



# **GUIDELINES FOR THE TREATMENT OF INHIBITORS IN HAEMOPHILIA A**

**Australian Haemophilia Centre Directors'  
Organisation**

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## **Disclaimer**

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (September 2004).

These guidelines will be reviewed in 2007.

## **1. INTRODUCTION**

The management of patients with Haemophilia A and inhibitors is complex and must be managed by a Haemophilia Treatment Centre (HTC). Major issues with treatment are firstly, the control of acute haemorrhage and secondly the eradication of the inhibitor (tolerisation). A systematic review of management of inhibitors in Haemophilia A has been recently published [1].

The incidence of inhibitors in those with severe Haemophilia B is much less common (1.5%) but requires more careful individual management in a HTC. Anaphylaxis can occur and is an additional complication. These guidelines do not apply to inhibitors in Haemophilia B.

These guidelines will be reviewed in 2007.

## **2. GENERAL COMMENTS**

Approximately 25% of patients with severe Haemophilia A develop inhibitors after initial treatment with factor VIII concentrates. Approximately half of these appear transient and disappear with continued therapy with factor VIII. Therefore the diagnosis of an inhibitor, irrespective of titre, requires active monitoring and treatment to determine whether the inhibitor progresses to a high titre inhibitor or is transient. The diagnosis of an inhibitor should be conducted using Bethesda criteria.

After initial diagnosis of a low titre inhibitor in a patient with Haemophilia A, routine doses of factor VIII may be as much as doubled and the clinical response and inhibitor titre monitored. Subsequent poor clinical response or rising titre levels indicate a non-transient inhibitor. The diagnosis of a high titre inhibitor which does not respond to factor VIII should be treated with an alternative product.

There is an incidence of inhibitors in those with mild Haemophilia A following treatment with factor VIII concentrates and the guidelines will also apply to those patients. DDAVP is occasionally used in mild to moderate haemophilia but is often ineffective.

## Definitions

Minor bleeds include muscle and joint haemarthrosis but are not trauma related.

Major bleeds include trauma related muscle or joint injury, severe spontaneous muscle bleeds eg psoas or iliacus, and haemorrhages affecting an organ.

Surgery which affects inhibitor patients includes dental procedures, insertion of intravenous access devices and emergency and major elective procedures. Both dental surgery and insertion of intravenous access devices require shorter durations of replacement therapy.

## **3. CONTROL OF HAEMORRHAGE**

### **3.1. Products Available**

In Australia the main products available are

- factor VIII, either recombinant or plasma-derived
- recombinant factor VIIa
- activated prothrombin complex concentrate (eg FEIBA)
- prothrombin complex concentrate (eg prothrombinex-HT)
- antifibrinolytics (eg tranexamic acid)

**Note:** Porcine factor VIII is no longer being manufactured and will only be available through the SAS until current world wide stocks are exhausted.

#### **3.1.1. Factor VIII**

In the case of life threatening haemorrhage infusion of factor VIII in large doses can be used to swamp the inhibitor. This therapy is mostly used in patients with low responding inhibitors (inhibitor titre is <5 BU/mL after infusion of factor VIII). In patients who are high responders, this treatment may be effective provided the inhibitor level is less than 5 BU/mL. Factor VIII levels should be observed to assess and monitor response. Anamnesis can

occur 5-7 days after therapy and make factor VIII ineffective. Recombinant and plasma-derived factor VIII are available.

### **3.1.2. Recombinant Factor VIIa**

This product has been widely used in Australia and has proved to be highly effective in the management of spontaneous bleeding episodes which are life or limb threatening. Evidence in the literature suggests that it is effective in 79-92% of such episodes [2]. In addition, there is evidence that it is effective in over 90% of cases of surgery [2].

Recombinant factor VIIa is infused as a bolus. Continuous infusion of recombinant factor VIIa may reduce the quantity and cost of treatment but evidence is conflicting. A recent study suggests continuous infusion of 50 µg/kg/hr is effective in surgery [3]. Antifibrinolytics are administered concurrently. The standard adult dose of recombinant factor VIIa is 90 µg/kg. However in children the mean half life is substantially reduced to 1.32 hours [2] and thus higher doses of up to 200-250 µg/kg may be required.

Present indications for funding of recombinant factor VIIa by the National Blood Authority (NBA) are for limb and life threatening haemorrhages. There is widespread evidence that recombinant factor VIIa is effective for treatment of all haemorrhage in patients with high responding factor VIII inhibitors. The appropriate treatment for all haemorrhages should be extended to all children and adults regardless of their State of residency.

### **3.1.3. Activated Prothrombin Complex Concentrates (APCCs) eg FEIBA VH**

Activated prothrombin complex concentrate, such as FEIBA VH, is effective in the treatment of 90% of bleeding episodes [2], and has been effective in the management of bleeding during major surgery [2]. An effective dose is 60-100 units/kg twice per day. The maximum daily dose of FEIBA is 200 units/kg/day. Antifibrinolytic agents, such as tranexamic acid, should not be administered concurrently with FEIBA. It should be noted that FEIBA contains small

amounts of factor VIII and therefore may cause elevation of inhibitor titres in some patients. The 1997 Working Party Report [4] did not recommend the use of these agents as first choice because they are plasma-derived rather than recombinant products; there is a reported high incidence of thrombosis associated with their use; and it is not possible to measure their activity in a standardised way. Nevertheless, AHCDO recommends that these products remain an option for treatment for complex cases in which alternative methods have proved ineffective.

In patients who are having frequent bleeds, a trial of FEIBA as prophylaxis should be considered. The suggested dose is 75-100 units/kg three times a week.

#### **3.1.4. Prothrombinex-HT**

Despite general scepticism about the effectiveness of prothrombinex-HT in the management of joint haemorrhage, some patients report benefit and continue to be treated with this product. There are concerns about the incidence of thrombosis when using repeated high doses, particularly in the presence of liver disease and when used in combination with antifibrinolytics. There is no evidence of efficacy in serious haemorrhages in surgery [2]. AHCDO recommends that recombinant factor VIIa is used in future for these patients.

#### **3.1.5. Antifibrinolytic therapy**

The recommended dose of tranexamic acid is 80-100 mg/kg/day, with a standard dose being 1g, *qid* given orally (recommended paediatric dose is 35 mg/kg/8hr). An intravenous preparation is available in Australia through the SAS. Intravenous epsilon aminocaproic acid (EACA) is no longer produced and not available.

#### **3.1.6. Plasmapheresis / Immunoabsorption**

Plasmapheresis can be used to reduce inhibitor titres to allow effective therapy with factor VIII. Specific immunoabsorption using the Malmo protocol [5] is not available in Australia.

There is as yet little information on the use of immunosuppression in patients with factor VIII inhibitors but some experimental protocols are being proposed. Immunosuppression has been associated with side effects including delayed wound healing and increased susceptibility to infection. Rituximab (anti CD 20 monoclonal antibody) therapy may be considered as an adjunct therapy to reduce inhibitor titres.

## **3.2. Treatment Regimens**

### **3.2.1. Low titre inhibitor (<5 BU/ml), low responder (see Algorithm A)**

Minor bleeding

The recommended dose of factor VIII is 50-100 IU/kg repeated every 8-12 hours. The response should be assessed clinically and factor VIII levels monitored.

Major bleeding

The recommended dose of factor VIII is 50-150 IU/kg repeated every 8-12 hours. The response should be assessed clinically and factor VIII levels monitored and maintained at > 50% until healing has completed.

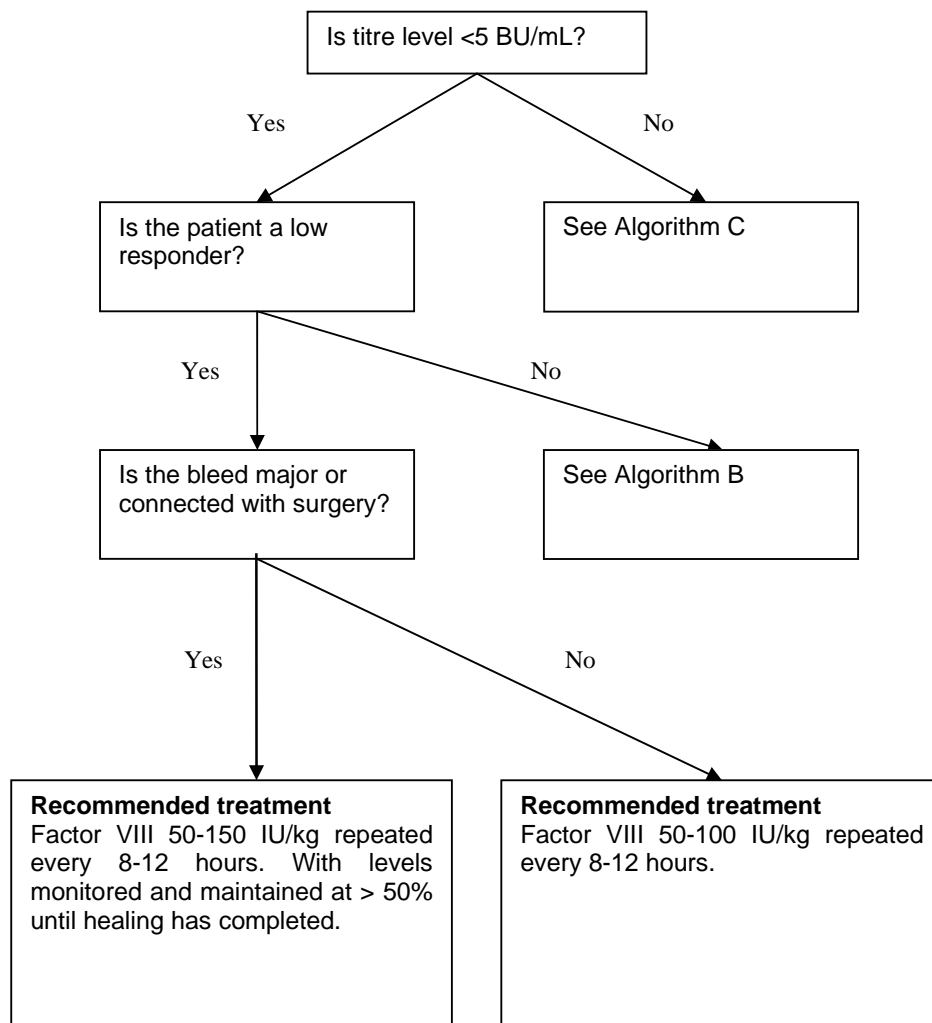
### **3.2.2. Low titre inhibitor (<5 BU/ml) but history of high responder (see Algorithm B)**

Minor bleeding

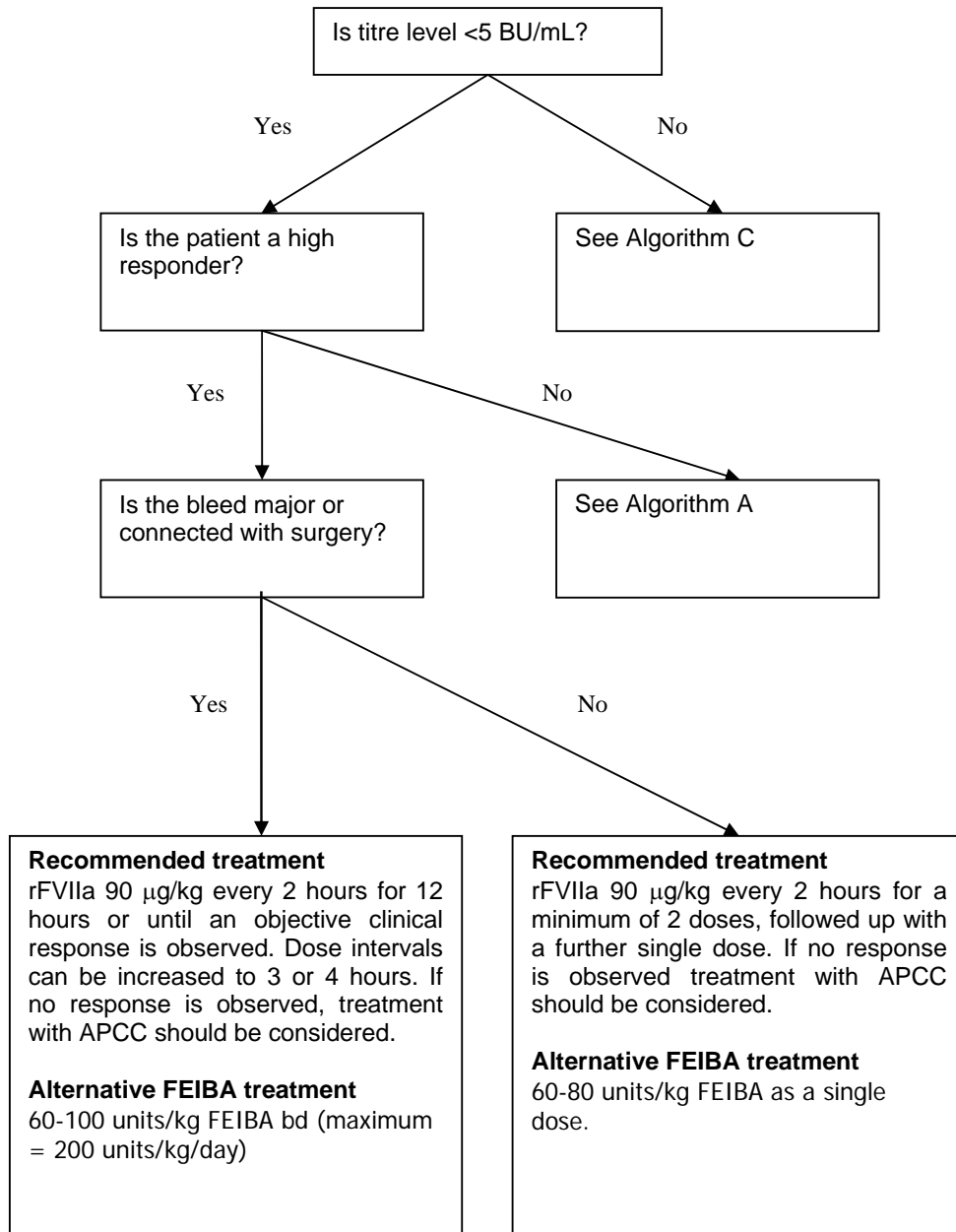
Infusions of factor VIII will cause an anamnestic rise of the levels of factor VIII inhibitor within 3-5 days rendering further therapy with factor VIII ineffective.

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended paediatric dose may be up to 200-250 µg/kg) at 2 hourly intervals for a minimum of 2 doses or until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

## Algorithm A- Low Titre Low Responder



## Algorithm B- Low Titre High Responder



**Footnote: Higher doses of rFVIIa are required for young children**

#### Major bleeding

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended paediatric dose may be up to 200-250 µg/kg) at 2 hourly intervals for 12 hours or until an objective clinical response is observed. Dose intervals can be increased to 3 or 4 hours. The duration of therapy depends on the extent of the initial haemorrhage. If no response is observed, treatment with APCC should be considered.

### **3.2.3. High titre inhibitor (>5 BU/ml) (see Algorithm C)**

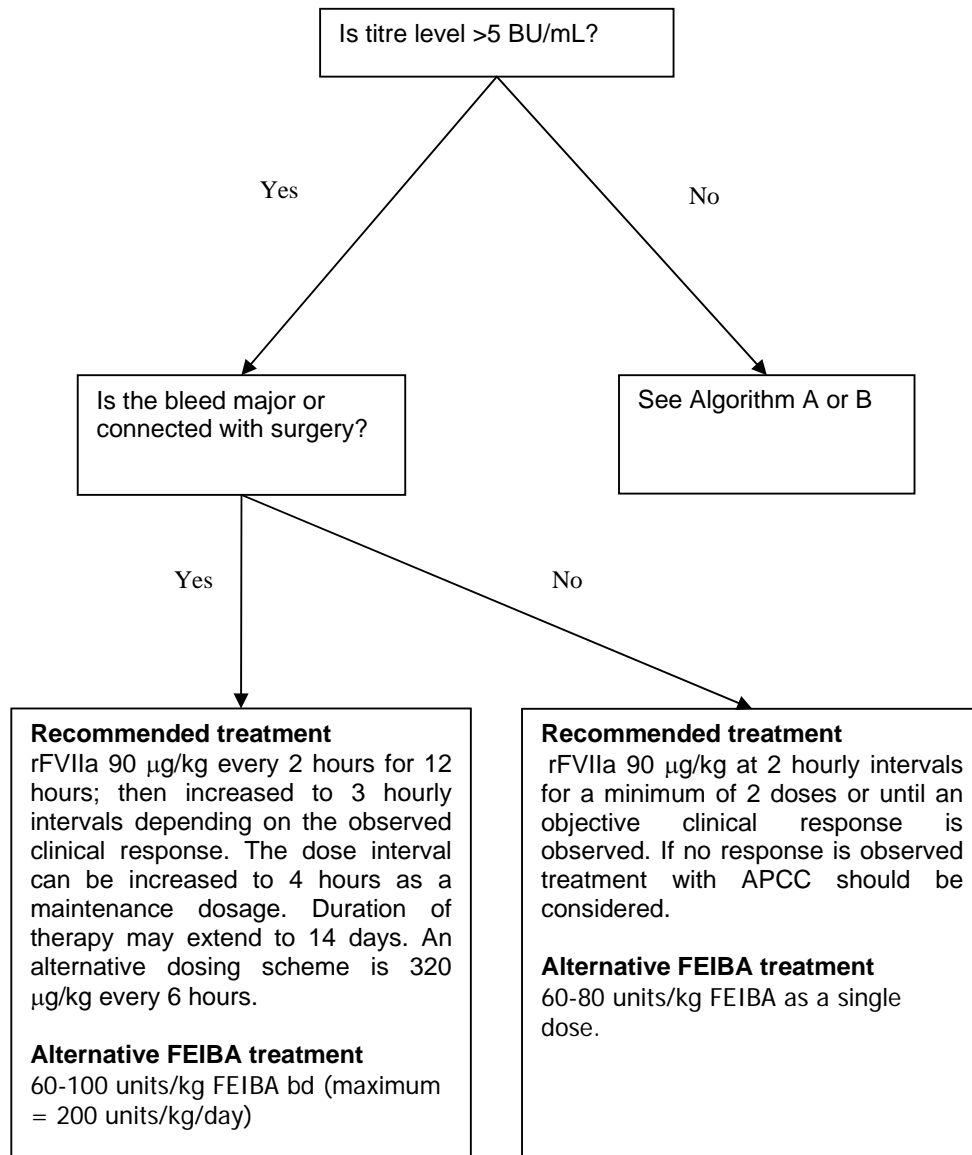
#### Minor bleeding

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended paediatric dose may be up to 200-250 µg/kg) at 2 hourly intervals for a minimum of 2 doses or until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

#### Major bleeding

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended paediatric dose may be up to 200-250 µg/kg) at 2 hourly intervals for 12 hours; then increased to 3 hourly intervals depending on the observed clinical response. If appropriate, the dose interval can be further increased to 4 hours as a maintenance dosage. The duration of therapy is dependent on the severity of the haemorrhage. If major surgery has been performed, the duration of therapy may extend to 14 days. An alternative dosing scheme is 320 µg/kg every 6 hours. If no response is observed, treatment with APCC should be considered.

## Algorithm C- High Titre



**Footnote: Higher doses of rFVIIa are required for young children**

### **3.2.4. Elective Major Surgery**

Major surgery in patients with inhibitors carries a high degree of risk and should only be carried out in recognised HTC after careful consultation and agreement with at least one other Australian haemophilia specialist. All such discussions should be documented. It is recommended that a pharmacokinetic study be undertaken before surgery. The dosage regimen is based on the regimen for major bleeds (Sections 3.2.1, 3.2.2 and 3.2.3 above).

Dental surgery and the insertion of IV access devices require 3-5 days of therapy and antifibrinolytics.

### **3.2.5. Emergency Major Surgery**

The dosage regimen is based on the regimen for major bleeds (Sections 3.2.1, 3.2.2 and 3.2.3 above). If time allows, there should be consultation and agreement with one other haemophilia specialist as in Elective Major Surgery. Any such discussion should be documented. The patient should be transferred to a recognised HTC as soon as practicable.

### **3.2.6. Home Therapy**

AHCDO recommends that home therapy only be considered with close monitoring and regular medical supervision.

## **4. TOLERISATION**

Tolerisation should be considered in all those patients with recent persisting inhibitors. Eradication of the inhibitor will allow the patient with haemophilia to be treated with factor VIII, either on demand or prophylactically, with an optimal outcome and improved quality of life. Immune tolerance induction (ITI) is demanding for both patients and parents, and written informed consent should be obtained before starting. Intensive replacement therapy for immune tolerance usually requires central venous access.

## **4.1. Haemophilia A**

The International Registry on Tolerisation [6] identifies better results in those patients with a lower age at the start of ITI; shorter elapsed time of inhibitor presence before ITI; lower maximum pre-treatment inhibitor titres and treatment with higher doses of factor VIII.

### **4.1.1. Participation in international clinical trial**

AHCDO strongly recommends participation in an international randomised trial of high dose versus low dose factor VIII tolerisation protocols. All patients considered eligible for the trial should be involved.

### **4.1.2. Treatment for patients who are ineligible for participation in clinical trial**

For patients who do not enter an international trial, there are a number of published tolerisation protocols that describe a variety of doses of FVIII (e.g. 50 IU/kg three times a week up to 200 IU/kg daily) as well as the use of immune suppression. Tolerisation should continue until eradication of the inhibitor demonstrated by a greater than 60% recovery and normal half-life of factor VIII. Tolerisation should only be attempted in consultation with a physician experienced in the management of patients with haemophilia and inhibitors.

## **4.2. Acquired Haemophilia A**

Immunosuppression is recommended for eradication of inhibitors in Acquired Haemophilia A.

## **4.3. Patients for whom tolerisation is not advised**

It is recommended that adults with severe haemophilia A who have had an inhibitor for many years, and in some instances decades, should be managed with treatment of haemorrhage by infusion of recombinant factor VIIa. Adult patients with mild or moderate Haemophilia A who develop inhibitors often have mild inhibitors which may decline with time. These patients should be

treated with desmopressin for minor bleeds and recombinant factor VIIa for more serious haemorrhages. Tolerisation may be considered if haemorrhages cannot be controlled by recombinant factor VIIa.

## REFERENCES

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