Congenital Haemophilia - Surveillance and Management of Inhibitors - Full Clinical Guideline

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1. Introduction

A serious and significant complication of the treatment of haemophilia is the development of an inhibitor (antibody) to FVIII or FIX. Most inhibitors occur in severe haemophilia, however, inhibitors can also occur in mild/moderate haemophilia. The highest risk period for the development of an inhibitor in severe haemophilia is during the first 20 exposures to factor concentrate. Inhibitor risk in mild haemophilia is not related to the number of exposures. The development of an inhibitor results in loss of efficacy to factor concentrate and should be suspected in a person with haemophilia who presents with bleeding despite adequate factor treatment. Inhibitors in haemophilia B may cause anaphylaxis following treatment with FIX concentrate.
Certain patients may have already been identified as being high risk for inhibitors eg known to carry a high risk genetic variant, or because of treatment related factors. These patients should always be discussed with a paediatric haematology consultant.

These guidelines are intended to be used within the Derby Haemophilia Centre. They are based on the UKHCDO guidelines (2013 and 2015) and refer to congenital haemophilia A and B patients. Patients with acquired haemophilia are excluded from this guideline.

These guidelines are a summary for Derby use. For detailed guidance, please refer to the full UKHCDO guidelines (see below for reference).

Treatment of inhibitors must be discussed and agreed with a Comprehensive Care Centre (Nottingham).

2. Aim and Purpose

To identify, manage and eliminate inhibitors to factor VIII and IX in congenital haemophilia A and B.

3. Definitions, Keywords

Inhibitor: antibody to factor VIII or IX. FEIBA: Factor Eight Inhibitor Bypassing Activity – activate Prothrombin Complex Concentrate. rVIIa: activated factor VII. Bethesda assay: a laboratory test designed to quantify the antibody titre. Immune tolerance induction: Giving large, frequent doses of factor VIII with the aim of suppressing the inhibitor.

4. Main body of Guidelines

Inhibitor surveillance

1. Mutation analysis

Mutation analysis gives prognostic information about the risk of inhibitor development.

1.1 All newly diagnosed patients with haemophilia should have mutation analysis as soon as possible after diagnosis.

1.2 Any patient with a diagnosis of haemophilia in whom mutation analysis has not been performed previously, should have analysis performed as soon as possible regardless of severity of haemophilia.

1.3 All mutations in mild and moderate haemophilia A should be checked on the relevant database to establish whether any association with inhibitor formation has been reported, and this information highlighted in the patient's record.

2. Inhibitor surveillance in severe haemophilia A

2.1 An inhibitor test should be performed in severely affected patients with haemophilia A at least every third exposure day (ED) or every 3 months until the 20th ED. After the 20th ED an inhibitor test should be done every 3–6 months up to 150 EDs.

2.2 Previously untreated and minimally treated patients with severe haemophilia A who have received an intensive FVIII exposure ≥ 5 exposure days (EDs)] should be closely monitored for inhibitor formation. Some consideration may be given to starting early prophylaxis.

2.3 Inhibitor testing should continue 1–2 times a year indefinitely.

2.4 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.

2.5 Inhibitor screening for patients on prophylaxis should include a trough Factor VIII level and an inhibitor screen.

2.6 Inhibitor screening must be performed prior to all invasive procedures.

2.7 Inhibitor screening must be done if unexpected bleeding or frequency of breakthrough bleeding increases in patients on prophylaxis.

2.8 Inhibitor screening should be done if the clinical or laboratory response to factor concentrate replacement is poor.

2.9 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.

3. Inhibitor surveillance in moderate and mild haemophilia A

3.1 An inhibitor test should be performed in mild and moderate haemophilia A yearly (if they have been exposed to FVIII).

3.2 An inhibitor test should be performed in mild and moderate haemophilia A after intensive exposure (≥ 5 EDs).

3.3 An inhibitor test should be performed in mild and moderate haemophilia A after surgery.

3.4 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.

4. Inhibitor surveillance in severe haemophilia B

4.1 An inhibitor test should be performed in severely affected patients with haemophilia B at least every third ED or every 3 months until the 20th ED. After the 20th ED an inhibitor test should be done every 3–6 months up to 150 EDs. Testing after 150 EDs is only required if clinically indicated.

4.2 FIX inhibitors are associated with allergic reactions to FIX, including life-threatening anaphylaxis especially in those with gene deletions. The first 20 exposures in patients with severe haemophilia B should be given in hospital with access to paediatric resuscitation facilities.

4.3 Any reaction to FIX concentrate should prompt inhibitor testing before further FIX exposure as even low-level FIX inhibitors may cause anaphylaxis.

5. All new inhibitors must be reported to the National Haemophilia Database

6. The presence of an inhibitor must be demonstrated on more than one occasion by an inhibitor screen and quantified by a Nijmegen-modified Bethesda assay. The presence of a low titre FVIII inhibitor is an elimination half-life of <7 h.

5. Treatment of inhibitors

Treatment of inhibitors must be discussed and agreed with a Comprehensive Care Centre (Nottingham).

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.

5.1 Treatment of bleeding episodes

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 the on call haematology team.
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

Severe haemophilia A

a. Bleeds may be managed with large doses of FVIII in low responders and FEIBA or rFVIIa in high responders.
b. FVIII can be considered for major bleeds in high responding patients with low-titre antibodies.

c. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII infusions rather than increase the dose.
d. Single dose FEIBA (50–100 iu/kg), single high dose (270 micrograms/kg) rFVIIa or 1–3 standard doses (90 micrograms/kg) of rFVIIa are all treatment options for early haemarthroses.
e. Treatment of non-joint bleeds should be with FVIII or standard doses of FEIBA or rFVIIa until further data are available.
f. 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.
g. Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose FVIII concentrate.
h. Combined treatment with rFVIIa and FEIBA should only be considered for life- or limb-threatening bleeds unresponsive to either agent used alone.

Severe haemophilia B

a. Patients who have experienced allergic reactions to FIX should be treated with rFVIIa.
b. Bleeds may be managed with large doses of IX in low responders and FEIBA or rFVIIa in high responders.
c. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FIX infusions rather than increase the dose.
d. Single dose FEIBA (50–100 iu/kg), single high dose (270 micrograms/kg) rFVIIa or 1–3 standard doses (90 micrograms/kg) of rFVIIa are all treatment options for early haemarthroses.
e. Treatment of non-joint bleeds should be with FIX or standard doses of FEIBA or rFVIIa until further data are available.
f. 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.
g. Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose IX concentrate.
h. Combined treatment with rFVIIa and FEIBA should only be considered for life- or limb-threatening bleeds unresponsive to either agent used alone.

Mild/moderate haemophilia A

a. Patients with mild/moderate haemophilia A with high inhibitor prevalence mutations or family history of inhibitor, should be treated with desmopressin wherever possible to avoid FVIII exposure.
b. Patients with mild/moderate haemophilia A and an inhibitor should have a desmopressin 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.

5.2 **Immune tolerance: Haemophilia A**

Patients with severe haemophilia A and a factor VIII inhibitor, demonstrated on more than one occasion by a Nijmegen-modified Bethesda assay, that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII.
These patients should undergo ITI to eliminate the inhibitor and restore normal clinical responsiveness to FVIII.

Timing of ITI
ITI should be started as soon as an inhibitor is confirmed irrespective of the titre.

Venous access
A central venous access device should be inserted if required to facilitate uninterrupted ITI.

Initial ITI regimens
First line ITI should be conducted using recombinant FVIII concentrate (unless as part of a clinical trial). This is usually with the product used by the patient at the time of inhibitor development.

Historic peak inhibitor titre	Regimen
< 5 BU	• Start ITI at a dose of 50 IU/kg on alternate days. • Escalate the frequency, then dose if necessary, to control haemarthroses and clinically significant breakthrough bleeds, initially using daily treatment and then increasing factor VIII dosage in increments of 50 IU/Kg/day up to 200 IU/kg/day. • If the inhibitor titre on this ITI regimen increases above 40 BU, increase dose immediately to 100 IU/kg/day. If the inhibitor titre increases above 200 BU increase the dose immediately to 200 IU/kg/day.
>5 and <200 BU	• Start ITI at a dose of 100 IU/kg/day. • Escalate the dose of FVIII, if necessary, to control haemarthroses and clinically significant breakthrough bleeds, by increments of 50 IU/Kg/day up to 200 IU/kg/day • If the inhibitor titre rises to >200 BU, increase dose immediately to 200 IU/kg/day.
>200 BU	• Start ITI at a dose of 200 IU/kg/day.

The ITI doses should not be interrupted once started because this will compromise the success of ITI.

Monitoring ITI
The inhibitor titre should be measured weekly after initiation of ITI to define the peak inhibitor titre. A Bethesda assay with Nijmegen modification and no washout period should be used.

Once peak titre has been defined, the inhibitor titre should be monitored monthly thereafter. ITI should be continued as long as there is a sustained downward trend in inhibitor titre.
If there is an upward trend in titre, or inadequate reduction in titre over a 6 month period - defined as a fall in Bethesda titre of less than 20% in a 6 month period - modify the regimen:

- If factor VIII dosage <200 IU/kg/day, increase to this dose.
- If factor VIII dosage 200 IU/kg/day, change to second line regimen (see below).

NOTE: port a cath infection can cause an increase in inhibitor titre or a poor response to ITI and should be excluded before assuming an inadequate response.

Dose tapering when Bethesda is negative

Dose tapering should not be attempted in poor risk patients (titre at start of ITI >10 BU, peak titre on ITI >200 BU) until the FVIII half-life is greater than 7 hours and dose reduction should then be undertaken cautiously.
In good risk patients (titre at start of ITI <10 BU, peak titre on ITI <200 BU), when the Bethesda assay after heat treatment (58°C for 60 minutes) is negative for 2 consecutive months continue ITI regimen unchanged but perform the following measurements monthly;.

- 24 hour trough factor VIII level
- In vivo recovery (IVR) (measured with a pre and a 15 minute post sample).

When 24 hour trough level is >1 IU/dL for 2 consecutive months dose reduction can be initiated;

- Reduce factor VIII dosage by available vial size increments, but maintain the 24 hour trough factor VIII level >1 IU/dL. If breakthrough bleeds occur, FVIII trough should be maintained at a higher level.
- To help guide dose tapering, the trough FVIII level is proportional to the dose if the half-life remains constant. Therefore if the dose is reduced by 50% the trough will also decrease by about 50%.
- The factor VIII dose should not be reduced by more than 50% at one time and the trough should be measured soon after the reduction to ensure a level above 1 IU/dL is maintained.
- Continue to measure Bethesda titre and 24 hour trough factor VIII level monthly and reduce FVIII dose further if trough is >1 IU/dL.
- Maintain the 24 hour trough >1 IU/dL during dose reduction.
- If the Bethesda titre becomes positive, the 24 hour trough factor VIII level is <1IU/dL, or a breakthrough bleed occurs, reintroduce the previous factor VIII dosage.
- When the factor VIII dose has been reduced to 50 IU/Kg/day and the 24 hour trough factor VIII level is >1 IU/dl, either continue daily infusions or switch to alternate day treatment. (Alternate day treatment is likely to require an increase in total factor VIII dose to maintain a 48 hour trough factor VIII level of > 1 IU/dl and pharmacokinetic studies will be helpful to plan the change in regimen).
- Continue to reduce factor VIII dose to maintain a 24 or 48 hour trough factor VIII level of > 1IU/dl and to prevent breakthrough bleeds.

Definition of tolerance

The patient is considered tolerant when a post washout Nijmegen Bethesda is negative and FVIII half-life is >7 hours.

A surrogate measure of a FVIII half-life >7 hours is when the FVIII dose has been reduced to ≤50 IU/kg on alternate day and the trough FVIII level is ≥1 IU/dL.

Partial remission

Partial remission is defined as Nijmegen Bethesda assay negative and trough FVIII level maintained >1 IU/dL on either daily or alternate day treatment, without fulfilling the additional half life and/or dose reduction thresholds defining complete tolerance.

Follow up

Prophylaxis should be continued indefinitely.

- Monitor the Bethesda titre and trough factor VIII level monthly for 6 months, then 2 monthly for 12 months and then routinely.
- Restart ITI immediately if relapse detected.

Poor responders and second line therapy

If there is an inadequate sustained downward trend in the inhibitor titre, consider alternative strategies;

- Options include FVIII dose increase, the introduction of plasma derived FVIII with a high vWF content (pdFVIII) or immunosuppression with rituximab.

Timelines for second-line therapy

- If there is no sustained downward trend after 6 months* of first line ITI, escalate to full dose (200 IU/kg/day)
- If there is no sustained downward trend after 6 months* of full dose ITI (200IU/kg/day), change to pd FVIII or immunosuppression for a further 6 months*
- NB; pd FVIII and and immunosuppression may be undertaken simultaneously or sequentially. If used sequentially and there is no downward trend after 6 months* with the 1st choice intervention, consider adding the alternate intervention with a further 6 months observation.
- If there is no sustained downward trend after 6 months of pd FVIII and immunosuppression and FVIII cannot be used to prevent and treat bleeds he ITI should be stopped.
  The final decision regarding cessation of ITI can be referred to a UKHCDO expert panel via the Inhibitor Working party Chairperson if uncertainty remains about interpreting response to 2nd line ITI strategies and/or future treatment planning with either FVIII concentrate or bypassing agents..

NOTE: time periods denoted by * indicate maximum time to wait before evaluation of
response. Earlier changes can be made if the inhibitor titre is increasing or a sustained downward trend is unlikely).

ITI outcome

All ITI treatments and the outcome of each intervention must be reported to the National Haemophilia Database every 3 months.

5.3 Immune tolerance: Haemophilia B

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 tolerisation has been reported and the addition of immunosuppression to the ITI has been associated with
the highest success rates

5.4 Immune tolerance mild/moderate haemophilia A

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.
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.

5. References

UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A: A protocol from the UKHCDO Inhibitor and Paediatric Working Parties (18th November 2015)

Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition) Peter W. Collins, Elizabeth Chalmers, Daniel P. Hart, Ri Liesner, Savita Rangarajan, Kate Talks, Mike Williams and Charles R. Hay British Journal of Haematology

6. Documentation Controls

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