1. Introduction and Who Guideline applies to

This guideline is for staff caring for people with haemophilia A and B who are at risk of or have developed inhibitory antibodies to their factor concentrate.

The haemophilia A treatment landscape continues to evolve, most recently with regulatory approval of the biphenotypic antibody emicizumab (Hemlibra®, Roche) for both inhibitor and non-inhibitor settings.

2. Guideline Standards and Procedures

These guidelines are intended for use within the UHL Haemophilia Comprehensive Care Centre. They are based on the UKHCDO guidelines (2013, 2015 and 2021) and refer to congenital haemophilia A and B patients. Patients with acquired haemophilia are excluded from this guideline. These guidelines are a summary for UHL use. For detailed guidance, please refer to the full UKHCDO guidelines.

Mutation analysis

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

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

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

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

Inhibitor surveillance in *severe* haemophilia A

1. In severely affected patients with haemophilia A, an inhibitor test should be performed at least every third exposure day (ED) (typically weekly) 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. If an infant or child has been commenced on emicizumab as the first prophylaxis agent, utilizing FVIII clotting factor concentrate (CFC) for on-demand treatment, inhibitor testing should be performed 2–6 weeks after every FVIII CFC treatment episode for the first 50EDs, then 3–6 monthly thereafter whether exposed to CFC or not in that period, as cases have been identified in the UK of inhibitors emerging in patients treated with emicizumab in the absence of recent FVIII exposure
3. Previously untreated and minimally treated patients (<20 ED) with severe haemophilia A who have received an intensive FVIII exposure 3+ exposure days (EDs), in vivo recovery (IVR) and inhibitor testing should be considered during the episode Some consideration may be given to starting early prophylaxis.

4. Inhibitor testing should continue 1–2 times a year indefinitely.
5. 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.
6. Inhibitor screening for patients on prophylaxis should include a trough Factor VIII level and an inhibitor screen.
7. Inhibitor screening must be performed before all invasive procedures.
8. Inhibitor screening must be done if unexpected bleeding or frequency of breakthrough bleeding increases in patients on prophylaxis.
9. Inhibitor screening should be done if the clinical or laboratory response to factor concentrate replacement is poor.

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.

Inhibitor surveillance in *moderate and mild* haemophilia A

1. An inhibitor test should be performed in mild and moderate haemophilia A yearly (if they have been exposed to FVIII).
2. An inhibitor test should be performed in mild and moderate haemophilia A after intensive exposure (≥ 5 EDs).
3. An inhibitor test should be performed in mild and moderate haemophilia A after surgery.
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.

Inhibitor surveillance in *severe* haemophilia B

1. In severely affected patients with haemophilia B, an inhibitor test should be performed at least every third ED (typically 2-3 weekly) 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 because inhibitor development after this time has not been reported.
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 hospitals with access to paediatric resuscitation facilities.
3. Any reaction to FIX concentrate should prompt inhibitor testing before further FIX exposure as even low-level FIX inhibitors may cause anaphylaxis.

All new inhibitors must be reported to the National Haemophilia Database

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 has an elimination half-life of <7 h.

Emicizumab interferes with the one stage FVIII assay and chromogenic FVIII assays using human coagulation factors. Once Emicizumab has been started a chromogenic FVIII assay using reagents containing bovine coagulation factors must be used to monitor FVIII replacement. The Bethesda assay utilising a bovine-based FVIII chromogenic assay must be used [5]. Before Emicizumab is started, samples should be taken to measure

anti-human and anti porcine FVIII inhibitor titres.

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.

New “non-factor” therapies (e.g. Emicizumab) should be considered for patients with inhibitors in order to provide effective bleed prophylaxis. This should be discussed at the haemophilia MDT and started as soon as the inhibitor is confirmed.

Treatment of bleeding episodes

Arrangements should be in place to treat bleeds within 2hrs, either at home or in the 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 with inhibitors – acute bleeding

a. Bleeds may be managed with large doses of FVIII in low responders and FEIBA or rFVIIa in high responders. N.B. CONCOMITANT PRESCRIPTION OF EMICIZUMAB AND FEIBA SHOULD BE AVOIDED DUE TO AN INCREASED RISK OF THROMBOTIC MICROANGIOPATHY

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 it is especially important for mucosal bleeds.

g. Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmapheresis 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 with inhibitors – acute bleeding

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 plasmapheresis 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 with inhibitors – acute bleeding

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. This agent, combined with tranexamic acid, should be used whenever possible to avoid FVIII exposure. Desmopression may lead to a 3-5-fold rise in FVIII, usually limiting clinical utility in moderate haemophilia A.

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 part of a clinical trial). This is usually with the product used by the patient at the time of inhibitor development. The ITI doses should not be interrupted once started because this will compromise the success of ITI.

Figure: 1

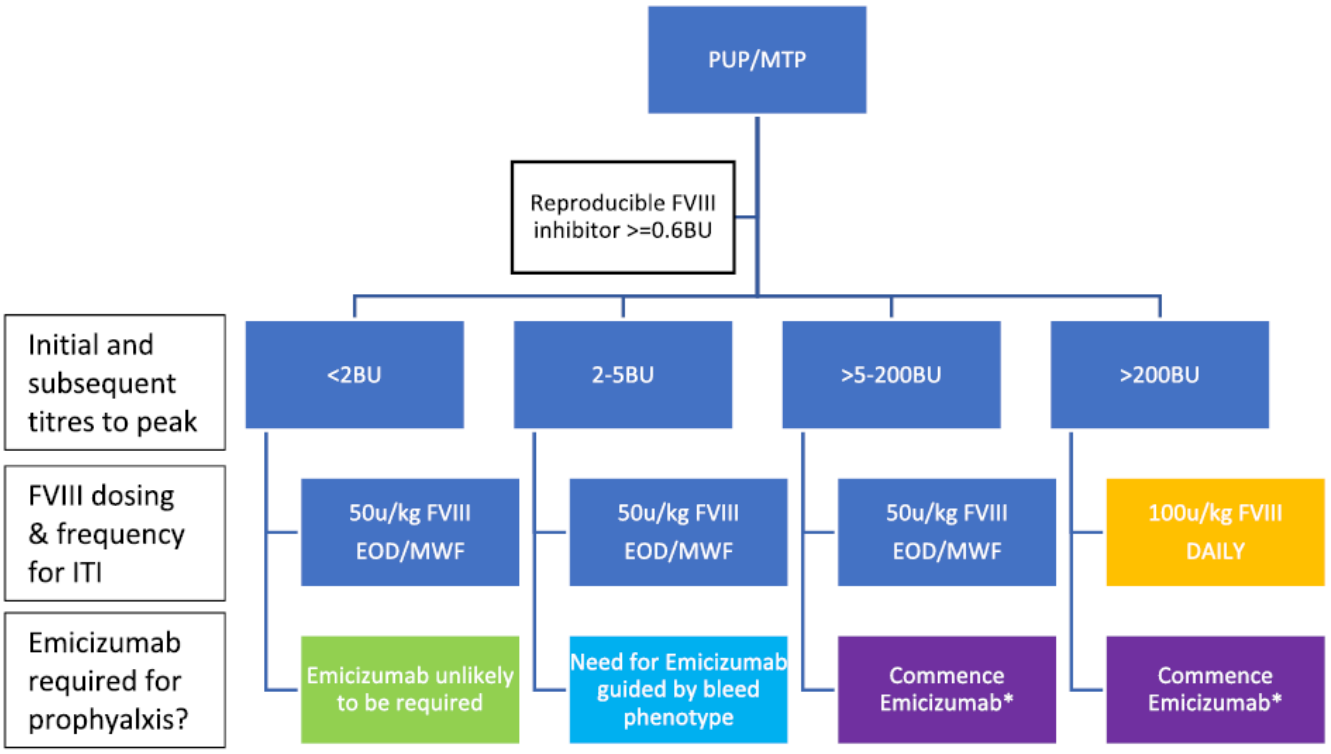

FIGURE 1 Initiation of Immune Tolerance Induction (ITI) in a minimally treated paediatric patient with severe haemophilia A and reproducible FVIII inhibitor > = .6BU. PUP, previously untreated patient; MTP, minimally treated patient; BU, Bethesda Unit; EOD, every other day; MWF, Monday, Wednesday, Friday; *Emicizumab loading and maintenance dosing should follow the accompanying manufacturer summary of product characteristics (SPC)

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.

If the patient was previously on (within last 6 months), remains on, or is being initiated on emicizumab, laboratory staff must be informed to ensure FVIII inhibitor levels are measured using chromogenic reagents containing bovine FIXa and FX components. FVIII activity and FVIII inhibitor estimation should not be measured by one-stage clotting assay in patients being treated with emicizumab, as the result is uninterpretable and invalid.

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 6 months - defined as a fall in Chromogenic Bethesda titre of less than 20% in 6 months - modify the regimen:

- If factor VIII dosage <100 IU/kg/day, increase to this dose.
- If factor VIII dosage 100 IU/kg/day, continue at this dose for a further 6 months ie complete 12 months at 100 U/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 two consecutive months continue ITI regimen unchanged but perform the following measurements monthly;.

- 24 hour trough factor VIII: C level
- In vivo recovery (IVR) (measured with a pre and a 15-minute post-sample) to ensure FVIII peaks maintained <150 iu/dl, decreasing FVIII dose if necessary to maintain peaks <150 iu/dl

When the 24-hour trough level is > = 2 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, 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.
- If breakthrough bleeds occur whilst on emicizumab a prophylaxis agent during ITI, check compliance and consider investigations for emicizumab anti-drug antibodies (ADA)

Definition of tolerance

1. Standard half-life FVIII

   A patient is considered tolerant when a post-washout Nijmegen Bethesda is negative, and the 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 48 hr trough FVIII level is ≥1 IU/dL.

2. Extended half-life FVIII

   A patient is considered tolerant when a post-wash-out Nijmegen Bethesda is negative, and the FVIII half-life is above the lower end of the normal range for children below the age of 6 years, or for the age of the child undergoing ITI for the concentrate being used.

   Once tolerance is achieved, FVIII CFC should be continued as prophylaxis to maintain tolerance. It is known that cessation of FVIII CFC and use of emicizumab prophylaxis carries a risk of inhibitor relapse. It is currently not known how high that risk is. The current UK consensus is that post-ITI prophylaxis should be with FVIII CFC

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/ ITI failure

Failure of ITI is defined as the inability to utilize FVIII CFC as the primary prophylaxis agent to satisfactorily prevent spontaneous bleeds, treat trauma and cover procedures and surgery safely.

Failure of ITI would necessitate stopping FVIII concentrate, continuing or re-initiating emicizumab as primary prophylaxis and utilising available BPA on demand to treat injury/bleed or cover surgery as per UKHCDO guidance.

Clinician and family/patient discussion will be required for second-line options which may include FVIII CFC product switch or immunomodulation (e.g. anti CD20mAb, Rituximab). Given the availability of an efficacious prophylaxis agent in the presence of chronic inhibitor, and the absence of robust data to support this second-line agent, it is unlikely 2nd line agents will be used other than in exceptional circumstances

ITI outcome

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

Emicizumab anti-drug antibody (ADA) screening

Clinical teams should be mindful of the possibility of ADA directed against emicizumab, particularly in the event of breakthrough bleeding.
Thought to occur in < 2% of cases, APTT and emicizumab level monitoring will aid interpretation if clinical concerns.
Poor compliance remains the most likely explanation for dropping/low emicizumab level and breakthrough bleeding can occur despite good compliance and satisfactory emicizumab levels. However, any combination of: dropping emicizumab levels; lengthening APTT; breakthrough bleeding of concern or no obvious explanation should prompt consideration of ADA screening.

It is currently not necessary to routinely screen for emicizumab ADA in the absence of clinical concern

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

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.

3.Education and Training

Nil

4. Monitoring Compliance

What will be	How will compliance be	Monitoring	Frequenc	Reporting

measured to monitor compliance	monitored	Lead	y	arrangements
Case review of patients with development of inhibitors	Case review	MDT lead	annual	MDT

5. Supporting References

1. 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)
2. 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, 2013, 160, 153–170
3. Hart D, Alamelu J, Bhatnagar N, et al. Immune tolerance induction in severe haemophilia A: a UKHCDO inhibitor and paediatric working party consensus update.. *Haemophilia*. 2021;27:932–937.

6. Key Words

Haemophilia, inhibitors, immune tolerance therapy, clotting factor

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr Sandhya Munireddy Guideline reviewed by Dr Sandhya Munireddy and Dr Shyamala Chinnabhadra	**Executive Lead**
Details of Changes made during review: **Sections on Emicizumab included. Figure 1 included**	