bjh guideline

Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B

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Methodology

This guideline was compiled according to the British Society for Haematology (BSH) process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf.
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. The references to support the recommendations are listed in the preceding discussion.

Literature review

The information contained in this review was gathered from several sources. These included references from a search of MEDLINE, EMBASE and the Cochrane databases to identify studies and reviews relevant to prophylaxis in patients with haemophilia, abstracts from international meetings and references known to the authors (Appendix S1).

Review of the manuscript

The writing group produced the draft guideline, which was subsequently revised by consensus. Review of the manuscript was performed by the BSH Guidelines Committee Haemostasis and Thrombosis Taskforce, the BSH Guidelines Committee and the Haemostasis and Thrombosis sounding board of the BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by members of the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Advisory Board, Haemophilia Nurses Association (HNA), Haemophilia Chartered Physiotherapists Association (HCPA); these organisations do not necessarily approve or endorse the contents.

Introduction

Coagulation factor replacement in people with haemophilia (PWH) A or B may be given either in response to a bleed [on-demand (OD) therapy] or regularly to prevent bleeding (prophylactic therapy). Guidelines for prophylactic treatment of children and adults with severe haemophilia A (SHA) were produced by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) in 2010, summarising the high-level, evidence-based studies of prophylaxis in boys and advising on the role of prophylaxis in adults with SHA.[1] This guideline builds on the former, accepting the clear evidence of benefit of prophylaxis in children with SHA. It addresses the optimum use of prophylaxis in children and adults with haemophilia A and B and gives evidence-based recommendations where appropriate. The guidance will be of value to healthcare professionals, laboratory scientists, patients and those with a responsibility for funding services.

What is the aim of prophylaxis in the management of a person with haemophilia (PWH)?

The primary goal of haemophilia care is to prevent bleeding; this is usually achieved by prophylaxis. In the UK prophylaxis is initiated at an increasingly young age and some adults, who did not have prophylaxis as a child, now start prophylaxis later in life to preserve musculoskeletal function. As outcome measures in these cohorts will clearly differ, the International Society of Thrombosis and Haemostasis (ISTH) have defined the aims of prophylaxis in relation to joint health at onset[2]:

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Primary prophylaxis

Commences in early childhood at the latest before the second joint bleed or the age of 3 years, in the absence of documented joint disease, with the aim that the child reaches maturity with normal joints.[3,4]

Secondary prophylaxis

Commences after two or more joint bleeds, but before the onset of proven joint disease. It is likely that these bleeds have caused subclinical but established, irreversible joint disease.[3] Prophylaxis aims to limit the consequence of this damage by preventing further bleeding, maximising function long-term.[4]

Tertiary prophylaxis

Commences after the onset of clinically/radiologically apparent joint disease and aims to slow down progression of joint disease, reducing pain and maintaining quality of life. It cannot, however, reverse established joint disease.[5]

Primary prophylaxis

Primary prophylaxis decreases the frequency of bleeding, preventing joint damage in boys with severe haemophilia (SH).[4,6] Prophylaxis also reduces the frequency of intracranial haemorrhage in people with SH who have no inhibitor.[7] The expected outcome is that, with optimised prophylaxis, a child with haemophilia (CWH) will reach adulthood with normal joints and live a full and active life, in the absence of bleeds.

Who should receive primary prophylaxis?

The bleeding phenotype and clinical outcomes can mostly be predicted from the level of factor VIII (FVII) or factor IX (FIX). Without prophylaxis, nearly all men with SHA (<1 iu/dl) and most of those with moderate haemophilia A (MHA) who have levels between 1 and 3 iu/dl will have at least one target joint and some degree of disability due to joint bleeds.[8,9] For those with MHA, a measured FVIII of 1–2 iu/dl has been associated with the highest risk of bleeding: median (interquartile range [IQR]) 2·9 (1·4–7·2) joint bleeds per year, despite prophylaxis in 40% compared to 1·4 (0·5–3·4) for those with a level of 3–5 iu/dl.[10] In the UK, adults with MHA (with a level <3 iu/dl) have very similar Haemophilia Joint Health Score (HJHS) to those with SH of the same age.[11] However, children with MHA have a worse HJHS than those with SHA, irrespective of whether they are taking prophylaxis, suggesting a discrepancy in the approach to the care of these two groups.[11]

As detailed previously, there is clear evidence for the use of primary, secondary and tertiary prophylaxis in SHA but little for MHA, although one randomised controlled trial (RCT) did include boys with both SHA and a level of 0–2 iu/dl.[3] However, current evidence suggests that those with a level <4 iu/dl develop significant joint damage and should be considered for primary prophylaxis.

Clinically, SHA and severe haemophilia B (SHB) are considered indistinguishable although some studies suggest that SHB might be associated with less severe outcomes.[12] Nonetheless, there are insufficient data to be able to treat this cohort differently to those with SHA and a similar approach to initiation and monitoring of prophylaxis is recommended.

Who should receive secondary prophylaxis?

In the ESPRIT trial of prophylaxis in SHA, secondary analysis showed that there were radiological signs of joint damage in none of the eight patients randomised to prophylaxis under the age of 36 months compared to three of 10 patients of the same age randomised to episodic therapy ($P < 0{\cdot}05$).[4] Six of 13 boys (46%) who started prophylaxis after the age of 36 months showed radiological signs of joint involvement compared to 10 of 12 (83%) of those on episodic therapy. This study demonstrates the benefit of both primary and secondary prophylaxis and the latter should be offered if a PWSH is not already established on primary prophylaxis.

Who should receive tertiary prophylaxis?

The SPINART study was an RCT comparing tertiary prophylaxis with on-demand therapy in PWSHA aged 12–50 years.[5] Those taking prophylaxis had a 94% reduction in bleeding events and a 54% reduction in chronic pain. As compared with OD treatment, prophylaxis was associated with improved function and quality of life, although magnetic resonance imaging (MRI) score changes did not differ.

The POTTER prospective open label study compared long-term tertiary prophylaxis with OD treatment in patients with SHA aged 12–55 years.[13] It demonstrated statistically significant improvement in joint scores and quality-of-life indicators, associated with a reduction in bleeding. A further open label, crossover study of tertiary prophylaxis following OD therapy in men aged 30–45 years with SHA showed a significant reduction in bleeding and improved Gilbert scores whilst on prophylaxis.[14]

Recommendations

- **All children with SHA or SHB should receive primary prophylaxis. Grade 1A**
- **Primary prophylaxis should be considered for all children with baseline factor levels of 1–3 iu/dl. Grade 2C**
- **Prophylaxis should be offered to any PWH who has sustained one or more spontaneous joint bleeds. Grade 2C**

- **Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B**

When should primary prophylactic factor replacement therapy begin in children with severe haemophilia?

The average age of the first joint bleed in SH is 1·49 years,[15] associated with ambulation. The optimum time to start prophylaxis is unclear[16] but, in principle, in order to prevent joint damage it should commence before the first joint bleed occurs.

In an RCT assessing the efficacy of prophylaxis *versus* episodic treatment, prophylaxis was introduced in boys with HA (0–2 iu/dl) aged 6–30 months who had experienced no more than two joint bleeds.[3] MRI assessment performed at 6 years demonstrated that 25 out of 27 (93%) in the prophylaxis group had normal joints compared to 16 out of 29 (55%) in the episodic-therapy group ($P = 0{\cdot}002$). Similar findings were reported in the ESPRIT trial[4] and cohort studies.[17,18] Many different prophylactic regimens were used, with respect to dose and interval, in these cohort studies but this did not seem to alter the impact of starting prophylaxis before the age of 3 years.

Prophylaxis should be started following completion of treatment for a spontaneous intracranial bleed, if not already established.[7]

Recommendations

- **In a person with SH or MH with a baseline level 1–3 iu/dl, primary prophylaxis should be started before or immediately after the first joint bleed. This will usually be at the time of ambulation, around 12 months of age and certainly before 24 months. Grade 2C**
- **Following initial treatment of a spontaneous intracranial haemorrhage, prophylaxis should be commenced and continued long term. Grade 1C**

Choice of product

Outside of clinical studies the choice of product in the UK is restricted to those on the national framework with European Medicines Agency (EMA) approval for use from birth onwards.

Treatment-related risk factors have been identified for inhibitor formation in SHA.[19] Differences in inhibitor rates have been reported for different recombinant FVIII (rFVIII) products in previously untreated patients (PUPs) in retrospective cohort analysis[20-22] and between plasma-derived (PD) and recombinant products in an RCT.[23] However, following review of the data from a European Haemophilia Safety Surveillance project (EUHASS),[24] the EMA concluded that there was no clear evidence of a difference in the incidence of inhibitor development between PD and rFVIII products.[25] The risk of transfusion-transmitted infection with PD products is low, but cannot be excluded, and should be taken into consideration when selecting a product.

Product choice may be influenced by patient preference, pharmacokinetic differences between products or economics. The national procurement process within the UK has resulted in many PWH switching between FVIII products with no observed increase in inhibitor formation.[26] Those with inhibitors to FVIII who have undergone successful immune tolerance therapy are usually maintained on the same product, so there are insufficient data to assess the safety of switching product in this group.

Use of extended half-life products

Extended half-life (EHL) products are available in the UK for both HA and HB and guidance on their use has been published in a consensus statement.[27] Studies have shown that both are efficacious, particularly EHL FIX, for which the half-life is significantly prolonged.[28-33] A definition of an EHL product proposed by Mahlangu *et al.*[34] includes three criteria: designed with technology to extend circulating biological half-life, demonstrate a difference from a standard rFVIII/rFVIX comparator for the majority of patients and have a half-life ratio of 1·3 or higher, based on modelling. Lower frequency of infusions is possible and may avoid the need for a central venous access device (CVAD). Alternatively, the frequency of infusions can be maintained, and a higher trough FVIII/FIX level achieved. Studies in PUPs with haemophilia (PUPWH) have not been conducted for all EHL products so recording of outcomes, including rates of inhibitor formation, in prospective registries is important.

Recommendations

- **The choice of factor replacement product must involve shared decision-making with the person with haemophilia and/or their parent/legal guardian. Grade 1C**
- **Switching between factor replacement products may be performed in patients with more than 150 exposure days and no prior inhibitor. Grade 1C**
- **Recombinant FVIII and FIX EHL products should be used according to published UKHCDO guidance and used only when they provide clear clinical benefit over standard half-life products. Grade 1C**

Emicizumab

Emicizumab is a recombinant humanised bispecific monoclonal antibody mimicking the co-factor function of activated

FVIII. It is licensed for the prevention of bleeding in SHA, both with and without inhibitors.

SHA with inhibitors

Emicizumab given weekly at a dose of 1.5 mg/kg is associated with lower annualised bleeding rate (ABR) compared to prophylaxis with bypassing agents (BPA), reducing the historical bleed rate in patients aged >12 years by 79% ($P < 0{\cdot}001$). In those with inhibitors previously treated OD the bleed rate was reduced by 87% ($P < 0{\cdot}001$), with an ABR (for treated bleeds) of 2·9 (95% confidence interval [CI], 1·7–5·0).[35] In a separate study, when the dosing interval was increased to 6 mg/kg every 4 weeks the ABR was 2·4 (95% CI 1·4–4·3).[36] In a paediatric study (non-randomised, open label) weekly emicizumab prophylaxis reduced the ABR by 99% (95% CI 97·4–99·4) for those on prior prophylaxis with BPA, the ABR being 0·3 (95% CI 0·17–0·50) and 77% had no treated bleeding events. All eight children aged <2 years received weekly prophylaxis. When the dosing interval was increased to fortnightly (3 mg/kg) or 4-weekly (6 mg/kg) the ABR was 0·2 (95% CI 0·03–1·72) and 2·2 (95% CI 0·69–6·81), respectively.[37]

SHA without inhibitors

In a randomised open label study in PWSHA aged >12 years, without inhibitors, weekly and bi-weekly emicizumab reduced the ABR to 1·5 (95% CI 0·9–2·5), 1·3 (0·8–2·3), respectively, compared to 38·2 (22·9–63·8) when treated OD.[38] This supports the role of emicizumab for prophylaxis in PWSHA over the age of 12 years. The limited data in children with SHA and an inhibitor suggest that emicizumab will be efficacious in non-inhibitor children.[37] Caution is advised in this age group, who may be significantly more active than the older cohort and the paediatric group with inhibitors, any increase in bleed frequency will adversely impact on joint health and quality of life. There are even more limited data on the safety and efficacy of emicizumab in children aged <2 years.[39]

Emicizumab is not licensed for use in MHA in the UK and, should not be substituted for FVIII prophylaxis outside of clinical trials. Emicizumab is licensed for MHA in some countries and for those with an inhibitor. There is no RCT comparing emicizumab with optimised FVIII prophylaxis, which is an important gap in the evidence base.

Adverse effects associated with emicizumab

From trial and emerging 'real world' data there have been reports of thrombotic events associated with emicizumab use. The UKHCDO requires that adverse events potentially associated with any treatment for haemophilia are submitted to the UK National Haemophilia Database. The Medical and Scientific Advisory Council (MASAC) has encouraged ongoing, prospective collection of data on emicizumab use in the USA patient population. Adverse events include:

Thrombosis

There have been several reports, including thrombotic microangiopathy and venous thrombosis, when activated prothrombin complex concentrate is co-administered at a dose >100 u/kg for >1 day with emicizumab.[35] Other reports are emerging and have been summarised.[40] It is important to recognise that all PWH with risk factors for thrombosis were excluded from clinical trials. There is one report of non-ST-elevation myocardial infarction and pulmonary embolism associated with co-administration of rFVIIa.[41] No thrombotic events have been reported in association with FVIII replacement, although the numbers treated to date are low and data in young children are very limited.[42,43]

Recurrence of inhibitors in people previously tolerized to FVIII

One patient in the HAVEN 3 trial was reported to have developed a persistent low titre inhibitor. This person had a past history of an inhibitor and had previously undergone immune tolerance.[38] The risk of inhibitor recurrence after stopping FVIII in apparently tolerant people is unknown but this possibility should be discussed, and inhibitor surveillance maintained. Some clinicians prefer to continue low-frequency FVIII exposure after switching to emicizumab, although there is no evidence to support this approach.

The UKHCDO has produced guidance on the use of emicizumab and management of bleeding episodes and invasive procedures.[44]

Recommendation

- **Emicizumab may be offered to a PWSHA aged >2 years without an inhibitor as an alternative to prophylaxis with FVIII**
- **Due to the limited data available for children aged <2 years, both for SHA with and without inhibitors, caution is advised when considering emicizumab in this age-group**
- **Counselling should be provided before changing treatment and consideration given to individual lifestyle, particularly with regard to high impact activity.**
- **In PWSHA and a past history of an inhibitor consideration should be given to continuing intermittent exposure to FVIII to maintain tolerance.**
- **National Guidance should be followed in the prescribing and monitoring of PWSHA using emicizumab prophylaxis and all adverse events should be reported to a national registry.**

How to start prophylaxis in children

There are different approaches to commencing prophylaxis in young children. It may be started at the standard full dose, that is, 20–40 u/kg on alternate days and tailored to prevent bleeding. Alternatively, it may be introduced at a reduced frequency, building up to the full dose as soon as possible or based on bleeding phenotype. The latter approach may avoid the need for a CVAD, but there is likely to be suboptimal protection against bleeding, which could have consequences in terms of long-term joint health.[45] Indeed, allowing joint bleeds to occur whilst using an incremental approach to primary prophylaxis, permitting up to two bleeds per joint in a 3-month period before intensification, has been shown to result in osteochondral changes on MRI at a median age of 8·8 years, demonstrating inadequate protection against joint damage.[6]

The multidisciplinary team (MDT) should support the introduction of prophylaxis in a CWH. Play therapy can be used to prepare, teach and distract the child, reducing difficulties around venous access.[46] Psychologists should support the families to address emotional and behavioural issues and anxieties, which might affect both delivery of prophylaxis and the family's quality of life.[47] Whether prophylaxis is administered through peripheral or central veins is dependent on the ease of venous access, the child and family. However, before inserting a CVAD, the risk of infection and thrombosis should be weighed against the relative ease of venous access.[48] Younger age and use of external CVAD are associated with higher rates of infections.[49]

Recommendations

- **Prophylaxis that is commenced at a reduced frequency should be escalated to full prophylaxis as soon as possible and immediately in the presence of any breakthrough haemarthrosis. Grade 1C**
- **When introducing a child to prophylaxis the psychosocial needs and social circumstances of the child and his family/carers should be addressed and supported by the haemophilia MDT. Grade 2C**
- **The route of administration should be agreed with the parent/guardian, according to ease of venous access, the child's compliance, technical abilities and social circumstances. Grade 2C**

Choosing the most appropriate regimen for prophylaxis - pharmacokinetics

The prophylactic regimen required to prevent bleeding varies between individuals according to differences in clinical and lifestyle characteristics.[50]

Prophylaxis assumes that an adequate plasma level of exogenous coagulation factor will protect the patient from bleeding.[8,51] The longer a person with SH spends with a factor level <1 iu/dl the more likely he is to bleed.[51] However, it is likely that the peak level is also of importance,[52] particularly for those participating in regular sporting activity.

Pharmacokinetic (PK) analysis of FVIII and FIX can be performed and used to help tailor an individual's regimen.[53] Previous standards set by the ISTH, for use in licensing studies, required multiple venepunctures at predefined times[54], as well as a washout period, which increases the likelihood of bleeding. As the PK of both FVIII and FIX change with increasing age, repeated analysis would be required in children.[55]

Subsequently, a population PK (Pop PK) model was built for rFVIII in those aged 1–65 years[56] and rFIX in those aged 0–69 years.[57] The Pop PK requires a few samples to be taken from many subjects. The PK model is then fitted to all data from all patients simultaneously, taking into consideration variations in patient characteristics such as age, bodyweight and inter-individual variability. This model is recommended for all age groups, reducing both the number of venepunctures and the laboratory costs of processing and assaying samples.[58]

Pop PK models have been developed for rFVIII[59-61] and for both rFIX and PD FIX, which have different PKs.[62,63] The PK of FVIII are affected by age, weight, von Willebrand factor level and blood group.[64-66] For FIX, weight and age are significant inter-individual variables for PK.[67] However, PK cannot be predicted from an individual's phenotypic characteristics alone.[64]

The ISTH has developed guidance for PK testing and interpretation.[58] Pop PK software has been developed (WAPPS-Hemo, www.wapps-hemo.org, my PKFit, www1.mypkfit.com) and can calculate an individual's product-specific PK. Graphs of factor level over time can be shared with the patient, facilitating shared decision-making and personalisation of prophylaxis.[68] For example, for highly active children, lower dose, daily prophylaxis may be preferable, whereas those with a more sedentary lifestyle may achieve efficacy with a less intense prophylactic regimen, targeting a minimum trough level. Peak levels can be tailored to coincide with times of intensive physical activity. Shared decision-making, using PK analyses, improves adherence and is a cost-effective way to deliver prophylaxis.[69]

As PK analysis is product-specific, it is recommended that pop PK analysis should be repeated when switching to an alternative product. The observed PK profile of an individual is also specific to the algorithm used; a recent review from the OPTI-CLOT group noted that different PK software analysis of the same data results in different PK outcomes.[70] PK assessment will be increasingly important in order to better understand the PK profile of EHL products, and to use them optimally.[71] The evidence for how frequently analyses should be repeated in children is not available, but a pragmatic approach would be to repeat analysis every 2–3 years or when there is a significant change in body weight.

Recommendations

- **Prophylaxis should aim to prevent all bleeds, especially in young children. Grade 2C**
- **The prophylaxis regimen should not be based on target peak and trough levels but should be tailored to prevent bleeding for an individual within his usual daily activity schedule. A trough of >1 iu/dl or even >3 iu/dl may be required in many cases to achieve this. Grade 2C**
- **The prophylaxis regimen should be individualised, determined jointly with the patient and based on PK data, patient activity and patient preferences. Grade 2C**
- **For small children, doses should be rounded up to the nearest vial size that prevents bleeding. Grade 2C**
- **A PK analysis using sparse sampling and a validated Pop PK software should be offered to patients when choosing a prophylaxis regimen. Grade 1C**
- **PK analysis should be repeated, if indicated by the software program used, when changing products, or, in children, with a significant change in weight. Grade 1C**

How long should prophylactic factor replacement continue?

Prophylaxis throughout childhood should result in the individual having normal musculoskeletal function and the goal of haemophilia care in adults should be to maintain that function by preventing bleeding. In a single-centre cohort study, where the joint outcomes of adults who discontinued prophylaxis were compared with those who continued, those who discontinued prophylaxis had a worse objective joint assessment score after 10 years.[72] There is no benefit to a PWH to stopping prophylaxis in adulthood and standard of care should be to continue life-long, unless the PWH chooses to stop.

The most cost-effective regimen required to prevent significant bleeds is unclear. The half-life of FVIII increases with age and there is marked inter-individual variation suggesting increased intervals between doses might be possible in some.[73] Repeated estimation of PK in an ageing individual should be considered, especially if he is bleed-free on his existing prophylaxis.

Recommendations

- **Life-long prophylaxis should be the standard of care and should be encouraged. Grade 1C**
- **If an adult discontinues prophylaxis, then it should be recommenced in the event of a spontaneous haemarthrosis or any bleeding that interferes with education or employment or quality of life. Grade 2C**

Monitoring the effectiveness of factor replacement therapy in the laboratory

The aim of laboratory monitoring is twofold: to look for inhibitor development as per published guidelines[74] and to facilitate determination of the ideal prophylactic regimen. The introduction of multiple new rFVIII and rFIX concentrates, as well as emicizumab, has increased the complexity of performing and interpreting factor assays.[27] Factor levels should be carried out in an accredited laboratory, in line with relevant national guidance.[75]

Recommendations

- **Surveillance for inhibitor formation should be undertaken in PWH to facilitate early detection and the appropriate management of bleeds**
- **An appropriate assay should be used to measure FVIII or FIX, according to the manufacturer's instructions, by a laboratory that is accredited by a regulatory authority. Grade 1C**

Assessment of clinical efficacy of a prophylaxis regimen

Bleeding rates

The goal of prophylaxis is for an individual to have no bleeds. For children who have commenced primary prophylaxis, achieving an ABR of zero is possible but requires a high level of commitment from a specialist MDT.[76] However, in those with established arthropathy assessment of bleeding is difficult for both patient and physician, and achieving zero bleed rates may be challenging.[4,77]

Reported bleeding episodes whilst on prophylaxis should be reviewed promptly by the MDT in order to review the prophylactic regimen and address musculoskeletal factors and psycho-social factors.

Bleeds should also prompt a review of adherence to the agreed prophylaxis regimen, using an on-line reporting tool, such as Haemtrack in the UK (https://apps.mdsas.nhs.uk/haemtrack). Barriers to compliance should be identified, as a greater level of adherence results in better outcomes.[78] The Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) tool allows assessment of adherence/concordance.[79]

Impact of haemophilia and treatment on daily life

The impact of haemophilia and prophylaxis on daily life can be assessed by direct questioning, for example, ability to perform hobbies and participate in sports, by recording key metrics such as days of work or education lost, and by the use of specially-designed questionnaires that assess quality of

life [A36 Hemofilia-QoL[80] and Children Haemophilia Outcome - Kids Assessment Tool (CHO-KLAT)][81,82] and activity.[83,84] There is interest in the use of accelerometry, a technique for quantifying movement patterns during walking, to assess activity.[85] Identifying and treating depression may influence adherence and improve outcomes.[86]

Musculoskeletal health

The role of the specialist haemophilia physiotherapist is to minimise the likelihood of bleeds by maximising strength and biomechanics through exercise, advice and prehabilitation. However, as children can develop arthropathy with no history of clinically overt joint bleeding[87,88], regular assessment of joint function is essential and can be done using targeted questioning (see above), physical examination and imaging.

Physical examination

Systematic musculoskeletal examination can reveal changes in gait, joints and muscles/ligaments/tendons due to arthropathy or maladaptive changes due to previous bleeds. This can inform rehabilitative regimens to improve joint function, reducing the likelihood of further bleeds and may also signal the need for an alteration in prophylaxis. This examination should be carried out by a physiotherapist skilled in musculoskeletal examination and with a good understanding of developmental norms.

Scoring

In order to encourage systematic assessment, provide a common language, monitor development of arthropathy and allow population comparisons, efforts have been made to apply scoring systems to physical examination.[89-91]

The HJHS can distinguish between children with severe and non-severe haemophilia[91] and between young adults on different intensities of prophylactic regimens.[92] It is more sensitive than the Gilbert score.[91] Early data suggest that an undifferentiated (i.e. not specific to a single joint) abnormal score may not be predictive of future joint problems[93] and the HJHS is not infrequently abnormal in the non-haemophilia population.[94] A deterioration in an individual's joint score should prompt a review of bleeding and the prophylaxis regimen.

Joint imaging

Joint imaging, initially plain radiography and latterly MRI, has been used as a means of documenting haemophilic arthropathy for several decades[95-97] and this has provoked interest in the use of imaging to monitor for early signs of arthropathy in patients receiving prophylaxis.[98] MRI has demonstrated utility in study populations, where joint imaging is used to compare the effectiveness of different treatment approaches.[99] Plain radiography, while cheap and relatively quick, is insensitive to early arthropathy[100] and current interest is focussed on MRI and ultrasonography (USS).

MRI

MRI scoring has been validated in haemophilic arthropathy, it has good intra- and inter-reader reproducibility[101], and correlates with physical examination,[98] bleeding history[98,102] and the Pettersson and Arnold–Hilgartner scoring for plain radiographs.[102,103] MRI scoring is more sensitive to early arthropathic lesions than clinical or X-ray scores[104], but is time-consuming and expensive. There are no longitudinal data showing the predictive value of early MRI changes or how MRI might aid the clinician in monitoring prophylaxis. In addition, young children may require general anaesthesia in order to acquire the imaging.

Ultrasonography

As well as helping to establish the diagnosis of acute haemarthrosis,[105] ultrasonography can detect joint effusions, synovial hypertrophy and osteochondral changes of developing arthropathy.[106] It can be delivered cheaply and simply in the clinic using a limited scanning protocol and has good inter-user consistency[107], but at present the clinical relevance of early ultrasound changes has not been established.

Recommendations

- **The nature and frequency of breakthrough bleeding should be carefully documented and monitored. Any suspected bleeds on a prophylactic regimen should prompt a clinical review. Grade 2C**
- **Adherence to prescribed prophylaxis should be recorded contemporaneously, with systems in place for the clinical team to be alerted to changes in bleeding frequency. Grade 2C**
- **The acceptability of a prophylactic regimen should be discussed with the individual, considering the impact of both haemophilia and prophylaxis on their quality of life, performance of daily activities and physical activity levels. Grade 2C**
- **PWH receiving prophylaxis should undergo annual, detailed musculoskeletal assessment by an appropriately trained physiotherapist using a validated objective scoring system. Grade 2C**
- **Radiological imaging should not be used to assess efficacy of prophylaxis: plain radiographs are insufficiently sensitive and neither MRI nor ultrasonography changes have yet been shown to be predictive of long-term joint function. Grade 2C**

Health promotion

PWH should be encouraged to engage in health promotion opportunities and to participate in screening programmes designed to identify early stage cancers. Clinical review at a haemophilia centre provides further opportunity for health promotion: smoking cessation; alcohol consumption; healthy diet; exercise; blood pressure control and bone health, which may influence prophylaxis through:-

Optimisation of bone and joint health

An increased body mass index has been shown to contribute to reduction in range of movement of joints.[108] Conversely, improvements in balance, joint health and pain are associated with regular exercise.[109] PWH are more likely to have low bone mineral density (BMD), likely due to haemophilic arthropathy resulting in reduced physical activity, and exacerbated by hepatitis C virus or human immunodeficiency virus seropositivity.[110] In a series of 49 PWMH and PWSH two-thirds of the patients aged >50 years had osteoporosis[110] and BMD showed significant correlation with the HJHS. PWH receiving anti-retroviral medication should be regularly screened for osteoporosis and tools are available such as FRAX (https://www.sheffield.ac.uk/FRAX/tool.aspx). In a study of PWH, whilst 78% had 25-hydroxyvitamin D concentration of <50 nmol/l, this was not correlated with BMD.[110] Indeed, systematic review and meta-analysis has shown no benefit of routine vitamin D supplementation[111] and vitamin D should only be used in conjunction with a validated risk assessment tool for osteoporosis or radiological evidence of osteoporosis.

Prevention and detection of co-morbidities that influence prophylaxis risk/benefit

PWH are at increased risk of hypertension[112] and intracerebral haemorrhage, and are at similar risk to the general population for atherosclerosis, ischaemic heart disease and atrial fibrillation.[113,114] The use of anti-platelet and anti-coagulant drugs increases the risk of bleeding in PWH.[115] Clinic reviews should incorporate screening to allow the early identification and treatment of these conditions, allowing provision of lifestyle advice to reduce risk, for example, smoking cessation.

Recommendation

- **Review of patient's general condition should include health promotion. Grade 2C**

Future directions

There are several new treatments for haemophilia on the horizon, which have not yet been studied in enough detail for this guideline to give any specific recommendations. Gene therapy studies in both HA and HB are moving into phase 3 clinical trials, as earlier studies have achieved sustainable levels of both FVIII and FIX that either normalise levels[116] or achieve sufficiently good levels that prophylaxis is no longer required.[117,118] In addition, several non-factor therapies are emerging.[119]

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Declaration of Interests

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All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. The following authors have undertaken advisory board, educational grant and speaker's fees: Susie Shapiro for Pfizer, Shire, Sobi, Bayer, Chugai/Roche, Novo Nordisk and Octapharma; Tina Biss for Bayer, Leo Pharma and Boehringer Ingelheim. Rachel Rayment, Elizabeth Chalmers, Katherine Forsyth, Richard Gooding, Anne M. Kelly, Kate Talks and Oliver Tunstall have no conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Literature review details.

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