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Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition)

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Introduction

This document updates UK Haemophilia Centre Doctors Organization (UKHCDO) guidelines on the management of factor VIII/IX (FVIII/IX) inhibitors in congenital haemophilia (Hay *et al*, 2000, 2006). Acquired haemophilia is excluded and will be covered separately. Most data apply to FVIII inhibitors and the recommendations for FIX inhibitors are sometimes extrapolated from this. Low titre inhibitors are defined as <5 Bethesda units (BU)/ml and high titre $\geq$5 BU/ml. These guidelines are targeted towards haemophilia treaters in the UK. Not all recommendations may be appropriate for other countries with different health care arrangements and resources.

Methods

The writing group reviewed publications known to them supplemented with papers identified through Pubmed, using index terms h(a)emophilia, factor VIII and IX, inhibitors, alloantibodies, rFVIIa, NovoSeven, FEIBA, aPCC, rituximab, management. The writing group produced the draft guideline which was reviewed and revised by members of the UKHCDO Advisory Board. The guideline was finally reviewed by a sounding board of approximately 50 UK haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committees and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found at http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html. The objective of this guideline is to provide healthcare professionals with pragmatic guidance on the management of patients with FVIII/FIX inhibitors although individual patient circumstances may dictate an alternative approach.

Basic principles

Patients with FVIII/IX inhibitors must be registered with, and have their treatment co-ordinated by a Comprehensive Care Haemophilia Centre (CCC) experienced in the management of inhibitors (National Service Specification available at www.ukhcdo.org). Centres must provide 24-h access to senior clinicians with experience in inhibitor management and laboratory services for the measurement of factor levels and inhibitor titres. Patients should be offered inclusion in appropriate clinical trials and reported to registries. UK patients must be registered with the National Haemophilia Database and details of their inhibitor reported as soon as they are confirmed.

Risk factors for inhibitor formation

Recognized and potential risk factors for inhibitor formation are listed in Table I. Clinicians are advised to check all mutations in mild and moderate haemophilia A on the Haemophilia A Mutation, Structure, Test and Resource Site (HAMSTeRs) database (www.hadb.org.uk) to establish whether any association with inhibitor formation has been reported. The International Study on aetiology of inhibitors in patients with moderate or mild forms of haemophilia A, influences of Immuno-Genetic and Haemophilia Treatment factors (INSIGHT) is expected to report imminently (Eckhardt *et al*, 2012). This study will provide the largest, unselected cohort of patients with mild/moderate haemophilia A, including exposure data, from which clinicians can gauge prevalence of inhibitors for a given mutation to inform

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Table I. Risk factors for inhibitor development.

Risk factor	Effect	References
Host-related		
Mutation	Severe haemophilia A: Highest risk: null mutations, large deletions and mutations inducing stop codons Medium risk: Intron 1 and 22 inversion, splice site Lower risk: small deletion/insertion and missense mutation Mild/moderate haemophilia A: Usually low risk but specific mutations associated with increased risk Severe haemophilia B: Increased risk with major deletions and null mutations Inhibitors are rare with point mutations	Oldenburg and Pavlova (2006), Gouw *et al* (2011), Boekhorst *et al* (2008), HAMSTeRs database (www.hadb.org.uk) Gouw *et al* (2012)
Ethnicity	Severe haemophilia A: 2- to 5-fold increased risk associated in patients of Hispanic and African origin compared with Caucasians	Viel *et al* (2009), Maclean *et al* (2011), Astermark *et al* (2001)
Family history	Severe haemophilia A: Increased risk with first degree family history Incidence with family history 48% (95% confidence interval: 35–62), incidence without family history 15% (11–21)	Astermark *et al* (2001)
Age	Severe haemophilia A: Age at first exposure does not appear to have an effect Risk is highest below the age of 5 years and increases after age of 60 years Mild haemophilia A: Risk increases with age	Gouw *et al* (2007a), Chalmers *et al* (2007), Santagostino *et al* (2005) Hay *et al* (2011) Mauser-Bunschoten *et al* (2012)
HIV status	Severe haemophilia A: Lower risk if human immunodeficiency virus positive	Hay *et al* (2011)
Treatment-related		
Previous exposure days (EDs)	Severe haemophilia A: Risk highest during early exposures with a median time of inhibitor presentation at about 10–15 EDs Risk lower after 150 EDs but may occur throughout life. Severe haemophilia B: Risk highest during early exposures with a median time of inhibitor presentation at about 11 EDs. Inhibitors are reported up to 180 EDs. Late inhibitors have not been reported	Bray *et al* (1994), Lusher *et al* (1993), Lusher *et al* (2003), Rothschild *et al* (1998), McMillan *et al* (1988), Shapiro *et al* (2005) Hay *et al* (2011)
Intense exposure	Severe haemophilia A: Risk increased with 5 or more EDs at first treatment Haemophilia B: No data Mild haemophilia A: Risked increased with intense exposure	Gouw *et al* (2007a), Gouw *et al* (2007b), Chalmers *et al* (2007), Maclean *et al* (2011) Mauser-Bunschoten *et al* (2012)
Prophylaxis	Severe haemophilia A: Early prophylaxis is associated with a decreased risk in some retrospective studies	Gouw *et al* (2007b)
Type of concentrate	Severe haemophilia A: No evidence of any difference in inhibitor risk between recombinant and plasma-derived concentrates There is no convincing evidence for a difference in inhibitor risk between different types of rFVIII	Franchini and Lippi (2010), Iorio *et al* (2010b), Aledort *et al* (2011a), Aledort *et al* (2011b), Iorio *et al* (2011),

Table I. (*Continued*)

Risk factor	Effect	References
Surgery	Severe haemophilia A: Risk increased if surgery combined with an intensive first exposure (>4 ED) compared to first exposure without surgery OR 4 (95% confidence interval, 2–8·4) Mild moderate haemophilia A: Risk increased by intensive exposure at the time of surgery especially associated with high-risk mutation	Eckhardt *et al* (2009), Eckhardt *et al* (2011), Mauser-Bunschoten *et al* (2012)

Table II. Potential factors that affect the outcome of immune toleration induction (ITI).

Risk	Effect	References
Historic peak titre	<200 BU/ml associated with increased chance of inducing tolerance	Mariani *et al* (1994), Kroner (1999), DiMichele and Kroner (2002)
Titre at start of ITI	<10 BU/ml	Mariani *et al* (1994), Kroner (1999), DiMichele and Kroner (2002) Mauser-Bunschoten *et al* (1995)
FVIII dose	Poor risk patients 100–200 iu/kg/d probably more effective Good risk patients No difference between 200 iu/kg/d and 50 iu/kg 3 times a week but tolerance achieved more rapidly with higher dose regimens and with less intercurrent bleeds	Mariani *et al* (1994) Kroner (1999), Mauser-Bunschoten *et al* (1995), Brackmann *et al* (1996), DiMichele and Kroner (2002) DiMichele (2003) Hay and DiMichele (2012)
Peak titre on ITI	Poor risk if >250 BU/ml The best indicator of success or failure of ITI on multivariate analysis of the International ITI study	Hay and DiMichele (2012)
FVIII type	No evidence of difference in first line ITI between plasma-derived (pd) and recombinant FVIII Uncontrolled reports of responses to pdFVIII after failure of first-line ITI	Kreuz *et al* (1996), Gringeri *et al* (2007), Kurth *et al* (2011)
Time from inhibitor presentation	<5 years between presentation and starting ITI associated with increased chance of tolerance	Kroner (1999), Brackmann *et al* (1996) Mauser-Bunschoten *et al* (1995)
Interruptions of ITI	Associated with decreased chance of tolerance	Lenk (1999)
Number of EDs before ITI	Large number of EDs associated with decreased chance of tolerance	Kreuz *et al* (1995), DiMichele (2003)
Ethnicity	No evidence of an effect	Hay *et al* (2012)
Infection in venous access device	No effect seen in good risk patients in I-ITI study	Hay *et al* (2012)

Good-risk patients are defined as having an inhibitor titre of <10 BU/ml and historic peak titre of <200 BU/ml. Poor-risk patients have an inhibitor titre >10 BU/ml or historic peak titre of >200 BU/ml.

future treatment decisions. Recognition that treatment-related factors can influence inhibitor development offers the possibility that treatment might be modified in order to reduce this risk. Desmopressin (DDAVP) should always be considered when appropriate in mild/moderate haemophilia A (Eckhardt *et al*, 2009, 2011). At the present time in severe haemophilia A, only prophylaxis has been shown to possibly reduce the risk of inhibitor development and whether this will be applicable to all patients remains to be defined (Gouw *et al*, 2007a; Auerswald *et al*, 2012).

Recommendations

- **FVIII/FIX mutation analysis should be undertaken in all patients with haemophilia A and B, especially newly diagnosed patients (Grade 2C).**
- **Previously untreated and minimally treated patients with severe haemophilia A who have received an intensive FVIII exposure [$\geq$ 5 exposure days (EDs)] should be closely monitored for inhibitor formation (Grade 1B). Some consideration may be given to starting early prophylaxis (Grade 2C).**

- **All patients who require replacement therapy with concentrate, including previously untreated patients, should be treated with recombinant FVIII/IX (Grade 1C).**

Diagnosis and investigation of factor VIII and IX inhibitors

Inhibitor testing should be performed if a patient has a poor clinical response to concentrate or lower FVIII/IX levels than expected after concentrate infusion.

Surveillance for inhibitors

Early detection of an inhibitor is crucial to minimize anamnesis and, if the inhibitor does not rise above 10 BU/ml, allow immune toleration induction (ITI) to be started without delay. Early detection will also limit exposure to sub-optimal treatment. Inhibitor testing is required before elective invasive procedures, when the clinical or laboratory response to concentrate is sub-optimal, before and after a switch of concentrate and 2–3 weeks after intensive treatment ($\geq$5 EDs) or surgery in mild or moderately affected patients.

Haemophilia A. An inhibitor screen should be performed in patients with severe haemophilia at least every third ED or every 3 months if concentrate exposure has occurred (whichever is sooner) until 20 EDs have been achieved. Thereafter, inhibitor testing should be undertaken every 3–6 months until 150 EDs. Most boys with severe haemophilia are established on prophylaxis by the 20th ED and the pragmatic approach is to measure trough levels at least every 3–6 months: if FVIII/IX is measurable further testing is not necessary but if <1 iu/dl, inhibitor testing is required. This strategy, however, may miss some low titre inhibitors and should not be regarded as a definition for the presence or absence of an inhibitor. Inhibitors may occur at any age and incidence increases again after the age of 60 years (Hay *et al*, 2011), therefore testing should continue 1–2 times a year indefinitely.

Mild/moderate Haemophilia A. Patients with mild or moderate haemophilia should be tested annually if exposed to concentrate and after any intensive exposure ($\geq$5 EDs) or surgery (Eckhardt *et al*, 2009, 2011; Mauser-Bunschoten *et al* 2012). Patients with mild/moderate haemophilia with a mutation judged to have an increased prevalence of inhibitor formation (see section 4) should be considered for testing after every exposure.

Haemophilia B

FIX inhibitors are associated with allergic reactions to FIX, including life-threatening anaphylaxis (Warrier *et al*, 1997; Warrier & Lusher, 1998; DiMichele, 2007; Recht *et al*, 2011), especially in those with gene deletions (Thorland *et al*, 1999). Any reaction should prompt inhibitor testing before further FIX exposure as even low-level FIX inhibitors may cause anaphylaxis. Patients should have their mutation established as soon as the diagnosis is made to identify the minority of patients with major gene deletions, since FIX inhibitor risk is almost completely confined to this group. The first 20 exposures in patients with severe haemophilia B should be given in hospital with access to paediatric resuscitation facilities, although this does not necessarily need to be in a haemophilia centre.

An inhibitor screen should be performed in patients with severe haemophilia B at least every third ED or every 3 months if concentrate exposure has occurred (whichever is sooner) until 20 EDs have been achieved, irrespective of the FIX mutation. Thereafter, inhibitor testing should be undertaken every 3–6 months until 150 EDs. FIX inhibitors have not been reported in patients with more than 150 EDs and so further testing is not required unless clinically indicated.

Laboratory methods

In this guideline, the term 'inhibitor testing' includes Bethesda assays, inhibitor screens, enzyme-linked immunosorbent assays (ELISAs) and a 48-h trough measurement on standard dose prophylaxis (20–50 iu/kg alternate day). Any positive test must be confirmed on a repeat sample as soon as possible.

Inhibitor testing. Inhibitor tests are most sensitive following a washout period where the factor level has returned to baseline for 24 h, because residual infused concentrate may mask or quench a low-titre inhibitor. FVIII inhibitors are time- and temperature-dependent. FIX inhibitors are not time-dependent. Inhibitor testing is commonly performed using a Nijmegen-Bethesda assay although this is relatively insensitive (Verbruggen *et al*, 1995). Activated partial thromboplastin time (APTT)-based methods are described (Ewing & Kasper, 1982) and, if used, each laboratory will need to standardize the assay to define an abnormal result. A screening method that determines inhibitory activity against the patient's factor concentrate has been described (Keeling *et al*, 2005). It is a useful screening test and appears to be more sensitive than a Bethesda assay, however, it may be less specific and associated with false-positive results (UK National Haemophilia Database, unpublished data). In patients using standard prophylaxis (20–50 iu/kg alternate days), a measureable FVIII trough level at 48 h can pragmatically be interpreted as a negative inhibitor screen because this is likely to be associated with a half-life >7 h.

In patients with mild or moderate haemophilia A the sensitivity of an inhibitor test may be improved by heating the plasma at 58°C for 90 min to inactive residual FVIII (Kitchen *et al*, 2009 and Miller *et al*, 2012).

Inhibitor quantification. FVIII/IX inhibitors should be quantified with a Bethesda assay (Kasper *et al*, 1975) with

Nijmegen modification for FVIII (Verbruggen *et al*, 1995). When recombinant B-domain-deleted porcine FVIII concentrate becomes available, appropriate quantification of cross-reactive inhibitors will also be required. An ELISA method may be useful if a lupus anticoagulant is present or for inhibitors which increase clearance rather than inhibiting activity (Sahud *et al*, 2007). However, an ELISA test may also detect non-inhibitory antibodies.

Factor VIII in vivo recovery

FVIII *in vivo* recovery (IVR) is calculated by subtracting the pre-infusion from the post-infusion level; it should be reported as the increase in iu/dl divided by the infused dose in iu/kg. Inaccuracies in measuring IVR (Björkman *et al*, 2007) will be exacerbated by the presence of an inhibitor. In haemophilia A, samples taken 1-h post-infusion underestimate the IVR in most patients lacking an inhibitor (Björkman *et al*, 2010). The optimal sampling time in the presence of a low titre inhibitor is unknown but it should be standardized so that serial results can be compared. By consensus, we recommend that the post-infusion sample be taken at 15 min. IVR is of limited use for monitoring the strength of an inhibitor but is important for guiding replacement therapy when treating bleeding episodes.

Factor VIII/FIX half-life studies

The most sensitive way to detect and quantify an inhibitor is to measure the clearance of FVIII/IX. An expert consensus has suggested that a FVIII inhibitor be considered to be present in very young children when the elimination half-life was <6 h. However, the only available published study in children aged 1–6 years, who had no detectable or past history of an inhibitor, (n = 54) reported a median (95% confidence interval) FVIII half-life of 9·4 (7·4–13·1) h (Blanchette *et al*, 2008) and methodological considerations related to the reduced blood sampling schedule suggest that this half-life may be an underestimate (Björkman *et al*, 2010). When these data were re-analysed using a population pharmacokinetic method the shortest half-life was about 7 h, even in children aged 1 year (Björkman *et al*, 2012). In addition, the normal half-life for an individual who has an inhibitor is very unlikely to be known because this will not have been measured prior to inhibitor development.

In view of these emerging data we suggest that a FVIII inhibitor should be considered to be present if the half-life is <7 h.

There are no consensus criteria for recognition of a FIX inhibitor because normal FIX half-life is uncertain; reports vary widely with values for plasma-derived (pd) FIX ranging from 29 to 43 h and for recombinant FIX (rFIX) from 18 to 24 h (Björkman, 2011). The half-life of rFIX in infants and young children is unknown (Shapiro *et al*, 2005).

For pharmacokinetic studies, 50 iu/kg of FVIII or 75 iu/kg of FIX are infused after a 3-d washout period. The International Society on Thrombosis and Haemostasis FVIII/FIX Scientific and Standardization Committee (ISTH SSC) recommendations state that samples should be taken; pre-dose, and at 10–15 min, 30 min, 1, 3, 6, 9, 24, 28, 32 and 48 h post-infusion for FVIII and an additional sample taken 72 h post-infusion for FIX (Lee *et al*, 2001). This is very difficult to achieve in young children and times of 1, 3, 6–8, 24 and 48 h are suggested for FVIII in these patients, although this results in an apparently shorter half-life compared to full sampling in non-inhibitor patients (Björkman *et al*, 2010). This may, therefore, suggest the presence of an inhibitor when none exists. The effect of reduced sampling time points is virtually eliminated by the use of population pharmacokinetic models (Björkman *et al*, 2012) but no population model is available for patients with low titre inhibitors at present.

International Society on Thrombosis and Haemostasis FVIII/FIX Scientific and Standardization Committee guidelines recommend that a series of simple linear regression models can reduce calculations involved in half-life estimation but they emphasize that rigorous statistical analysis is required in order to assign the correct regression function (Lee *et al*, 2001). A number of computer programs can be used to estimate FVIII half-life but none have been validated for the measurement of half-life in the presence of an inhibitor. The calculation of an accurate half-life in the presence of a low titre inhibitor is a highly specialized procedure, beyond the ability of most centres. If half-life needs to be measured, the sampling schedule and methodology for calculation (Win-Non-Lin software; Pharsight, St Louis, MO, USA) used in the International ITI (I-ITI) study should be used so that patient outcomes can be compared to the results of that study (Hay & DiMichele, 2012). It should be recognized, however, that this sampling schedule (pre, 0·25–0·5, 1, 2, 4, 6, 24 and 48 h) may underestimate the half-life (Björkman *et al*, 2010).

A definition of an inhibitor based on half-life is the hardest and most sensitive measure but is difficult to apply in most routine clinical circumstances. In view of this, and because of the challenge of measuring FVIII half-life in patients with low titre inhibitors in routine practice, we will use a pragmatic and clinically relevant surrogate measure of normal FVIII pharmacokinetics in this guideline, as a FVIII level $\geq$1 iu/dl at 48 h in an individual receiving standard prophylaxis (20–50 iu/kg on alternate days).

Recommendations

- **An inhibitor test should be performed in severely affected patients with haemophilia A or B at least every third ED or every 3 months until the 20th ED (Grade 2C). After the 20th ED an inhibitor test should be done every 3–6 months up to 150 EDs. For haemophilia A,**

inhibitor testing should continue 1–2 times a year indefinitely (Grade 1C). For haemophilia B, testing after 150 EDs is only required if clinically indicated.

- **An inhibitor test should be performed in all patients with haemophilia A before any change in concentrate and at least twice in the first 6 months after the change or if there is any change in bleeding pattern or response to FVIII (Grade 2C).**
- **An inhibitor test should be performed in mild and moderate haemophilia A yearly (if they have been exposed to FVIII) or after intensive exposure ($\geq$5 EDs) or after surgery (Grade 1C).**
- **Patients with mild/moderate haemophilia A and a mutation with high inhibitor prevalence and/or family history of inhibitors should undergo inhibitor testing after all exposures (Grade 1C).**
- **Patients with haemophilia B should be tested after an allergic reaction to replacement therapy before any further FIX exposure occurs (Grade 1B).**
- **Tests to detect the presence or titre of an inhibitor should be done after a washout that ensures that the baseline factor level has been reached (Grade 1B).**
- **With currently available methodology it is difficult to accurately monitor FVIII half-life in patients with low titre inhibitors in routine clinical practice. If required, half-life should be measured by the methods described in the International Immune Tolerance study (Grade 2C). The current consensus definition for a FVIII inhibitor is an elimination half-life of <6 h, but this is likely to be an underestimate (Grade 2B) and the definition suggested in this guideline is <7 h (Grade 2B).**
- **We suggest that a pragmatic and clinically relevant surrogate measure of normal pharmacokinetics is a FVIII level $\geq$1 iu/dl at 48 h in an individual receiving standard prophylaxis (20–50 iu/kg on alternate days) (Grade 2C).**
- **There is no criterion for recognition of a FIX inhibitor other than the presence of a positive Bethesda assay (Grade 2C).**
- **IVR is a relatively inaccurate method to assess the strength of an inhibitor but is useful for guiding replacement therapy (Grade 2B).**

Treatment of inhibitors

Inhibitor treatment involves the control and prevention of bleeds and strategies to eradicate the inhibitor. Immune tolerance induction (ITI) must be viewed as a long-term investment and the high initial cost compared with the cost of life-long treatment in the presence of a persistent inhibitor.

Inhibitor eradication

Patients with a FVIII inhibitor, measured on more than one occasion, that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII should undergo ITI to eliminate the inhibitor and restore normal clinical responsiveness to FVIII. Factors that potentially affect the outcome of ITI are listed in Table II. Good risk patients are defined as having an inhibitor titre <10 BU/ml and an historic peak titre <200 BU/ml.

It is important to avoid interruption to ITI and to follow a protocol closely because the first attempt at ITI carries a considerably greater chance of achieving long-term tolerance than rescue therapy (Lenk, 1999). ITI regimens should be reviewed by a haemophilia clinician every month, and more formally reviewed every 3 months by a clinician with expertise in ITI.

Previous reports have suggested that most patients achieve tolerance within 6–12 months and a minority may take 1–3 years or more (Kreuz *et al*, 1995; Brackmann *et al*, 1996). The International ITI Study, however, found that, in good risk patients, the median time on ITI in the low-dose arm was 16·4 months and in the high-dose arm 14·2 months (Hay & DiMichele, 2012).

Patients who are super-high responders (inhibitor titre rises to >500 BU/ml after starting ITI) usually have a poor outcome (DiMichele & Kroner, 2002; Hay & DiMichele, 2012). ITI can be abandoned in such patients after 6–9 months and second-line therapy considered (see section 6.1.7.) unless there is evidence of a significant ongoing decline in inhibitor titre (at least a 20% fall in inhibitor titre in each 6 month period).

Choice of FVIII. Uncontrolled data have suggested that tolerance may be more readily achieved using low-purity pdFVIII than with recombinant FVIII (rFVIII) (Kreuz *et al*, 1996; Gringeri *et al*, 2007; Kurth *et al*, 2011). This remains controversial and there are a number of studies showing that the reported success-rates for ITI do not appear to be influenced by the product-type (Mauser-Bunschoten *et al*, 1995; Brackmann *et al*, 1996; Batlle *et al*, 1999; Rocino & de Biasi, 1999; Smith *et al*, 1999). A randomized comparison of the efficacy of high-dose pdFVIII or rFVIII for ITI in poor-risk patients is in progress (Gringeri, 2007). First-line ITI should be conducted using rFVIII concentrate, unless as part of a clinical trial, and is usually performed with the product used by the patient at the time of inhibitor development.

Inhibitor titre at the start of ITI. Starting titre is the most powerful predictor of ITI success (Mariani *et al*, 1994; DiMichele & Kroner, 2002) and regimens that delay treatment until the inhibitor has fallen below 10 BU/ml show very high success-rates (Mauser-Bunschoten *et al*, 1995; Rocino & de Biasi, 1999; Smith *et al*, 1999). It took a median of 5 months from diagnosis for titres to fall to <10 BU/ml in the I-ITI study (Hay & DiMichele, 2012). Rate of response to ITI did not decline until ITI had been delayed for 5 years from the time of diagnosis in the North American ITI registry (NAITR) (DiMichele & Kroner, 2002). Inhibitors that fail to fall to <10 BU/ml over 12–24 months often respond less

well to ITI. Bleeds should be treated with activated recombinant FVII (rFVIIa) during this time to avoid an anamnestic response.

Immune toleration induction should therefore be delayed until the inhibitor titre has fallen below 10 BU/ml. If the inhibitor is <10 BU/ml when first detected, and does not rise above 10 BU/ml in the subsequent 1–2 weeks, ITI should be started promptly, highlighting one of the benefits of good surveillance and early inhibitor detection. Commencement of ITI should also be considered if the inhibitor titre has not fallen below 10 BU/ml within 1 year, or if there has not been a downward trend in titre during these first 12 months.

Venous access. A central venous access device (CVAD) is usually inserted to facilitate ITI. Some centres attempt ITI without the use of a CVAD, because infection has been suggested to adversely affect the outcome of ITI, especially in poor risk patients. The I-ITI study observed that, in good-risk patients, infection or CVAD placement had no effect on either the proportion achieving tolerance or the time taken to become tolerant (Hay & DiMichele, 2012). Implantable CVADs are significantly less likely to become infected during ITI than external lines, such as Hickman or Broviac catheters (Hay & DiMichele, 2012).

ITI regimen. The choice of ITI regimen remains problematic. The I-ITI and NAITI suggest that poor-risk patients (peak titre >200 BU/ml, starting titre >10 BU/ml) are best tolerized using a high-dose regimen (100–200 iu/kg/d FVIII) (Mariani *et al*, 1994; DiMichele & Kroner, 2002). These registries and the I-ITI study suggest that high dose and low-dose (50 iu/kg three times weekly) regimens are equally effective in inducing tolerance in good risk patients (Mariani *et al*, 1994; Mauser-Bunschoten *et al*, 1995; DiMichele & Kroner, 2002; Hay & DiMichele, 2012). By implication, therefore, 200 and 100 iu/kg/d can be assumed to be equally efficacious for inducing tolerance in good risk patients (Hay & DiMichele, 2012) but the relative effect of these high dose regimens on bleeding is unknown.

Low-dose ITI (50 iu/kg three times a week or on alternate days) takes longer to achieve a negative Bethesda titre (DiMichele & Kroner, 2002; Hay & DiMichele, 2012) and is associated with significantly more intercurrent bleeding before the Bethesda titre becomes negative, a period during which 85% of intercurrent bleeding on ITI takes place (Hay & DiMichele, 2012).

Low-titre inhibitors (historic peak titre <5 BU/ml) are usually readily tolerized using a low-dose regimen (50 iu/kg alternate day) (Ter Avest *et al*, 2010).

Dose adjustment during ITI. Most published ITI regimens, with occasional exceptions (Smith *et al*, 1999), maintain the same dose of FVIII until the patient is considered tolerant. Dose tailoring, however, has been used on an empirical basis by some clinicians and three observations from the I-ITI study are relevant to this: (i) the outcome of ITI is unrelated to dose in good risk patients; (ii) high-dose ITI is associated with a statistically significant reduction in bleeding only in the early phase of ITI; (iii) although high-dose patients achieve a negative Bethesda titre three times faster than low-dose, the time taken to achieve the subsequent milestones of normal recovery and half-life were similar (Hay & DiMichele, 2012). These findings suggests that it might be possible, having started with high-dose ITI, to reduce the dose of FVIII during the course of ITI without affecting the time taken to achieve tolerance, as long as intercurrent bleeding is minimized and joint function preserved.

It is important to note that, in the I-ITI study, the number of bleeds occurring between the time of the first negative Bethesda assay and tolerance was 56 in the low-dose arm and 7 in the high-dose. This did not reach statistical significance as there were relatively few patients available for analysis during these phases of the trial and the study may not have had sufficient power to detect a difference. The effect on long-term joint outcome of this difference in bleed number is not known.

Most clinicians consider that all patients with a historic peak titre >5 BU/ml requiring ITI should be started with high-dose to minimize inter-current bleeding. However, in good risk patients, dose reduction in stages can reduce costs as long as there is no subsequent increase in break-through bleeds that require by-passing therapy. This strategy would not be expected to increase the time taken to achieve tolerance (Hay & DiMichele, 2012). Although not tested in a controlled trial, a similar regimen has been reported to be successful in a small series of patients (Smith *et al*, 1999).

Practical management of induction of immune tolerance. There is limited evidence to guide recommendations for the conduct of ITI and the following is a pragmatic, practical consensus method. It recognizes the fact that the accurate measurement of FVIII half-life in patients with low-titre inhibitors is difficult for most haemophilia centres, that the normal FVIII half-life of an individual patient is unknown and that a FVIII half-life of 6 h is likely to be too short to be a suitable criterion for tolerance. The definition used for restoration of normal pharmacokinetics is, therefore, a post-washout half-life of >7 h or a measureable FVIII trough level at 48 h in an individual receiving standard prophylaxis (20–50 iu/kg).

The regimen supports the consideration of dose reduction, whilst aiming to minimize joint bleeds and preserving long-term joint status, by tailoring to a 24- or 48-h- trough level $\geq$1 iu/dl, once these have become measurable (Collins *et al*, 2009a).

Initial regimen. If the historic peak inhibitor titre is <5 BU/ml, ITI should be started at a dose of 50 iu/kg on alternate days. The dose and frequency should be escalated if there are break-through bleeds; this may require daily treatment. If the inhibitor titre on ITI increases above 40 BU/ml,

the dose should be increased to 200 iu/kg/d (Mauser-Bunschoten *et al*, 1995; Ter Avest *et al*, 2010).

If the inhibitor titre is 5–10 BU/ml and the historic peak between 5 and 200 BU/ml, ITI should commence with 100 iu/kg/d. If a patient experiences haemarthroses or other significant bleeds, or if the inhibitor titre increases to >200 BU/ml, ITI should be increased to 200 iu/kg/d.

If the inhibitor titre is $\geq$10 BU/ml or the historic peak >200 BU/ml, ITI should commence with 200 iu/kg/d.

Monitoring and milestones. The inhibitor titre, without a washout, should initially be measured weekly to define the peak titre after commencing ITI and then monthly to follow the response to ITI. If a downward trend is observed (20% fall in a 6-month period after the peak inhibitor titre has been reached) the regimen should be continued. If the trend is upwards, or an adequate downward trend is not seen over a 6-month period, consideration should be given to modifying the regimen or stopping ITI. If the regimen is <200 iu/kg/d it should be increased to this level. If already at this level, second-line therapy should be introduced (see section 6.1.7.).

The following milestones suggest that ITI is inducing tolerance and should, therefore, be continued.

1 Fall in inhibitor titre of at least 20% over each 6-month period after the peak titre has been reached.
2 Inhibitor titre becomes negative without washout.

When the Bethesda titre without a washout is negative, treatment should continue unchanged. The 24-h trough level should be measured at least monthly and at the same time the IVR recorded. The 24h trough level will initially be <1 iu/dl and IVR low. As the inhibitor titre falls further the IVR will increase and as half-life lengthens the 24-h trough level will first become measureable and then increase. The IVR is useful for planning FVIII replacement therapy if bleeds occur.

3 Trough level at 24 h $\geq$1 iu/dl after ITI FVIII dose.

Once the 24 h trough is measureable, the inhibitor titre after a washout (such that baseline has been reached), should be measured. If this titre is positive, dose tapering should not be attempted but if the inhibitor titre is negative on two consecutive occasions then reduction of the ITI dose can be considered.

4 Dose tapering.

Dose tapering should not be considered in poor risk patients and the regimen of 200 iu/kg/d should be continued until tolerance is achieved.

Some clinicians consider dose tapering in good-risk patients once the Bethesda titre is reproducibly negative, others prefer to continue with full dose ITI in this situation. If dose tapering is used the Bethesda titre and 24 h FVIII trough level should continue to be measured at least monthly. Once the 24-h trough level is persistently measureable, and the post-washout inhibitor titre is negative on two consecutive occasions, the daily dose of FVIII can be tapered whilst maintaining a 24-h trough level >1 iu/dl and to prevent bleeds.

5 After a dose reduction is undertaken the Bethesda titre and 24-h trough FVIII level should be measured. If the Bethesda titre becomes positive, or the 24-h trough falls below 1 iu/dl or break-through bleeds occur, then the previous FVIII dose should be re-introduced.
6 Switch to alternate day dosing.

Once the FVIII dose has been reduced to about 50 iu/kg/d and the 24-h trough remains above 1 iu/dl, a switch to alternate day treatment can be considered. When this happens it is likely that an increase in total FVIII dose will be required to maintain a measureable 48-h trough level. The alternate day dose can then be slowly tapered to maintain a measureable 48-h trough level and to prevent bleeds.

7 Return to routine prophylaxis and confirmation of tolerance.

Tolerance can be confirmed by demonstrating a post-washout half-life of $\geq$7 h. Alternatively, when the alternate day dose has been tapered to 50 iu/kg or less and the 48-h trough is measurable the patient can be considered tolerant. At this stage routine prophylaxis should be continued indefinitely. Children with a past history of an inhibitor have required higher than normal doses of FVIII concentrate during prophylaxis to sustain a measureable trough level (UKHCDO annual returns available www.ukhcdo.org) and this is probably because they have a shortened half-life due to a residual very low titre inhibitor, below the limit of detection.

8 Surveillance for potential relapse.

Estimates of the risk of relapse after ITI vary depending on the length of follow-up and the definitions used. Mariani *et al* (1994) reported 15% gross relapse after 25 years follow-up. The I-ITI study reported 8% relapse within 12 months, using a sensitive pharmacokinetic definition of success (Hay & DiMichele, 2012). Based on this, we suggest monthly estimations of both Bethesda titre and 48-h trough FVIII levels for at least 6 months, followed by 2 monthly monitoring for up to a year in order to detect early relapse. If relapse does occur, consideration should be given to restarting ITI immediately.

Inadequate response to ITI/failed first-line therapy. If first-line therapy is considered not to be effective or to have failed, the strategy should be reviewed without interrupting ITI. Second line options to be considered include abandoning ITI, increasing the dose of FVIII to 200 iu/kg/d, changing to a pdFVIII with high von Willebrand factor (VWF) content, adding immunosuppression or a combination of these strategies.

Use of pdFVIII with a high VWF content has been associated with anecdotal reports of success and the risks associated with the presence of a long-term inhibitor are likely to

outweigh the very small potential risk of transfusion-transmitted disease. There are also anecdotal reports of the use of rituximab in patients who have failed conventional ITI with mixed responses (Mathias *et al*, 2004; Carcao *et al*, 2006; Collins *et al*, 2009b). A consecutive national cohort of 15 patients receiving rituximab as rescue therapy after failure of first line ITI reported that rituximab alone was unlikely to be successful and treatment should be combined with standard ITI regimens. Only a minority (14%) of patients achieved a complete and stable remission but 58% of those treated with rituximab and FVIII experienced a fall in inhibitor titre such that bleeds could be prevented and treated using FVIII concentrate (Collins *et al*, 2009b).

Mild/moderate haemophilia A. Patients with mild/moderate haemophilia A who develop an inhibitor respond less well to immune tolerance compared to those with severe haemophilia A (Hay *et al*, 1998). In some patients the inhibitor cross-reacts and leads to a fall in baseline FVIII and a worsening of the bleeding phenotype. Avoidance of FVIII concentrate will often allow the inhibitor titre to decline and the plasma FVIII level to return to baseline, however, tolerance is not likely and re-exposure will often result in a return of the inhibitor. ITI should not be used as a first line treatment but reserved for those who have recurrent bleeds. ITI can be considered in patients who need elective surgery but the potential benefit of tolerization must be weighed against the risk of boosting the inhibitor titre and reducing the baseline FVIII level. In patients who have an acquired haemophilia bleeding pattern, immune suppression may be considered.

Immune tolerance induction: haemophilia B. Immune toleration induction for haemophilia B must be carefully considered because the success rate is low (25%) and there are risks of anaphylaxis and irreversible nephrotic syndrome (Ewenstein *et al*, 1997; Warrier, 1998; DiMichele & Kroner, 2002). Regimens analogous to those used in haemophilia A have been used, including low- and high-dose FIX concentrate and a modified Malmo regimen. The NAITR reported 31% success (5/16) using a median dose of 100 iu/kg/d. There was insufficient data to differentiate outcome between differing dose regimens but patients with an allergic phenotype and a family history of inhibitors had a poorer outcome (DiMichele & Kroner, 2002; DiMichele, 2009).

Successful ITI using the Malmo protocol has been reported in six of seven patients although two required two or more ITI courses and one relapsed after 6 months (Freiburghaus *et al*, 1999). Individual case reports further support the role of immunosuppression as a component of the ITI regimen used in patients with haemophilia B. Success was reported in a patient with an allergic phenotype using initial densensitization with steroids, intravenous immunoglobulin and escalating doses of FIX, followed by the Malmo regimen (Curry *et al*, 2007) and further success in 2/4 patients using the same approach has been seen (unpublished observations, Liesner R.). This approach requires intensive inpatient monitoring and daily urinalysis. Others have reported successful desensitization to FIX, facilitating FIX infusions as part of ITI (Alexander *et al*, 2008; Chuansumrit *et al*, 2008). Mycophenolate mofetil combined with dexamethasone, intravenous immunoglobulin and high-dose FIX has also been used in a few patients with success (Klarmann *et al*, 2008a,b). Ciclosporin has been used successfully in one patient (Cross & Van den Berg, 2007) and rituximab has been used as part of the treatment regimen with variable outcomes in single case reports or small series (Mathias *et al*, 2004; Fox *et al*, 2006; Alexander *et al*, 2008; Chuansumrit *et al*, 2008; Beutel *et al*, 2009).

Recommendations

- **Immune toleration induction is recommended for patients with severe haemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (Grade 1B).**
- **The probability of good ITI outcome may be estimated using the peak historical inhibitor titre and starting titre (good-risk: <200 and <10 BU/ml, respectively) (Grade 1C).**
- **Immune toleration induction should be started as soon as possible after the inhibitor has been confirmed and when the titre is <10 BU/ml (Grade 1B).**
- **If the inhibitor titre is >10 BU/ml at diagnosis, the start of ITI should be deferred until it has fallen below 10 BU/ml (Grade 1B). If this has not happened after 1 year, consideration should be given to commencing ITI (Grade 2C).**
- **If the historic peak inhibitor titre is <5 BU/ml, ITI should be started at a dose of 50 iu/kg on alternate days (Grade 2B).**
- **If the starting inhibitor titre is <10 BU/ml and the historic peak <200 BU/ml ITI should commence with 100 iu/kg/d unless peak is <5 BU/ml (see above) (Grade 2B).**
- **If the starting inhibitor titre is >10 BU/ml or the historic peak >200 BU/ml ITI should commence with 200 iu/kg/d (Grade 2B).**
- **If the ITI regimen of 50 iu/kg alternate days or 100 iu/kg/d is complicated by bleeding episodes the dose should be increased in stages up to 200 iu/kg/d to control bleeds (Grade 2B).**
- **Immune toleration induction should continue as long as there is a convincing downward trend in inhibitor titre (20% in a 6 month period after the peak inhibitor titre has been reached) and interruptions in ITI should be avoided (Grade 2C).**
- **Dose tapering may be considered in good risk patients once the post-washout Bethesda titre is negative on two consecutive occasions and the 24-h FVIII trough level is $\geq$1 iu/dl. The FVIII dose should be reduced whilst maintaining a 24-h trough level $\geq$1 iu/dl and minimizing break-through bleeds (Grade 2C).**

- **Once the FVIII dose has been reduced to $\leq$50 iu/kg on alternate day whilst maintaining a trough FVIII level $\geq$1 iu/dl or the FVIII half-life after a washout is >7 h, the patient can be considered tolerant (Grade 2C).**
- **If there is an inadequate decrease in the inhibitor titre (20% reduction over a 6-month period) an alternative strategy may be considered. Options include FVIII dose increase, the introduction of pdFVIII, immunosuppression with rituximab, or stopping ITI (Grade 2C). If there is no adequate response within 6 months after introduction of second-line therapy ITI should be stopped (Grade 2C).**
- **Careful consideration should be given to attempting to induce immune tolerance in patients with haemophilia B, given the relatively poor response rate and risk of anaphylaxis and the nephrotic syndrome. Successful tolerization has been reported and the addition of immunosuppression to the ITI has been associated with the highest success rates (Grade 2C).**
- **In patients with mild/moderate haemophilia A and an inhibitor, a trial of on-demand bypassing therapy should precede consideration of ITI, the success rate of which is low in this group. (Grade 1C).**
- **In patients with mild/moderate haemophilia A and an inhibitor associated with a bleeding phenotype similar to acquired haemophilia A, a trial of immunosuppression should be considered (Grade 2C).**
- **Immune toleration induction should be conducted under the supervision of a Haemophilia Comprehensive Care Centre with expertise in inhibitor treatment, as defined by the National Service Specification. (Grade 1C).**

Treatment of bleeds

Regular clinical review by experienced clinicians is essential with assessment at least daily. More serious bleeds require more intensive supervision and in-patient care may be necessary to ensure timely administration of haemostatic agents. Bleeds should be treated early (within 2 h) (Salaj *et al*, 2009; Kavakli *et al*, 2010; Berntrop, 2011) to minimize their extent and associated morbidity and to reduce the amount of haemostatic agent required. Patients and their families should be established on home treatment as early as possible and be educated to recognize the early symptoms of bleeds and instructed on initial treatment regimens. Patients and families need 24-h access to experienced clinicians for advice and clinical review. Non-responsive bleeds should be identified objectively and treatment changed early (Berntrop *et al*, 2011).

Haemostatic agents. Since the previous guidelines (Hay *et al*, 2006), no new agents have become available although a number are in development.

Patients with low-titre inhibitors may respond to higher than usual doses of FVIII/FIX. Patients who are high responders usually have FVIII/FIX concentrate given only for severe bleeding. The dose required to neutralize the inhibitor and increase the FVIII/FIX level varies widely and various (unvalidated) dosing algorithms exist (Gringeri & Mannucci, 2005; Kempton & White, 2009). Patients treated with FVIII/FIX should have regular (at least daily) monitoring of FVIII/FIX levels to detect any increase in inhibitor activity.

Patients with mild haemophilia A and an inhibitor should have a DDAVP trial with pre- and post- (0·5, 1 and 4 h) FVIII levels being measured. If the response is adequate, this agent combined with tranexamic acid should be used for bleeds likely to respond. It is important to avoid FVIII exposure in patients with mild haemophilia A and a history of an inhibitor, if possible, to reduce the risk of stimulating a cross-reacting inhibitor that depresses the baseline FVIII level and worsens the patient's bleeding phenotype. This can be achieved with the use of activated recombinant FVII (rFVIIa) or DDAVP, depending on the severity of the bleed and documented DDAVP response.

For patients who do not respond to FVIII/FIX, or in whom avoidance of FVIII/FIX is necessary, rFVIIa or activated prothrombin complex concentrates (aPCC) are the treatments of choice. The only currently available aPCC is FVIII Inhibitor Bypassing Activity (FEIBA). Both bypassing agents are effective in minor and major haemorrhage and a bleed may respond to one product where the other has failed to achieve haemostasis. Studies have addressed dosage regimens for rFVIIa and compared the efficacy of FEIBA and rFVIIa in the management of early haemarthroses. Studies in other types of bleeds and severe haemarthroses have not been performed.

Dose and frequency of rFVIIa. Randomized trials have compared multiple standard doses of rFVIIa (90 μg/kg) with a single higher dose to treat haemarthroses. The studies have been small and used different measures of effectiveness, but suggest that a single dose of rFVIIa (270 μg/kg) is as effective and as safe as three doses of 90 μg/kg. A randomized study compared these regimens in 18 patients and showed similar success rates and median rFVIIa usage (Santagostino *et al*, 2006). Similar results were obtained in a randomized, crossover, double-blind study (Kavalki *et al*, 2006). Comparative studies of a single dose of rFVIIa 270 μg/kg compared with one or two doses of rFVIIa 90 μg/kg have not been undertaken, although the median number of infusions required to treat haemarthroses has previously been reported to be 2·4 (including one consolidation treatment) (Key *et al*, 1998), and this must be recognized in any cost effectiveness analysis.

Comparison of rFVIIa and FEIBA. A prospective, randomized, non-blinded crossover study compared FEIBA (75–100 iu/kg) with two doses of rFVIIa (90–120 μg/kg 2 h apart) for home-treated haemarthroses. Similar efficacy was observed although the study's pre-defined statistical criteria

for equivalence were not met. Neither product was superior at any time point (Astermark *et al*, 2007).

A three-way comparison of high dose rFVIIa, standard dose rFVIIa and FEIBA to treat early haemarthroses has been reported in a randomized, crossover double-blind study involving 27 patients. The two rFVIIa groups had a similar requirement for additional haemostatic treatment. The FEIBA group required significantly more additional treatment compared with the high dose rFVIIa group and a trend towards more additional treatment when compared with standard dose (90 μg/kg) rFVIIa. In a Cochrane Review of the efficacy of rFVIIa and aPCC, these were the only studies identified as eligible for analysis from 10 trials identified. However, the authors identified methodological flaws in both studies and concluded that there was similar haemostatic efficacy between FEIBA and rFVIIa (Iorio *et al*, 2010a).

A number of factors could influence the results and conclusions of these studies, including the small numbers of patients, varying severity of bleeding phenotype, the presence of target joints, subjectivity of patient assessment of treatment effectiveness, the blinded or non-blinded nature of some studies and the differing entry criteria. Factors that could influence response to bypassing agents have recently been summarized (Berntorp, 2009).

Conclusions. In early haemarthroses treated at home, a single dose of rFVIIa 270 μg/kg is as effective and safe as three doses of rFVIIa 90 μg/kg. Comparative studies of a single dose of rFVIIa 270 μg/kg compared with one or two doses of rFVIIa 90 μg/kg have not been undertaken. A single dose of FEIBA appears to be as effective as two standard doses of rFVIIa 2 h apart. A single high dose of rFVIIa may be more effective than a single dose of FEIBA at 9-h post-treatment.

Other treatment options. Treatment modalities, such as plasma exchange with immunoadsorption and high dose FVIII, should be considered, depending on the clinical circumstances and especially if response to bypassing agents is inadequate, although facilities for this mode of treatment are not widely available.

Tranexamic acid should be considered for all bleeds treated with rFVIIa but is especially important for mucosal bleeds. Concerns about concomitant use of tranexamic acid with FEIBA exist but reports of complications are very rare and many clinicians use tranexamic acid in combination with FEIBA (Tuyet Tran *et al*, 2011; Holmström *et al*, 2012).

Patients receiving bypassing agents are at risk of thrombosis, particularly adults with associated co-morbidities, and should be regularly monitored clinically for such events (Aledort, 2004; Sumner *et al*, 2007; Baudo *et al*, 2012).

Sequential or combined therapy. Combination treatment with rFVIIa and FEIBA may act synergistically in some patients and can be considered for life or limb-threatening bleeding unresponsive to treatment with either bypassing agent alone. Bypassing agents can be administered sequentially or in combination (Schneiderman *et al*, 2007; Martinowitz *et al*, 2009; Gringeri *et al*, 2011). This treatment strategy is unlicensed, has been reported in only a small number of patients and has the potential for causing venous and arterial thromboses, especially in older patients and in those with acquired thrombotic risk factors. The authors are aware of unpublished venous thrombotic events associated with combined treatment and this should only be considered in exceptional circumstances (Ingerslev & Sørensen, 2011). A consensus statement has discussed the potential role of sequential combined therapy (Teitel *et al*, 2007).

FIX inhibitors associated with allergic reactions. Patients who have had severe reactions associated with FIX-containing concentrates should have bleeds treated with rFVIIa (Warrier, 1998; Chitlur *et al*, 2009).

Treatment of specific bleeding problems

Recommendations are proposed for specific clinical situations but in the absence of clinic trials these are necessarily by consensus.

Soft tissue bleeds. Either rFVIIa 90 μg/kg 2–3 hourly with assessment after each dose or FEIBA 50–100 u/kg with review after 8 h. If partial response after three doses of rFVIIa or 8 h after FEIBA consider either continuing with the same treatment and reassessing after 24 h or increasing the dose or frequency of treatment. Total doses of FEIBA should not exceed 200 iu/kg/d. If no response is seen, or the bleed worsens, switch to the alternate bypassing agent. Treatment should be continued until full recovery of muscle function, with dose and frequency of treatment being tapered as improvement occurs.

Joint bleed. Consideration should be given to immobilization of the affected joint and the use of ice packs. Uncomplicated haemarthroses should be treated with the same treatment protocol as soft tissue bleeds and treatment should be continued until full joint recovery, again reducing dose and frequency with improvement to the joint. Early haemarthroses may be treated with a single infusion of rFVIIa 270 μg/kg and assessed after 4–6 h.

Intracerebral bleed. Treatment should be commenced with rFVIIa or FEIBA as soon as the diagnosis is suspected (rFVIIa 90–120 μg/kg 2 hourly and response assessed after two treatments or FEIBA 100 iu/kg with assessment after 4 h). If the inhibitor titre is low, rFVIII/IX concentrate should be considered with regular FVIII/IX monitoring and switch to a bypassing agent if the inhibitor titre rises. Dose or frequency should be increased if partial response and treatment should be switched to an alternate agent if no response or deterioration is observed. The maximum dose of

200 iu/kg/d of FEIBA is likely to be exceeded in these circumstances and this is reasonable on a case by case basis. If response to the alternate agent is not adequate, sequential treatment with these two products can be considered. Intensive treatment should be continued for at least 5 days, and regular radiological assessment is recommended. A slow tapering of dose and frequency can be undertaken as improvement occurs. An efficacy rate of 100% for extracerebral haemorrhage and 82% for intracerebral haemorrhage using 'standard' dosing of rFVIIa has recently been reported (Nakar *et al*, 2010).

Treatment modalities, such as rFVIII/IX with plasma exchange, should be considered depending on the clinical circumstances and response. Prophylactic treatment with rFVIIa or FEIBA should be started once resolution of the intracerebral bleed has occurred and continued for at least 6 months.

Recommendations

- **Arrangements should be in place to treat bleeds within 2 h, either at home or in hospital. Patients should be on home treatment with agreed initial regimens as soon as is practically possible, combined with arrangements for rapid access to hospital review and or advice from an experienced clinician (Grade 2C).**
- **Bleeds may be managed with large doses of FVIII/IX in low responders and FEIBA or rFVIIa in high responders. FVIII can be considered for major bleeds in high-responding patients with low-titre antibodies. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII/FIX infusions rather than increase the dose (Grade 2C).**
- **Patients who have experienced allergic reactions to FIX should be treated with rFVIIa (Grade 1C).**
- **Single dose FEIBA (50–100 μg/kg), single high dose (270 μg/kg) rFVIIa or 1–3 standard doses (90 μg/kg) of rFVIIa are all treatment options for early haemarthroses (Grade 1B).**
- **Treatment of non-joint bleeds should be with FVIII/FIX or standard doses of FEIBA or rFVIIa until further data are available (Grade 2C).**
- **Tranexamic acid should be considered in all patients who are not receiving high doses of FEIBA (>200 iu/kg/d) but is especially important for mucosal bleeds (Grade 2C).**
- **Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose FVIII/IX concentrate (Grade 2B).**
- **Combined treatment with rFVIIa and FEIBA should only be considered for life- or limb-threatening bleeds unresponsive to either agent used alone (Grade 2C).**
- **Patients with mild/moderate haemophilia A with high inhibitor prevalence mutations or family history of inhibitor, should be treated with DDAVP wherever possible to avoid FVIII exposure (Grade 1C).**
- **Patients with mild/moderate haemophilia A and an inhibitor should have a DDAVP trial, including a 4-h fall off FVIII level and this agent, combined with tranexamic acid, should be used whenever possible to avoid FVIII exposure (Grade 2C).**
- **Management of a bleed depends on its site and severity, knowledge of the inhibitor titre and previous response to bypassing agents and whether the patient is a low or high responder (Grade 2C).**

Surgery

Surgery in inhibitor patients is a high-risk procedure that should not be undertaken lightly, as no product can guarantee haemostasis. In some circumstances it may be in the patient's best interests not to undertake a procedure. Haemostasis must be adequate in the peri- and post-operative periods to facilitate wound healing and for an extended period to allow physiotherapy and rehabilitation after major joint surgery.

If the patient has a low-titre antibody, high and frequent doses of FVIII/IX may be used. Patients should be closely monitored with FVIII/IX levels and observed for development of an anamnestic response, which may rapidly render FVIII/IX ineffective. In patients with mild/moderate haemophilia and a previous inhibitor, rFVIIa should be considered to avoid an anamnestic response. Minor procedures may be covered with DDAVP if response is adequate.

Both rFVIIa and FEIBA have been used successfully to cover surgery and many authorities believe that they may be used interchangeably because both seem to offer effective haemostasis in 80–90% of patients (Quintana-Molina *et al*, 2004; Tjønnfjord, 2004; Obergfell *et al*, 2008; Teitel *et al*, 2009; Rodríguez- Merchan *et al*, 2010; Takedani *et al*, 2010; Rangarajan *et al*, 2011).

The dose and duration of use for these products for various types of surgery is not standardized. A consensus protocol for the use of rFVIIa in elective orthopaedic surgery has been published (Giangrande *et al*, 2009). Administration of rFVIIa by continuous infusion has been reported in the setting of clinical studies, but the data regarding its efficacy are inconsistent and this approach is not licensed (Smith *et al*, 2001; Ludlam *et al*, 2003; Pruthi *et al*, 2007). FEIBA is usually used at doses of 75–100 units 8–12 hourly.

The choice of bypassing agent for a particular individual requiring surgery depends on the response of the patient to bypassing agents for previous bleed treatment, experience of the treating centre, venous access, history of anamnesis with FEIBA and cost considerations. In severe haemophilia A, anamnesis will not change the bleeding phenotype or response to FEIBA but removes the option to use FVIII as a short-term measure to treat uncontrolled bleeding. Hybrid

protocols using rFVIIa in the initial peri-operative period with switch to FEIBA for extended post-operative rehabilitation have been used successfully in a few cases (Teitel *et al*, 2009). Young children awaiting ITI should have surgical procedures managed with rFVIIa.

Both products are potentially thrombogenic, and thrombotic events have been reported in individuals with additional risk factors and/or when the dose administered has exceeded licensed recommendations (Aledort, 2004; Teitel & Poon, 2004). Antifibrinolytic agents, such as tranexamic acid, can be used with rFVIIa (Schulman *et al*, 1998). The use of tranexamic acid with FEIBA is not recommended according to the summary of product characteristics, but has been used in this setting without adverse events (Holmström *et al*, 2012).

Recommendations

- **Surgery in patients with inhibitors should be conducted at a CCC with experience in surgery in inhibitor patients and 24-h specialist consultant cover (Grade 1C). Haemostasis cannot be guaranteed with any available haemostatic agent, therefore, surgical procedures should be undertaken only after a careful assessment of the potential risks and benefits (Grade 1B).**
- **FVIII/IX can be used if satisfactory plasma levels can be achieved (Grade 1C).**
- **rFVIIa or FEIBA can be used at recommended licensed doses (Grade 2C). If the original bypassing therapy fails, then the alternate bypass agent may be used.**

Prophylaxis for inhibitor patients

Most inhibitor patients cannot use FVIII/FIX for prophylaxis because the half-life is too short, although daily or twice daily treatment may be effective for low-titre inhibitors. Studies with FEIBA and rFVIIa have shown a decreased bleed frequency, maintenance or improvement in joint scores and improvements in quality of life (Table III). FEIBA is associated with anamnesis and should not be used in those whom ITI is planned.

Two prospective studies have been published. The ProFEIBA study compared prophylaxis with FEIBA 85 iu/kg 3 days a week with on-demand treatment and showed a decrease in mean total bleeds from about 13 to 5 during a 6-month period. The study had a randomized cross-over design. The mean number of haemarthroses during 6 months prophylaxis was 4·2 and 6/26 evaluable patients had no bleeds during prophylaxis (Leissinger *et al*, 2011). A prospective study with rFVIIa showed a decrease in joint bleeds from a mean of about 14 in a 3-month period of on demand therapy to a mean of about 8 and 4 in 3 months for 90 or 270 μg/kg/d respectively. There was no statistically

Table III. Studies investigating prophylaxis with bypassing agents.

Study	Patients	Regimen	Outcome
Leissinger *et al* (2011)	26 adults and children	FEIBA 85 iu/kg ± 15% on 3 non-consecutive days per week	62% reduction in all bleeds, 61% reduction in joint bleeds compared with on demand treatment
Konkle *et al* (2007)	22 cases 5·1–50·5 years	rFVIIa 90 vs. 270 μg/kg/d, 3 months treatment and 3 months follow-up	45% and 59% reduction in bleeding
Kreuz *et al* (2000)	22 children 0·1–6 years	FEIBA during ITI 50–100 iu/kg/d	Median annual incidence of haemarthrosis 1 (0–6)
Valentino (2004)	9 children 6 on ITI	FEIBA 75–100 iu/kg	Reduced haemarthrosis during FEIBA treatment
Hilgartner *et al* (2003)	7 children	FEIBA 50–100 iu/kg Alternate days or × 3/week	5/7 progression of arthropathy 4/7 new target joints affected
DiMichele and Négrier (2006)	14 patients	FEIBA 15–100 iu/kg Daily-×1/week	Joint bleeding reduced in 83% 8/13 joint status maintained, 3/13 joint status improved
Leissinger *et al* (2007)	5 patients 3–16 years	FEIBA 5–75 iu/kg/week or 100 iu/kg/d	Reduced joint bleeding Maintenance or improvement of joint score
Valentino (2009)	6 patients 3·7–24 years	FEIBA 100 iu/kg/d or 50–75 iu/kg every 3rd d	Reduced haemorrhages Improved orthopaedic status Improved quality of life
Morfini *et al* (2007)	13 adults and children	rFVIIa 200 μg/kg/d –week	Reduced frequency of bleeding

ITI, immune toleration induction; FEIBA, Factor VIII Inhibitor Bypassing Activity; rFVIIa, recombinant activated factor VII.

significant difference between the 90 and 270 μg/kg doses (Konkle *et al*, 2007). This study did not have a randomized cross-over design. The data, therefore, are less robust and the finding that the reduced bleed rate continued after the rFVIIa prophylaxis had been stopped may have been a chance finding. Neither bypassing agent completely prevented bleeds in most patients although both showed a significant reduction in frequency but the results cannot be compared. It is not known whether the reduction in bleeds translates into benefit in terms of joint pathology but, given the number of haemarthoses observed, prevention of progression of arthropathy would be unlikely. It is also not known whether the bleed rate would decrease further with a longer period of prophylaxis or whether lower dose regimens would be as efficacious.

Unsurprisingly, the two prospective studies have inferior outcomes compared to most of the published literature, although both studies only recruited patients with high bleed frequencies. Available data strongly support the view that prophylaxis with a bypassing agent is not as efficacious as FVIII/IX, strengthening the recommendation to tolerize an inhibitor early.

As in patients without inhibitors, the best chance of preventing arthropathy is with primary prophylaxis commenced in young children with no significant pre-existing joint damage. Many of the published studies on inhibitor prophylaxis have been performed in older patients with significant arthropathy, where benefit may be more difficult to demonstrate. Studies in children with good baseline joint function will be required to address this issue.

There is wide variation in reported prophylactic regimens, in terms of both dose and frequency of infusion. Optimal regimens for both agents remain to be established and deciding factors include potential ITI, the frequency of infusions, previous response to bypassing agents and treatment cost. The longer half-life of FEIBA may make this a more practical option for many patients.

In patients in whom ITI is underway, or if ITI has been unsuccessful, either rFVIIa or FEIBA can be used. Commonly used regimens are; rFVIIa at 90 μg/kg daily or FEIBA at 50–85 iu/kg alternate day or three times a week. Some patients respond to much lower doses, such as FEIBA 10–15 iu/d. If initial treatment is unsuccessful then increasing the frequency of infusions of FEIBA whilst maintaining the same overall dose will be a more cost-effective option than escalating the dose. Similarly, with rFVIIa, if bleeds continue despite 90 μg/kg rFVIIa daily dose escalation has been shown to be ineffective (Konkle *et al*, 2007) and an increase in dose frequency is a more logical approach.

Recommendations

- **Prophylaxis with a bypassing agent should be considered in young children after the first haemarthosis to reduce the risk of arthropathy (Grade 2C).**
- **If prophylaxis is required in patients awaiting ITI, rFVIIa should be used (Grade 2C).**
- **Prophylaxis with bypassing agents in patients on ITI should undergo a trial reduction when FVIII recovery is measureable and stopped when the Bethesda titre is negative, assuming significant break-through bleeds do not result (Grade 2C).**
- **Prophylaxis may be considered in older patients with recurrent bleeds or progressive arthropathy (Grade 2C).**
- **The choice of product for prophylaxis should be considered on an individual basis, taking into account previous response to treatment, logistics of administration and cost (Grade 2C).**
- **If the initial regimen is unsuccessful, increasing the frequency of infusion is more likely to be effective than increasing the dose (Grade 2C).**

Monitoring bypassing agents

There are no validated laboratory tests to monitor bypassing agents in the setting of bleeds or during surgery for inhibitor patients. Tests such as Thrombin Generation Assay (TGA), Calibrated Automated Thrombography (CAT) and Thrombelastography (TEG)/Thromboelastometry (ROTEM) have all been used as research tools (Dargaud *et al*, 2010). These tests are not standardized in terms of reagents and technique and therefore the results cannot be compared (Dargaud *et al*, 2007; Lewis *et al*, 2007; van Veen *et al*, 2008). The FVIII/FIX SSC of the ISTH has established working parties to facilitate standardization. In the case of TGA and CAT, rFVIIa and FEIBA cannot be directly compared (van Veen *et al*, 2008) and thrombin generation with rFVIIa cannot be assessed in platelet poor plasma (Dargaud *et al*, 2008; van Veen *et al*, 2008).

Recommendation

- **The use of laboratory tests to monitor and determine dose of bypassing agent therapy in patients with inhibitors is not recommended outside of clinical trials (Grade 2C).**

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.

Date for guideline review

The guideline will be reviewed after 5 years or earlier if significant developments occur.

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