Haemophilia Prophylaxis UHL Haematology Guideline	University Hospitals of Leicester NHS NHS Trust Trust Reference Number:C10/2020

1. Introduction and Who Guideline applies to

This guideline is for staff managing people with haemophilia A and B who require prophylactic clotting factor concentrate (CFC) to prevent spontaneous bleeding problems.

2. Guideline Standards and Procedures

Introduction and background

Coagulation factor replacement in patients with haemophilia A or B maybe given in response to a bleed (on-demand therapy) or given regularly to prevent such bleeds (prophylactic therapy).

The goal of prophylactic treatment is to prevent bleeding, primarily into the joints, with subsequent development of arthropathy. Importantly, prophylactic treatment will also offer protection from other serious bleeds such as intracranial bleeds, muscle bleeds and intra-abdominal bleeds. Prophylaxis may be given as primary or secondary, or as episodic. High level evidence-based studies of prophylaxis in boys with haemophilia A have been published and there is now a widespread recognition of the efficacy of the early implementation of prophylaxis in the prevention of arthropathy in children and young adults (Manco-Johnson et al, 2007; Gringeri et al, 2009). There is less evidence for prophylaxis in haemophilia B, but consensus among haemophilia treaters is that children with severe haemophilia B should be treated similarly (with important considerations for initiation of prophylaxis. Primary prophylaxis is started prior to initiation of joint disease usually well before the age of 2 or after the first joint bleed. The rationale behind an early start is that even a small number of joint bleeds can result in irreversible damage, and that damage may progress despite prophylactic therapy. It has also been shown that the time point at which prophylaxis is begun is an independent factor for good joint outcome.

Choice of factor concentrate.

Current practice in the UK is to treat all previously untreated patients (PUPs) with a recombinant factor concentrate. Recent evidence from the SIPPET study comparing inhibitor rates between PUPs treated with recombinant vs plasma derived concentrates may be discussed with parents/carers depending on the clinical context. A decision should be made regarding the product to be used in advance of the child requiring any treatment with recombinant factor VIII. This should be discussed with the child's parents and documented in the notes and on the HCIS (Haemophilia Centre Information System) front sheet.

Initiation of prophylaxis

Prophylaxis should be commenced at the latest after the 1st joint bleed or significant soft tissue bleed. The decision of when to start prophylaxis for a child over the age of one who has not experienced any bleeds should be made on an individual basis. Indications to start prophylaxis prior to the second joint bleed/significant soft tissue bleed include:

- Following treatment for an intracranial haemorrhage
- Following an early intensive treatment episode, e.g. treatment to cover a surgical procedure
- If a child is requiring frequent on-demand treatment for injuries such as minor soft tissue injuries and minor head injuries

Severe haemophilia A

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In most circumstances prophylaxis should be commenced at a dose of 25-50 iu/kg factor VIII every other day or 3 times per week (round up to the nearest whole vial size). This may be administered via a peripheral vein or a central venous access device. Both options should be discussed with and offered to parents/carers. If circumstances dictate otherwise, such as the child needing to attend the haemophilia unit for prophylaxis, a 3 times per week regimen can be used. If prophylaxis is commenced following treatment of an intracranial haemorrhage or an intensive treatment episode, it should be initiated at a dose of 50 iu/kg (round up to the nearest whole vial size) administered at least every 48 hours (dosing should then be guided by trough levels and/or PK measurement)

Severe haemophilia B

There is a lack of evidence to guide the initiation of prophylaxis in children with severe haemophilia B. It is reasonable to initiate prophylaxis with recombinant factor IX 50 iu/kg once weekly for most patients (an exception would be if prophylaxis was commenced after treatment of an intracranial haemorrhage) and escalate to twice weekly administration of factor concentrate at a dose of 25-50 iu/kg. As for children with severe haemophilia A, the prophylaxis dose should be rounded up to the nearest whole vial size. As with haemophilia A, a CVAD should be considered and discussed.

NOTE: Factor IX inhibitors are associated with allergic/anaphylactic reactions to recombinant factor IX. The 1st 20 doses of recombinant factor IX should be given in a clinical area where paediatric resuscitation facilities are available. If any allergic reaction occurs, an inhibitor should be excluded prior to further factor IX exposure. Monitoring of children on prophylaxis

Monitoring for inhibitors

An important consideration when using factor concentrates is the development of inhibitors. This is particularly relevant for prophylaxis in haemophilia A, but important in mild and moderate haemophilia A if/when CFCs are used.

For further details on inhibitor screening and management, see Inhibitors to FVIII and FIX guideline.

Monitoring for efficacy

A combination of clinical and laboratory monitoring is required for children on prophylaxis:

- All parents/carers/children on prophylaxis will record their treatment using the online system Haemtrack. This will record all prophylactic treatment and also document bleeding episodes and response to treatment. Haemtrack records will be reviewed at each routine clinic visit and in the haemophilia MDT. If bleeds are occurring, the haemophilia team will be alerted by the online system allowing the opportunity to review treatment outside of usual clinic visits.
- All patients with severe haemophilia should have their own personalised treatment plan documenting their current prophylactic regime as well as dose recommendations for any breakthrough bleeding episodes. A copy of this plan will be available in the patient's hospital record and given to the patient/parent/carer. The plan should be updated at each routine clinic visit.
- All patients receiving prophylaxis over the age of 4 years will have a Haemophilia Joint Health Score recorded at least once a year. Younger children should have a clinical assessment by an experienced haemophilia physiotherapist recorded at each routine clinic visit.
- Trough factor levels should be measured at routine clinic visits (at least 6 monthly). A target of trough factor level > 1% has historically been used. This may not be sufficient to prevent bleeding in all patients depending on phenotype and level of physical activity. In addition, some patients with trough levels <1% may not experience breakthrough bleeds. Prophylaxis should be personalised to each individual depending on various factors such

as activity levels, bleeding phenotype, venous access etc. The use of population PK modelling where available (currently only MyPKFit for patients on Advate) is increasingly being used to tailor prophylaxis and should be used when possible.

- Prophylaxis should be tailored to provide maximum protection for physical activity and schooling. In most cases treatment should be administered in the morning to optimise factor levels for maximum benefit.

Home treatment

Adherence to a prescribed regimen of prophylaxis is essential to ensure the full benefits of prophylaxis are realised. Much of the burden of prophylaxis administration in children is unseen as it is undertaken by parents and then by the child when he is able to be taught self-administration. This is a significant commitment for any lay person.

Successful prophylaxis involves several key components:

- Competent venous access techniques
- Ensuring an available supply of clotting factor concentrate and other disposable equipment
- Knowledge of appropriate storage and safe disposal of used items
- Detailed data collection
- Sensitivity to deal with psychological and emotional distress in the child
- Knowledge of symptoms of specific spontaneous and traumatic bleeds and their necessary treatment
- Knowledge of how and when to seek professional advice from haemophilia specialists.

All children will be offered home treatment and parents/carers will be provided with appropriate training delivered by a haemophilia nurse specialist in order to achieve this. All patients on prophylaxis will be offered home delivery of their factor concentrate once compliance with the online Haemtrack system has been demonstrated. The home delivery company will provide services for delivery of factor product and any peripheral products required as well as removal and disposal of used items.

Parents/carers and later patients will be provided with appropriate education of how to recognise and treat bleeding episodes. Information will be provided (verbal, written and online) of how to contact the centre 24 hours a day for advice. Each patient will have a copy of their own personalised treatment plan for easy reference. Relevant support for emotional or psychological difficulties associated with prophylaxis will be offered to the child and their parents/carers eg play specialists, clinical psychology. An experienced haemophilia physiotherapist is available to advise on appropriate physical activities for children of all ages. The importance of avoidance of head injury from contact sports and activities will be emphasised in an ongoing and age appropriate fashion.

3.Education and Training

Training is in line with expected continuing professional development whilst working in this area.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements

Use of CVDs	Rate	MDT lead	annual	MDT minutes
Inhibitor development	Rate	MDT lead	annual	MDT minutes
Bleed rates (spontaneous) and joint scores	Rate	MDT lead	annual	MDT minutes

5. Supporting References

1. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson, ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew

P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H & Evatt BL. (2007) Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. New England Journal of Medicine, 357, 535–544.

2. Gringeri A, Lundin B, von Mackensen S, Mantovani LG & Mannucci PM. (2009) Primary and secondary prophylaxis in children with haemophilia A reduces bleeding frequency and arthropathy development compared to on-demand treatment: a 10-year, randomized, clinical trial. Journal of Thrombosis and Haemostasis, 7(Suppl. 2), 114–115 (Abstract OC-MO-034).

3. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V, Hanley J. (2010) A United Kingdom Haemophilia Doctors' Organization Guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. British Journal of Haematology, 149, 498-507.

4. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. (1992) Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med, 232, 25–32.

5. Fischer K, Van De Bom JG, Molho P et al. (2002) Prophylactic versus on-demand treatment strategies was in for severe haemophilia: a comparison of costs and long-term outcome. Haemophilia, 8, 745–52.

6. Collins P, Chalmers E, Hart D, Liesner R, Rangarajan S, Talks K, Williams M, Hay C. (2013) Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia. British Journal of Haematology, 160, 153-170.

6. Key Words

List of words, phrases that may be used by staff searching for the Guidelines on PAGL. If none – state none.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr Richard Gooding	**Executive Lead**
Details of Changes made during review:	