network is to regroup bring together all aspects of care in inherited bleeding diseases whatever their severity. The MHEMO's mission is : to coordinate actions between the network's members and his various partners, to inform patients, relatives, general public and all healthcare professionals, to bring together all the actors around a common project, and to facilitate exchanges within the network. To meet this objective, the MHEMO network has set up a management's structure comprising 3 committees (Coordinating Committee, Medical and Scientific Council and College of Practitioners and Users). Furthermore, the French Ministry of Health has set 3 common missions to rare diseases health's networks: the improvement of care for people with rare diseases, the development of translational, clinical

and organizational research, and the development of education, training and information. In this context, the MHEMO network has defined 14 actions. Each of them is carried out by a working group composed of actors issued from hemophilia treatment centers, the patients' association, the FranceCoag Network, research units, diagnostic laboratories and hospital pharmacies. The MHEMO network also has the support of several partners such as representatives of health professionals, scientific societies and European reference networks.

M-P-160 (710) | Perception of patients with hemophilia and von Willebrand's disease of the care received, for unspecialized care centers in Colombia

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Introduction and Objectives: We all know about the experience and "knowledge" that patients with hemophilia have, Von Willebrand and their families of these diseases. Nonconformities of patients about inadequate management in unspecialized health institutions, it is evidence of the limitations in the training of responsible professionals. It is necessary to propose curricular modifications in undergraduate and postgraduate courses in the faculties of health sciences in order to improve care for these patients.

Materials and Methods: 12 surveys were applied to patients and caregivers aged between 6 and over; Three with mild hemophilia, one moderate, four severe; four with Von Willebrand disease; 4 in pharmacological prophylaxis and the rest in treatment on demand; All receive comprehensive care by the multidisciplinary care team.

Results: The 67% were diagnosed more than 19 years ago, all have been hospitalized at least once, the 17% ensure that health professionals are trained to manage their illnesses, while 83% say no; of this 83%, 41.6% add that most professionals prefer to refer them to other care centers. 58.3% report that they have not been adequately treated, with the following observations: Factor concentrates were applied incorrectly; untimely attention, the hematologist was not consulted, application of intramuscular drugs, administration of oral contraindicated medications and denial of attention for fear of causing iatrogenic.

Conclusions: The perspective of the patients adduces the lack of knowledge on the part of health professionals, suggests designing and carrying out formal training plans in conjunction with training centers for patients, caregivers and health professionals in order to improve the quality of care of this group.

W-P-177 (142) | A pilot program to improve sexual health communication for healthcare professionals treating people with hemophilia (PWH)

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Introduction and Objective: HERO (Hemophilia Experiences, Results and Opportunities) participants provided the first-ever extensive, evidence-based data set about sexuality in haemophilia. In Canada (n = 18) 50% of PWH reported hemophilia affected the quality of their sex lives negatively and only 6% talked to their doctor or their clinical team about sexual intimacy. The Canadian HERO National Advisory Board (NAB) examined this issue in 2013 and through a series of activities guided the process leading to a pilot training program for healthcare professionals (HCPs). Based on the Canadian findings, sexual health is not routinely discussed with all patients at Hemophilia Treatment Centers (HTCs). Training and the availability of educational materials are lacking. Learning how to communicate more effectively and comfortably with people with hemophilia about sexual health is important to HCPs but without specialized training many are ill equipped to discuss this effectively with patients. The NAB recognized the importance of sexual health as a part of the overall health of people with hemophilia resulting in an initiative designed to help HCPs learn ways to communicate more effectively about sexual health with patients and amongst the team.

Materials and Methods: The pilot program, entitled "Sexual Health: Strategies for Effective Communication", took the form of 2, 3 hour workshops, in October 2016 and February 2017. The training was conducted by a local expert from the Calgary Sexual Health Center who was briefed on the issues related to people with hemophilia and sexuality, and also on the unique challenges facing a multi-disciplinary team as they treat clients with time and privacy challenges. Both sessions were a combination of lecture and case scenarios that had been prepared specifically related to hemophilia.

Results: Seven HCPs working in the pediatric and adult hemophilia clinics from Calgary's Alberta Children's and Foothills Hospitals attended the 2 sessions. Participants completed evaluations after both workshops and reported improvements in knowledge, skills and comfort level.

Conclusion: Feedback was positive and has resulted in interest for training from other HTCs in Canada.

32-NURSES' ISSUES

S-NUR-005 (49) | Nurses' experience of Using PK Profiling to promote personalised prophylaxis

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Introduction: It is widely accepted that prophylaxis regimens offer optimal care for people with haemophilia. Personalised prophylaxis regimens incorporate individual lifestyle factors, bleeding phenotypes, half-life of infused clotting factor concentrates (CFC) and patient preferences. Pharmacokinetic profiling (PKP) is a key component when developing individualised prophylaxis plans. The nurse's role within the multi-disciplinary team includes interpreting results, supporting patients to set treatment goals and assisting transition to the new treatment regimen.

Methods: Haemophilia Nurse Specialists in two London hospitals have collaborated to share experiences of using PKP to engage patients in decisions about prophylaxis regimens. Opportunities to engage patients in discussions about their expectations, experiences and health beliefs were identified. Patient factors linked to uptake of PKP were identified along with barriers. Patient outcomes were recorded and categorised.

Results: 19/92 adult patients with severe haemophilia A (without inhibitors) underwent PKP; 16/19 were treating prophylactically. Primary outcomes were categorised as: Swapped from on-demand to prophylaxis (3/19); Reduced frequency of infusions (5/19); Achieved increased trough levels (12/19); Reduced dose of prophylaxis (2/19); Did not change prophylaxis regimen (4/19). Factors identified that motivated patients to engage in PKP: switching factor concentrate; to reduce frequency of infusions; preparing for surgery; treatment tailored to their lifestyle; time invested in the patient; concerns about spontaneous/breakthrough bleeding. Barriers to uptake of PKP include: full-time employment/self-employment; travelling distance to hospital; low annual bleed rate (ABR).

Discussion: It is important to recognise opportunities when patients may be receptive to PKP. PKP gives nurses an opportunity to explore how patients make decisions about their treatment and to reconcile evidence-based practice with the patients' expectations and goals. Nurses have a unique role to play in supporting patients and are ideally placed to lead discussions about medicine optimisation due to their clinical knowledge, accessibility and communication skills. However, PKP requires a number of blood samples at specific time intervals over a number of days and is often inconvenient for patients due to the time commitment required. Further strategies are needed to enable patients to undertake PKP; these may include home/workplace visits for venepuncture or availability of weekend appointments.

W-P-139 (688) | Nurses educational needs in bleeding disorders: Results from an international, mixed-methods study

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Introduction and Objectives: The importance of integrated, multidisciplinary care for bleeding disorders was highlighted in the second Team Haemophilia Education Meeting (2016). Despite nurses' systematic involvement in patient management, limited data exists regarding clinical challenges and educational needs of nurses. A mixed-method, ethics-approved study was conducted to identify practice gaps and challenges faced by nurses working in haemostatic disorders, with the objective to inform the development of educational programs.

Materials and Methods: Phase 1 consisted of semi-structured interviews with nurses and patients/ caregivers. The interviews were conducted to identify challenges in providing or receiving care for haemostatic disorders. The key themes identified served to inform Phase 2, an online survey to validate Phase 1 findings, and identify causalities (lack of knowledge, skills) with a larger sample of nurses. Data were triangulated, and final mixed-methods findings were interpreted by clinical and educational experts.

Results: Two hundred thirty four participants (212 nurses and 22 patients/caregivers) participated in the study (Argentina (n = 25), Australia (n = 21), Canada (n = 25), China (n = 24), France (n = 24), Germany (n = 26), Spain (n = 25), U.S. (n = 38), and the UK (n = 26)). Most nurses had at least 10 years of practice (59%), and were from academic/specialized centers (72%). Five clinical challenges were identified by nurses: (1) challenges in conducting patient assessment (46% reported sub-optimal skills assessing bleeding risk); (2) low understanding of von Willebrand disease (54% reported sub-optimal knowledge of disease criteria); (3) challenges gathering relevant patient history (37% reported sub-optimal knowledge of which elements of patient history to gather); (4) low understanding of inhibitors (52% reported sub-optimal knowledge of inhibitor treatment goals); and (5) challenges individualizing communication and care (57% reported difficulty determining what information to provide to the patient). Nurses also perceived a lack of support in skill development by senior staff. Findings specific to country, years of practice, and practice setting, were also identified.

Conclusions: Future educational programs in bleeding disorders should be designed to address the priority challenges identified in this study. A more systemic intervention is needed to improve how nurses are supported in their professional skills development.

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W-P-140 (90) | Application of attention destruction techniques during factor concentrates infusion to children with Hemophilia

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The majority of children with severe hemophilia-A (HA) are routinely treated by intra venous (IV) infusions of prophylactic replacement therapy. Such treatment may become a traumatic experience as fear; cry and aggressive children's behavior are often noted in the nurses treatment room. Due to children's anxiety, coping with the behavioral/emotional response to the infusions creates a challenge by itself for the patients, parents and caregivers. Attempts are currently being made by to reduce children's anxiety using methods like verbal explanations, positive reinforcements following the infusion and gentle or forced hugging; however, this attitude often fails. Our study aimed at anxiety reduction during IV factor treatment, by using unique attention destruction techniques.

Methods: Children with hemophilia, aged 1-12 years, treated at our center, were eligible for study participation if their caregivers signed informed consents. A special unit of attention distractors was developed, designed and built, and has been installed in different locations in the infusion room's ceiling, just above and in front the children's head during the infusion. The operation of the remote-control unit, by study coordinator, psychologist or nurse, triggers the appearance of toys/objects approaching the child. Children were first assigned to IV infusion without any attention drawer, and then on another infusion their attention was drawn to the small objects (e.g.: toys, TV figures) surprisingly going down from the ceiling in front of them. Objective parameters of behavior and any emotional responses were captured on video and later analyzed. An objective psychological test, Yale Preoperative Anxiety Scale (m-YPAS), was applied to quantify the children's situational anxiety and stress.

Results: Results of 5 patients aged 1-4.5 years show a significant reduction of the m-YPAS parameters that quantify children's fear, anxiety and anger when they were exposed to the attention distractors, when compared to the baseline infusion.

Conclusion: The pilot study results support the hypothesis that attention distraction can reduce fear, anger and stress in children with hemophilia during therapeutic infusions.

W-P-141 (268) | Let's talk period: nursing outreach in Grade 9 females, a pilot project

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Introduction: Educating the general public about normal vs. abnormal bleeding can be a difficult task, particularly for menstrual bleeding. Letstalkperiod.ca is a website (with aligned social media posts) that provides information about bleeding and aims to raise awareness about inherited bleeding disorders. To date, 19,888 people have accessed the website and 171,976 people in 115 countries have been reached through social media.

Objective: The goal of this pilot study was to develop and implement an educational program for Grade 9 health classes in a local high school in order to raise awareness about abnormal bleeding symptoms, particularly menorrhagia, and the consequences including symptoms of iron deficiency.

Materials and Methods: Permission was obtained from a Grade 9 girl's health class at a local high school to teach as part of their curriculum discussing bleeding symptoms and inherited bleeding disorders using the Let's Talk Period platform as the mode of presentation. Multiple meetings were held amongst expert stakeholders to develop and refine the educational materials.

Results: The nursing role was to provide leadership in the development of educational materials and to present information in class about normal and abnormal bleeding through teaching about the menstrual cycle, demonstration of sanitary protection products, discussion of methods to monitor menstruation and strategies to decrease menstrual blood loss. This presentation was given to two female grade 9 health classes that included 30 girls age 14, representing 2 hours of teaching time on the topic of symptoms of inherited bleeding disorders, normal and abnormal bleeding and iron deficiency.

Conclusion: This pilot project was well received and requests from the schools have been made to have this presentation repeated in future classes. Future directions would be to expand the number of schools and to create an online learning module to complement the Let's Talk Period campaign.

W-P-142 (739) | Successful multidisciplinary strategy for obtaining peripheral venous access in young children with hemophilia: Experience of a Brazilian Hemophilia Treatment Center (HTC)

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Introduction and Objectives: Hemophilia patients require venous access for regular infusion of coagulation factor concentrates. The frequent venipunctures, particularly in young children, represent a challenge due to the lack of suitable peripheral venous access and often result in psychological trauma for the children and their relatives. The use of central venous access device (CVAD) can be an alternative. However, the need of insertion procedure and the occurrence of catheter-related complications makes this option less attractive. In this report, we aimed to describe strategies performed in a Brazilian HTC in order to guarantee intravenous-based treatment and avoid the use of CVADs for hemophilia children.

Material and Methods: We retrospectively assessed the number of children (up to 12yo) with severe or moderately severe hemophilia (factor VIII or IX ≤ 2 IU/dL) seen in our HTC from 2007 to 2017 who needed at least 3 venipunctures per week either for prophylaxis or for immune tolerance induction (ITI). Strategies performed in the daily practice of the multidisciplinary team in order to enable successful peripheral venous punctures were described.

Results: 92/385 (24%) of the people with hemophilia followed in our center are younger than 12y. Among them, 53/92 (58%) had FVIII or FIX ≤ 2 IU/dL and were receiving at least 3 intravenous injections of factor concentrates per week. Only 4 children (7.5%) underwent CVAD insertion, which means that the procedure was avoided in 49 (92.5%) patients. The strategy adopted by the multidisciplinary team for punctures included the participation of the parents. They were encouraged to sit the child upright, allowing them to interact with healthcare providers and handle some materials used during the procedure, such as vacuum tubes, factor concentrate boxes and tourniquets. Music and videos for children were also used during the procedure, in order to make it more playful and less stressful or psychologically traumatic.

Conclusion: Parents' education and actions to familiarize young patients to venous punctures are useful to avoid CVAD insertion in children with hemophilia who need frequent injections of factor concentrate for prophylaxis or ITI protocol.

W-P-143 (671) | Value of the specialist nurse

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Introduction: Specialist nurses consistently rate higher than other healthcare professionals due to understanding patients' needs and being a key point of contact for all involved in a chronic disease patient pathway. Yet UK specialist nurses face redundancies, service cuts, downgrading of bands, confusion around titles and expansion of responsibilities. The aim with this evaluation was to establish the cost effectiveness of the UK Haemophilia Specialist Nurse role.

Methods: Initially presented at the 2017 Haemophilia Nurses Association annual conference, a proposal was set out to evaluate members' job roles; this was accepted by the members in attendance. Utilising the Apollo Nursing Resource, a UK wide evaluation of members was conducted. Members self-evaluated their role with the job description tool.

Results: Take up was initially poor due to the comprehensiveness of the tool and the time required completing it. Results revealed the varying role and the comments from members involved an increased self-recognition of the number of activities undertaken which are invisible to management but make a huge impact of patient outcomes. Telephone activity played a major part in their working week and preventing patients accessing care elsewhere such as the emergency department or general practice. A key role they play within the team is one of education, this was both for families and for other healthcare professionals.

Conclusions: The role of the specialist nurse within the UK is under threat through funding cuts and pressures on services, but it is clear that their role is essential in maintaining safe patient pathways through the multifaceted role they play. Without recognition on a national, European and International stage of what a difference this role makes to peoples' lives we are likely to lose this key member of the multidisciplinary team. Further evaluations of this type to confirm these findings and save this role for future generations of people with bleeding disorders and our future workforce are required.

W-P-144 (747) | Development of a nurse-led pharmacokinetic sampling clinic for patients with Factor VIII deficiency

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Background: Standard weight based prophylactic regimens fail to account for inter-individual variability in factor VIII (FVIII) half-life.

Pharmacokinetic (PK) guided prophylactic regimens have shown promise in efforts to personalise prophylactic treatment. PK sampling may be onerous on patients as it requires attendance at specific time-points post treatment in order to calculate FVIII clearance and half-life.

Aim: Development of a structured nurse-led PK sampling clinic for patients with FVIII deficiency and determination of the number of successful PK profiles generated in comparison to previous efforts at PK sampling.

Methods: Patients with Factor VIII deficiency were invited to attend for PK sampling. From the historical cohort, 11 point PK sampling was performed in line with the ISTH guidance on PK[1]. For the prospective cohort, Bayesian analysis of PK sampling on Advate® was employed using my PKFiT™ to minimise blood draws. Two samples were obtained at 3 hours and at 24-32 hours post prophylaxis[2]. Upon completion of the study, patients were followed in the general haemophilia clinic and alterations to prophylactic regimens made (if required) based on timed PK samples and my PKFiT™ output.

Results: From the historical cohort on 10 point PK sampling, attendance was low with only 11 patients recruited in the study period (1.5 years). In contrast, Bayesian analysis of PK sampling on Advate®, 31 patients attended over 10 months with a complete PK profile obtained in 19 patients. Initially appointments were scheduled on the same day as medical review, with two timed attendances required to complete the profile. This was subsequently optimised to coordinate with haemophilia clinic attendance. Patients were advised to take prophylaxis on the day prior to clinic and a 24-32 hour sample was taken in the morning before clinic. Following administration of a repeat prophylaxis dose the 3 hour sample was obtained after clinic. This allowed completion of the PK profile in one visit, with greater patient and staff satisfaction levels.

Conclusion: Nurse-led PK sampling clinics offer a structured approach to the introduction of routine PK sampling in a haemophilia setting. PK sampling offers both opportunities to personalise treatment for patients with haemophilia and important insights into individual rates of FVIII clearance.

33-PAIN MANAGEMENT

S-NUR-001 (427) | A new tool to improve clinical communication about pain, Pain Treatment Planning Questionnaire: results from a randomized controlled trial

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Introduction and Objective: Pain is common in adults attending outpatient bleeding disorder treatment programs (BDTPs) with approximately 57% reporting daily chronic pain. Over half of adults rely on the BDTP for pain management advice and 39% report their pain is not well managed. Management of chronic pain may require pharmacological and non-pharmacological strategies and interdisciplinary approaches to care. The Pain Treatment Planning Questionnaire (PTPQ) was developed at a Canadian provincial BDTP with clinician and patient input to meet an identified need for improved pain management communication. The PTPQ is a 28-item patient-reported outcome tool for assessment of patients' pain experiences and treatment approaches. The objective of this study was to examine the effect of the PTPQ on therapeutic alliance scores between a usual care group and a group in which the PTPQ was used by BDTP clinicians to discuss pain in addition to usual care.

Materials and Methods: Participants with haemophilia or von Willebrand's Diseases (n = 42) were recruited during clinic visits. Block randomization by disease and severity ensured equal group allocation. All participants completed the questionnaire battery (PTPQ, SF-36, Chronic Pain Grade Scale [CPGS], modified brief California Psychotherapy Alliance Scale, and clinical feasibility). Group therapeutic alliance scores were compared by t-test.

Results: Mean participant age was 46.7 years with 62% males and mean usual pain score of 2.4 (0-10 scale with 10 being maximum pain). The intervention group had statistically significantly higher therapeutic alliance scores than the control group (δ = 0.6, P = 0.026, 95% CI = 0.1-1.2). There was convergent validity between the PTPQ pain scales and SF-36 Bodily Pain Scale (Pearson's r = −0.76, P < .001), and statistically significant differences in the average of 4 pain questions (P < .001, 95% CI = 1.5, 3.3), number of descriptive words selected (P = 0.010; 95% CI = 0.1, 5.5), interference of pain with activities (Chi square = 4.7; P = 0.029), and pain effect on mood (Chi square = 8.1; P = 0.005) between low and high pain/disability groupings of the CPGS. Median completion time of the PTPQ was 5-7 minutes.

Conclusions: The PTPQ is a clinically feasible, condition-specific, patient-reported outcome instrument that improves therapeutic alliance when used to guide pain management discussions between patients and clinicians in an outpatient BDTP.

W-MP-152 (179) | 77% of haemophilia patients experience pain: A global snap-shot study

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Introduction and Objective: Haemophilia patients often have recurrent bleeds in weight-bearing joints. Pain from a (joint) bleed and pain from subsequent arthropathy is common and a burden for haemophilia patients, impacts quality of life and worsens with age. To prevent joint bleeds, people with severe haemophilia in high-income

countries receive prophylaxis with regular FVIII/IX infusions. To establish a baseline knowledge of experienced pain, we investigated the annualized pain ratio (APR) and efficacy of pain therapies in haemophilia patients.

Materials and Methods: Ten consecutive haemophilia patients per participating haemophilia treatment centre (HTC) for any reason (bleed, trial visit, routine visit) completed an anonymous questionnaire about pain, medication and pain relief methods within the past 28 days. The EQ5D questionnaire for adults and the EQ5D-Y questionnaire for those aged <18 years was used to assess their quality of life (QOL).

Results: 209 persons from 20 HTCs in 11 countries participated in this study, with a median age of 36 (range 8-84). 181 patients had hemophilia A, 25 patients hemophilia B, 3 did not know (in total; 71% severe, 13% moderate, 15% mild). 28 respondents had an inhibitor. Most patients (n = 121) were on prophylaxis, 61 on demand, 20 had a combination and 7 did not know. Unfortunately, 161 patients (77%) experienced a total of 1.927 days (162.17 days per year) of pain (APR 0.44). These patients most often had pain in joints (66.6%) and muscle pain (28%). There was no significant differences in pain incidence between countries or races. Median pain severity was 4.5 VAS. Remarkably, 59% of patients aged 8-12 years suffered from pain. 74% of patients on prophylaxis still reported pain. Paracetamol was used by 46% of patients but did not effectively relieve pain. 47% used pain medication without medical consultation. Alternative reported pain relief strategies were rest (57%) and physiotherapy (40%) crutches (25%) and alcohol or marihuana (15%). Although 90% of patients were asked about pain during regular consultation, advice on pain management was often not satisfactorily given.

Conclusions: The burden of pain in haemophilia patients is enormous, and the current treatment strategies (including prophylaxis) are inadequate. Pain management for haemophilia patients requires more attention and awareness.

Keywords: Haemophilia, pain, EQ5D, medication.

W-MP-153 (619) | The pain of hemophilia in childhood

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Introduction and Objective: We note that hemophiliac children have different experiences of pain produced both by the hemorrhagic episodes and by the treatment with coagulation factor. For some children the pain is unbearable while for others it is not a problem. We also observe that the experience of pain varies in the same child at different times of his life. This let us to wonder about the child's relationship with hemophilia and pain.

Materials and Methods: The data comes from 68 children and their families and they have been obtained through clinical interviews, parent group sessions, family programs and hospital work.

Results: Hemophilia involves physical manifestations and actions in the child's body, from explorations to treatment with coagulation factor. Some of these situations can become for the child an "instant of seeing": the subject is perplexed by a situation that he does not understand and that affects him. This pushes him to an elaboration to give himself an explanation. One situation becomes an "instant of seeing" and inaugurates a subjective path of logical times (instant of seeing – time to understanding – moment of conclusion), when it must affect the child and his body. Hemophilia, which implies the experience of pain, contributes to it. During the "time to understanding" there is usually the pain and the child refuses to be injected. But he also starts to think hypothesis to understand what is happening. The child begins a construction about what hemophilia is for him. It is not about the knowledge of the disease in a medical level, but about the child understands the hemophilia in relation with his/her history and his/her own world. Thus, the child reaches a "moment of conclusion" in which he assumes his hemophilia, and the subjective experience of pain becomes calm.

Conclusions: The pain of the puncture, or better the subjective experience of pain, is closely related to the development that that the child makes about his own hemophilia. That is why the experience of pain changes according to how it is experienced.

W-P-154 (125) | Audit of Intra articular steroid injection: Results from haemophilia clinic

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Introduction and Objective: Joint arthropathy in severe haemophilia is common. Recurrent bleeds into joints causes synovitis, cartilage damage, joint degeneration and pain. While intra articular corticosteroid injections are commonly used to treat synovitis and pain in inflammatory joint disease, the potential benefits are unclear in haemophilia. The purpose of this audit was to investigate the effects of intra articular corticosteroid injection in haemophilia patients with ankle pain.

Method and Materials: Patients reporting increasing ankle pain were imaged using MRI. The results were discussed within the multidisciplinary team. If steroid injection was indicated this took place in the Haemophilia centre as an outpatient. Patients were counselled to the possible risks and benefits. Intra articular triamcinolone acetamide with lignocaine was used to inject the talo-cural and or the sub-talar joint in each subject. Subjects were given questionnaires pre-intervention, at 3 and 6 months following the procedure. Questionnaires used were the Visual analogue Scale for pain (VAS), Haemophilia Activity index (HAL), EQ 5D 5L, Functional ankle activity measure (FAAM) and the Haemophilia joint health score (HJHS) at pre and 6 months.

Results: 11 patients were included in the audit with 13 ankles injected. The median age was 29 years. A clinically significant reduction in median VAS pain scale was seen at 3 and 6 months, 3 and 3.5 points respectively with *P* values of *P* = .007 at 3 months and *P* = .091 at 6 months; with no changes in EQ 5D 5L. There was an initial improvement in FAAM values at 3 months which then reverted to baseline by 6 months. HAL values showed a slight reduction, although HJHS improved over the time scale.

Conclusions: These findings provide support for the use of intra-articular corticosteroid in the management of severe ankle pain in haemophilic arthropathy. The beneficial effect though appears to be short term.

W-P-155 (576) | Differences of subjective and semi-objective pain assessments in patients with haemophilia

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Introduction: Pain is a major problem in patients with haemophilia (PwH) affecting quality of life, psychological well-being and physical performance. In the field of haemophilia, pain is often subjectively assessed on the basis of numeric (NRS) or visual analog scales, which are influenced by many factors.

Material and Methods: Thirty-six patients with moderate to severe haemophilia A or B and 36 age-matched controls were included. All participants underwent a standardized examination consisting of semi-objective assessment of pressure pain thresholds (PPT), as an indicator for the individual pain sensitivity, at 11 landmarks across both knee joints (e.g. medial joint space, infrapatellar distal). Additionally, the subjective pain condition (at the moment, 6 weeks and 3 months on average) at these 11 points were recorded via NRS (0 = "no pain" – 10 = "worst possible pain"). For each assessed landmark, the 95%-confidence interval (95%-CI) of control-knees were used to determine pathological PPT values in PwH, indicating clinical relevant alterations of the pain condition. 72% of the PPT-data of PwH were beyond the 95%-CI of the control group and were further used for correlation analyses of PPT and NRS for each of the 11 landmarks.

Results: Pathophysiological PPT and NRS values for the medial joint space (e.g. pain at the moment: $r = -0.398$, $P = .003$) and the medial femur condyle (e.g. pain at the moment: $r = -0.461$, $P = .001$) showed moderate correlations. Weak correlations of semi-objective and subjective pain values were determined for 5 landmarks. Four landmarks showed no statistical connection between pathophysiological PPT and NRS values ($P > .05$).

Conclusion: This study revealed that pathological pain conditions, assessed by PPT, were not detected when PwH were asked to rate their pain intensity, based on the NRS, at the moment, in the last 6 weeks or last 3 months. Chronic pain might lead to a diffuse condition. Therefore, a sufficient, differentiated pain diagnostic based on subjective pain ratings is difficult to achieve. The results should be considered in the pain management in PwH in order to treat pain related alterations as early as possible.

W-P-156 (579) | Conditioned pain modulation (CPM) in patients with haemophilia

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Introduction: Patients with haemophilia (PwH) suffer from haemophilic arthropathy which is associated with enhanced pain sensitivity. Based on the "pain inhibits pain"-paradigm, Conditioned Pain Modulation (CPM) asses the endogenous pain modulation. Recent studies showed a decreased pain inhibitory function in other chronic pain conditions. The role of the descending pain modulatory system in the pain condition of PwH has not been analyzed to date.

Material and Methods: Thirty patients with moderate to severe haemophilia A or B (severe A = 25, B = 2; moderate A = 2, B = 1; mean age: 50 ± 10 years) and 27 healthy controls (mean age: 50 ± 11 years) were examined in terms of CPM. Additionally, the WFH joint score and the WFH pain score were assessed. The CPM effect was evaluated calculating the difference of rating the intensity of A) a standalone heat pain stimulus (test stimulus) and B) rating the intensity of the same heat pain stimulus under the influence of a cold pain stimulus (conditioned stimulus). Pain ratings were assessed by the numeric rating scale (0 = "no pain" – 100 = "worst possible pain"). The heat pain stimulus was applied on the dominant forearm by a thermode. Cold pain was induced by immersion of the contralateral forearm into cold water.

Results: PwH showed a more impaired total WFH joint score (mean score: PwH: 22.3 ± 8.3 / controls: 8.7 ± 2.7; $P \leq .001$) and an increased pain score ($P \leq .001$) in comparison to controls. The mean CPM effect was 21 ± 12 NRS points in the control group, whereas PwH showed a mean CPM effect of 12 ± 11 NRS points. Therefore, PwH showed a statistically significant reduced endogenous pain inhibition when compared to controls ($P = .008$). In reference to a large effect size ($d = 0.862$), a clinical relevant difference between the groups was detected.

Conclusion: Our study shows for the first time that a dysfunctional endogenous pain modulation might play a role regarding the enhanced pain sensitivity in PwH. Further studies should confirm these findings. If the results will be further verified, pain relieving interventions, targeting the endogenous pain modulation, could be a new approach in the pain management in PwH.

34-PERSONAL AND SOCIAL DEVELOPMENT

T-P-132 (744) | The effects of swimming on the social adaptation of hemophiliacs: A qualified research

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Objective: Swimming is not considered to be a physical problem for people with hemophilia (PwH). However, PwH who are thought to reduce activities or reduce the activation of these activities are unfortunately more and more inactive. This study was planned to observe the possible effects of swimming sports on the self-esteem of PwH and as well as the ability of swimming to welcome of new individuals.

Methods: Of the 61 hemophilia campers in different age groups and socio-economic segments who participate in the Turkish Hemophilia Summer Camp was observed and analyzed on a total of 12 hours of swimming and pool activities on 4 consecutive days. The Fully Participated Observation Method used enables the examination of whether by virtue of swimming there is any difference and increase in adaptation to the community the PwH is in.

Results: It was observed that swimming and physical activities which involve water reduced the anxiety levels and increase the enjoyment obtained from the activity in comparison to other sports activities. There was also a marked increase in the frequency and intensity of activity participation.

Conclusion: By establishing the interest and participation of PwHs in water sports, they are able to better use their bodies, thus reducing their anxiety levels and increasing their confidence. In the same way, it was found that with their participation in swimming sports there is a significant increase in their participation in group activities and their sense of belonging. It has been determined that two sessions of swimming per day for a minimum of 3 days significantly increase the efficiency of the activity and the physical performance of the PwH.

T-P-133 (457) | Tokyo Medical University Hospital-sponsored hemophilia summer camp: Achievements over 34 years

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Introduction: The hemophilia summer camp offered by Tokyo Medical University Hospital targets patients with congenital coagulation disorders, mainly hemophilia. The activities are supported by medical doctors, paramedical staff members (such as nurses, pharmacists and physical therapists), university medical and nursing student volunteers and others who were going to support these disorders. We herein review the achievements of this activity for a 34-year span regarding the ingenuity required to keep these patients safe and discuss influences that have been introduced to hemophilia care.

Materials and Methods: This review is based on analyses of information contained in stored records and charts in the administration files.

Results: There were a median of 22.5 participants and 31 staff members per camp over these years. The oldest participant of the 34th Summer Camp was 45 years of age and had taken part in all 34 camps. Activities in the camp included tasteful recreation, such as cooking with firewood, water play, night hikes, and campfires. In the planned camp activity in consideration of the bleeding risk, all participants had no special behavioral restrictions. In the history of the summer camps, no participant left earlier due to a bleeding event. In addition, the opportunity to observe the injection procedure at the time of scheduled replacement therapy was able to be offered to promote the self injection. With the consent of senior patients who were able to perform self-injection, younger patients were able to watch the real world of self treatment, like the senior's experiences perhaps when they were urged to start the self-injection.

Conclusion: These summer camps provided an opportunity to encourage outdoor activities that hemophiliac patients find it difficult to experience in their daily lives while ensuring their safety through adequate cooperation of the staff. The activities included an introduction to, and encouragement of, self-injection with peer counseling. As a result, the camp experience contributes to the physically and mentally healthy growth of the patients. COI Y. Chikasawa has received honoraria for participation in advisory boards from Bayer, Novo Nordisk, Shire; has received honoraria for speaking from Bayer, Bioverativ, Novo Nordisk, Pfizer, Shire, outside of the submitted work. K. Amano hold concurrent posts as professors for the department of Molecular Genetics of Coagulation Disorders without additional salary; is a board member of the Factor Eight Inhibitor Bypass Activity Post Marketing Surveillance Study Board in Japan organized by Baxalta; has received honoraria for speaking from Baxalta, Bayer, Biogen, Kaketsuken, Novo Nordisk, and Pfizer; has

received honoraria for consulting with Baxalta, Bayer, CSL Behring, Kaketsuken, Novo Nordisk, Chugai and Pfizer; and has received unrestricted grants supporting research from Pfizer, outside the submitted work. M. Bingo has received honoraria for participation in advisory boards from Bayer, Bioverativ, Kaketsuken, Novo Nordisk, Shire; has received honoraria for speaking from Bayer, Bioverativ, Novo Nordisk, Pfizer, Shire, outside of the submitted work. K. Shinozawa is an endowed assistant professor funded by CSL Behring, has received payment for lectures from Baxalta, Novo Nordisk, Pfizer, and Bioverativ, and has received the Award from Baxter Coagulation Research Fund in Japan. H. Inaba has received honoraria for participation in advisory boards from CSL Behring; has received speaking fees from Biogen and Bayer, outside of the submitted work. K. Fukutake hold concurrent posts as a professor for the department of Molecular Genetics of Coagulation Disorders supported by CSL Behring without additional salary; is advisory committee member of Chugai Parm. and consultant of Chugai Parm., SRL Inc. and LSI Medience; has received research funding from Baxalta, Bayer, Biogen/Bioverativ, CMIC, EPS, Hitachi, Kaketsuken, Novo Nordisk, Ortho, Pfizer and Sysmex; has received honoraria for consulting, speaker or advisor from Abbott, Baxalta, Bayer, Biogen/Bioverativ, Chugai Pharm./Roche, CSL Behring, Japan Blood Products, Kaketsuken, MSD, Novo Nordisk, Octapharma, Ortho, Pfizer, Roche Diagnostic, Sekisui Medical and Torii Pharm.

T-P-134 (571) | Empowerment through transition – A qualitative exploration of young people's experiences

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Introduction and Objectives: During adolescence a young person has many biological, social and emotional changes to manage including significant hormonal changes, choosing a career and moving out of the home. A young person with haemophilia has other significant demands including an expectation they will have increased responsibility for the management of their condition and a physical transfer of care from the familiar paediatric setting to a new adult setting. With this complexity in mind, the Edinburgh haemophilia nursing and psychological support team decided to ask young people in Scotland about their experience of transition and what role the centre could play in supporting them.

Materials and Methods: Young people (aged 15-25) with moderate to severe Haemophilia registered at all Scottish Haemophilia Centres were sent an invitation letter for them and/or their prime caregiver to attend a focus group in Edinburgh. A semi-structured questionnaire was utilised to explore participants' experience of transition. The conversations were audio-recorded, transcribed verbatim and analysed for recurrent themes using thematic analysis.

Results: Six patients and one caregiver attended the event. Here, we present three inter-related recurrent themes all concerning the empowerment of the young person: "education and re-education", "advocating for self" and "choosing appropriate support networks". Young people highlighted the importance of continuous education throughout their healthcare journey emphasising that re-education about prophylaxis and bleeds on numerous occasions is necessary. This is particularly important in the adolescence years as there are many competing demands. All participants described the challenges of being able to advocate for themselves, describing a lack of confidence and experience in speaking to new medical professionals. Young people further described a need for different types of supports from different avenues throughout the transition process.

Conclusions: The young people described the transition process as both a physical transfer of care and a journey of empowerment, with the aim being to become an expert in the self-management of their condition. There is much the haemophilia care team can do to support this journey through a well-planned and structured transition process.

T-P-135 (183) | Living your life in a bubble

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Introduction and Purpose: The Nova Scotia Chapter of the Canadian Hemophilia Society runs a summer camp for children with Bleeding Disorders (Maritime Adventures Camp or MAC). The mission of the camp is to "improve the quality of life of children living with a bleeding disorder". The nurses at MAC organize educational sessions to help the children gain insight and develop coping strategies. This summer, the campers played "Bubble soccer", a game where the children were enclosed in inflated bubbles and rolled around the soccer field without threat of injury. From this game the nurses took the opportunity to explore the topic of "Living Life in a Bubble".

Material and Methods: After the game of Bubble soccer, 36 campers, aged 6-15 ((boys and girls), gathered for a discussion. The nurses did a short power point presentation, the children were separated into two groups and were given 15 minutes to discuss and answer the following two questions 1) What does it mean when we say "Living your life in a Bubble"? 2) Do you ever feel like you are living your life in a bubble?

Results: The children came back together. They grasped the concept of "Living in a Bubble" amazingly well. They shared some very mature and intuitive answers to these two questions. For question #1 some shared that they "felt safe and protected" while others felt nervous, scared to try new activities and hesitated to take risks. It was also expressed that some felt introverted and hesitated to share their feelings. For question #2 more than one camper said that they

felt they couldn't do some activities, or were not included in certain games. One even said that he sometimes felt invisible. The discussion was continued until all the campers had the opportunity to express their opinions. Possible coping strategies were also discussed.
Conclusion: The feeling of "Living life in a Bubble" is common amongst many with chronic illness. Helping children express their feelings and develop coping strategies is of utmost importance. Camp is the perfect place to discuss and allow this to happen.

35-PHYSIO

W-FPMSK-002 (366) | Inter-rater variability of global gait score assessment using the HJHS criteria

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Introduction and Objectives: UK guidelines state all persons with moderate/severe haemophilia are evaluated with the Haemophilia Joint Health Score (HJHS) at yearly intervals. Global Gait Score (GGS) within HJHS is an observational section with skills of walking, stair climbing, running and hopping scored between 0 and 4 for skills not within normal limits. This study investigated whether training reduces the variability of scoring in physiotherapists assessing the gait component of HJHS in paediatric and adult patients.
Method: 17 physiotherapists (adult) (mean haemophilia experience 4.27 years) and 18 (paediatric) (mean haemophilia experience 4.82 years) attended an HJHS training day. Each used the GGS criteria of the HJHS to assess two children or two adults with haemophilia, before and after training using the HJHS instruction video. Variability of scores together with concordance with an experienced HJHS user was analysed using descriptive statistics.
Results: Mean adult GGS prior to training was 1.76 ± 1.56 (SEM; 0.27), following training increased to 3.35 ± 1.09 (SEM; 0.19). Mean paediatric GGS prior to training was 2.14 ± 1.40 (SEM; 0.23), following training increased to 2.58 ± 1.48 (SEM; 0.21). Before training, agreement with an experienced HJHS user was 19% for paediatric and 32% for adult therapists. Post training, agreement was 39% and 71% respectively. Post training, 33% of paediatric and 9% of adult therapists differed from the expert by more than 3 points. Therapists within 1 point agreement had more years haemophilia experience (mean years; 6.0 paediatric, 5.5 adult) than those with disagreement of 2 or more points (mean years; 3.1 paediatric and 1.8 adult).
Conclusions: Training of the GGS component of the HJHS reduces variability and improves accuracy of scoring amongst UK physiotherapists. The GGS is underestimated by both paediatric and adult physiotherapists; this underestimation is reduced following specific GGS training. Concordance of therapists with an expert rater doubled following training, but high variability remained when assessing children despite training, perhaps due to differences in knowledge of childhood development and maturation. Nevertheless, regular training and validation of users of the HJHS is essential, particularly if the tool is used in multi-centre and comparative studies.

W-FPMSK-003 (599) | Initial results of the real world haemophilia early detection ultrasound (HEAD US) study

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Introduction and Objectives: Advances in technology, reduced costs and the need for an objective and meaningful assessment of joint health have seen an increase in the adoption of point of care ultrasound as an assessment tool within haemophilia care. The Haemophilia Early Arthropathy Detection Ultrasound (HEAD-US) protocol has been developed as a simple clinical tool for the use of clinicians rather than radiologists. The primary aim of this study is to identify whether the use of the HEAD-US protocol influences clinical decision-making in haemophilia care.
Materials and Methods: Patients were assessed during routine clinical appointments by a consultant haematologist and changes to clinical management were recorded and categorised. Patients were then assessed by a physiotherapist. Patients were randomised to be assessed by physical examination involving the use of the Haemophilia Joint Health Score or examination using the HEAD-US protocol. Patients were then re-assessed using the other assessment modality within the same clinic appointment. After completion of each modality clinical findings were discussed with the haematologist. Any further changes to clinical management were recorded and categorised. Initial results: 27 patients (to date) with either severe or moderate haemophilia A or B have been assessed, median age 29 (range 21-65). 37% of participants' clinical management were altered as a result of ultrasound examination. 3.7% changed treatment regime, 14.8% received further advice or education, 11.1% were referred on for further diagnostic tests, 7.4% changed their physiotherapy or exercise regime and 3.7% received some other medical or non-medical intervention. 53% percent of patients remained unchanged by HEAD-US. Clinicians did report that ultrasound provided further justification for management decisions in 14.8% of these cases. 22% of participants' clinical management was altered following physical examination.

Conclusions: These are preliminary findings from a single site of a multi-site clinical study. The initial results support the effectiveness on adopting the HEAD-US protocol as a clinical assessment tool in haemophilia care.

W-FPMSK-006 (163) | The pediatric hemophilia activities list: towards a next generation of activities and participation assessment

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Introduction and Objective: The pediatric Hemophilia Activities List (pedHAL) assesses self-reported limitations in activities in children with hemophilia (child and parent forms). The pedHAL contains 53 items, divided in seven domains. The present study aimed to explore patient-parent agreement, assessment of social participation and identify non-informative items.

Materials and Methods: We analyzed cross-sectional pedHAL data collected at the annual routine assessment at the Van Creveldkliniek (University Medical Center Utrecht, The Netherlands) between October 2010 - June 2017. Patients (4-18 years) with moderate/severe hemophilia A/B and their parents completing ≥1 pedHAL were included. We determined the distribution of scoring per item with descriptive analyses and patient-parent agreement per domain with limits of agreement and Wilcoxon signed-rank tests. In addition, 7 children, 4 parents and 11 health care professionals rated the relevance of all 15 participation items of the domains 'use of transport', 'household tasks' and 'leisure activities and sports'.

Results: Eighty-two patients with hemophilia A/B (severe 94%, median 13.1 years [range 5.4-18.0]) were included. Mean domain scores ranged between 98 and 92. Limits of agreement of domain scores of patients and parents (n = 69 pairs) varied from 8 ('selfcare', mean score 98) to 19 ('functions of the legs', mean score 93). In parents 15 items were scored as 'never problems' in >90% and 28 items were scored as 'never problems' in 80-90%. The 13 most informative items (<80% 'never problems') belonged to the domains 'sitting/kneeling/standing', 'functions of the legs' and 'leisure activities and sports'. The evaluation of participation items showed that sports items were considered most relevant; sports items were scored as relevant by >64% of the participants.

Conclusions: Patient-parent agreement for the pedHAL was acceptable. This explorative analysis of single-center data identified several non-informative items. In addition, participation assessment will be further evaluated in focus groups. Item reduction is expected enhance feasibility of the pedHAL for research and clinical proposes, but can only be performed after testing in other populations.

W-FPMSK-007 (252) | A novel physiotherapy led musculoskeletal clinic – The perceptions of persons with haemophilia

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Introduction: In the UK, guidelines recommend that patients with severe and moderate haemophilia (PWH) are regularly reviewed by physiotherapists with regards to their joint health and function. Currently this is achieved at routine 15-30 minute outpatient appointments in which the patient is reviewed first by the haematologist, then the nurse, then the physiotherapist. This typical delivery of care poses challenges in terms of space, time to complete a full musculoskeletal (MSK) review and little time for multidisciplinary discussion and patient education. At the Royal London Hospital, we established a new model of delivery that involves an additional clinic appointment at a separate physiotherapy led MSK clinic to monitor patient's MSK health and provide relevant education and treatment, using the Haemophilia Joint Health Score (HJHS), Haemophilia Activities List (HAL) and the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US).

Materials and Methods: To explore patient perception of the MSK clinic, all patients who attended were sent a closed format questionnaire by post, email or by hand. Using a 4-level Likert scale, patients were asked for their perspectives on the usefulness, knowledge gained and willingness to attend future MSK clinics.

Results: 24 (51%) patients completed the questionnaire. Almost all (>95%) found the clinic useful and would attend an additional MSK clinic each year, where the focus could be specifically on their MSK health. The majority of patients (66.7%) also reported a better understanding of their disease after attending the clinic and would recommend the clinic to other PWH (87.5%). Patients (87.50%) reported point-of-care ultrasound examination (HEAD-US) the most valued and informative component of the clinic, followed by the HJHS and then the HAL.

Conclusions: A novel physiotherapy led MSK clinic focused on individual joint health and education is positively perceived by PWH. This model of individualised care, in particular, the use of point-of-care ultrasound utilising the HEAD-US tool was perceived as high value to PWH, and attributed to increasing their understanding of joint health. Further data is required to determine the cost effectiveness of maintaining a service of this nature.

T-P-142 (378) | "In the Driver's Seat": A patient education resource to guide individualized decision-making about physical activities

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Introduction: It is well-documented that persons with bleeding disorder (PBD) benefit from physical activity. Previous physical activity resources for PBD are primarily didactic and based on an incomplete assessment

of sport risk. They do not incorporate an evaluation of an individual's physical function and limitations that may impact their risk for injury or bleed. Currently, in more privileged countries, prophylaxis is common to manage the bleeding disorder. PBD, with high severity, are now participating in more high-risk activities, despite the recommendations. Additionally, current practice in chronic disease management encourages self-efficacy and collaborative partnership between healthcare provider and the patient. Therefore, a resource for PBD is needed which encourages informed decision-making about physical activity for PBD.

Objective: The objective of this project is to develop a user-friendly workbook to guide PBD in evaluating their health and activities of choice, and to minimize the risks associated with the activity.

Method: Members of the Canadian Physiotherapists in Hemophilia Care (CPHC) formed a working group to address the gaps were identified in the available patient resources for activity recommendations. Learning objectives were identified: 1. Self assessment 2. Assessment of the activity of choice 3. Risk Reduction 4. Activity Planning. The workbook is based on health behavior change theory, patient-centred learning, management of joint health, and epidemiology and prevention of sport injury. It was written in consultation with experts in health education design.

Results: The workbook is divided into four sections: *Assessing yourself*, *Choosing physical activities*, *Reducing risks*, and *Making an activity plan*. Each section introduces the topic, followed by questions to engage the reader in critically evaluating their chosen activity, and the potential effects it may have on their body. End-users (PBD and parents of PBD) were involved in the development process. The workbook has been published and distributed to all hemophilia treatment centres in Canada in both English and French and is also available electronically.

Conclusion: Successful outcomes for patients with chronic conditions, requires a collaborative relationship with healthcare providers and self-management tools. This workbook incorporates current evidence and patient-centre care principles and presents a novel resource for PBD and physical activity recommendations.

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T-P-143 (126) | Engagement with physiotherapy services in a cohort of persons with haemophilia at a treatment centre in Kerala, India

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Introduction and Objective: There is limited access to regular prophylaxis with clotting factor concentrate (CFC) in resource-limited settings resulting in a high prevalence of haemophilia-related arthropathy. Physiotherapy is an important means of managing acute haemarthrosis, providing rehabilitation after a bleed and maximising functional status. The aim of this report was to describe the engagement with physiotherapy services in a cohort of persons with haemophilia (PWH) at Aluva Hemophilia Treatment Centre, Kerala, India.

Materials and Methods: This study was a retrospective review of physiotherapy workload over a period of 24 months starting from April 2014.

Results: 633 PWH were registered for care at the centre, 519 with haemophilia A and 114 with haemophilia B. 71.4% had severe haemophilia and 40 subjects (0.06%) had an inhibitor. There were a total number of 8688 physiotherapy sessions. Among 144 subjects with established arthropathy, the predominant affected joint was; Knee in 70.4%, ankle in 19.4% and elbow in 10.2%. Regular physiotherapy sessions (on average 7 hours/week) were attended by 97 (64.6%) of those with arthropathy whereas 47 (35.4%) only attended sporadically (on average 1 hour/week). Physiotherapy treatment components included proprioception, muscle strengthening and general exercises. Haemophilia Joint Health Scores (HJHS) and Functional Independence Score in Haemophilia (FISH) were routinely recorded at baseline and 6 monthly.

Conclusions: There is an incomplete uptake of physiotherapy treatment in PWH even in those with established arthropathy. Measures that have been identified which may improve engagement are the establishment and training of outreach haemophilia treatment centres in the state of Kerala and education of PWH about the benefits of physiotherapy in terms of their joint health.



FIGURE 1. Predominant affected joint in 144 individuals with haemophilia at Aluva Hemophilia Treatment Centre, Kerala, India.

T-P-144 (96) | Safety and efficacy of fascial therapy in the treatment of hemophilic arthropathy of elbow: a pilot study

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Introduction and Objective: Hemophilic arthropathy is characterized by loss of function and chronic pain. Fascial therapy mobilizes

the connective tissue, intervening in the state of the injured fascial complex and the surrounding tissues. The objective of the study was to evaluate the safety and effectiveness of a physiotherapy program through fascial therapy in patients with hemophilic elbow arthropathy.

Material and Methods: Fourteen adult patients with hemophilia from over 18 years old were recruited. The intervention consisted of three sessions of 45-minute fascial therapy for three consecutive weeks. Assessment was carried out at baseline and after the treatment and follow-up period. The study variables were bleeding frequency (using a self-registration of bleeding), joint pain (thought visual analogue scale), range of motion (with a universal goniometer) and joint status (assessed with *Hemophilia Joint Health Score*). The mean difference was calculated using the t-student test. The effect size was calculated using Cohen's formula. Using a repeated measures ANOVA, means were compared in both groups in all three evaluations.

Results: None of the patients included in experimental group developed muscle or joint bleeding during the treatment or follow up period. After treatment, significant improvements in joint pain were observed in both elbows (P = .08 and P = .037 in right and left elbow, respectively). Similarly, we found improvement in flexion (P = .04) and joint status (P = .047) in right elbow.

Conclusions: The application of physiotherapy through fascial therapy does not produce muscle or joint hemorrhages in persons with hemophilic arthropathy of elbow. This treatment of fascial therapy can improve joint pain, range of motion and elbow status in adult patients with hemophilia. The authors state that this work has received financial support from Baxalta now part of Shire.

T-P-145 (162) | Usefulness of a simple self-administered condition assessment sheet for knee and ankle joints in the management of children with hemophilia

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Introduction and Objective: Hemophilic arthropathy is the serious complication of hemophilia deteriorating quality of life. Recently, a simple self-administered joint condition assessment sheet for the management of hemophilic arthropathy was developed and validated for adults. The objective of the work is to verify the sheet for children with hemophilia.

Materials and Methods: From 2012 to 2017, 140 knee and ankle joints of 35 patients (27 children with hemophilia A and 8 children with hemophilia B, 5 inhibitor positive) were enrolled in this research. The average age of them were 10.5 (4-20) years old. The patients were asked to answer the self-administered sheet regarding to the condition of each joints. The sheet comprises four items about bleeding, swelling, pain and physical impairment. At the same time, the joints are evaluated with Hemophilia Joint Health Score (HJHS) 2.1, DePalma radiological classification and Arnold-Hilgartner (A-H) grading system. Each items of the sheet were correlated with those evaluations using Spearman's rank correlation.

Results: Three of four items were correlated with HJHS 2.1 in knee joints. Two of four items correlated with it in ankle joint. Especially, the item for pain was strongly correlated with HJHS 2.1 in knee and ankle joint (correlation coefficient: 0.77 and 0.77, respectively). The item for swelling was moderately correlated in both joints (0.49 and 0.40 in knee and ankle joint, respectively). In ankle joint, the item for bleeding moderately correlated with DePalma classification (0.55) and A-H grading system (0.53). As for elbow joints, however it could not be analyzed the correlation between items of assessment sheet and HJHS2.1 because the HJHS 2.1 positive joints number is small.

Conclusions: To the best of our knowledge, this is the first research correlating of the sheet with already well validated physical and radiological evaluations in children with hemophilia. Using this concise self-administered joint condition assessment sheet would be helpful in the management of children with hemophilia.

T-P-146 (221) | Validity of a depth camera for elbow range of motion measurement in haemophilic patients: The first step for a telemedicine approach

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Introduction and Objective: Telemedicine is becoming a valuable tool for stimulating the performance of home-based exercises in haemophilic patients. In addition, systematized ways of measuring range of movement (ROM) for remote supervising their progression, especially after a bleed, are needed. This work proposes a complementary method to classical goniometry based on motion sensing technology to monitor elbow ROM in haemophilic patients.

Materials and Methods: This observational study was carried out at the University of Valencia. 10 healthy

controls (CG) (age = 35.20 ± 6.23 years; BMI = 22.25 ± 1.97 kg/m^2) and 10 haemophilic patients (HG) (age = 36.80 ± 10.49 years; BMI = 27.94 ± 7.36 kg/m^2) with different grade of elbow arthropathy (HJHS average in elbows = 10.20 ± 9.11) participated. Microsoft Kinect V2 (MKV2) depth camera and goniometer were used to measure the elbow ROM from the maximum extension to the maximum flexion in increments of 10°. To improve MKV2 accuracy, a measurement correction model (cubic polynomial fit) was applied. MKV2 validity was assessed comparing MKV2 and goniometer measurements using the Bland-Altman method. Differences in the ROM between CG and HG were analysed with Wilcoxon test.

Results: Before adjustment, the mean error of the MKV2 with respect to the goniometer was 7.87° (limits of agreement (LoA) = −10.28°;26.02°) in the CG and 9.49° (LoA = −7.92°;26.89°) in the HG. After applying the fitting model, the mean error was reduced to −0.08° (LoA = −8.10°; 7.93°) in the CG and to −0.73° (LoA = −10.70°; 9.25°) in the HG. This reduction of the error was statistically significant ($P < .001$). Regarding the ROM, the HG showed a significantly ($P < .001$) lower extension and flexion of the elbow than the CG, both with the goniometer and with the MKV2 measurements. There were no statistically significant differences between measurements performed with the goniometer and with MKV2, except for the extension in the HG ($P = .008$).

Conclusions: Results indicate that the angle-corrected MKV2 is a valid tool to measure elbow ROM of haemophilic patients. Therefore, this telemedicine tool, in addition to its gaming use, can complement classical goniometry allowing the clinicians to remotely measure the patients' ROM, especially post bleeding, when an accurate control of a therapeutic program is needed. Moreover, MKV2 can reduce patients' hospital dependence.

T-P-147 (216) | Interaction of dual task in haemophiliac and non-haemophiliac subjects in postural control during quiet stance

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Introduction: The most common consequences of haemophilia are joint damages, principally the lower limb (knee and ankle) affecting range of motion, force and proprioception. Recently, it has been proposed that haemophilic arthropathy is accompanied with poor automatic postural control strategies. One form to study the automated process in postural control is the dual task paradigm. The main objective of this study is to probe the following hypothesis: haemophilic patient have less automatic postural control during cognitive dual task.

Methods: Eighteen adult patients with severe haemophilic and fifteen non-haemophilic patients were assessed. Each participant was invited to maintain a quiet stance during 30 seconds three times with deprivation of visual stimulus in single task (maintain bipodal posture) and cognitive dual task (bipodal posture and mathematical task). The postural sway was assessed by triaxial accelerometer at L5. The sway analysis consisted in measure two variables, the acceleration of center of mass and irregularity of acceleration signal through sample entropy to assess the automatic process of postural control. The two-way ANOVA was applied by group (haemophiliac and non-haemophiliac) and conditions factors (close eyes and dual task). If interaction was significant the par-comparison was applied with Bonferroni post-hoc.

Results: The two-way ANOVA showed a significant interaction in sample entropy between group and conditions only in mediolateral axis ($P = .038$). Also, we found a significant difference in the factor group ($P < .001$) and conditions ($P = .008$). The post-hoc analysis exhibited a higher sample entropy during dual-task in non-haemophilic group ($P = .006$), however in haemophiliac patients the sample entropy was maintained without change between conditions ($P = .900$).

Conclusion: The results suggest that haemophiliac patients has lees automatic control in the dual task condition during quiet stance. The poor automatic adaptation during dual task propose that is necessary postural exercise to optimize the automatic adjustments during different physical and cognitive conditions.

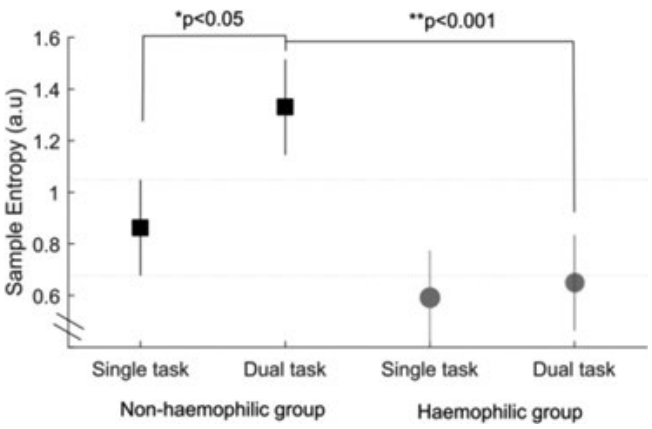


FIGURE 1. Interaction of group and conditions during quiet stance.

T-P-148 (566) | Weekend group rehabilitation course increasing range of motion in patients with hemophilic arthropathy of the knee

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Introduction and Objectives: Hemophilia is an X-linked recessive bleeding disorder. Repeated joint bleeding leads to hemophilic arthropathy with chronic synovitis, cartilage damage and bony destruction, which are associated with pain, reduced range of motion (ROM), muscle atrophy, functional impairment, and poor quality of life. The aim of the study was to investigate the effectiveness of 3 months Weekend Group Rehabilitation Course (WGRC) in patients with hemophilic arthropathy of the knee.
Patients and Methods: 14 severe hemophilia A patients with hemophilic arthropathy of the knee at our center were recruited. Every participant received 30-minute modality treatment, 45-minute group exercise and 15-minute personal manual therapy, in every Saturday morning for 3 months. We collected clinical information including age, height, weight and history of inhibitor. Bilateral knees joints were evaluated by plain X-ray and scored with Pettersson scale. The primary outcome was ROM measured by a goniometer. Secondary clinical outcomes included pain, stiffness and daily activity limitation, ranging from 0 (no symptom) to 10 (extremely severe). Change of Hemophilia Joint Health Score (HJHS) was also recorded at baseline and 3 months later.
Results: The patients' median age was 46.5 years old with a range from 20 to 62 years. Two patients had factor VIII inhibitors. The median BMI was 24.0 kg/m^2 (range, 19.0-37.0). The median Pettersson score of the knee was 9 (range, 2-13). ROM of the knee was significantly improved after 3 months WGRC (right knee, from 74.8 ± 16.8 to 89.2 ± 19.6, $P < .01$; left knee, from 78.2 ± 28.2 to 92. 9 ± 26.0, $P < .01$). There were no significant difference between the baseline and after 3 months WGRC in terms of pain ($P = .358$), stiffness ($P = .203$), daily activity limitation ($P = .424$) and HJHS.
Conclusions: Our study demonstrates that 3 months WGRC could improve knee ROM in patients with hemophilic arthropathy of the knee. WGRC may be an alternative strategy for patients who cannot receive physical therapy during weekday due to work or school.

T-P-149 (358) | Osteoporosis and sarcopenia in haemophilics who underwent orthopedic major surgery: An observational study

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Introduction and Objective: A decreased or impaired mobility is the most frequently suggested mechanism for the lower bone mineral density (BMD) in patients with haemophilia (PWH). According to the physiology of the muscle-bone development, limited physical activity leads to sarcopenia, that in turn increases the risk to develop osteopenia/osteoporosis. In this study we aimed to determine the prevalence of osteoporosis/osteopenia and sarcopenia in PWH.
Materials and Methods: We included adults (n = 54) with haemophilia A or B hospitalized in Rehabilitation Unit after orthopedic major surgery (total knee, ankle and hip replacement; osteosynthesis and leg amputation). Lumbar and femoral dual-energy X-ray absorptiometry (DXA) was performed to analyze BMD. Skeletal muscle mass was estimated by bioelectrical impedance analysis (BIA 101-Akern) and skeletal mass index (SMI) was calculated with Bodygram PLUS software to classify sarcopenia (n = 34). Handgrip strength was evaluated with Jamar dynamometer (n = 34). Vitamin D deficiency was also investigated (n = 50).
Results: According to World Health Organization criteria to define osteoporosis, we divided patients in two groups: < of 50 years (median age 38 ys, Body Mass Index 24.07 kg/m^2) and > of 50 years (median age 58 ys, Body Mass Index 24.1 kg/m^2). Among patients < 50 ys, 14.8% had osteoporosis (Z score less than −2), 40.7% presented osteopenia (Z score within the range −1 and −2). 88% had vitamin D below 30 ng/dl and 20% showed severe vitamin D deficiency. On the basis of European consensus on definition of Sarcopenia, according to SMI cut off, 83.3% had mild-moderate sarcopenia and 16.7% severe sarcopenia; 22.2% showed low handgrip strength (<30 kg). Among patients > 50 ys, 18.5% had osteoporosis (T score less than −2.5) and 59.3% osteopenia (T score within the range −1 and −2.5). 90.5% showed vitamin D below 30 ng/dl and 38.1% had severe vitamin D deficiency. 50% presented mild-moderate sarcopenia and 50% severe sarcopenia; 73.3% exhibited low handgrip strength.
Conclusions: Both young and older PWH who underwent orthopedic surgery showed very high prevalence of sarcopenia and vitamin D deficiency. Low BMD occurs in adults with haemophilia more frequently than in general population.

T-P-150 (444) | Gait testing and training using the C-Mill Motek™ treadmill in hemophilia patients: a pilot study

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Background: The C-Mill is a treadmill for evaluation and training of impaired gait and balance using augmented and virtual reality. The advantages of using the C-Mill is that it trains functional walking with targeted treatment options. It has repeatable and variable training possibilities and allows the assessment of the patient's gait and gait adaptability. Due to repeated joint bleed, joint arthropathy and joint arthroplasty in adult Hemophilia patients, gait parameters are often impaired. Treatment goals include improvement of gait parameters. The C-Mill Motek treadmill incorporates objective testing, training and re-testing and aids in the improvement of the patient's gait.

Participants: Five Hemophilia A male patients ages 32-42.
Methods: A protocol was initiated which included a test, training period and re-test. The test and re-test consisted of the patient walking at his comfortable speed for three minutes, stepping on stepping stones symmetrically for two minutes and an obstacle course for two minutes. The training consisted of weight shift using a virtual reality screen, an obstacle course and stepping on or avoiding objects placed at different intervals. The training was based on a medium range of difficulty and took 13 minutes to complete.
Results: There were improvements in temporal and spatial gait parameters by 20-30%. Symmetry and accuracy improved 8-10%. The center of pressure improved in all but one of the participant's gait parameters. Conclusion: The use of the C-Mill Motek treadmill can be successfully used to build protocols that will improve gait parameters in the Hemophilia patient. There is implicit learning, feedback and the ability to vary training options. Author has no disclosures.

36-PSYCHOSOCIAL ISSUES

T-FPMTD-004 (534) | Evaluation of the Scottish haemophilia psychological support service

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Introduction and Objectives: The burden of mental health issues among people with haemophilia is well recognised. The World Federation of Haemophilia's Guidelines for the management of haemophilia specify "attention to psychosocial health" as a key priority in the comprehensive care of people with haemophilia. Guidelines in the United Kingdom recommend that patients should have access to counselling services. In 2016, with strong support from patients through Haemophilia Scotland, the Scottish Government funded a pilot for a Psychological Support Service (PSS) to attempt to address these needs. The PSS comprises one full time clinical psychologist and part time psychiatrist. The service provides direct clinical care, clinical consultation to teams and educational programmes for multidisciplinary clinic staff.
Materials and Methods: A mixed methods design was utilised to explore the impact of introducing a PSS to a Haemophilia Centre. Patients referred to the service completed a number of psychometric tests including the HADS, CORE-10, General Self-Efficacy Scale, Self-efficacy for managing chronic disease scale, and EuroQol-5D upon entry and completion of treatment. Qualitative interviews were conducted with patients and staff members to explore people's experience of the PSS.
Results: At time of referral, 88% of patients had clinically significant psychological distress, 18% scored within diagnostic range for clinical depression and 59% for diagnosable anxiety disorder. Treatment led to statistically significant improvements in anxiety ($P = .001$), depression ($P < .05$), and psychological distress ($P < .001$). There was a non-significant trend towards improvement in overall quality of life ($P = .064$) and self-efficacy scores (Overall SE $P = .138$; Health SE $P = .256$). Analysis of qualitative patient interviews identified the benefits for patients of PSS input for self-management and adherence to treatment, increasing coping skills, anxiety management and adjusting to the impact of bleeding disorders on quality of life. Staff interviews highlighted the diverse role a PSS can play through individual patient support, collaborative working, and the impact on healthcare professionals' own practice.
Conclusions: The Scottish pilot has demonstrated that the introduction of PSS has a positive impact upon patients' well-being and is well received by both patients and staff. Data collection is ongoing. Future challenges include rolling out the service to remote areas.

W-MP-159 (204) | Assessment of depressive disorders among people with hemophilia A inhibitors

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Introduction and Objective: Depression is associated with poor quality of life, lower functioning, and decreased treatment adherence. The impact of depression in persons with hemophilia A (PWHA) is less frequently addressed. We compared the depressive disorders among PWHA with and without inhibitors.
Materials and Methods: PWHA inhibitors who participated in two 2016 USA Inhibitor Education Summits serve as the inhibitor group. The non-inhibitor group included PWHA without inhibitor history from the Hemophilia Utilization Group Studies part Va (HUGS Va), a two-year observational study conducted during 2005-2007. Data on sociodemographic and clinical characteristics, and 12-Item Short Form Health Survey (SF-12) were collected for both groups. Depressive disorders were assessed by the SF-12 mental component score (MCS), a validated population-based measure including depressive disorders. MCS≤45 has been identified as a depressive symptom threshold suggestive of a disorder. MCS≤36 indicates persons with more severe psychological symptomatology and/or impairment. Descriptive statistics were compared between inhibitor and non-inhibitor groups, using propensity score adjustment for sample selection bias. The EQ-5D-3L was administered only in the inhibitor group. Depression identified from EQ-5D-3L in the inhibitor group was compared to the USA general population.
Results: Twenty-two participants (47.9% adults) were in the inhibitor group and 278 (50.8% adults) in the non-inhibitor group.

Self-reported joint pain (85% vs. 72%, $P = .0002$) was significantly higher in the inhibitor group than the non-inhibitor group. Mean MCS was significantly lower in the inhibitor group (mean±SD: 45.0 ± 38.5 vs. 50.7 ± 10.7, $P = .04$). The inhibitor group was more likely to report "feeling down hearted and blue" in the SF-12 (85% vs. 67% $P < .0001$); had MCS≤45 (47% vs. 28%, $P = .0002$); and had MCS≤36 (21% vs. 11%, $P = .0002$). Persons in the inhibitor group reported more problems than the general USA population in five areas of the EQ-5D-3L: measures of mobility (50% vs. 18%), self-care (25% vs. 4%), usual activities (55% vs. 15%), pain/discomfort (80% vs. 41%), and anxiety/depression (45% vs. 27%).

Conclusions: Our study indicates higher rates of potentially depressive disorders identified by SF-12 in a sample of PWHA inhibitors. The inhibitor group reported higher proportion of impaired health status identified by EQ-5D-3L compared to the general USA population.

Conflict of interest: Joanne Wu and Mimi Lou received financial support through the project funding provided by Genentech Inc. Randall Curtis and Brenda Riske received consultant fee through the project funding provided by Genentech Inc. Judith Baker, Megan Ullman, and Marion Koerper have no significant conflicts of interest to declare. Yaping Xu is an employee of Genentech Inc. and Roche Stocks holder. Michael B. Nichol is a principle investigator for the HUGS studies received grant funding from multiple sources including Genentech Inc., Bioverativ (formerly Biogen Idec), Pfizer, Baxter, Bayer, CSL Behring, and Novo Nordisk. He is a consultant for Bayer.

T-P-002 (453) | Psychological profile of carriers and need for active genetic counseling for female family members of hemophilia

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Introduction: Hemophilia A (HA) and B (HB) are sex-linked recessively inherited disorder. Its diagnosis, inheritance pattern, and treatment regimens have well been established. However, satisfactory genetic counselling for the carriers have not been easily available in dealing with accurate information of carrier status, psychological impact of being carrier, and decision-making process for family planning.

Objectives: In order to study the awareness of carrier status and the scope of the psychological profile among female family members of hemophilia, we surveyed their understanding of being a carrier status before and after group education session and individual genetic counseling service.

Materials and Methods: Of 158 patients with hemophilia A and B we followed, 48 families were identified as having carriers. Among these, 16 subjects in 10 families with 5 hemophilic pts, 4 wives of hemophilic pts, 4 daughters of hemophiliac fathers and 3 daughters of hemophiliac carrier mothers consented to participate in the survey of genetic counseling program for hemophilia using the questionnaires concerning the knowledge of genetic inheritance and psychological profiles. Questionnaire was filled out before and after the group education session and individual genetic counseling.

Results: All participants showed lack of accurate information regarding their carrier status as to obligate vs. at risk and revealed "fear" from the possibility of carrying hemophilic child, which resulted in avoiding healthy relationship with partners or child bearing. Obligate carrier daughters from hemophilic fathers were suffering more from than the carriers at risk from carrier mothers. After the education and genetic counseling, improvement of understanding lack of communications with their fathers with accurate information on the mode of inheritance and carrier status led to a reduced undue fear, being able to comprehend sufficient knowledge to make informed choices toward future relationship with partners and for childbearing.

Conclusions: While the therapeutic intervention for hemophilic patients are well established and enjoy the benefit of improved treatment, their carrier members of hemophilia are suffering from undue fear due to the lack of accurate genetic information and warrant active genetic counseling to overcome the psychological barrier and burden to make a better informed decision on their reproductive options.

W-P-088 (507) | How "good" a healthcare professional should be? An empirical study on the acquired and required psychosocial competences for comprehensive haemophilia care

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Introduction and Objective: The comprehensive care (CC) model promoted by the WFH is nowadays widely acknowledged, although its actual implementation is subject to considerable variations among Countries and/or Centres, due to socio-cultural aspects and resources availability. In this framework, healthcare professionals (HCPs) are asked to acquire psychosocial competences, which are transversal to various professions, but are also expressed and contextualised depending on the professional specificities and circumstances. This study, which is part of a two-year research project, aims to identify and describe such non-technical competences in relation to five major domains that a previous study recognised as representative of HCPs' experiences in working with haemophilia: dealing with policies, resources and stakeholders in the local care system; challenges when caring for impaired adult PWHs; diagnosis and counselling about reproductive choices;

challenges when coping with adolescent PWHs; considering the impact of family dynamics.

Materials and Methods: Structured interviews with haemophilia HCPs, people with haemophilia (PWHs) and their family members, from seven different countries, were content analysed. Technical and non-technical competences and needs associated with different actors (i.e. HCPs, PWHs, family members) in the five domains were coded. Details about the interviewee (i.e. role, Country) were also considered in order to reflect on cultural and organisational specificities.

Results: The triangulation between the perspectives of the main actors involved in haemophilia care led to the identification of relevant needs and cross-professional and non-technical competences supporting the CC model. The representation of the HCPs' work will be described through the identification of the challenges to be addressed and the competences to be developed in each domain, introducing some reflections about how professional and cultural specificities may affect the CC model.

Conclusions: Overall, this research project contributes to improve knowledge and awareness of the different psychosocial aspects that the CC model requires to be fully achieved. Such knowledge can be integrated in research designs and can become the basis for further developments in interventions (e.g. training paths, work organisation in haemophilia CC centres). It can also be used for constructing a cross-professional and cross-national "core curriculum" in order to promote CC in haemophilia.

W-P-160 (203) | Group therapy for parents of young children improves coping with hemophilia

Helena Landa; Gaby Golan; Dalia Bashari; Tami Barazani - Brutman; Gili Kenet

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Introduction and Objective: Hemophilia comprehensive care throughout life is provided at our national HTC for about 670 patients. One of the techniques successfully used by us is group therapy, starting as soon as the diagnosis is made. We currently lead four organized groups of parents of hemophilic children in various ages. Group formation, management, type of support and special events handling are presented for our cohorts in this paper.

Methods: once hemophilia diagnosis is made patients are referred to our tertiary national HTC. During the first meetings with pediatric hematologists, nurses, the psychosocial team is introduced, and parents are invited to join a currently running or a newly formed group. Our center currently runs 4 different groups, one of them already running for 13 years (!) and others for 7 years, 3 years and 1 year. The parents meet outside the department and support each other in difficult times. One of the unique techniques used in our groups is that each one of the caregiver's team joins one of the group meetings to supply information about their expertise, in order to reduce anxiety and deal with the feelings aroused.

Results: The current groups include a total of 24 families, coming from various areas of our country. Group members deal with their mutual problems, giving support and comfort to each other, guided by two co-therapists, the social worker and psychologist. The group enables reduction of the psychosocial burden of the disease while at the same time amplifying coping resources, becoming, in time, a self-support group. When compared with families of similar aged hemophilia patients that do not take part in the support groups, group members are more confident, more knowledgeable about disease and treatment, start prophylaxis earlier, ask for more referrals to in vitro fertilization and PGD and are more involved in their patient association activities.

Conclusion: Group intervention offers the families a therapeutic option to handle situations of sickness and disability and better cope with challenges of health and life.

W-P-161 (151) | Psychological support to families: The effect on family structure of patients with hemophilia

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Introduction: Chronic diseases such as hemophilia go beyond the containment of institutional health care systems and affect not only personal daily life but also social networks. This situation is even more difficult when the affected patient is a child; the initial diagnosis impacts heavily on the family disrupting its homeostasis. Space for the whole family to deal with this situation can be found from a psychological point of view. This is done at the foundation of Hemophilia through psychotherapy.

On the other hand, the "Accompanying Parents" (AcP) programme created in 1998 and composed of volunteer parents whose sons suffer from severe hemophilia, functions as a backup system for recently diagnosed families and families in crisis. The *objective* of this study is to analyze and to compare the family structure in a sample of parents whose children suffer from hemophilia.

Materials and methods: To do this research the Family Adaptability and Cohesion Evaluation Scales (FACES III) was handed out. Thirty parents of pediatric patients with hemophilia participated in the study, divided in three groups: people attending psychotherapy sessions (G1), families without psychotherapy (G2) and the AcP members (G3). Psychological therapy was offered to G2 -for parents, children with hemophilia and/or their siblings, according with each case-.

Results: In the cohesion indexes, all groups presented a semi-related structure. Concerning their adaptability, no adaptation level differences were evinced; all the groups showed a rigid one. Regarding the family structure, G1 and G3 have an extreme family structure;

G2 has a medium range structure. Besides, significant differences on statistical level were found between G2 and G3 as far as cohesion and family type. The intervention of AcP produced a 100% healthy impact on the accompanied families. This is the result of a survey made for that purpose.

Conclusions: The sudden diagnosis of hemophilia generates psychological vulnerability in the family group. According with WFH recommendations, the present study shows that to recover a healthy balance and improve the quality of family life, integral and sustained psychological work for the entire family is needed.

Keywords: Family structure, Psychotherapy treatment, Accompanying Parents, Cohesion, Adaptability.

W-P-162 (235) | Go Dutch with Ethic; using a Moral Deliberation Forum to structure and discuss an ethical dilemma

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Introduction and Objective: People with hemophilia (PWH) tend to bleed longer due to the missing clotting factor. Treatment by injecting the missing clotting factor is very effective. With adequate treatment and proper care, PWH can relatively live healthy lives. Worldwide, only 25% of estimated 400.000 PWH have access to appropriate healthcare. The lack of access to care and clotting factor in under-developed countries is an important world health challenge. This knowledge, combined with the high costs of clotting factor concentrate results in developed countries ethical dilemmas for hemophilia health care providers.

Aim: To define and discuss an ethical dilemma among nurse practitioners working in 5 different hemophilia treatment centers in the Netherlands.

Methods: With the help of an expert moderator using a structured methodology each nurse practitioner shared an ethical dilemma and reviewed literature about this dilemma. A moral deliberation can focus on two outcomes: 1. solution-oriented; standards are central: What should I do? 2. attitude-oriented; values are central: Who do I want to be? What do I want to do and why? Several methods during a moral summit can be used like; Dilemma method or Nijmegen method. Each method uses a number of successive steps to reach a morally responsible decision.

Results: An ethical dilemma is often a problem without a satisfactory resolution. The significance of ethical decision-making is that different ethical choices regarding the same ethical dilemma can be made. Ethics involve doing "good" and "causing no harm". It seems an utopia to conduct a code of ethics which promotes moral behavior and could act as a guideline for ethical decision making, enhances the reputation of an organization, prevents negative legal effects, encourages positive relationships and prevents discrimination or harassment, which highlights the values between members of a hemophilia treatment team must uphold. The decisions we make on a daily base are affected by many factors. Principles learned in education, regulations of the HTC, health care insurance companies, national government regimes, personal beliefs, values and experiences have all influence.

Conclusion: Ethical dilemmas in hemophilia care exists. Organizing a Moral Deliberation Forum offer clarity and structure.

W-P-163 (248) | A psychological wellbeing needs assessment for haemophilia patients at Newcastle Haemophilia Centre

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Introduction and Objectives: Rates of psychological difficulties are thought to be two to three times higher in people with long term conditions. Due to the potential impact of mental health on pain, life expectancy, treatment adherence and quality of life, it is important that people with haemophilia (PWH) experiencing psychological difficulties are identified and offered intervention.

Materials and Methods: An opportunity sample of adult haemophilia patients was recruited from attendees at Newcastle Haemophilia Centre over a three-month period. Participants completed the Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder Assessment (GAD-7) regarding symptoms of depression and anxiety, the Haemophilia Quality of Life measure (Haem-A-QoL) and four additional questions regarding perceived relationships between mood and haemophilia and engagement in psychological services.

Results: At the point of abstract submission this needs assessment was ongoing. Preliminary results from 27 participants found mean scores of 9.5/27 and 6.5/21 on the PHQ-9 and GAD-7 respectively. While these scores fall within 'mild' clinical categories, 40% scored in the 'moderate-severe' or 'severe' categories for symptoms of low mood and 22% indicated recent experience of suicidal ideation. 59.26% of participants stated their haemophilia had "previously" impacted on their mental health, which would not be reflected in current psychometrics. 51.85% of participants also felt that their mood had impacted on their management of haemophilia. Patients with severe haemophilia rated the perceived impact of haemophilia on psychological wellbeing and the impact of mood on condition management significantly higher than patients with mild or moderate haemophilia. PHQ-9 and GAD-7 scores were positively correlated with Haem-A-QoL total scores, which had a mean of 49.17. While 51.58% of participants had engaged in mental health services, 15% suggested this support had never been offered.

Conclusions: In addition to physical symptoms and complications, these results show a proportion of PWH also experience psychological and social implications of living with this chronic condition. This supports other studies that have suggested up to half of PWH have feelings of anxiety or depression and highlights the importance of routine psychological screening. Identification of such needs has implications for the provision of specialist psychosocial support across haemophilia treatment centres.

W-P-164 (359) | Health care professionals at haemophilia center and Shelter Institution working together: Case study of a nine-year-old boy with severe haemophilia A

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Objectives: 1) Illustrate the team work of different carers, both health care professionals and pedagogic assistants of a shelter delivered throughout 2017 to save the cognitive and emotional state of an abandoned child. 2) Describe the strategies used to create a team work and the psychosocial interventions like psycho-education, play therapy, creative school notebooks and customized homework.

Backgrounds: Comprehensive care involves taking care of the patient's psychosocial story. F, a 9-year-old severe hemophilia A boy living in a shelter presented a high level of illiteracy. Although our social worker had followed up the patient through subsequent home visits, interviews with the single mother and siblings, consultations to orient, support and facilitate adherence in treatment, the child was not included in school. F had born in an unstructured family and due to lack of good parenting care he was hospitalized several times for severe bleedings –the last one was in March 2016 staying for four months. In June 2016 he was sent to a shelter. Although this was a traumatic event, it was also the beginning of real care for him.

Materials and methods: His learning of hemophilia and self-infusion trough psycho-education was on track, but the fact that he was not able to read and write shown us the importance to intervene as a multidisciplinary team using the collaboration of the pedagogic assistants of the shelter. Several meetings occurred with the implementation of a reinforcement program. Different techniques to teach him the basics of language were used with success. A fluid communication between the psychologist, social worker, nurse and shelter carers started to follow up his gradual learning and preparation to enter school in July 2017.

Results and conclusion: After 8 months of collaborative work including our little boy's, we are all proud of our team work and of the good results: F is adapted in classroom and has been able to step out of illiteracy. This is an example that comprehensive care includes other institutions and that the role of multidisciplinary team goes beyond our hemophilia center's walls.

37-QUALITY OF LIFE

S-NUR-005 (40) | Assessing the burden of treatment for adult people with haemophilia (PWH)

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Introduction and Objective: Currently available infusion treatments for PWH have significantly improved quality of life. However, PWH are still experiencing considerable burden due to technical, physical, logistical, and other aspects of self-administering intravenous infusions. Subcutaneous treatment options that may reduce this burden are currently in development. This study investigated the burden associated with home-based intravenous treatment among adult PWH, and the experiences of PWH who received a subcutaneously injectable treatment in a clinical trial setting.

Materials and Methods: Semi-structured, qualitative interviews were conducted in-person or by telephone in the US and UK with 14 adult males with severe haemophilia, with or without inhibitors. Eleven self-infused intravenously prophylactically or on demand; three received subcutaneous injections in a clinical trial. Transcripts were thematically analyzed with an adapted grounded theory approach commonly used in qualitative research. Ethics approval was granted by an Independent Review Board.

Results: Participants who self-infused intravenously reported treatment burden issues across six domains: 1) adherence, including keeping track of the infusion schedule (36%); 2) treatment concerns, including venous access (73%), mixing/reconstituting factor (55%), and infection risk (27%); 3) physical impacts, including physical scarring (64%), infusion site pain/soreness (27%), blown veins (18%), port complications (27%), and inhibitor development (18%); 4) emotional impacts, including worry (64%) and annoyance (18%); 5) interference in daily life, particularly daily activities (55%) and travel (73%); and 6) work impacts, primarily absenteeism (55%). Forty-five percent of these participants expressed the desire for a non-intravenous treatment option. All three participants who received subcutaneous injections considered it to be more convenient, easier to use, and faster to prepare and administer than intravenous infusions. Two further reported reduced burden of pain, scarring, and venous access. All three reported that they would prefer to continue on a subcutaneous treatment, if available.

Conclusions: Intravenous haemophilia treatment can be physically and emotionally burdensome and interfere with daily activities and work. The reported findings suggest this burden can be reduced with a subcutaneous delivery mode. Further investigations into patient experiences with subcutaneous injection for haemophilia treatment are necessary to better understand its impact on patient outcomes and identify optimal endpoints for future studies.

Conflict of interest disclosure: Funding for this research was provided by Novo Nordisk A/S.

T-FPMTD-007 (752) | Impact of pain on health-related quality of life in persons with hemophilia from the hemophilia utilization group studies part VI (HUGS VI): USA experience

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Introduction and Objective: Patient reported data on health-related quality of life (HRQoL) should help optimize hemophilia management. We report on the association of pain and HRQoL in persons with hemophilia.

Materials and Methods: An on-going factor adherence study (HUGS VI) collected data on socio-demographic and clinical characteristics, pain, bleeding episodes, and adherence to prescribed treatment at 8 Hemophilia Treatment Centers in the USA. HRQoL was obtained from 12-item short form survey (SF-12, adults ≥ 18 years) and Pediatric Quality of Life Inventory (PedsQL, children 6-17 years). Health utility SF-6D was derived from SF-12. Multivariable regression models with stepwise selection were used to investigate characteristics associated with HRQoL.

Results: The analysis included 147 participants with A or B (112 adults and 35 children), 86% had hemophilia A, 90% had severe hemophilia, and 86% received prophylactic treatment. Mean adult physical (PCS), mental component scores (MCS), and SF-6D were 44.60 ± 10.38, 52.16 ± 8.75, and 0.76 ± 0.14, respectively. Regression analyses found chronic pain was the most important variable associated with PCS ($P < .0001$), MCS ($P < .001$), and SF-6D ($P < .0001$); increased age was associated with decreased PCS ($P = .0006$) and SF-6D ($P = .02$); bleeding-related pain was associated with a lower SF-6D ($P = .04$). Children had mean total PedsQL, physical health, and psychosocial health scores of 83.23 ± 20.02, 84.83 ± 24.69, and 82.43 ± 19.23, respectively. Multivariable regression models for the child sample showed that bleeding related pain was the most important variable associated with lower physical health, and chronic pain and having public insurance were associated with reduced psychosocial health.

Conclusions: In a sample of persons with predominantly severe hemophilia, adults had lower PCS than the general USA population. Children had HRQoL comparable to the general USA child population. Chronic pain was the most important variable associated with reduced HRQoL in adults and decreased psychosocial health in children. Bleeding-related pain was the most important variable associated with reduced physical health in children. These findings reinforce the importance of chronic pain for adults and children, and bleeding-related pain for children in hemophilia treatment. More research must be done to understand the nature of pain in impacting QOL differently in adults and children.

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M-MP-164 (190) | The impact of hemophilia on the social status and quality of life among Lebanese persons with hemophilia

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Introduction and Objectives: Although many studies of the impact of hemophilia on the quality of life (QoL) and social status were conducted all over the world, specific data pertaining to Lebanese persons with hemophilia (PWH) are lacking. The current study assesses the impact of hemophilia on QoL and social status of Lebanese PWH compared to reference population, with further collection of data on the disease's characteristics (severity and type of hemophilia, bleeding per month, target joints and treatment).

Materials and Methods: In this case-control study, cases were identified from the Lebanese association of hemophilia database, with 60 respondents (60% of all patients with severe and moderate hemophilia above 18 years old), and 112 random healthy male controls.

Detailed socio-demographic data and disease characteristics were collected and QoL was assessed using SF-36 questionnaire.

Results: Cases and controls had comparable age and BMI. The percentage of married persons was similar in both groups (33.3% vs. 38.4%). A greater proportion of controls attained a higher educational level than cases (88.4% vs. 59.3% respectively, $P < .001$). PWH were more likely to have a job requiring activity than controls (55.9% vs. 31.4%), and more likely to be unemployed (10.2% vs. 1.0% respectively, $P < .001$), whereas more controls have higher socioeconomic jobs (10.5% vs. 1.7%). PWH had significantly ($P < .001$) worse scores in all SF-36 domains (physical functioning, role-physical, role-emotional, emotional well-being, social functioning, pain, general health) except for energy/fatigue domain. Among PWH, 90% had a severe disease, correlating significantly with SF36 physical functioning domain score and social functioning score. On average PWH had 2.7 ± 1.5 affected targeted joints, inversely correlating with all SF36 domains except role-emotional, energy/fatigue and emotional well-being. Monthly bleeding frequency was 2.9 ± 2.4, inversely correlated with SF36 pain domain. Only 26.7% of PWH walk normally, and walking abnormalities were inversely correlated with all SF36 domains except role-emotional and emotional well-being.

Conclusions: The majority of Lebanese PWH has difficulties in social integration, have severe physical limitations and psychological impairments, suggesting they are not coping well with their chronic disease.

M-P-165 (656) | Health-related quality of life and health status in persons with hemophilia A (PwHA) without inhibitors: Prospective, non-interventional study (NIS) from a real-world setting

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Introduction and Objectives: Little real-world data have been published for PwHA. A global, prospective, non-interventional study (NIS; NCT02476942) evaluated clinical and health-related outcomes in PwHA receiving routine treatment. Presented here are health-related quality of life (HRQoL) outcomes in adult/adolescent PwHA without inhibitors receiving factor VIII (FVIII) therapy in this NIS.

TABLE 1. Hemophilia-specific QoL in adult/adolescent PwHA on FVIII therapy: Total and domain scores at Week 1.

Haem-A-QoL* (age ≥18 years) Domain and Total scores, mean (SD)	Episodic (n = 34)	Prophylaxis (n = 41)
Physical Health	50 (21)	28 (19)
Feeling	36 (27)	17 (19)
View of Self	42 (24)	30 (20)
Sport and Leisure	**64 (26)**	**41 (27)**
Work/School	26 (23)	14 (16)
Dealing	19 (15)	21 (21)
Treatment	42 (21)	32 (17)
Future	44 (23)	32 (21
Family	42 (33)	19 (26)
Relationships/Partnerships	21 (31)	13 (22)
Haem-A-QoL Total score	40 (17)	27 (15)
Haemo-QoL-SF1 (age 12-17 years) Domain and Total scores, mean (SD)	**Episodic (*n* = 6)**	**Prophylaxis (*n* = 5)**
Physical Health	22 (9)	24 (24)
Feelings	22 (25)	11 (11)
View of Self	26 (28)	14 (12)
Family	50 (25)	34 (30)
Friends	26 (39)	**37 (13)**
Other People	13 (11)	8 (7)
Sports and School	**52 (27)**	36 (20)
Dealing	34 (37)	6 (11)
Treatment	36 (21)	11 (13)
Haemo-QoL-SF Total score	31 (9)	20 (9)

Domains with the greatest impairment highlighted in bold.
[1] Scales range from 0 to 100 (0 indicates no impairment; higher values indicate greater impairment).

Methods: All participants continued to receive usual care (episodic or prophylactic FVIII), with no experimental interventions. Outcomes assessed monthly: Haem-A-QoL (range 0-100); Haemo-QoL-SF (range 0-100); EQ-5D-5L index utility score (IUS; range 0-1), EQ-visual analogue scale (VAS; range 0-100); days work/school missed; and days hospitalized. EQ-5D-5L IUS and EQ VAS also assessed on bleeding days. Haem-A-QoL and Haemo-QoL-SF: 0 indicates no impairment, higher scores indicate greater impairment. EQ-5D-5L and EQ-VAS: higher scores indicate less impairment.

Results: Ninety-four PwHA on episodic (n = 45) or prophylactic (n = 49) regimens were enrolled. Median (range) observation time: 27.7 (15.4-47.7) weeks for episodic and 30.4 (12.4-45.1) weeks for prophylactic. Mean Total and domain scores for Haem-A-QoL and Haemo-QoL-SF at Week 1 are in Table 1; most scores indicated greater impairment in episodic group. At Week 1, in episodic and prophylactic groups, respectively, mean (SD) EQ-VAS was 85 (11.3) and 85 (15.1), and mean (SD) IUS was 0.8 (0.14) and 0.9 (0.15). There were no substantial variations with time in any outcome through Week 29. Mean EQ-VAS and IUS scores suggested greater impairment on bleeding days than on scheduled reporting days. Over the observation period, in episodic and prophylactic groups, respectively, mean proportion of school days

missed was 16% and 3%, mean proportion of work days missed was 10% and 3%, and mean days hospitalized was 0.0 and 0.41.

Conclusions: In this real-world setting, PwHA without inhibitors experienced impairments in their health status, which may be worse on bleeding days. Overall, HRQoL was notably poorer with episodic versus prophylactic FVIII treatment; specific impairment was observed in several domains.

Conflicts of Interest: JO: Consultant: Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi; Speaker bureau: Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi; Research funding: Baxalta, Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma. HT: Speaker honoraria: Bayer, Novo Nordisk, Pfizer, Shire. FP: Honoraria or consulting fees: Biopharma, Freeline, Kedrion, LFB, Octapharma; Honoraria for speaking at educational meetings: Ablynx, Bayer, Grifols, Novo Nordisk, Sobi; Member of advisory board: Ablynx and F. Hoffmann-La Roche Ltd. RN: Member of advisory board: Bayer, LFB, Sobi; Speaker honoraria: Grifols, Novo Nordisk, Octapharma, Roche, Shire. PT: Employee: Genentech, Inc.; Shareholder: Genentech, Inc. SC and ML: Employee: Roche. JNM: Consultant/advisory committee: Alnylam, Baxalta, Biogen, CSL Behring, Novo Nordisk, Roche, Shire; Grant/research support: Alnylam, Bayer, Biogen, Catalyst Biosciences, CSL Behring, Novo Nordisk, Roche; Speaker bureau: Alnylam, Amgen, Bayer, Biogen, Biotest, CLS Behring, Roche. VJ-Y: Grants/research support: Novo Nordisk and Shire; Honoraria/consulting fees: Novo Nordisk, Roche, Shire. SvM: Consultant: Roche. This study was sponsored by F. Hoffmann-La Roche Ltd.

M-P-166 (731) | Hydrotherapy: Experience in Rawson Hospital, San Juan, Argentina

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Introduction: Musculoskeletal disorders continue to be amongst the most serious and invalidating in hemophilia. Hydrotherapy could be an appropriate treatment given its physical and psychosocial benefits.

Objectives: The subject matter of this work is to evaluate the effect of hydrotherapy in a physical, psychosocial level in outpatients suffering from type A Hemophilia who are in prophylactic treatment.

Materials and Methods: 20 patients with severe type A Hemophilia diagnosis on prophylactic treatment were evaluated. Ages are between 3 and 65 years old. A Program of Physical exercise in a Water Environment (PPEWE) was developed. The program took place in an acclimatized pool, cost-free, with proper tools provided. To evaluate muscle strength, Lovett Valoration Scale was used monthly, A Goniometric exam to evaluate joint amplitude, flexibility and movement coordination. Were as environment adaptation, water safety and social skills were evaluated using an observational test. The test took place in a 12 month continued period: Patients took one hour long classes weekly. The activity was organized in 4 age groups: A: 3-6 years, B: 7-12 years, C: 13-21 years and D: 22-65 years. Before the test took place the patient were evaluated in their physical and psychological status. Taking into account the patients' activity, adherence and previous experience in a water environment. Each one was given an answer: "Good", "Regular", "Poor" or "Bad Response".

Results: Of the 35 patients that originally enrolled in the study only 20 completed it (57.14%). The 15 patients who presented lack of adherence were 80% due to lack of commitment by their parents and 20% due to economic reasons related to transportation. Only one patient had had previous experience with this form of rehabilitation. In 90% of the patients there was an improvement in environment adaptation, achieving higher confidence and better social skills, Moreover all physical parameters improved in at least 20% of all patients.

Conclusion: Hydrotherapy is a complete therapy from a Physical and psychosocial point of view, improving patient's quality of life. Lack of adherence was attributed to the parents lack of understanding of the benefits, which is why these should be more emphasized.

M-P-167 (765) | Health-related quality of life among children and adolescent patients with hemophilia: A study in Argentinian population

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Introduction: Hemophilia A and B are life-long X-linked recessive conditions. Improvements in coagulation replacement therapy and prophylaxis have led to a progressive increase in life expectancy. A growing need to address patients' psychological and social factors related to HRQoL is recognized.

Objective: The objective of this cross-sectional, multicentric, national-wide study was to evaluate the HRQoL in Argentinian children and adolescents with severe hemophilia through the Spanish version of the age-specific, validated Haemo-QoL questionnaire.

Material and Methods: This was a cross-sectional study carried out in pediatric hemophilia out patients attending 15 centers in Argentina, including the Central region, North-West region, Patagonia region, Cuyo region and North-East region. Enrollment criteria included age between 0 and 18 years, a diagnosis of severe hemophilia including presence of

inhibitors and type of treatment (prophylaxis or on-demand therapy). Participants were stratified in three ages groups. Scores were calculated for each domain, scores values were transformed to a scale from 0 to 100 to allow better comparisons between answers.

Results: Data from 175 children and adolescents were available; 153 questionnaires (87.42%) HRQoL scores were found to be for most dimensions above 50 points in a transformed scale. In Children I group, significantly higher scores were calculated for "physical" and "family" domains when compared with older children and adolescent. A trend to worse scoring in "feeling" domain was also identified in younger children, as well. Other domains scoring were similar across all age-defined groups. When "perceived support" and "dealing" domains were compared between Children II and adolescent groups, no statistically differences were found.

Discussion: One hundred and fifty three participants were included. Total mean scores were above 40 in our participants, which seems consistent with previous research in non-developed countries. Strategies for improving HRQoL are recommended. HRQoL refers to different physical, psychological, and social domains of health that are influenced by patients' experiences, beliefs, expectations, and perceptions.

Conclusion: HRQoL in Argentinian hemophilic children and adolescents needs improving in most dimensions. This objective need cooperation of an integrated team of healthcare professionals to properly assess and improve HRQoL.

M-P-168 (295) | Effect of monitoring daily physical activity on quality of life in adult patients with haemophilic arthropathy

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Introduction and Objective: In order to increase the quality of life (QoL) related to health and reduce the risk of suffering diseases typical of a sedentary lifestyle, it is necessary to promote the physical activity (PA) in the haemophilic population. Activity wristbands such as Fitbit have been shown to be effective to monitor activity levels and to increase exercise adherence. Therefore, the objective of this work is to evaluate the effect that the use of activity wristbands has on the QoL in haemophilic patients.

Material and Methods: 27 subjects with severe haemophilia in prophylaxis treatment [type A/B: 26/1; age: 36.07 (9.36) years old; weight: 78.23 (19.61) kg; height 1.75 (0.07) m and HJHS total score: 28.52 (16.58)] were included. Fitbit Charge HR was used to monitor daily PA for a full year. Participants were encouraged to try to comply with the goal of 10,000 steps/day and follow their progress. The QoL was evaluated at the beginning of the study and after the year follow-up using the A36 Hemofilia-QoL® questionnaire. This instrument consists of 36 items (values can range from 0 to 4) grouped into 9 subscales (Table 1). The pre-post differences in the questionnaire scores were analysed using t-test or Wilcoxon test depending on the normality of the data.

Results: During the year follow-up, the average daily steps of the participants were 10379.05 (2781.99) and 17 of the 27 subjects achieved a daily annual average greater than 10,000 steps. Regarding QoL, an increase in the scores of all the subscales was observed except on the subscale "difficulties with treatment" (Table 1). However, only statistically significant differences were found in the subscale "physical health" ($P = .007$).

Conclusions: In general, self-monitoring of daily PA using a fitness tracker improves QoL in haemophilic adults, especially in the subscale "physical health".

TABLE 1. A36 Hemofilia-QoL results (mean and standard deviation).

QoL subscale	Pre	Post	Diff [95% CI]	*P*-value
Physical health	22.11 (4.21)	24.26 (3.71)	2.15 [−3.65; −0.64]	**.007**
Daily activities	10.70 (3.50)	11.15 (4.07)	0.44 [−1.61;0.72]	.342
Joints	7.48 (2.06)	7.59 (2.08)	0.11 [−0.78;0.56]	.360
Pain	4.52 (1.91)	4.78 (1.60)	0.26 [−1.07;0.56]	.520
Satisfaction with treatment	6.81 (1.52)	7.00 (1.27)	0.19 [−0.66;0.29]	.694
Difficulties with treatment	12.67 (2.88)	12.63 (2.56)	−0.04 [−0.88;0.96]	.821
Emotional functioning	13.33 (4.25)	13.81 (4.69)	0.48 [−1.68;0.72]	.418
Mental health	8.19 (2.09)	8.70 (2.37)	0.52 [−1.38;0.34]	.226
Relationships and social activity	16.59 (2.98)	16.70 (3.77)	0.11 [−1.26;1.04]	.694
Total score QoL	102.41 (18.14)	106.63 (19.68)	4.22 [−10.11;1.66]	.152

Diff: Differences; CI: Confidence interval.

M-P-169 (184) | Understanding gender-specific isease burden of US females with hemophilia A or B: Insights from the results of the CHOICE Project into gynecological, obstetric, and quality of life issues

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Introduction and Objective: This analysis describes gender-specific disease burdens of females with hemophilia A or B (FWH) using data from the CHOICE Project, a survey-based surveillance initiative run by Hemophilia Federation of America (HFA) and supported by the Centers for Disease Control and Prevention (CDC).

Materials and Methods: Demographic and clinical information was collected through the CHOICE survey in the US from 04/2013-07/2015 among adults (≥18 years, male/female) and caregivers of children (male/female) with bleeding disorders. Participants took a 20-minute survey in English or Spanish, online or on paper. Undiagnosed females with hemophilia symptoms could participate.

Results: Of the 576 participants reporting a single diagnosis of hemophilia A (HA) or hemophilia B (HB), FWH accounted for 20% (n = 113, HA n = 94, HB n = 18). For FWH, average age of first period was 12.4 years; 90% report ever having a heavy period starting at an average age of 14.2; 75% currently change menstrual hygiene products at least every 2 hours; 90% experience menstrual cramping. Of FWH, 31% have lost work/school/recreation days due to menstrual bleeding in the past 12 months; 46% reported a diagnosis of depression; over 63% of FWH reported receiving care for their hemophilia at least once per year; 23% receive care only prior to a medical procedure. Related to pregnancy, 82% have been pregnant with an average number of pregnancies of 3.9; of these pregnancies, an average of 2.0 were full-term; 36% tried to get pregnant for a full year without becoming pregnant. Hysterectomy rates among FWH is 32% at an average age of 38.6 with FWH between the ages of 35-55 (35%) and 56+ (43%) reporting the highest rate of hysterectomies.

Conclusions: Preliminary data from CHOICE offers new insights into gender-specific disease burdens of US FWH. Further investigation is needed into how to improve FWH's access to care and address depression, fertility issues, and the rate of hysterectomies. This sample does not necessarily represent all US FWH, as targeted outreach in some regions may have led to over-representation of some participant characteristics.

Disclosures: The authors have no conflicts of interest to disclosure.

M-P-170 (594) | Sedentary work vs. manual work: A comparison of Health-Related Quality of Life (HRQoL) and work-related problems in severe haemophilia

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Introduction and Objectives: Improvements in treatment options has ensured a greater array of career choices are now available to people with severe haemophilia. The purpose of this study is to judge whether people with severe haemophilia in manual work (MW) experience reduced HRQoL outcomes and increased work-related problems compared to those in involved in sedentary work (SW).

Materials and Methods: Data on haemophilia patients without inhibitors were drawn from the 'Cost of Haemophilia across Europe – a Socioeconomic Survey' (CHESS) study, a cost-of-illness assessment in severe haemophilia A and B across five European countries (France, Germany, Italy, Spain, and the UK). Physicians provided clinical and sociodemographic information for 1,285 adult patients, 551 of whom completed corresponding questionnaires, including EQ-5D-3L and EQ VAS. Individuals who were not currently in employment or retired were excluded from this analysis.

Results: 302 patients currently in full or part time work provided information on employment type, 229 (75.8%) and 73 (24.1%) individuals were employed in SW and MW respectively. Mean reported EQ-5D index score for SW patients was 0.740 (standard deviation (SD) 0.235); and 0.803 (SD 0.218) for patients in MW. Compared to individuals in SW, MW was associated with a greater EQ-5D (0.0614; SD 0.0312; $P < .05$) when age was controlled for. Individuals employed in MW reported a greater number of days of work missed due to haemophilia compared with those in SW; 10.44 days (SD = 9.34) and 10.35 (SD = 18.09) respectively. Of these days missed 4.06 days (SD = 4.99) and 5.78 days (SD = 5.76) were a result of a bleed in the SW and MW groups.

Conclusion: Although individuals in MW did not report a lower HRQoL compared to those in SW; there was an association between work type and days missed due to haemophilia, this may be due to a lack of flexibility in this sector. It is important to expand guidance and support for haemophilia patients to understand the impact of haemophilia on education and employment and ensure that the needs of people with severe haemophilia are being adequately addressed proactively to avoid work-related problems in the future.

M-P-171 (312) | Health-related outcomes and caregiver burden in pediatric persons with hemophilia A (PwHA) with inhibitors: prospective, non-interventional study (NIS) in a real-world setting

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Introduction and Objectives: Limited published data exist around real-world experiences of PwHA. Greater insights are needed into the impact of the disease and its treatment on health-related outcomes for pediatric PwHA with inhibitors to factor VIII replacement therapies, and accompanying caregiver burden. A global, prospective, non-interventional study (NIS; NCT02476942) evaluated bleeding, adverse events, and health-related quality of life (HRQoL) in PwHA treated according to local routine clinical practice; here we present HRQoL outcomes and aspects related to caregiver burden in the pediatric (aged <12 years) PwHA with inhibitors cohort from this NIS.

Methods: All participants continued to receive usual care (episodic or prophylactic bypassing agents [BPAs]), with no experimental interventions. Median (range) observation time: 31.2 (21.3–44.1) weeks for episodic; 17.9 (8.7–36.4) weeks for prophylactic.

Outcomes: Hemophilia-specific measures: Haemo-QoL-SF (age 8-11 years) and Adapted Inhib-QoL with Aspects of Caregiver Burden; days school/day-care missed; and days hospitalized. Haemo-QoL-SF and Adapted Inhib-QoL scales range from 0-100; 0 indicates no impairment, higher scores indicate greater impairment.

Results: Twenty-four pediatric PwHA were enrolled (episodic, n = 10; prophylaxis, n = 14); 11 aged 8-11 years (episodic, n = 3; prophylaxis, n = 8). Mean Total and domain scores for Haemo-QoL-SF and Adapted Inhib-QoL at Week 1 are in the Table. Greatest impairments in children and caregivers, respectively, were in 'Sports/School' and 'Dealing with Inhibitor'. There were no substantial variations with time in any outcome through Week 29. Mean proportion of days school/day-care missed (days missed/days expected) was 9% and 25% in episodic and prophylactic groups, respectively; mean (SD) days hospitalized were 2.7 (4.9) and 10.1 (24.0), respectively.

Table 1 Health-related outcomes and caregiver burden in pediatric persons with hemophilia A (PwHA) with inhibitors: prospective, non-interventional study (NIS) in a real-world setting

Hemophilia-specific QoL in pediatric PwHA on BPAs and their caregivers: Total and domain scores at Week 1		
Haemo-QoL-SF[a] Domain and Total scores, mean (SD)	**Episodic (n = 3)[b]**	**Prophylaxis (n = 8)[b]**
Physical health	50 (13)	29 (26)
Feelings	23 (25)	38 (25)
View of self	29 (19)	39 (18)
Family	65 (13)	41 (22)
Friends	50 (38)	31 (28)
People	38 (13)	23 (13)
Sports/School	**71 (10)**	**59 (27)**
Dealing	17 (24)	26 (21)
Treatment	40 (10)	43 (24)
Haemo-QoL-SF total score	42 (8)	37 (14)
Adapted Inhib-QoL[a] Domain and Total scores, mean (SD)	Episodic (n = 9)[d]	Prophylaxis (n = 14)
Physical health	42 (13)	44 (21)
Treatment	42 (34)	31 (29)
Perceive condition[c]	42 (18)	40 (24)
Dealing with inhibitorc	**63 (14)**	**64 (20)**
Perceived treatment	37 (20)	53 (9)
Family life[c]	41 (19)	42 (21)
Siblings	13 (25)	21 (22)
Contact with others	35 (39)	24 (28)
Adapted Inhib-QoL total score	44 (11)	46 (15)

Domains with the greatest impairment highlighted in **bold**. [a] Scale ranges from 0 to 100 (0 indicates no impairment; higher values indicate greater impairment). [b] Only patients aged 8-11 years completed this questionnaire. [c] These domains reflect caregiver burden. [d] One caregiver did not complete the form at Week 1.

Conclusions: In this real-world setting, HRQoL scores indicated moderate to severe impairment in several areas of function. This NIS suggests that the burden of disease and treatment for pediatric PwHA with inhibitors has a substantial negative impact on children's daily lives and adds considerable burden to caregivers.

Conflicts of Interest: MEM: Consultant: Bayer HealthCare, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Roche, Sobi/Biogen; Speaker bureau: Baxalta/Shire, Bayer HealthCare, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Sobi/Biogen. VJ-Y: Grants/research support: Novo Nordisk, Shire; Honoraria/consulting fees: Novo Nordisk, Roche, Shire. PT: Employee: Genentech, Inc. SC and ML: Employee: Roche. JNM: Consultant/advisory committee: Alnylam, Baxalta, Biogen, CSL Behring, Novo Nordisk, Roche, Shire; Grant/research support: Alnylam, Bayer, Biogen, Catalyst Biosciences, CSL Behring, Novo Nordisk, Roche; Speaker bureau: Alnylam, Amgen, Bayer, Biogen, Biotest, CLS Behring, Roche. JO: Consultant: Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi; Speaker bureau: Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi;

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[Correction added on 7 August 2018, after first online publication: a table has been inserted in this current version of abstract M-P-171 (312).]

M-P-172 (258) | The PROBE Data Dashboard – A new tool for real-time data visualization and analysis of patient reported outcomes

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Introduction and Objectives: The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project developed a standardised questionnaire and a dedicated research network to generate and continuously update PROBE reference data. PROBE was developed with direct patient involvement through collaborations with non-governmental haemophilia patient organizations. Project feasibility, questionnaire development and validation have been previously reported. The objective of this work was to develop an analytics tool and visualization dashboard for PROBE study data utilizing the PROBE Score.

Materials and Methods: The PROBE data dashboard utilizes Microsoft Power BI software for business analytics. The first 2100 questionnaires collected in 21 countries were used to develop and locally test global and individual country dashboards. The psychometric properties of the PROBE questionnaire were assessed, and a composite PROBE Score developed. Dashboard version 2.0 incorporates analytics to calculate the PROBE Score.

Results: Each dashboard is divided into two main components - filters and graphs (visualization views). The visualization views provide graphic results for the selected outcome of interest (e.g., current health status, mobility aids, pain (including medication, acute and chronic pain), independence, joint surgery or another invasive procedure, employment and school life). Filters are divided into three subgroups such as personal, health problems and haemophilia related. Each subgroup allows refinement of the data sample for demographic variables (e.g., region of the world, diagnoses, disease severity, inhibitor history, treatment regimen). Comparator data from those not personally affected by a bleeding disorder (controls) are also depicted. The graphs are interactive allowing comparison of outcomes using the demographic variables.

Conclusions: The results of the feature-rich dashboard indicate an integral interaction between the analytical tool Power BI and PROBE study data. The dashboard allows participating organizations easy, secure and large-scale external as well as internal access to PROBE study data. The properties of the PROBE questionnaire are suited for differentiating PWH with better or worse health status. The immediate use of the PROBE dashboard incorporating the PROBE Score will be in cross-sectional comparisons among different settings, e.g. different levels of care.

M-P-173 (521) | Pharmacokinetic education improves patient activation and quality of life whilst reducing treatment concerns in severe haemophilia A

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Introduction: The Patient Activation Measure (PAM) gauges the knowledge, skills and confidence essential for managing one's health/healthcare. The UK-PK clinical trial captured changes in patient reported outcome measures and regimen decisions made after patient education and personalised pharmacokinetic (PK) guided treatment discussions.

Primary Objective: Identify whether PAM predicts outcomes, and whether PAM changes post-intervention.

Materials and Methods: 50 severe haemophilia A patients from 16 UK haemophilia centres completed the intervention which included a standardised patient education package, explaining PK and personalised prophylaxis, followed by modelling of patients' own PK using myPKFiT® and discussion of personalised dosing options. PAM, health-related QoL (EQ5D), haemophilia-related QoL (HAEMA-QoL-A), Beliefs about Medicines (BMQ), and adherence (VERITAS-Pro) were assessed using a questionnaire completed by participants pre-intervention (Q1) and again 6 (Q3) and 12 months (Q4) later. An intervention evaluation questionnaire was completed directly after the intervention (Q2).

Results: PAM scores and levels significantly increased after the intervention (Table 1). Higher pre- and post-intervention PAM significantly correlated with better QoL and fewer concerns about prophylaxis, but not with adherence. Negative intervention evaluations (Q2) were associated with lower post-intervention PAM and adherence, lower pre- and post-QoL and greater pre- and post concerns about prophylaxis. When both pre-intervention concerns about prophylaxis and negative intervention evaluations were entered into a regression model (χ^2=34.9, df = 2, P = .005), only negative evaluations were significantly associated with decreases in PAM (β = 0.572, P = .003).

Conclusions: Although PAM did not predict intervention evaluations, it did significantly correlate with QoL and concerns about prophylaxis. Patient education and personalised PK-guided dosing discussions could be an important tool in improving QoL and PAM and reducing treatment concerns. However, It is crucial to be proactive to prevent negative experiences during interventions, as these can lead to worse outcomes.

M-P-174 (645) | Cultural adaptation and validation of a Brazilian Portuguese translation of the paediatric version of the Haemophilia Activities List (PedHAL)

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Introduction and Objective: Musculoskeletal impairment due to recurrent bleeding is an important cause of functional capacity limitation for children with hemophilia. Worldwide, children with hemophilia have been affected from limitation in performing activities of daily living. In order to assess such limitations, the Paediatric version of the Haemophilia Activities List (PedHAL) was created and tested in the Netherlands. The aim of this study was to evaluate the Brazilian version of the PedHAL questionnaire, assessing its translation, cross-cultural adaptation and psychometric properties.

Materials and Methods: The PedHAL questionnaire was translated into Brazilian Portuguese in a process composed by two translations and back-translations, carried out by independent evaluators. A cultural adaptation to Brazilian children was also performed according to an international methodology. In order to evaluate reproducibility, patients were interviewed twice within a period of 15 days. Patients were also submitted to physical evaluation with the Hemophilia Joint Health Score (HJHS) and the Functional Independence Score in Hemophilia (FISH). Spearman's correlation coefficient was used to correlate our translated questionnaire with the previous mentioned tests, and to evaluate the inter and intra-rater reproducibility. The internal consistency was assessed by Cronbach's alpha coefficient.

Results: Thirty-three patients were evaluated, including 26 with severe hemophilia A and 7 with severe hemophilia B. The mean age ± standard deviation (SD) was 12.2 ± 3.5 years. The mean ± SD of the PedHAL score was 91.4 ± 8.8. The Brazilian version of PedHAL showed a moderate correlation with the HJHS (r_s = −0.45). The domains "arm function", "transport" and "sport and leisure activities" showed a moderate correlation with r_s = −0.44, r_s = −0.43 and r_s = −0.46, respectively. The correlation was weak between results of PedHAL and FISH (r_s = 0.23). The internal consistency of domains and sum of scores ranged from high to moderate (α = 0.70-0.86), except for "transportation", "personal care" and "household chores" which had α<0.70. As for the inter and intra-rater reproducibility, a strong and moderate positive correlation was observed, with r_s = 0.48-0.71, except for item of transport.

Conclusion: The Brazilian Portuguese version of the PedHAL is a reproducible and valid tool for the evaluation of functional ability in Brazilian children with hemophilia.

M-P-175 (650) | Influence of health care professionals on the embodiment of persons with hemophilia: a bioethical perspective

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Introduction and Objective: Some research has provided evidences of beneficial effects of physical activity for the development of embodiment in persons with hemophilia (PWH). Embodiment is the subjective perception of body (somatic modes of attention) and it is also a methodological field that studies the relation between the body and its perception in the world. However, there is few discussions about the influence of health care professionals on the embodiment of PWH in a bioethical perspective. The objective of this study is to understand the influence of health care professionals' health care on PWH corporeality/embodiment in a approach with some bioethical principles.

Materials and Methods: A focal group with 8 PWH (age between 18 and 37) was conducted and ordered by a topic guide. The interview lasted approximately 90 minutes and was recorded in audio and video, after consent, in Rare Diseases Observatory - University of Brasília. The interview was analyzed using a discourse analysis strategy.

Results: The participants' responses differed in how they cope with hemophilia and how they perceived their body subjectively. They have ascertained how each PWH should particularly know its disease. They reported that some professionals recommend, and others don't recommend practicing sports and an active lifestyle. In some cases, the health care professional didn't know about hemophilia. PWH said they experienced a better quality of life when they were motivated to adopt an active life. They also responded that a multidisciplinary team specialized in hemophilia treatment is an important factor in the adoption of this lifestyle. Topics such as autonomy, self care, discrimination, justice, equity appeared in the speeches of the research participants.

Conclusion: The interviewed affirmed that health care professionals influence their subjective perceptions of their bodies. This influence can be positive or negative and also impacts the autonomy of the PWH. This suggests ethical repercussions in the relationship of health professionals with PWH also in the field of embodiment. Lastly, a multidisciplinary treatment team facilitates the adoption of an active lifestyle by PWH.

M-P-176 (821) | Quality of life in adults with hemophilia in a Colombian population

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Introduction: Hemophilia is a hereditary disorder, caused by a deficiency of clotting Factors VIII or IX, with hemorrhagic manifestations that produce important complications such as arthropathy with chronic pain and long-term damage to joints. These characteristics make hemophilia a chronic and disabling disease with physical, psychological and social impact that affects the quality of life of patients. In Colombia, the effect of the disease on the quality of life is unknown.
Objective: To establish the quality of life of adults with hemophilia in a Colombian population.
Methods: Cross-sectional analytical study, which evaluated the quality of life related to health in adult patients with hemophilia through the application of the Hemolatin QoL questionnaire, validated as a specific psychometric test for the evaluation of quality of life in this population. In 27 questions, the physical, emotional and social functioning, pain, mental health and environmental conditions were estimated.
Results: 56 patients with hemophilia accepted to participate, 89.3% with Hemophilia A and 10.7% with Hemophilia B. 60.7% had severe, 21.4% moderate and 17.9% mild hemophilia. The average global index of quality of life in patients is 71.1 points (95% CI 66.4 - 75.7), which classifies patients between a regular and improved quality of life. The domains of environmental conditions (9.8 / 16) and mental health (6.8 / 11) are the most affected. Patients with moderate and severe hemophilia are more compromised with a lower quality of life index (64.7% and 62.6%) compared to those with mild hemophilia (78.2%) with statistically significant differences ($P < .01$ and $P < .02$).
Conclusion: Hemophilic patients have an increased probability of having a poor quality of life depending on its severity. The environment and mental health conditions were the most affected domains.

T-P-128 (191) | Steps to healthier habits

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Introduction: Lower levels of physical activity are associated with patients with haemophilia. A recent audit confirmed this for patients attending the Haemophilia Centre at Belfast City Hospital. This, together with higher obesity levels, contributes to additional health issues for Patients.
Objective: 1) to increase awareness of the benefits of healthy eating and increasing physical activity levels, and 2) to signpost patients towards opportunities to facilitate a more active lifestyle.
Materials and Methods: Patients with bleeding disorders, who attend the NI Haemophilia Comprehensive Care Centre, were invited to participate. The course was held over 8 sessions (April-June 2017). Topics covered included: The Eatwell Guide; portion sizes; food labels; reducing salt, sugar and fat intake; benefits of being active; dangers of sedentary behaviour; physical activity guidelines; measuring physical activity; increasing physical activity levels; overcoming barriers to physical activity; local physical activity opportunities. All participants completed: 1) questionnaires relating to eating habits, physical activity levels and self-efficacy; 2) Multiple choice questionnaire (MCQ) to assess understanding of the key messages delivered.
Results: 16 participants. Severe Haemophilia A (n = 8); mean BMI 33 (29-41.7). Haemophilia A carriers (n = 4). Partners (n = 4). 13 completed the programme. 2 participants did not return after the first session. 1 participant was unable to continue after week 2 due to a joint bleed. His wife continued to attend and they both completed the MCQ and contributed to feedback. 92% scored >85% in the final MCQ. 100% reported positive changes to their eating habits and 77% reported positive changes to their physical activity levels.
Conclusion: Preliminary results are encouraging. A number of participants have demonstrated commitment to increasing their physical activity levels. Two accepted referrals to local Physical activity schemes. One commenced a physiotherapy-led exercise programme designed to bridge the gap between rehab and exercise in the community. One was referred to the MacMillan 'Move More' programme. Two continue to receive one-to-one coaching support. Further review will be undertaken at each participant's regular clinic appointments. Further outcomes for consideration at that time will be the impact on BMI, activity levels, pre-existing musculoskeletal pathology and uptake of physical activity opportunities.

T-P-129 (611) | Barriers and enablers to self-care (or self-management) for adults with inherited bleeding disorders

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Introduction and Objective: Self-care (or self-management) is simply defined as a sustainable way of living with a long-term condition. Self-care studies predominate in children with haemophilia and for adults with bleeding disorders focus on quality of life and compliance with medical management. We explored with our patients and families, living with inherited bleeding disorders, what strategies are helpful for them to develop or promote self-care, focusing on what matters to individuals. Identifying barriers to self-care and how to develop patients and families expertise in self-care (based on what matters to them).

Materials and Methods: Semi –structured interviews using emotional touch points to identify what is working to promote self-care (or self-management) and what the barriers are. Thirty patients or family members were selected at random for interview and results thematically reviewed using a mixed methodology of qualitative and quantitative data analysis. Action research methods were used to identify areas of service co-design, which was guided by patient experience.

Results: Initial thematic review of semi-structured interviews identified three main issues; Firstly communication between specialists healthcare professionals, Secondly, clinicians being unprepared for consultations with expert patients and finally attending non specialist bleeding disorder services increased levels of stress. Full results pending at time of submitting abstract.

Conclusions: Initial findings to date indicate main areas of barriers to self-care (or self-management) are inadequate communication between professionals and patients and accessing acute mainstream services. Main enablers for self-care are being trusted and respected by healthcare professionals. Experiential based co-design in development focusing on methods to improve communication between professionals and patients.

38-SELF-INFUSION

S-NUR-007 (760) | Go Blue Infusion U: strategizing self-infusion training for pediatric patients: An innovative approach to transition

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The National Hemophilia Program Coordinating Center (NHPCC) was funded by the Health Resources and Services Administration (HRSA) to coordinate and collaborate with regional networks and to establish standardized national efforts to identify gaps in care, establish national priorities for quality improvement and collect metrics. Improved transition to adulthood is a priority for Healthy People 2020 outcomes. Self-infusion is a critical skill for patients with severe bleeding disorders and a necessary milestone in preparing for adulthood. Done on an individual basis, this can be difficult to accomplish. Our Hemophilia Treatment Center partnered with our local Foundation to present an interactive educational program which included learning basic concepts of bleeding disorders and training in self-infusion techniques with the ultimate goal of transferring skills to the home environment. Children on home infusion were recruited for five weekly classes under the direction of hemophilia nurses. Dinner and beverages were provided. Educational concepts were presented during an interactive discussion and were reinforced throughout the program. Parents attended a concurrent session during the first meeting and a "graduation ceremony" at the final session. Instruction was provided in a calm environment without interruptions. To minimize distraction, only nurses and children were present during teaching. Attendees performed mock infusions on artificial arms followed by self-infusion, with time provided for feedback and reflection. Brief homework assignments were reviewed at each session. Thirteen eligible children were invited and eight attended, ages 7-14 years. Two children had inhibitors and two were exclusively using ports. Parents completed pre and post program questionnaires. All children were able to perform peripheral infusion in class; 54 independent self- infusions were done by six children at home during the 6-week period. This program provided ample opportunity for nurses to identify and address barriers to learning. Working in a group gave children a sense of belonging, increasing their motivation to learn. Repetitive sessions supported the development of skills and provided opportunity for practice and reinforcement. The program was designed to be easily replicated by other HTCs with simple instructional materials, contributing to our national initiative on enhancing adolescent to adult transition.

W-P-170 (399) | Establishment of a comprehensive hemophilia clinic, Chiang Mai University Hospital: 5-year experience

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Introduction and Objectives: Hemophilia is an inherited bleeding disorder which causes recurrent bleeding in musculoskeletal (MSK) system. Prophylactic treatment and early factor concentrate administration after bleeding episode is the main treatment to delay the long-term sequel. Moreover, comprehensive education about self-care for persons with hemophilia (PWH) and their families are also important. This project is to report the improvement of patients' care after the establishment of the Comprehensive Hemophilia Clinic (CHC), Chiang Mai University (CMU) Hospital.

Materials and Methods: The CHC, CMU Hospital has been established since 2012 to gather all PWH and their families together and allow the multidisciplinary hemophilia team to educate them comprehensively with all aspects of hemophilia care. The regular visit for CHC is every 2 months to receiving the factor concentrate and patients' education. In addition, the nurses in Pediatric Hematology Ward were educated for hemophilia care and able to teach the PWH and their families when the PWH were admitted to the hospital for serious bleeding episodes.

Results: Twenty-one PWH had been followed up in CHC, CMU hospital. Seventy-one percent had hemophilia A and 71% of all PWH had severe disease. The age of patient ranged between 1 and 40 years. After the establishment of CHC, 48% of all PWH were on continuous prophylaxis (secondary and tertiary) while 24% were on intermittent prophylaxis for 3 months after life-threatening

bleeding or surgery. The rates of admission due to acute bleeding were decreased in the last 5 years. To succeed in prophylactic treatment, the process of self-infusion of factor concentrate was educated to PWH and their families. However, the competency for self-infusion by themselves or their parents was achieved in 8/21 (38%). The barriers of the success were poor venous access in young children and not feeling confident to do the self-infusion.

Conclusions: Establishment of CHC improves the care of PWH through the initiation of prophylaxis and comprehensive education. Self-infusion of factor concentrate is one of the indicators for the achievement of hemophilia care. However, there are some gaps that have to be filled up for the better care.

W-P-171 (322) | Collaborative model of home delivery program in haemophilia through an association of patients

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Introduction and Objectives: Most of the clotting factor (CF) dispensations to patients with hemophilia in Valencian Community are centralized in only one hospital, generating frequent visits to hospital, and requiring long travel distances.

Material and Methods: Since 2011 the Outpatient Pharmaceutical Care Unit (OPCU) established collaboration with the Hemophilia Patients Association of the Valencian Community (ASHECOVA) to develop together a home delivery program, allowing patients an easiest and convenient access to their treatments. ASHECOVA developed a specific software to communicate the programmed requirements CF for each patient, through a delegated prescription, and the dispensation is prepared in advance. Pharmaceutical care includes treatment validation of prescription, review of medical records, healthcare continuity, treatment safety, traceability and cold chain preservation. An ASHECOVA member collects medication and delivers it to patient's home in optimal, accredited conditions. Data since December 2011 to November 2017 included: baseline characteristics, number of patients, deliveries and medication dispensed. A satisfaction survey was conducted, asking about benefits and suggestions about the program.

Results: During the study period, 47 patients were included, 46 with hemophilia A & 1 with hemophilia B. The table summarizes data of home deliveries. There have not been any reported incident. In some patients, home delivery was also used to deliver antiretroviral drugs.

Year	Patients	Deliveries	Dispensations
Total 2011	**5**	**2**	**5**
1T12	14	33	79
2T12	15	53	124
3T12	15	46	119
4T12	18	59	155
Total 2012	**18**	**191**	**477**
1T13	19	66	167
2T13	21	75	197
3T13	25	77	231
4T13	29	94	275
Total 2013	**29**	**312**	**870**
1T14	31	99	284
2T14	31	102	301
3T14	30	95	277
4T14	35	123	361
Total 2014	**35**	**419**	**1223**
1T15	36	115	314
2T15	36	112	305
3T15	36	111	293
4T15	39	121	320
Total 2015	**39**	**459**	**1232**
1T16	40	125	340
2T16	40	129	344
3T16	41	132	343
4T16	42	138	347
Total 2016	**43**	**524**	**1374**
1T17	46	146	355
2T17	47	157	366
3T17	46	100	220
4T17[1]	46	73	179
Total 20171	**47**	**476**	**1120**
Total 2011-2017	**47**	**2381**	**6296**

[1] Data until 09/11/17.

The survey performed in January 2017 showed that all patients were satisfied with the service. The benefits reported were mostly related to less frequent visits to hospital, reducing time and costs spent in transportation, absenteeism in the workplace, and dispensation waiting times. Most of the patients agreed with the program without any change suggested.

Conclusions: Home delivery program guarantees a proper follow-up of treatments, obtaining full satisfaction evaluation from patients. This program improves patient's convenience, as well as allows OPCU to achieve a better pharmaceutical care, traceability of the process and optimization of working times and CF stock management.

W-P-172 (249) | Patient experiences of recording treatments and bleeds at home: Barriers and facilitators

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Introduction and Objectives: Standards of care recommend home treatment for many patients with severe haemophilia. Although this self-management approach promotes improved quality of life for patients and reduced costs for services, it demands responsibility in terms of adherence to treatment regimens, monitoring and treating bleeds, and recording this activity to inform care decisions. Poor return of these records highlights a need for better understanding of barriers and facilitators to this self-management behavior.

Materials and Methods: All Newcastle Haemophilia Treatment Centre (HTC) patients aged 16 + on home treatment were invited to participate via post or in person. Parents/guardians of younger patients who do not record their own treatment were also invited. Participants were given an anonymous questionnaire regarding their experience of recording treatment/bleeds, understanding of its value, potential barriers and reminder methods.

Results: Of the thirty-nine participants (32 patients, 7 parents/guardians), 61.54% reported recording "whenever I treat", while 20.51% acknowledged doing this "infrequently". Regularity of recording treatments was associated with regularity of recording bleeds. There was a significantly higher perceived value of recording treatment/bleeds for the HTC than for patients themselves ($P < .01$). Similarly, participants scored significantly lower for awareness of specific benefits relating to them than for the HTC ($P < .05$). Participants who reported recording whenever they have a treatment/bleed scored significantly higher for awareness of specific benefits both overall and for themselves ($P < .01$). Infrequent recorders identified significantly more barriers ($P < .01$), with "I often forget" being endorsed by 100% of these participants. Parents/guardians reported more frequent recording, indicated higher awareness of specific benefits both overall and for their children, and identified fewer barriers ($P < .01$). Although letters were the most common reminder method (69.23%), a preference for emails was indicated. 67% of participants were interested in further education on recording treatments/bleeds, with a preference for information leaflets.

Conclusions: The results suggest that unreliable recording behavior may be due to a combination of barriers such as 'forgetting' and poor appreciation of its value. While reminder procedures may be reviewed, knowledge and understanding are key to behavior change. It is therefore important to consider approaches to educate patients around the value of this self-management activity.

W-P-173 (587) | Arterio-Venous Fistula in adults with severe bleeding disorders – A single centre experience

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Introduction: Good venous access is critical for successful treatment of haemophilia. While peripheral veins are the preferred route of administration of clotting factor for most people with haemophilia (PWH) it is challenging for those with poor venous access or physical difficulties accessing veins due to limited upper limb mobility as a result of haemophilic arthropathy. Poor venous access may lead to compromised compliance with prescribed treatment regimens and removes a patient's autonomy and independence, resulting in poor outcomes. An arteriovenous fistula (AVF) is an alternative option to insertion of central venous access devices (CVADs) such as a port-a cath®. An AVF is fashioned on the arm and once matured, veins are easy to access quickly and independently by patients and carers.

Objective: To review and evaluate the effective use of AVF for regular venous access in people with severe bleeding disorders on a home treatment programme in a single comprehensive care centre.

Method: Patients' were identified from searching the Centre's database. In 9 years (2008-17) 10 patients (aged 35-76) had 16 surgical procedures relating to AV fistula creation. 7 had SHA, 2 with high titre inhibitor, 2 had SHB, 1 had Type 3 vWD.

Results: 8 of 10 patients have functioning AVF's. 2 failed to mature. From the 2 who had failed fistulae, 1 of them now has a port-a-cath®. Of the 8 successful AVF, 2 required 2 surgical attempts and one succeeded on the third attempt. Two patients required surgical revision of the same fistula with good outcomes.

Conclusion: Successful creation of AVF in people with IBD's relies on good multi-disciplinary communication between haemostasis and surgical teams. A named vascular consultant developing a special interest in PWH has improved outcomes. Those patients with compromised venous access are now identified and referred earlier to optimize success as good quality vessels are required to create AVF's. Specialist nurses in Haemophilia Centres are best placed to assess venous access, identify issues early and provide education and support for suitable patients. Successfully functioning AVF's have improved adherence and facilitated prophylaxis and home treatment. This has resulted in fewer hospital visits and greater independence.

39-SOCIAL MEDIA AND ELECTRONIC COMMUNICATIONS

W-P-178 (385) | Patients' priorities for enhancing access to person-centered hemophilia care and support via electronic means

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Introduction: Advances in technology offer new avenues for improvements in patient-centered care. Social media platforms can be used to provide programming and supports to defined clinical populations, such as people with hemophilia. Since 2015, ongoing studies have been conducted in whole or part at the British Columbia (BC) Adult Hemophilia Program. While varying in purpose, these studies are linked through their attention to understanding the potential of technology-mediated approaches to hemophilia support, both from clinical and patient perspectives. These approaches could increase access to the provider team by over 30% of the BC adult hemophilia population who reside more than 3 hours from the Centre. This presentation summarizes some key findings and emerging research directions.

Methods: The authors draw upon findings from two surveys of men with hemophilia, and a series of in-depth qualitative interviews. Survey 1: 75 respondents from 3 Canadian Treatment Centers. Survey 2: 29 respondents, from the BC adult program. The current project seeks to gain depth on technology-related questions in rural and remote areas through 10 targeted qualitative interviews conducted with BC adult clients via Skype or FaceTime which specifically address priorities for on-line education, programming, and support. Qualitative results are analyzed using interpretive description.

Results: Survey respondents were familiar with on-line education and programming, with 72% having used e-learning in school, and 52% at their place of work. 44% of respondents indicated interest in information and education about vocational issues delivered on-line. Interviews elaborate upon these findings; qualitative results will capture priorities for expanding e-health services, reveal challenges to the use of electronic services, and document any concerns related to the employment of technologies for e-health and social support.

Conclusions: Persons with hemophilia affiliated with the BC Adult Treatment Program are experienced technology users who welcome ways to access additional educational opportunities, and potentially other supports, using web-based platforms. Ongoing collection of data regarding patient perspectives guides clinicians in how they can adapt practices to the information age and increase access to services traditionally confined to within the clinic walls.

W-P-179 (277) | Improvement in reporting of bleeds and infusions via a mobile application

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Background: Bleeding events and infusions in patients with bleeding disorders have traditionally been recorded on paper in our institution. ZeroBleeds is a novel mobile application designed to enhance recording of bleeding events and infusions. This mobile application allows real-time, accurate recording of events, which can be retrieved online by healthcare providers, enabling effective management of patients by tailoring treatment protocols according to bleeding frequency.

Aims: 1. To track the use of ZeroBleeds application in the recording of bleeds, infusions and as a tool to monitor compliance with prophylaxis. 2. To compare the quality of data obtained via a mobile application as compared to traditional physical records.

Methods: Available functions from ZeroBleeds include: 1) Logging bleeds with details of bleed position, date, time, bleed type, cause, activities, pain scale, treatment with the ability to log a photograph of the bleed site 2) Logging of infusions including date, time, product used, dosage, infusion reason, infusion site, and vial lot number. 3) Scheduling calendar to help with infusion schedules. The quality of data obtained from ZeroBleeds was compared to data collected from paper records.

Results: Since January 2017, 31 out of 89 patients (35%) in our institution are using the mobile application. 25 patients who are on prophylaxis were 100% compliant with logging infusions in the first 3 months. The compliance rate dropped slightly to 90% after an average of 6 months. Reasons included data submission failure, login failure and changes in prophylaxis schedules. Patients who were treated on-demand logged in an average of 4 bleeds, of which 100% indicated details of treatment. Data recorded could be retrieved for all patients and used to determine treatment decisions during clinic reviews. For patients using paper records, compliance with logging in bleed or infusion details was 50%. Details of bleeds or infusions were frequently missing from paper records. Patients often did not bring paper records during clinic visits.

Conclusion: The quality of bleeding and infusion data obtained from the ZeroBleeds mobile application is superior to paper records. A high rate of compliance to logging in of treatment details was sustained beyond the first 3 months of use.

W-P-180 (782) | Starting the conversation with people living with mild hemophilia: A worldwide innovation with the first MOOC ever built with and for patients

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Introduction and Objective: In France, therapeutic education (TE) is very much on the rise but programmes practically never cover mild haemophilia. Needs of patients with mild haemophilia (PWMH) are not well known, even if they represent more than 50% of patients with haemophilia. In order to determine the most appropriate educational approach, needs expressed by PWMH have been explored.
Materials and Methods
Four main educational and skills emerged from a study conducted, in 2014, under the aegis of the French interdisciplinary working group on TE: The Therapeutic Education Patients, Parents, Professionals (ThE-3P group). To improve care management for PWMH, thE-3P group studied their educational needs and deduce new educational strategies (structured programme, exchanges with peers, social accompaniment). and development of appropriate tools. The format should be adapted to a group that infrequently consults health professionals (HP). Avenues of digital learning solutions to reinforce the educational workshops for people with mild haemophilia were projected. In 2016, the AFH decided to launch a Massive On-line Open Course (MOOC) dedicated to PWMH: men and women (carriers).
Results: HemoMOOC contained 5 pedagogic objectives **during 7 weeks** (spring 2017) :- Knowing mild haemophilia and how to recognize the symptoms and reacting in appropriate manner. How to react in an emergency situation and exceptional situations- **How to** express needs and being understood by HP (general practitioners, emergency doctors, gynecologists)- How to express feelings about the disease in order to be able to set back to help - How to live the daily life with mild haemophilia **524** people registered to HemoMOOC. **470** have been active at least once onto the platform. Parents represents 16.36%; PWMH: 24.55%; Women with mild haemophilia: 14.55%; HP: 21.82%; Social workers: 3.64%; PWH (severe or moderate): 9.09%; Others: 10%, **184** Social exchange network between patients and HP, **1083** seen on one Facebook/Live with 47 comments.
Conclusion: A MOOC seems to be a useful alternative to PWMH and can (re)-establish a link with HP. It is a real innovative tool for patients who don't feel ill but needs information and education.

W-P-181 (219) | Sports participation in adult haemophilia patients: An age-related comparison between intermediate and high dose prophylaxis

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Introduction and Objective: Differences in joint status have been observed between patients treated with intermediate-dose (Dutch) or high-dose (Swedish) prophylaxis, but sports participation has not been compared between these groups so far. The present study compared sports participation between Dutch and Swedish persons with haemophilia (PWH) and age-matched peers.
Materials and Methods: Adults with severe haemophilia treated in Malmö, Stockholm or Utrecht completed a questionnaire on the type and frequency (per week) of sports performed. PWH were compared with age-matched peers. Physical Activity (IPAQ), Health related quality of life (HRQoL; SF-36 – physical functioning: 0-100), joint health (HJHS: 0-144) and self-reported limitations in activities (HAL: 0-100), as well as bleeding and clotting factor consumption were assessed for PWH. Injury risk was classified according to the NHF classification (5 risk categories). Dutch and Swedish PWH and peers were compared according to age (18-22, 23-29, 30-40 years old) using non-parametric tests. Spearman's correlations between bleeds, factor consumption and sports participation were calculated.
Results: All participants performed some kind of sports at least 1x/week, including high-risk sports (57.6%). Type and frequency of sports participation were similar between PWH and peers in both countries. Dutch patients aged 30-40 showed a significant age-related decline in (high-risk) sports participation (from 7x/week at age 23-29 years to 2x/week at age 30-40), joint health (HJHS: from median 2.0 to 15.5) and HRQoL (median SF-36_{PF}: 100 to 77.5), while Swedish patients remained stable. Dutch and Swedish PWH showed similar sports participation and outcome, except for the oldest group, where Dutch patients had higher HAL scores (median 94 vs. 99.5) and performed high risk sports less frequently (0 vs. 2x/week) than Swedish. Sports participation was not associated with bleeding or clotting factor consumption.
Conclusion: All participants performed sports at least once weekly, including 57.6% in high-risk sports. Dutch PWH on "intermediate dose prophylaxis" showed an age-related decrease in (high-risk) sports participation, joint status and HRQoL that was not observed in the Swedish "high dose" patients. Differences between countries were only observed for PWH aged 30-40.

W-P-182 (319) | Perceptions of physical activity among young men with haemophilia

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Introduction and Objectives: Historically, physical activity was contraindicated in those with haemophilia. A recent Cochrane review concluded that most exercise produced improvement in outcomes (including pain, strength, walking tolerance) but that the quality of the evidence was poor. Physical activity is now known to increase strength and flexibility, reduce the risk of metabolic and cardiovascular disease, osteoporosis, arthropathy and intramuscular or joint bleeds. This study explores the reasons why young men show risk-adverse behaviour and do not undertake exercise, and what part previous injuries play in their perception that exercise is harmful.

Materials and Methods: Qualitative interviews were conducted with 10 young men aged 17-25 years with haemophilia of varying severity and type. Open-ended questions prompted discussion to capture opinions of physical activity and the degree to which haemophilia has an impact. Interview recordings were transcribed and analysed for themes.

Results: All participants were aware of the benefits of physical activity in regard to managing haemophilia and wanted to do more. The group varied widely in the extent to which they engaged in daily activity: 5/10 (50%) described themselves as very physically active, 3/10 (30%) as moderately physically active, and 2/10 (20%) as not very active; 4/10 (40%) described themselves as "not gym confident". Most had sustained sports-related injuries linked to their haemophilia and were aware of their limitations; all understood the need for prophylaxis before taking exercise. All had been encouraged by their physiotherapists to be more active in order to augment the efficacy of their treatment but 5/10 of the interviewees failed to follow this advice. Comments suggested the reasons were lack of motivation, fear of pain, previous experience of injuries or because they found the usual "prescription" of stretches and exercises to be unappealing.

Conclusion: Results indicated varied motivation to engage in physical activity motivation. There may be a need to establish a more tailored approach to exercise, focusing on identifying and addressing an individual's underlying medical and psychological issues. This may result in greater long-term adherence to physical activity among young men with haemophilia.

W-P-183 (732) | Quadriceps hematoma in mild hemophilia after sport injury: Case series in two subjects

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Introduction: Mild hemophilia is when factor level range between 5-40%. There is a paucity of information on patients with mild hemophilia (PWMH) with muscular hematomas. Reports indicate 10-25% of bleeding episodes occur in the intra/intermuscularly in severe hemophilia.

Objectives: To present a case series regarding the management and follow-up of two PWMH who presented with muscular hematoma following sports related trauma.

Materials and Methods: Retrospective analysis of treatment and bleeds from the medical record and Canadian Bleeding Disorders Registry (CBDR/MyCBDR). Case 1: 17 year old male with mild hemophilia A with a factor VIII level of 31% who sustained a left quadriceps hematoma following a collision in a soccer match. He presented to the hemophilia clinic 3 days post injury with swelling, warmth, decreased range of motion and pain in his left thigh . The initial ultrasound (US) showed an intramuscular hematoma within vastus intermedius with minimal effusion. He was treated with two doses of DDAVP (0.3 mcg/kg) followed by physiotherapy. He had a total of 5 serial US for follow-up. On week 4, multiple calcifications were noted adjacent to the hematoma. The third US found calcifications decreased in size and in number with physiotherapy. At 4 months post trauma a single calcification remained with resolution of hematoma. Despite these US findings, the patient was asymptomatic 8 weeks post trauma. Case 2: 15 year old male with mild hemophilia B with a factor IX level of 9% who sustained a trauma to his left thigh resulting in a hematoma while playing a hockey game. He was treated with FIX (45 IU/kg) and received 17 infusions for this bleeding episode. He returned to physical activity 4 weeks post-trauma with continued factor prophylaxis. Serial of US's were completed weekly over 3 months then monthly until resolution at 5 months post-trauma.

Conclusion: Patient with mild hemophilia often engage in intense physical activity without the direction of the hemophilia clinic. In our case series, radiological resolution of hematomas was prolonged and did not correlate with their symptoms or activity. Physiotherapy showed a good progress in both cases despite the radiological findings.

W-P-184 (504) | How the assessment of subjective physical functioning reflects objective data concerning physical fitness – Pilot-testing results of the fit-for-life activity in children and adults with haemophilia in Germany

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Introduction and Objectives: *Fit-for Life* is an activity specially designed for people with haemophilia (PWH) assessing their physical fitness. Objectives of this pilot-study were to examine subjectively and objectively physical functioning and physical fitness in PWH and to analyse how these measures are correlated. Moreover, we wanted to compare these findings with healthy controls.

Materials and Methods: All PWH (> 5 years) participating in the *fit-for-life activity* in Munich performed a five-stage fitness test covering sport-specific motor capacities (coordination, strength, aerobic fitness, mobility, body composition). In addition PWH completed an instrument for the subjective assessment of physical functioning (HEP-Test-Q); some clinical data were collected. The HEP-Test-Q consists of 25 items pertaining to four dimensions ('mobility', 'strength & coordination', 'endurance' and 'body perception'). As controls healthy male siblings or relatives were asked to fill-in the HEP-Test-Q.

Results: Fourteen PWH with a median age of 11 years (range 5-32) participated in the pilot-study; 12 paediatric and 2 adult PWH. 78.6% PWH had haemophilia A and 92.9% were severely affected; 92.9% were physically active. In addition 10 healthy controls (2 siblings, 8 adults) were included. PWH were below reference values of normal population in the mobility (42.9%) and endurance test (64.3%). In body composition and coordination PWH were above the reference values. No differences were found for back strength and overall fitness (16.7/50% of children/adults were below fitness reference values). Paediatric PWH reported good subjective physical functioning in the 'HEP-Test-Q Total Score' (M = 82.25 ± 9.6); being quite similar to their healthy siblings (M = 82.25 ± 9.6). By contrast adult PWH showed impairments in their 'HEP-Test-Q Total Score' (M = 54.5 ± 20.5) which was worse than that of healthy controls (M = 72.85 ± 9.1). A medium correlation was found between subjective and objective measures in terms of 'Total HEP-Test-Q' and back strength (r = 0.444) and 'body perception' and overall fitness (r = 0.461). Participants with an overall fitness below reference values reported worse subjective physical functioning (P < .037).

Conclusions: Paediatric PWH had good subjective and objective physical functioning comparable to healthy controls. By contrast, adult PWH showed impairments in subjective and objective physical functioning. To compensate or prevent impairments in fitness individualised exercise programmes and awareness trainings are recommended.

Keywords: haemophilia, physical functioning, HEP-Test-Q, exercise, physical fitness.

41-TREATMENT PRODUCTS

T-MP-169 (132) | Establishment of plasma fractionation center for the production of plasma-derived factor VIII concentrate by the National Blood Center, Thai Red Cross Society: an achieving self-reliance

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Background: The National Blood Center, Thai Red Cross Society has established a fractionation center to produce albumin, intravenous immunoglobulin and factor VIII concentrate with the aim of self-reliance.

Objectives: To study the safety and efficacy of locally-produced factor VIII concentrate among Thai patients with hemophilia A.

Methods: Previously-treated patients with hemophilia A for more than 150 days were enrolled in the study. After a 5-day wash-out period, they received 500 units of factor VIII concentrate. The vital signs and clinical manifestations were closely monitored before and at 1, 2 and 4 hours. Factor VIII clotting activity (FVIII:C) was determined before and 30 minutes after factor VIII concentrate administration. Then 500 units of factor VIII concentrate twice weekly was prescribed as a low dose prophylaxis regimen for 3 months. In cases of any bleeding episodes, patients received only these locally-produced factor VIII concentrates. The infectious markers of HIV, hepatitis A, B and C viruses were screened before and after 3 months of factor VIII administration. Also, the pharmacokinetics of FVIII:C was studied among 10 patients.

Results: In all, 50 patients with severe and moderate hemophilia A were enrolled in the study. Their mean (SD) age was 20.4 (6.9) years old. The mean (SD) incremental FVIII:C after receiving one unit of factor VIII concentrate per BW (kg) was 2.3% (0.5). Pharmacokinetics analysis revealed a half-life of F VIII:C at 12.7 hours. The efficacy of bleeding control among 42 episodes found in 18 patients was designated as excellent (n = 1), good (n = 39) and moderate (n = 2). All patients required one dose of factor VIII concentrate at a mean dose (SD)

of 10.9 (9.9) units/kg except 2 patients with moderate response requiring 2 and 3 doses, respectively. Neither of the patients required hospitalization. Mild adverse reactions were found in 2 patients, unrelated to the administered factor concentrate. No seroconversion related to HIV, hepatitis A, B and C viruses was found after a 3-month period.

Conclusion: Factor VIII concentrate produced by the National Blood Center, Thai Red Cross Society showed safety and efficacy in bleeding control among Thai hemophilia A patients with severe and moderate degrees.

T-P-170 (632) | The factor concentrate redistribution program: A 10 year review

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Introduction and Background: The Factor Concentrate Redistribution Program (FCRP) has been in operation since May of 2007. The role of the FCRP in the province of Ontario, Canada is to ensure little to no wasting of clotting factor concentrates (CFC). In the past 10 years the program has seen many changes, has been able to reach numerous hospitals in Ontario, and saved millions of dollars' worth of CFC. Community hospitals maintain an inventory of CFC for known patients in the area and possible emergency treatment. However, if the CFC is not used before expiry, it's discarded, and new product ordered to re-stock. The shelf life of CFCs is anywhere from 1 to 3 years and the cost per IU is from $0.53 (CDN) to $10.80 (CDN). St Michael's Hospital still remains the main Hemophilia Treatment Centre (HTC) used to ensure short dated products are being used before expiring. The objective is to reduce wasting of an expensive product by moving it to a centre with a known patient who can utilize the CFC before expiry.

Methods: Through a partnership with the Ontario Regional Blood Coordinating Network, our programs move all short dating plasma protein products around Ontario with the FCRP responsible for the CFCs. Transfusion Medicine Services reports monthly to the FCRP, any product that will expire within the next 6 months. The FRCP staff work together to monitor inventory, move product safely and promote the program amongst all Ontario hospitals.

Results: In the past 10 years, the FCRP has redistributed over 7.4 million IUs of CFCs that would have been otherwise been discarded. The FCRP has allowed for CFCs to be stored at community hospitals without concern of waste or expiry.

T-P-171 (434) | Emergency drugs, health geography interest to study spatial accessibility: Application for clotting factor concentrates

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Clotting Factor Concentrates (CFC), used as a replacement therapy for haemophilia or other rare bleeding disorders are expensive drugs. The cost of emergency stock can be an obstacle to keeping them in the hospital pharmacy. This study has two aims, the first one is to carry out an exhaustive inventory of CFC emergency doses distribution. The second aim is to determine their accessibility on Rhone-Alpes region (France), around 44 665 km². Data on the availability of CFC were collected using a questionnaire sent to hospital pharmacists. An expert opinion, composed of an emergency physician, and a haemophilia specialist, has considered that a haemophiliac should be treated urgently by a CFC in less than 30 minutes. The analysis and the cartographic modelling were then carried out thanks to a Geographical Information System (GIS) from patients address to hospitals pharmacies. The GIS analysis allows maps realization, accessibility evaluation, according to emergency criteria. The FVIII accessibility area under 30 minutes represents an area of 20,376 km^2, or 45.6% of the total area of the region. As for FIX, only 13,616 km^2 of the region territory is accessible, representing 30.5% of the total area. If every pharmacy would have the emergency stock defined as 4 000 IU for FVIII and 7 000 IU for FIX, 50.3% would be accessible for FVIII and 52.5% for FIX, a respective increase of 4.7% and 22% of the CFC accessibility area. In conclusion, this exhaustive inventory of CFC emergency stocks teaches us that a more efficient management of the CFC would allow a better accessibility on the regional territory and increase the proportion of PWH that can be treated within 30 minutes. Cartographic design is a real decision-making tool with public health issues. The geography of health brings a major interest in this analysis of accessibility to treatments. It would be interesting to be able to transpose this study of the accessibility to emergency treatment to other rare diseases, concerned by similar problems.

T-P-172 (262) | Audit of the Laboratory Management of Coagulation Factor Concentrates in a National Paediatric Centre for Haemophilia

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Our Lady's Children's Hospital, Crumlin (OLCHC) is the national paediatric centre for haemophilia in Ireland. The Blood Transfusion laboratory

at OLCHC has responsibility for the management of Coagulation Factor Concentrates (CFCs) for patients in the in-patient and day care setting.
Objective: An audit was performed to quantify the laboratory's workload associated with haemophilia patients between 2006 and 2016. Included was the number of patients treated in hospital, the total quantity of CFC vials issued from the laboratory and the number of vials wasted over this period.
Results: The number of patients receiving CFC as inpatients or day cases increased from 35 in 2006 to 91 in both 2015 and 2016. The number of vials issued annually ranged from 1084 in 2006 to a maximum of 2520 in 2011 with 2132 vials used in 2016. Between 2008 and 2016 16,826 vials of CFC were used with 66 vials discarded having expired in the laboratory or been wasted in the clinical area, this represents 0.4% of all CFCs managed by the laboratory. In 2014 the hospital began enrolling patients in CFC clinical trials. The laboratory managed the CFCs for patients receiving product in the hospital for eight clinical trials between 2014 and 2016. Initially 13 patients received trial CFC in the hospital this rose to 21 patients in 2016. The amount of trial CFC used over the three years represented between 21 and 27% of all CFCs used in hospital.
Conclusion: The audit found that the laboratory workload associated with the treatment of haemophilia patients in the hospital setting has increased significantly since 2006 while CFC wastage and expiry rates are maintained at minimal levels. A significant portion of the CFCs managed by the laboratory since 2014 were clinical trial products.

T-P-173 (280) | The global initiative on local preparation of viral inactivated cryoprecipitate: An update

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Introduction and Objectives: In developing countries (with low-Human Development Index, l-HDI), treatment of patients with bleeding disorders is inadequate or absent and the dramatic situation has not changed significantly during the past 20 to 30 years. Past experience has shown that clotting factor concentrates (CFC) alone cannot solve the existing supply problems in l-HDI. Recently, significant developments have occurred which have the potential to change the disastrous situation in therapy delivery to "hemophiliacs" in developing countries: blood systems in many l-HDI have tangibly improved and novel technologies for viral inactivation (VI) of labile blood components have been developed and are now marketed (amotosalen, riboflavin, solvent-detergent…). In a few l-HDI, local preparation of viral inactivated cryoprecipitate (Cryo-VI) has been introduced and has proven to be a safe, effective therapeutic for patients with bleeding disorders, at an affordable cost. Nonetheless, the use of VI-technology to render cryoprecipitate safe remains very limited; therefore, major coordinated actions are needed to promote Cryo-VI in l-HDI and to facilitate its implementation.
Materials and Methods: A Global Initiative on local production of cryoprecipitate, viral inactivated with solvent-detergent, in l-HDI has been launched end of 2016 as a collaborative effort with international partnering organizations (like WHO, ISBT and others) and national stakeholders in l-HDI. An update is given of the core interventions in the Global Initiative: revise and update existing guidelines and standards on "anti-hemophilic" treatment; give high priority in policies and strategies to "Local Cryo-VI in l-HDI"; organize strong advocacy and promotion; run a pilot project in several sites; establish an expansion programme; support activities for implementation and sustainability of it.
Results: The Global Initiative is an ongoing programme, making stepwise progress and an update on progress will be given.
Conclusions: The Global Initiative on "Local Cryo-VI in l-HDI" is intended to be complementary to existing relief activities (e.g. product donations) and will result in additional supply of safe and effective haemostatic products to treat patients with bleeding disorders in resource limited countries. At the same time, it will contribute to significantly lower the incidence of inhibitor formation in previously untreated patients with severe hemophilia A.

42-WOMEN AND BLEEDING DISORDERS

T-P-001 (351) | Successful carrier identification by messenger RNA analysis for one hemophilia A family without found DNA mutations

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Introduction and Objectives: Identifying carrier status for female members in a hemophilia family is important for genetic counseling. There are 2~7% of Hemophilia A (HA) patients whose mutations cannot be found by DNA-based analysis of F8 gene. For those patients without found DNA mutations, identification of carrier status for female members is very difficult because of the existing wild-type X-chromosome. We aimed to share our experience to identify the carrier status by mRNA analysis with customized primers in a HA family with skipped exon 19 transcript.
Materials and Methods: Two brothers, at age of 28 and 30 years, with moderate-type HA, whose FVIII:C was 2.4% and 3.6% respectively. No detectable F8 mutation was found by DNA-based analysis. RNA was extracted from 200 μl buffy coat according to QIAamp RNA Blood Mini Kit. Total cellular RNA was reverse-transcribed to cDNA. F8 cDNA was amplified as eight fragments using nested PCR. The two brothers were found to have aberrant transcripts of skipped

exon 19 by mRNA analysis. For the patients' two marriageable sisters, we designed specific primers to determine the mutation region. The customized reverse primer (5′-3′CAGGGGAGTCTGACACTCTG) was complementary across exons 18 to 20 in F8 cDNA. In this family with a transcription error resulting in skipped exon 19 in cDNA, the carrier status was determined by mRNA analysis of customized primer.

Results: The two HA patients had both PCR products of 359 bp and 710 bp, which indicated they carried aberrant transcript of skipped exon 19 and normal transcript. One of their two sisters had only 710 bp PCR product, which indicated her non-carrier status. In contrast, the other sister was found to have presence of both 359 bp and 710 bp PCR products, which was consistent with her carrier identity.

Conclusions: We successfully clarified the carrier status of the two sisters from this HA family without detectable DNA mutation by mRNA analysis. This method with customized primers was an effective tool to detect female carriers with skipped exon transcript.

T-P-176 (254) | Carrier status, HA related bleeding symptoms in carriers and changing approaches to the diagnosis and treatment of women with haemophilia

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Introduction: Recent discussions have started to move away from Haemophilia related bleeding symptoms in carriers to acceptance of the diagnosis of (predominantly) mild haemophilia in women. This has implications for the way women and the healthcare professionals they encounter, understand and respond to symptoms of bleeding, and the treatments made available.

Objective: The objective of this paper is to explore the experiences and understandings of women experiencing bleeding as a result of haemophilia.

Method: This paper draws on data from a qualitative interview-based study exploring the experiences of people living with haemophilia in Ireland. As part of this, semi-structured interviews were conducted with 8 women carriers of haemophilia focusing on their experiences of the condition. All interviews were recorded, transcribed verbatim and underwent thematic analysis. The data in this paper is presented by way of 3 illustrative narrative accounts.

Results: The narratives exemplify the ways in which approaches to bleeding symptoms in women are changing. The first relates to Woman 1, a carrier who is recently married with a father and nephew with haemophilia. She self identifies as a non-symptomatic carrier. Her story focuses on the potential of having a son with haemophilia. Woman 2 is a carrier with a family history of haemophilia who provides expert care for her father (mild haemophilia) but lacks expertise around her own condition despite experiencing heavy bleeding monthly. Woman 3 has a family history of haemophilia, was identified as a 'carrier with low levels' aged 8 and was recently diagnosed with mild haemophilia. She attends a support group and self identifies as the only woman attending with a haemophilia diagnosis.

Conclusion: These three narratives illustrate many of the common issues around carrier status, family history, the carer role, and a lack of knowledge and expertise about normal and abnormal bleeding patterns amongst women with haemophilia. In addition, they illustrate the changing status of haemophilia related bleeding in women and have implications for treatment and awareness raising.

T-P-177 (473) | The female factors: Women's resources as education tools

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Introduction and Objective: Consultation with Australian women with bleeding disorders indicates that many non-haemophilia health professionals lack knowledge of bleeding disorders in females. As a result, women have not been referred to Haemophilia Treatment Centres (HTCs) and experienced avoidable bleeding problems with menorrhagia and after invasive procedures and childbirth. Many experience isolation and fears about their health. The Haemophilia Foundation Australia (HFA) The Female Factors (TFF) project aims to produce high quality evidence-based information resources that women with bleeding disorders can use to inform themselves about self-advocacy in the health care setting and show to their health care practitioners.

Materials and Methods: By 2017 HFA had published two TFF booklets: a snapshot of bleeding disorders in females with information on working with HTCs and other health care practitioners; and another on carrying the gene for haemophilia with some common reactions to diagnosis and where to go for support. Importantly, they include personal stories and tips from other affected women as peer education and support. For credibility with health professionals, the evidence-based references and expert reviewers are printed clearly in the booklets. The booklets have a magazine-style design, are printed on high-quality paper and also available online. Print booklets were distributed widely through haemophilia foundation newsletters and HTCs; and promoted through social media and e-news.

Results: Uptake was very high: by November 2017 4,164 print copies of the snapshot had been distributed, including 146 copies requested by individuals for their medical team, workplace, school and siblings. This is approx. 80% more than other HFA print booklets. 2,663 copies were downloaded. Booklets were used to initiate discussion in women's groups; women spoke of the importance of being acknowledged; some women with mild disorders identified themselves and connected with other women and HTCs. A community survey to further evaluate usage and impact will be conducted by early 2018 and results reported in this presentation.

Conclusions: High-quality evidence-based information resources with tips and personal stories are effective in enabling women to connect to other women and HTCs and feel supported; and provide a tool they can use to educate their other health care professionals.

T-P-178 (558) | Review of a multidisciplinary clinic for women with inherited bleeding disorders

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Introduction and Objectives: Women with inherited bleeding disorders are at risk of gynaecological disorders. Guidelines from the UKHCDO advocate management by a multidisciplinary team. We undertook a review of the joint gynaecology/haematology clinic at Royal London Hospital with the aims to understand the clinic population and how we may develop this model to meet the needs of this population.

Materials and Methods: All patients with inherited bleeding disorders attending the clinic between January 2013 to October 2017 were selected. Data was retrospectively collected through the EMIS database, including demographic data, referrer, patient diagnosis, presenting symptom and number of appointments at the joint clinic. Both gynaecological and haematological treatments were recorded.

Results: 72 patients were seen. 20/72 (28%) were 12-18 years, 19 (26%) 18-30 years, 18 (25%) 31-40 years, 14 (19%) 41-49 years and 1 (1%) over 50 years. 64/72 (89%) were referred from the haemophilia centre, 7 (10%) by gynaecology. 57/72 (79%) of patients presented with menorrhagia. 32/72 (44%) had Von Willebrand's disease. Additionally, there were a 5/72 (7%) with rare coagulation disorders and 8/72 (11%) with Glanzmann's. Treatment given was either medical only 59/72 (82%), 1 patient surgical only (1%) or both (6 patients, 8%), though 6 (8%) had only discussion or referral. 22/72 (31%) patients received tranexamic acid, 22/72 (31%) COCP, 8/72 (11%) POP, 11/72 (15%) IUS and 11/72 (15%) other hormonal therapies.

Conclusions: This multidisciplinary clinic treats patients with a wide range of inherited bleeding disorders, including those with rare bleeding disorders. Over a quarter of patients were adolescent, highlighting an unmet need for an adolescent gynaecology haemophilia clinic which could begin with pre-menarche counselling. Cross-specialty decisions involving the patient could be immediately acted upon, with the potential to improve both patient safety and treatment outcomes. Surgical treatment rates are low, with improved safety due to specialised haematology input.

T-P-179 (654) | Management and outcomes of heavy menstrual bleeding in adolescents with bleeding disorders

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Introduction and Objectives: While heavy menstrual bleeding (HMB) is common in adolescent girls and often attributed to anovulation, a significant number may have an underlying bleeding disorder (4-36%). The optimal menstrual bleeding reduction strategies have not been studied in a prospective manner and expert opinions vary on the approach to medical management of HMB. Furthermore, management of HMB may be more challenging in those with a bleeding disorder. Here we describe our single institution experience in evaluation and subsequent management of adolescent females with HMB and a newly diagnosed bleeding disorder.

Materials and Methods: A retrospective cohort of adolescents seen at Children's Healthcare of Atlanta (CHOA) Hemophilia Treatment Center diagnosed with HMB and a bleeding disorder were identified between January 2016 and November 2017. Demographic and clinical details related to presentation and treatment were abstracted from chart review. HMB was defined per the CDC. Low von Willebrand factor (VWF) was defined as VWF:Ag or VWF:RCo of 40-50% and von Willebrand disease (VWD) as VWF:Ag or VWF:RCo of <40% on 2 occasions. Factor deficiency was defined as <50% and qualitative platelet dysfunction was defined as abnormality in whole blood impedance on 2 occasions.

Results: Our cohort (n = 40) was mostly Caucasian (57.5%), with a median age at menarche of 11 years (9-14 years). The most common bleeding disorders were low VWF (35%), VWD (30%), qualitative platelet function defect (25%) and factor VII deficiency (10%). Of the 23% initially presenting to the hospital, primary treatments included intravenous estrogen (78%), combined oral estrogen/progesterone (COC) (44%) and/or anti-fibrinolytics (33%). Of the 78% initially presenting to our clinic, the most common treatments were COC (58%), anti-fibrinolytics (48%), norethindrone (26%) and injectable progesterone (16%). Treatment at 3-month follow-up included COC (37.5%), norethindrone (35%) and/or anti-fibrinolytics (40%) and injectable progesterone (12.5%). At 3-month follow-up, patients documented their menstrual cycle as normal (42.5%), amenorrhea secondary to hormone therapy (27.5%) or continued HMB (22.5%).

Conclusions: HMB in adolescents with mild bleeding disorders can be successfully managed with hormonal therapies with or without anti-fibrinolytic agents.

T-P-180 (715) | Women with all bleeding disorder require education

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Introduction and Objectives: Women have long been an underserved population within the bleeding disorders community. The common conception is that only men have hemophilia, even within sections of the bleeding disorder community. Medical professionals discount women's claims of abnormal bleeding, leaving us to feel undervalued and demeaned. Within the last decade, increased studies support what women have known all along-WE bleed. In the US, annual, national meetings feature a women's track, through the assistance of Hemophilia Federation of America local chapter meetings feature women only retreats. Our collective voices are at last being heard!

Materials and Methods: To propel all women with bleeding disorders issues to the forefront, we set out in 2016, by partnering with three local chapters to offer a one-day LadyBugs Program. Sessions on FVIII/FIX carrier status, stress reduction to include mindfulness and yoga, self-infusion, and a rap session. Session and program evaluations were distributed to determine participant satisfaction. These programs were well received in their communities, but the request remained: We Need More. To accomplish this, the first national LadyBugs Women's Summit was offered for an entire weekend in November 2017, that included breakout sessions for vWD, FVIII/FIX, and other related blood disorders to include: FV, GT, FX, FXI and Storage Pool deficiency. For the national LadyBugs Summit, program and session evaluations were dispensed to evaluate satisfaction. A pre-and post-program survey was distributed to evaluate efficacy.

Results: Cumulative program evaluations from the one day, 2016 LadyBugs programs indicated a 96.7% satisfaction rating based on 32 attendees. The 2017 national LadyBugs Women's Summit indicated a 96.9% overall satisfaction rating based on 20 attendees. Pre- and post-survey data indicated a 5%-30% increase in participant's understanding of their own condition, their ability to self-advocate and creation of a strong support network.

Conclusions: Women with all bleeding disorders need and are demanding a voice when it comes to diagnosis, identification and treatment respective to their own health. National programs organized by and for women with any bleeding disorder deserve the attention and resources necessary to elevate their treatment to the same level as men with bleeding disorders.

T-P-181 (808) | Understanding and finding symptomatic undiagnosed women

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Introduction and Objectives: Up to an estimated 1% of women in the United States have a bleeding disorder, but many with symptoms go undiagnosed. The National Hemophilia Foundation (NHF) conducted a needs assessment of currently diagnosed women to understand their path to diagnosis to help inform creation of an awareness campaign called Better You Know.

Materials and Methods: In 2015, NHF fielded a survey of diagnosed women, yielding 184 responses. Informed by the needs assessment and input from a working group of medical providers and consumers, NHF launched the Better You Know campaign in 2016, which includes a website with a validated screening tool, resources on where to find providers on the path to diagnosis and treatment, outreach videos, social media posts, promotional postcards, paid media articles, accredited medical provider webinars, and mini-grants to select chapters for local outreach.

Results: NHF found that women finally sought care for their symptoms for the following reasons: significant bleeding incident (surgery, childbirth, etc.), symptoms got too bad, or a family member was diagnosed. Women reported seeing the following providers first on their path to diagnosis: 38% hematologist; 23% primary care physician, 16% OB/GYN, and 15% pediatrician. About 80% of women also reported going to other people they know with a bleeding disorder for information and support. This lead to the creation of betteryouknow.org and other related campaign elements. From launch in July 2016 through October 2017, the website drew 4,107 sessions, with 413 completing the screening tool and 86% of those being at risk. There were 108 clinicians who received accreditation for the provider webinars. NHF has developed partnerships with feminine hygiene product companies to spread the word, and pushes out campaign messaging via social media, chapters and some paid media. Total audience (website visits, social media impressions, etc.) for the campaign to date is over 252,500,000.

Conclusions: Undiagnosed women with bleeding disorders face true challenges due to their bleeding symptoms. NHF will continue to raise awareness with providers and women, utilizing findings for effective methods of communication and education, through the Better You Know campaign.