Guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A

A UKHCDO Guideline approved by the British Committee for Standards in Haematology

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Date for guideline review  September 2014

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SUMMARY
Evidence-based guidelines are presented on the role of prophylactic administration of factor VIII concentrate in children and adults with severe haemophilia A. The timing of initiation of prophylaxis, the choice of prophylactic regimen, monitoring, management of breakthrough bleeding and education of the patient and family are discussed.

Keywords: haemophilia A, factor VIII, prophylaxis, child, adult

INTRODUCTION
Coagulation factor replacement in patients with haemophilia A or B may be given in response to a bleed (on-demand therapy) or given regularly to prevent such bleeds (prophylactic therapy). Guidelines for prophylactic treatment of children with haemophilia A or B were last produced by the UKHCDO in 1994 and were mostly based on the prophylactic regimens used successfully in Sweden since the 1960s. In the last 15 years, significant information has been derived from international studies which have resulted in changes in the practice of prophylaxis. High level evidence based studies of prophylaxis in boys have been published recently 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. The role of prophylaxis in adults is evolving, but prophylaxis will be of benefit in many individuals.

These guidelines address the optimum use of prophylaxis in children and adults with haemophilia A and give evidence based recommendations where appropriate. Similar recommendations for patients with haemophilia B are not provided given the paucity of published evidence. The guidance will be of value to physicians, nurses, laboratory scientists and patients and those with a responsibility for funding services.

METHODOLOGY
The information contained in this review was gathered from an appropriate literature search. The writing group produced the draft guideline which was subsequently revised by consensus by members of the UKHCDO Advisory Board. It was reviewed by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH) and the sounding board of the British Society of Haematology, comments being incorporated where appropriate. Grading of evidence was assigned according to the recommendations of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group (Atkins et al, 2004).
INTRODUCTION.

The aim of prophylactic administration of factor VIII to patients with haemophilia A is to reduce their number of bleeds. Compared with on demand treatment, prophylaxis results in a reduction in the frequency of haemarthroses which has been demonstrated to protect joints from the development and progression of arthropathy. This may in part reflect a reduction in the incidence of sub-clinical joint bleeds. A protective effect of prophylaxis in reducing the frequency of intracranial haemorrhage in patients over the age of 2 years with severe haemophilia and no inhibitor has also recently been demonstrated (Witmer et al. 2008). The practice of prophylaxis can be considered in four phases:

- the initial introduction of prophylaxis to a child during the first three years of life,
- the establishment of a regular pattern of factor administration in an older child,
- the modification of prophylaxis to compensate for enhanced physical activity in the teenage years and
- the potential for modification to reduced intensity prophylaxis in adults.

EVIDENCE FOR PROPHYLAXIS REGIMENS IN CHILDREN WITH SEVERE HAEMOPHILIA A


Manco-Johnson et al reported a study in which sixty-five boys with haemophilia were randomly assigned to prophylaxis (32 boys) or enhanced on-demand therapy (33 boys) (Manco-Johnson et al, 2007). Eligibility criteria included an age of less than 30 months, a factor VIII activity level of <2 iu/dl, a history of <2 haemorrhages into each index joint and normal baseline joint imaging. The mean age at enrolment in both groups was 1.6 years. A previous haemarthrosis had been sustained in 56% of the prophylaxis group and 39% of the on-demand
group. The factor VIII dose in the prophylactic regimen was 25 iu/kg body weight on alternate days; the enhanced on-demand infusion schedule consisted of at least three doses totalling a minimum of 80 iu/kg of factor VIII at the time of a joint haemorrhage. When assessed at the age of 6 years, of the 32 patients in the prophylaxis group, one (4%) had evidence of joint damage by plain radiography and 2 (7%) by Magnetic Resonance Imaging (MRI) in contrast to 5 (19%) and 13 (45%) in the on-demand group (p=0.006). The relative risk of MRI-detected joint damage with on-demand therapy as compared with prophylaxis was 6.1 (95% confidence interval, 1.5 to 24.4). The mean annual numbers of joint bleeds and total haemorrhages were higher at study exit in the on-demand group than in the prophylaxis group (p<0.001 for both comparisons). The annual use of factor VIII in the prophylaxis group was 6000 iu/kg in contrast to approximately 2500 iu/kg in the on-demand group.

There was only a weak correlation between the numbers of haemarthroses with MRI scores; joint abnormalities were not apparent on physical examination. The history of previous haemarthroses in some patients at trial entry implies that some joint damage may have existed at this time point; this may have contributed to the MRI appearances seen at completion of the study. However, the evidence of joint disease by MRI assessment at completion of the study was lower in the prophylaxis group despite a higher incidence of previous joint bleeds at study entry. The authors proposed that chronic micro-haemorrhage into the joints or subchondral bone in young boys with haemophilia may cause deterioration of joints without clinical evidence of haemarthroses and that prophylaxis prevents this subclinical process (Manco-Johnson et al, 2007).

Preliminary data from the Italian ESPRIT (Evaluation Study on Prophylaxis: a Randomized Italian Trial) have been published in abstract form (Gringeri et al, 2009). Forty children with severe haemophilia A (FVIII <1 iu/dl), aged < 7 years (median 2 years), with negative clinical-radiological joint scores at entry and at least 1 bleed during the previous 6 months were randomized to receive prophylactic factor VIII 25 iu/kg body weight 3 times a week or on-demand treatment with 25 iu/kg body weight daily until complete resolution of the bleed. Ten of 21 children on prophylaxis required indwelling catheters compared to none of 19 children receiving on-demand treatment. Children on prophylactic treatment showed a significantly lower total number of breakthrough bleeds compared to children treated on-demand (0.52 vs.1.08 bleeds/patient/month respectively, p < 0.05) and fewer joint bleeds/month (0.20 vs.0.52, p < 0.02). Radiological evaluation showed signs of haemophilic arthropathy in 6 patients on prophylaxis (29%) (median Pettersson score 5; range: 3–14) and in 14 on-demand patients (74%) (median score 8; range: 2–12) (p < 0.05). Prophylaxis was more effective when started at younger ages (≤ 36 months).

The higher factor VIII consumption associated with prophylaxis would suggest that this option will be more expensive than using on-demand therapy. However, studies of young adult patients have indicated that the annual factor consumption in patients who are currently and have always been treated on-demand is no
different from the consumption in those on long term intermediate dose prophylaxis, although the on-demand cohort was noted to have more severe arthropathy (Fischer, 2003). Patients with demonstrable joint damage may need increasing coagulation factor support as arthropathy deteriorates and the need for joint replacement emerges. In contrast, patients who have received prophylaxis who have better preserved joints may have a more stable factor requirement and improved school and work attendance. This suggests that in the long term prophylaxis may be clinically and economically more attractive than on-demand treatment.

A recently published multinational cohort study, the CANAL study, has suggested that prophylaxis introduced at a median number of exposure days of 16 (inter-quartile range 8-28 days) was associated with a 60% reduction in the risk of inhibitor development compared to on-demand therapy (Gouw et al 2007). This has not yet been substantiated by further adequately powered studies.

**RECOMMENDATION**

It is recommended that children with severe haemophilia receive prophylactic infusions of factor VIII with the aim of preventing haemarthroses and other bleeding episodes. (Grade of evidence: High).

**PROPHYLACTIC REGIMENS IN CHILDREN.**

Recent studies have provided additional data about factor VIII pharmacokinetics in younger children and the role of trough factor VIII levels in the prevention of bleeds; these data have implications for the practice of prophylaxis. It has been established that there is significant variability of factor VIII pharmacokinetics in children. One study has demonstrated that the half life of a recombinant factor VIII concentrate varied from 6.8-15.4 hours in a group of children between 1 and 6 years and increasing age was associated with increasing half-life (Blanchette et al, 2008). A recent study has suggested that the number of soft tissue bleeds and haemarthroses which occur in children on prophylaxis is related to the period of time spent with plasma factor VIII concentrations <1 iu/dl. Although in this study a lack of adherence to prophylaxis was an important contributor to low plasma factor VIII levels, the rate of bleeding in children aged 1-6 years was also influenced by factor VIII half-life and clearance (Collins et al, 2009). This study provides confirmation that, for patients on prophylaxis, increasing time with a low factor VIII increases the risk of bleeding but does not necessarily imply that all patients should have their factor VIII level maintained above 1 iu/dl.

In patients who are phenotypically severe, it is unclear how many joint bleeds are needed to cause arthropathy and this may be subject to inter-individual variation. Although it is theoretically attractive to introduce prophylaxis at an early age before the first joint bleed, this may present practical difficulties; the technical challenge posed by the intravenous administration of coagulation products in
young children may necessitate the insertion of a permanent indwelling intravenous catheter. It has also been recognised that individuals with severe haemophilia may exhibit clinical phenotypes of varying severity. This has been reflected in the variable age at which patients with severe haemophilia suffer their first bleed and the variable time period which may elapse before they experience their second bleed. These observations have prompted the concept of individualised therapy, whereby patients with a mild clinical phenotype may be able to start prophylaxis at a later age and receive concentrate at less frequent intervals, using less concentrate to achieve a bleed-free existence (Astermark et al, 1999, Astermark, 2003, Petrini, 2001).

Although the principle of prophylaxis in severe haemophilia is widely accepted, the details of concentrate administration in prophylactic regimens vary internationally. There have been no prospective randomised studies comparing the efficacy of different regimens. Retrospective cohort studies exist that have compared the outcomes of children within a single country treated during successive time periods, whilst other comparisons have been made between the outcomes of similar patients in different countries. The two principal models of prophylaxis that have been used are (i) administration of factor concentrate with combined clinical and pharmacokinetic monitoring to prevent bleeds (Swedish model) and (ii) factor concentrate dose based on clinical end points (Dutch model).

i) The practice of prophylaxis in Sweden has been to initiate factor administration when the patient is 1-2 years of age, to administer treatment either on alternate days or a minimum of three times a week, at a dose sufficient to prevent bleeding. This group reported a trend in improving orthopaedic and radiological joint scores over a twenty year review period (Lofqvist et al, 1997). The last two cohorts of nine and six patients (each of which included one patient with haemophilia B) started treatment at the age (range) 1.3 years (1-2) and 1.2 years (1-1.5) respectively; annual consumption of factor VIII/IX concentrate / kg body weight (range) was 5741 iu (4730 to 7817) for the older of the two groups and 6354 iu (5305 to 8915) for the younger group. These patients had no evidence of joint damage as assessed by clinical examination or plain radiology at the age of 7-10 years. No benefit from the increased factor consumption in the youngest cohort has been demonstrated within the current follow up period.

ii) The experience in the Netherlands has also been reported (van den Berg et al, 2001). The time period during which treatment was started in the most recent Dutch cohort overlaps that relevant to the most recent Swedish cohort. Prophylaxis was started after one or two joint bleeds or when more than two other bleeds per month required treatment. The mean age of starting treatment was 3.9 years in the 27 patients. The mean (standard error) clinical orthopaedic score when assessed at 7.9 (0.4) years was 0.2 (0.2) and the Pettersson radiological score 1.1 (0.4). The mean annual product consumption was 2900 iu/kg/year.
A comparison of the Swedish and Dutch experience indicated that patients receiving prophylaxis in Sweden had fewer joint bleeds over a period of 3 years and a slight reduction of arthropathy after 17 years of follow-up but with significantly higher treatment costs (Fischer et al, 2002).

A study of prophylaxis introduction is currently underway in Canada in which tailored increase in factor VIII dosing is dependent on breakthrough bleeding (Feldman et al, 2006). Concentrate administration is introduced at a dose of 50 iu/kg once weekly and is escalated through two steps to prophylaxis at a dose of 25 iu/kg factor VIII on alternate days. An interim analysis of an inception cohort with a median follow up period of 55 months indicated median clinical joint scores (range) of 0 out of 56 (0-15) for knees, 0 out of 52 (0-13) for elbows and 2 out of 56 (0-22) for ankles (Blanchette et al, 2009).

The descriptions of the various models of prophylaxis outline differences in the thresholds used for introduction of treatment, in the concentrate dose used and the manner in which prophylaxis is introduced. Outcome measures have varied; one study has used MRI and the remainder clinical assessment and plain radiology. Although there is evidence to suggest that MRI is a more sensitive tool to detect joint damage, its significance in predicting progressive arthropathy and functional impairment is unclear.

Pharmacokinetic modelling suggests that the maintenance of trough factor VIII levels above a desired level is achieved more effectively and at a lower cost using an alternate day regimen compared to three times a week (Collins et al 2008a).

**RECOMMENDATIONS**

1. Prophylaxis should be commenced by the second joint bleed or significant soft tissue bleed. (Grade of evidence: Low).
2. Prophylaxis may be introduced by initially administering factor concentrate once weekly but escalating treatment rapidly to more frequent administration as venous access permits in order to prevent the occurrence of any joint or soft tissue bleeds. (Grade of evidence: Low).
3. Prophylaxis should consist of a factor VIII concentrate dose (25-50 iu/kg) administered ideally every 48 hours unless circumstances dictate otherwise such as the need for attendance at the haemophilia centre for prophylaxis administration. If three times a week administration is used, the practice of giving a higher dose on the third day is not recommended. An additional dose should be considered in order to ensure that the maximum interval between doses does not exceed 48 hours. (Grade of evidence: Low).
4. The minimum dosage of factor concentrate which prevents breakthrough bleeds should be used. Daily injections can significantly reduce the amount of concentrate required to prevent bleeds and maintain trough
factor levels >1 iu/dl and should be considered in very active older boys or where breakthrough bleeds are occurring on a less frequent prophylactic regimen. (Grade of evidence: Low).

5. Prophylactic doses should be tailored to provide maximum cover for particular physical activities, e.g. school, physical education lessons, sport training sessions. Prophylaxis should be administered ideally in the morning to optimize factor VIII levels (Grade of evidence: Low).

6. Children and neonates with severe haemophilia who have had a spontaneous central nervous system bleed should continue long term prophylaxis following initial treatment of the bleeding episode. (Grade of evidence: Very low).

7. Insertion of an indwelling venous access device should be considered if venous access and/or adherence to treatment are difficult. (Grade of evidence: Low).

8. The prophylaxis dose should be rounded up to the nearest whole vial size. (Grade of evidence: Very low).

MONITORING OF PROPHYLAXIS

The use of a single mode of monitoring prophylaxis is inadequate; the combination of clinical, laboratory and radiological methods provides a more effective approach.

a) Clinical monitoring

Clinical monitoring is currently the single most informative mode for the evaluation of prophylaxis. It includes the regular physical assessment of the patient and the accurate evaluation of breakthrough bleeds, the latter including the number of breakthrough bleeds, the nature and cause of the bleeds, the number of days taken off school or work and days away from regular physical activities. In addition it is essential that the number and quantity of extra treatments given for breakthrough bleeds are recorded. As patients on prophylaxis are usually on home treatment programmes, the monitoring of adherence to the prophylaxis regimen and of the recognition, documentation and treatment of breakthrough bleeds are dependent on good quality treatment records being kept by the patients or their carers.

The regular clinical assessment of a patient receiving prophylaxis should include well-defined physical examination scores designed to identify not only progressive haemophilic arthropathy but the early detection and quantification of joint disease. Physical examination scales designed in the 1980s are now too insensitive for the detection of early signs of joint disease in children receiving regular prophylaxis and modifications to such scores have been introduced in the USA and Europe (Manco-Johnson et al 2004). A Haemophilia Joint Health Score has been proposed by an expert international group of treaters (International Prophylaxis Study Group, IPSG) which consolidates the American and European systems and has been shown to have high intra and inter-rater reliability (Hilliard
et al 2006). Prospective use of this system will be necessary to confirm its potential for detecting joint problems in children receiving long term prophylaxis.

b) Laboratory monitoring
Laboratory assessment of prophylaxis includes the assay of trough levels of factor VIII and the determination of factor half life. More detailed pharmacokinetic studies are difficult to perform in children given the frequency of blood sampling required with standard methods. Although there is no doubt that laboratory monitoring is of crucial importance in ongoing checks of a prophylaxis programme it is essential that results are interpreted alongside evidence of clinical efficacy.

i) Trough levels. As one of the principal purposes of prophylaxis is to convert the severity of haemophilia from severe to moderate (factor level ≥ 1 iu/dl), it has been routine practice in many haemophilia centres to monitor whether this has been achieved. Monitoring is most often performed by measuring the ‘trough’ level of FVIII taken 48 or 72 hours after the last dose of concentrate and just before the next dose is due so that the lowest level of FVIII between treatments is measured. Review visits should be planned with parents and the child in such a way that prophylaxis is due on the day the patient attends. This enables a representative trough level to be taken prior to the due prophylaxis dose being given. Sensitive inhibitor screening should be considered when the 48 hour trough FVIII level is <1iu/dl.

ii) Half life studies. Factor VIII half life studies may be helpful in guiding individualised dosing and frequency of prophylaxis. It is often difficult in practice to obtain sufficient data points for standard half life calculations but for patients with sparse data, a Bayesian approach may be more applicable (Ahnström et al, 2004). Shortened half life results require formal inhibitor studies (Lee et al, 2001, Shapiro et al, 2005, van Dijk et al, 2005a, Bjorkman and Berntrop, 2001).

c) Radiological monitoring.
The main benefit of widespread radiological monitoring is likely to be in the setting of prospective studies. Radiology is useful in assessing the joint in certain clinical situations such as the presence of target joints or chronic synovitis.

RECOMMENDATIONS
1. A combination of clinical and laboratory monitoring is required for children on prophylaxis. (Grade of evidence: Low).
2. Standardised clinical examination scores should be incorporated into the prospective assessment of patients receiving prophylaxis such as the HJHS score. (Grade of evidence: Low).
3. Adherence and bleed history should be recorded. (Grade of evidence: Very low).
4. Trough factor levels should be measured at routine clinic visits. In the absence of bleeds, maintenance of trough levels >1 iu/dl is not always necessary. (Grade of evidence: Low). Half life studies may be useful if trough factor VIII levels remain <1 iu/dl in the absence of an inhibitor. (Grade of evidence: Low).

5. There is no requirement for radiological surveillance of joints unless there is a specific clinical indication. (Grade of evidence: Very low).

MANAGEMENT OF BREAKTHROUGH BLEEDING IN HAEMOPHILIA PATIENTS RECEIVING REGULAR PROPHYLAXIS.

There is a wide variation in the factor VIII doses used for breakthrough bleeds in patients receiving prophylaxis (Gringeri, 1999, Feldman et al, 2006, Manco-Johnson et al, 2007, Gringeri et al, 2009). The efficacy of these treatment schedules for breakthrough bleeds is unknown. Adequate treatment to ensure complete resolution of the bleed and return of the joint to normal function is essential.

RECOMMENDATIONS

1. Breakthrough bleeds should be treated according to site and severity until complete resolution. (Grade of evidence: Low).
2. The prophylaxis regimen should be reviewed accordingly. (Grade of evidence: Low).

HOME TREATMENT AND PROPHYLAXIS

Adherence to a prescribed regimen of prophylaxis is essential to ensure the full benefits of prophylaxis are realised (Hacker et al 2001). 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.
The needs of individual families will differ depending on the age of initiation of prophylaxis, the personalities involved and the family dynamics. Achieving competence and confidence in parents and older patients requires formal education, supervision and on-going support to families which in turn provides reassurance to these families and also accountability to healthcare professionals. (Vidler, 1999). The multidisciplinary team framework which underpins the successful management of patients with haemophilia is essential in ensuring this education and support for parents. Education about prophylaxis and involvement in treatment should begin with the first treatment administered; if possible, both parents should be involved in venous access training and treatment administration (Herrick et al 2004).

Rarely, there are complicating factors that affect the ability of families to administer effective prophylaxis. These can range from anxiety and distress in the child which renders intravenous access difficult to non-adherence caused by complex family dynamics and circumstances.

Prophylaxis does much to improve the quality of life of the individual with haemophilia (Fischer et al, 2002) but does not cure the disorder; it offers the possibility of participation in many sporting and leisure activities that would previously have been considered to be dangerous. A dilemma is then created as to the most appropriate level of participation in such sporting activities and which sporting activities are considered to carry a low level of risk of injury (Seuser et al, 2007). Careful consideration and discussion are needed between healthcare professionals and the family if the sporting activities being pursued result in coagulation factor consumption in excess of that needed for routine prophylaxis. This can lead to tension when the family’s expectations of a “normal” lifestyle have to be reconciled with the responsibilities of health care professionals to ensure the appropriate utilisation of expensive resources. The use of lower dose daily prophylaxis may partly address this issue.

RECOMMENDATIONS

1. Early education and training for prophylaxis is an essential component of haemophilia care in the young child and their family and is best provided within the Multidisciplinary framework of the Haemophilia Service. (Grade of evidence: Very low).

2. Involvement of both parents in this process should be encouraged where possible. (Grade of evidence: Very low).

3. Continuing and regular contact with the family together with the regular review of prophylaxis are essential for the early recognition of problems with home prophylaxis programmes. (Grade of evidence: Very low).

4. Agreement is essential with individuals and their families about physical activities and sports. Competitive contact sports particularly in patients
aged over 10 years will increase the risk of haemarthroses and arthropathy; sports with a high risk of head injury should be avoided at all ages. Alternative activities such as racket sports, athletics or swimming should be encouraged, facilitating full participation in school activities with peers and promoting musculoskeletal development and general good health. (Grade of evidence: Very low).

PROPHYLAXIS IN ADULT PATIENTS
The use of prophylaxis is becoming more common in adults. Patients may continue taking routine prophylaxis after adolescence, may use intermittent prophylaxis tailored to their sporting activities and potential traumatic episodes or may start secondary prophylaxis later in life either short term or for prolonged periods.

a) Management of young adults treated with prophylaxis in childhood
Most people with severe haemophilia reaching adulthood in the UK will have received prophylactic treatment during childhood. Prophylactic regimens will have been started at different ages and with variable intensity resulting in variable numbers of joint bleeds during childhood, as a consequence some patients reaching adulthood will have near normal joints and others will have evidence of arthropathy. Adults are often less physically active than children and hence less prone to trauma induced bleeds. It is also possible that normal adult joints may be less vulnerable to bleed induced arthropathy than developing joints (Roosendaal et al, 2000). However the existence of arthropathy may increase the risk of haemarthroses in older patients. It has been shown that approximately 30% of young adults with severe haemophilia can stop regular prophylaxis; these patients continue with targeted prophylaxis for specific activities (Fischer et al, 2001, van Dijk et al, 2005, Richards et al, 2007).

It is standard practice to involve the individual adult patient in a discussion regarding potential modification of prophylaxis in early adult life. Reduction in the intensity of prophylaxis carries attendant risks if those patients with milder clinical phenotypes cannot be reliably identified. Haemarthroses occurring during reduced prophylaxis may cause damage in joints, the health of which had been preserved throughout childhood and adolescence by consistent prophylaxis. In some individuals who have demonstrated a much milder phenotype, modification of prophylaxis may be appropriate. Intermittent prophylaxis should be maintained for sport or other potential traumatic events. Careful monitoring is essential if a change of prophylaxis is introduced; full prophylaxis should be reinstated if spontaneous bleeds occur that interfere with education or employment or significant haemarthroses occur that carry the risk of development of arthropathy.

b) Secondary prophylaxis in adults
Secondary prophylaxis may be short term to treat a target joint or long term. There are very few published data relating to secondary prophylaxis in adults
with haemophilic arthropathy (Valentino, 2004). Patients with longstanding arthropathy and disability may benefit from prophylactic treatment if recurrent bleeding episodes are interfering with mobility or employment. A prolonged period free of bleeds may improve quality of life, mobility and musculature by allowing more intensive physiotherapy (Loverin et al, 2000). Initially, relatively high prophylactic doses may be required to prevent bleeds but smaller or less frequent infusions of concentrate may be sufficient to prevent haemarthroses after a period of sustained prophylaxis. Prophylaxis in this context decreases bleeding episodes leading to improved mobility, less pain, fewer days off work and improved quality of life (Miners et al, 1998, Tagliaferri et al, 2008, Loverin et al, 2000, Fischer et al, 2005, Saba et al, 2000, Collins et al, 2008b). There are only limited data related to whether prevention of bleeds in adults with established arthropathy delays progression of joint disease as has been shown in children. One study suggests that prolonged prophylaxis in this patient group did delay progression of joint disease (Fischer et al, 2005). More data are required to investigate the effect of secondary prophylaxis on progression of haemophilic arthropathy, mobility, pain, employment, quality of life and cost effectiveness.

c) Prophylactic regimens and dose adjustment in adult patients
The standard prophylaxis regimens used in children may not be appropriate for adult patients although comparative data are not available. Adult patients with severe haemophilia have a wide variation in pharmacokinetics following an infusion of factor VIII, the half life varying between 8 and 23 hours (Bjorkman, 2003, Morfini, 2003). The longer factor VIII half life in adults compared to children results in a reduced total weekly requirement of factor VIII to achieve a given trough level. In order to attain a specified target trough factor VIII level in an individual, widely varying amounts of concentrate will be required. More frequent infusions result in a reduced factor concentrate requirement to sustain a target factor VIII level (Carlsson, 1997, Bjorkman, 2003). Knowledge of an individual patient’s pharmacokinetics is likely to improve cost effectiveness of prophylactic dosing. Adult patients usually tolerate more regular infusions and more detailed pharmacokinetic analyses than children and are better able to discuss individualised prophylactic regimens.
Prophylactic regimens in adults should be individualised to bleeding phenotype and pharmacokinetics. The infusion frequency may vary between every 3-4 days for individuals with a long factor half life to alternate day or low dose daily treatment for those with shorter factor half lives. Factor VIII doses prescribed to ideal weight for height may be more appropriate than using actual weight.

RECOMMENDATIONS

1. Adolescent and adult patients with severe haemophilia should be encouraged to continue regular prophylaxis at least until they have reached physical maturity. (Grade of evidence: Low).
2. In some individuals who have demonstrated a much milder phenotype, adapting formal prophylaxis to a more targeted policy may be considered but in such cases, there must be an agreed plan for monitoring and reintroduction of prophylaxis if necessary. (Grade of evidence: Low).

3. If significant haemarthroses occur after discontinuing prophylaxis, prophylaxis should be reinstated to prevent joint damage and to maintain quality of life. Prophylaxis should particularly be restarted if bleeding interferes with education or employment. (Grade of evidence: Low).

4. The dose and frequency of infusions should be adjusted, based on bleeding phenotype and ideally individual pharmacokinetics. The minimum amount of concentrate should be used to prevent haemarthroses irrespective of trough levels. (Grade of evidence: Low).

5. Pharmacokinetic studies may help dose adjustment and improve cost effectiveness. At a minimum, trough levels should be monitored but more information can be obtained from half life studies over a period of 48-72 hours. (Grade of evidence: Low).

6. Patients on long term prophylaxis should have their regimens critically reviewed at least every 6 months. If no break through bleeds have occurred a trial of dose reduction is appropriate, especially if the trough level >1 iu/dl. (Grade of evidence: Low).

7. Short or long term secondary prophylaxis should be considered in patients with advanced arthropathy if recurrent bleeding episodes significantly interfere with work or mobility. (Grade of evidence: Low).

8. Long term secondary prophylaxis is indicated following intracranial haemorrhage if no underlying cause can be corrected(Grade of evidence: Low).

DISCLOSURES
Disclosures made annually by all authors to Chairman of UKHCDO.

DISCLAIMER
While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UKHCDO, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
REFERENCES


