CHAPTER

96

Current Management of Hemophilia

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INTRODUCTION

Haemophilia is an X-linked congenital bleeding disorder caused by a deficiency of clotting factor VIII (Haemophilia A) or factor IX (Haemophilia B). In haemophilia, the FIXa/ VIIIa complex fails to form on the platelet surface and does not activate sufficient FX for a large burst of thrombin. Without this thrombin burst, the subsequent conversion of fibrinogen to fibrin, the haemostatic plug is unstable, leading to prolonged bleeding (Figure 1).

EPIDEMIOLOGY

The worldwide incidence of hemophilia A is 1 in 5000 male live births, and that of hemophilia B is 1 in 30,000 males. The number of people with haemophilia in the world, based on WFH's annual global survey of 2014 is approximately 1, 78,500. India has the highest disease burden of 17,470 patients including 14,450 with Haemophilia A, which constitutes only about 23% of the actual number of cases; due to under diagnosis.

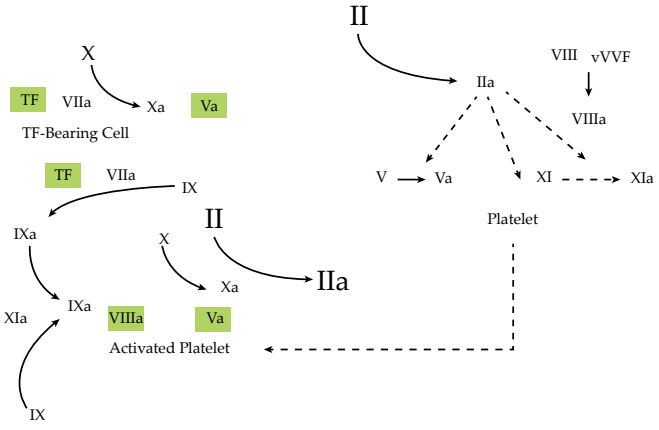


Fig. 1: FactorVIII function

GENETICS

Haemophilia is an X-linked recessive disorder and is more likely to manifest in males. A female who carries the defective gene on one X chromosome will be a carrier (heterozygous) and on both X chromosomes will have Haemophilia (homozygous). Some carriers may have clotting factor level so low that they fall within the moderate-to-severe range of haemophilia due to a phenomenon called 'extreme lyonisation'.

One-third of cases may arise from spontaneous mutation of the F8 and F9 genes.

CLINICAL FEATURES

Typical history includes recurrent bleeding symptoms that may occur spontaneously or due to any trivial injury. Depending on the site and severity of bleeding, bleeds are classified as mild to moderate and severe/major/ life threatening in nature.

Mild to Moderate Bleeds

- Joint bleed
- Muscle bleed (Figures 3 & 4)
- Mucocutaneous bleed

Major or Life Threatening or Severe Bleeds

- Gastro-intestinal
- Genito-urinary
- Intracranial

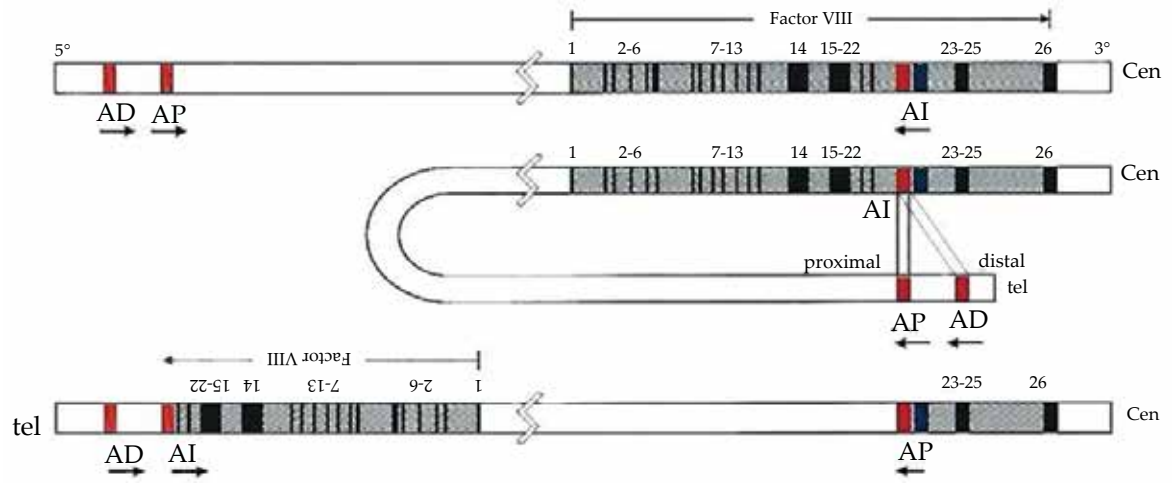


Fig. 2: intron 22 inversion-most common genetic abnormality in Haemophilia A

- Intra-abdominal
- Retroperitoneal
- Bleeding from neck, throat, chest

The difference betweeen platelet and coagulation disorders are enumerated in Table 1. Common sites of bleeding are listed in Table 2.

DIAGNOSIS

Screening tests reveal isolated prolongation of aPTT in haemophilia (Table 3). However, a normal aPTT does not exclude haemophilia because of its relative insensitivity.

A FVIII (normal 50-150%) and or FIX assay should be requested to confirm the diagnosis of haemophilia.

COMPLICATIONS OF HAEMOPHILIA

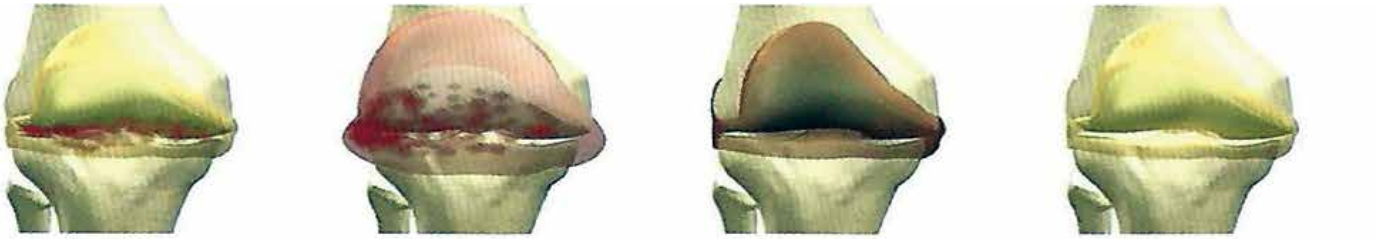
- Joint bleeds (haemarthrosis) and disability
- Synovitis
- Pseudotumor(muscle hematoma)
- Chronic hemophilic arthropathy
- Fractures
- Transfusion related (anaphylaxis and viral infections)
- Psychosocial impact

MANAGEMENT OF HAEMOPHILIA

The primary goal of haemophilia therapy is to prevent

Table 1: Difference between platelet and coagulation disorders

	Platelet Disorders	Coagulation Factor Disorder
Site of bleeding	Skin, mucous membrane and soft tissue	Deep in soft tissues (joints and muscles)
Physical Finding	Petechiae, ecchymoses	Hematoma, Hemarthrosis
Bleeding after cuts and scratches	Yes	No
Bleeding after surgery and trauma	Immediate, usually mild	Delayed (1-2 days), often severe



Bleeding starts within the joint

As blood accumulates in the joint, it swells, become warm to the touch and may be painful. Appropriate treatment at this state will stop further bleeding in to the joint

The synovium breaks down the bleed and absorbs it from the joint

After about a week, all the blood is absorbed and the joint returns to its pre-bleeds state

Fig. 3: Short term impact of joint bleeds

A Single bleeding event may be sufficient to provoke inflammation (synovitis)

Recurrent bleeding leads to swelling of the joint and ongoing synovitis

Growth of the joint lining (synovium) leads to an inflammed, vascular, and fragile tissue that is more likely to bleed. Further bleeds can destroy the cartilage

Destruction of cartilage leads to long - lasting joint damage, resulting in arthritis and stiffened joints

In later stages, there is complete loss of cartilage and the bone may become deformed, changing the shape of the joint

Fig. 4: Long term impact of joint bleeds

and treat bleeding with the deficient clotting factor; and whenever possible should be treated with specific factor concentrate. Acute bleeds should be treated as quickly as possible, preferably within 2 hours. If in doubt, treat.

FIRST AID MEASURES

- P - Protection (Splint)
- R - Rest - avoid weight bearing / restrict movement
- I – Ice (crushed, indirect, 3-4x/day)
- C – Compression
- E – Elevation

REPLACEMENT THERAPY AND DIFFERENT TYPES OF CLOTTING FACTORS (FIGURE 5)

Replacement therapy is done by providing concentrates of deficient clotting factors and is preferred over the use of cryoprecipitate and fresh frozen plasma.

CLOTTING FACTOR CONCENTRATES

They are of two types-

- Plasma Derived
- Recombinant Therapy (Figure 6)

1 unit/kg factor concentrate increases factor VIII level by 2IU/dL, and factor IX level by 0.8 IU/dL in the absence of an inhibitor.

Table 2: Common sites of bleeding in haemophilia

Site of Bleeding	Approximate Frequency
Hemarthrosis • more common into hinged joints: ankles, knees and elbows • less common into multi-axial joints: shoulder, wrists, hips	70%-80%
Muscle	10%-20%
Other major bleeds	5%-10%
Central nervous system (CNS)	<5%

The patient's factor level should be measured 15 minutes after the infusion, to verify the calculated dose. Factor concentrates should be infused by slow IV injection at a rate not exceeding 3mL/min in adults.

Dose Required = Body Weight x Desired Factor Level (IU/dL) x 0.5 (Haemophilia A)
Dose Required = Body Weight x Desired Factor Level (IU/dL) x 1.25 (Haemophilia B)

Prothrombin complex concentrates which contain factor IX along with activated clotting factors such as II VII & X may predispose to thromboembolism and so not preferred in treatment of Factor IX deficiency.

OTHER PLASMA PRODUCTS

Fresh Frozen Plasma

It contains all coagulations factors but is poor in factor VII. 1 ml of FFP contains 1 unit of factor activity. Acceptable starting dose is 15-20ml/kg.

Cryoprecipitate

It is rich in Factor VIII, XIII, vWF and fibrinogen. It is preferable to FFP for the treatment of haemophilia A in situations where clotting factor concentrates are not available

PROPHYLAXIS

The goal of prophylaxis is to prevent bleeding events and joint degeneration to preserve normal musculoskeletal function. The World Health Organisation (WHO) and WHF guidelines recommend prophylactic therapy as the gold standard of management.

Two prophylaxis protocol are supported by long-term data (Tables 5 & 6).

DOSAGE

- 25-40 IU/kg as per MALMO protocol per dose
- 15-30 IU/kg as per UTRECHT protocol per dose
- administered three times a week for those with

Table 3: Interpretation of screening test

Possible Diagnosis	PT	APTT*	BT	Platelet Count
Normal	Normal	Normal	Normal	Normal
Hemophilia A or B**	Normal	Prolonged*	Normal	Normal
VWD	Normal	Normal or prolonged*	Normal or prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or prolonged	Normal or reduced

Table 4: Category of Bleeding Tendency for People with Haemophilia A

Category	FVIII concentration (Relative %)	Clinical presentation
Severe	<0.01 IU/mL (<1% of normal)	Spontaneous joint and muscle bleeding; bleeding after injuries, accidents, and surgeries
Moderate	0.01 – 0.05 IU/mL (1-5% of normal)	Bleeding into joint and muscles after minor injuries; excessive bleeding after surgery and dental extraction
Mild	>0.05 – 0.40 IU/mL (5-40% of normal)	Spontaneous bleeding does not occur; bleeding after surgery, dental extraction, and trauma

haemophilia A, and twice a week for those with haemophilia B

ON-DEMAND TREATMENT

OTHER PHARMACOLOGICAL OPTIONS

Desmopressin (DDAVP)

Desmopressin, a synthetic analogue of the vasopressin may be the treatment of choice in mild or moderate haemophilia. It enhances the interaction of FVIII and vWF and elevates FVIII three to six times the baseline levels to control bleeding. A single dose of 0.3ug/kg body weight, either by intravenous or subcutaneous route, may be given.

Tranexamic acid

It is an antifibrinolytic agent and is usually given as an oral tablet 3 to 4 times daily. It may be given alone or together with factor VII concentrates.

Epsilon aminocaproic acid (EACA)

It is similar to tranexamic acid and is given to adults orally or intravenously every 4 to 6 hours up to a maximum of 24 g/day in an adult.

Other Management Options

Adjuvant treatment and other supportive strategies used in the management of haemophilia are shown in Tables 7 & 8 below.

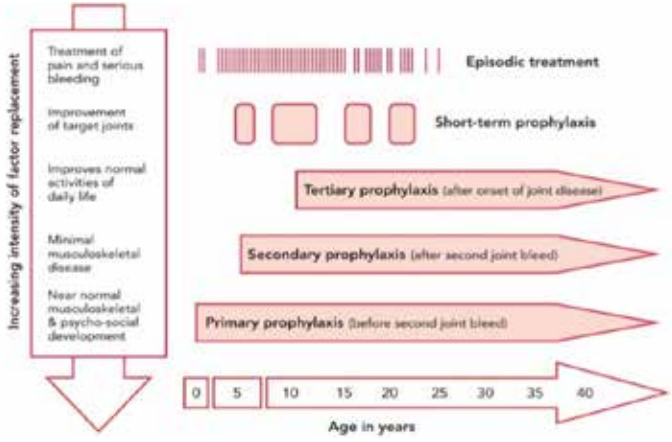


Fig. 5: Strategies for clotting factor replacement at different ages and impact on outcomes

COMPLICATIONS OF HAEMOPHILIA TREATMENT

Inhibitors

Inhibitors are allogenic IgG antibodies that neutralise clotting factors. Inhibitor development occurs in 20-30% of patients with severe haemophilia A and 2-3% with haemophilia B who are on prophylaxis. Confirmation and quantification of an inhibitor is performed in the laboratory using the Nijmegan-Modified Bethesda assay.

When to screen for Inhibitors

- Once every 5 exposure days until 20 exposure days and every 10 exposure days between 21 & 50 exposure days, then 2/year
- Intensively treated for >5 days, within 4 wks of the last infusion
- Prior to surgery
- Recovery assays are not as expected
- Clinical response is sub-optimal in the post-operative period

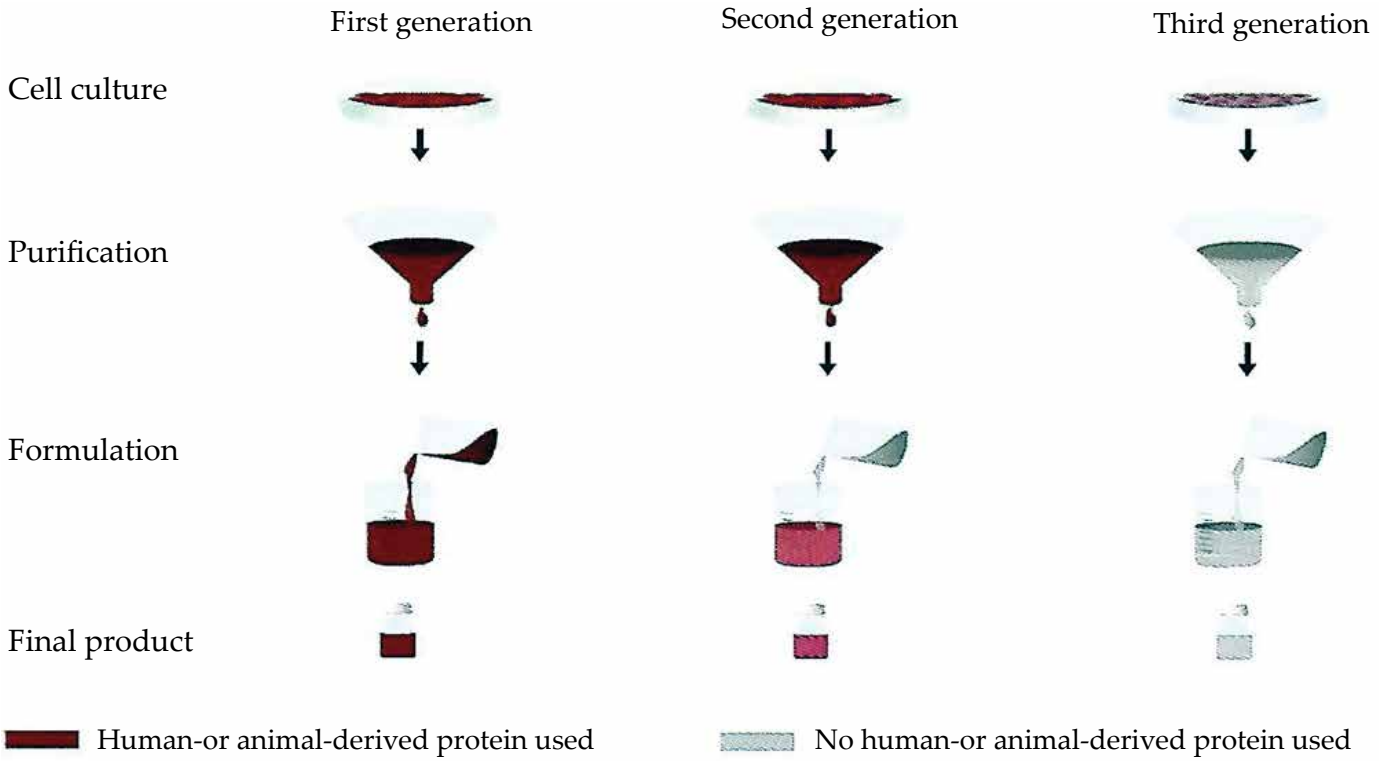


Fig. 6: Types of recombinant therapy

Table 5: Plasma Factor Replacement Target for Haemophilia A and B (when there is no significant resource constraint)

		Hemophilia A		Hemophilia B
Types of Hemorrhage	**Desired Level (IU/DL)**	**Duration (Days)**	**Desired Level (IU/DL)**	**Duration (Days)**
Joint	40-60	1-2, may be longer if response is inadequate	40-60	1-2, may be longer if response is inadequate
Superficial muscle/no NV compromise (except iliopsoas)	40-60	2-3, sometimes longer if response is inadequate	40-60	2-3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
• initial	80-100	1-2	60-80	1-2
• maintenance	30-60	3-5, sometimes longer as secondary prophylaxis during physiotherapy	30-60	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
• initial	80-100	1-7	60-80	1-7
• maintenance	50	8-21	30	8-21
Throat and neck				
• initial	80-100	1-7	60-80	1-7
• maintenance	50	8-14	30	8-14
Gastrointestinal				
• initial	80-100	7-14	60-80	7-14
• maintenance	50		30	
Renal	50	3-5	40	3-5
Deep laceration	50	5-7	40	5-7
Surgery (major)				
• Pre-op	80-100		60-80	
• Post-op	60-80	1-3	40-60	1-3
	40-60	4-6	30-50	4-6
	30-50	7-14	20-40	7-14
Surgery (minor)				
• Pre-op	50-80		50-80	
• Post-op	30-80	1-5, depending on type of procedure	30-80	1-5, depending on type of procedure

Management of Bleeding in Patients with Inhibitors

Patients with low-titre inhibitors (<5 Bethesda Units (BU)) may be treated with specific factor replacement at a much higher dose (50-200 IU/kg/dose) to overcome inhibitors and control bleeding. Options for management of high-titre inhibitors (>5BU) are summarised below in Table 9.

BLOOD-BORNE INFECTIONS (INCLUDING HEPATITIS C AND HIV)

Viral inactivation procedures have virtually eliminated the risk of transmission of enveloped viruses (i.e. hepatitis B and C viruses and HIV) in plasma-derived concentrates. There is still possibility of transmission of non-lipid enveloped viruses (e.g. parvovirus B19), prions, and undetectable pathogens in plasma-derived concentrates.

RECOMBINANT FACTOR CONCENTRATES

First- generation (Recombinate)

Animal and human derived proteins are used in cell culture medium and human albumin is used to stabilise the final product.

Second- generation (Kogenate FS)

Animal and human derived proteins are used in cell culture medium and sucrose instead of human albumin is used to stabilise the final product.

Table 6: Plasma Factor Replacement Target for Haemophilia A and B (when there is significant resource constraint)

Types of Hemorrhage	Hemophilia A		Hemophilia B	
	Desired Level (IU/DL)	Duration (Days)	Desired Level (IU/DL)	Duration (Days)
Joint	10-20	1-2 may be longer if response is inadequate	10-20	1-2, may be longer if response is inadequate
Superficial muscle/no NV compromise (except iliopsoas)	10-20	2-3, sometimes longer if response is inadequate	10-20	2-3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
• initial	20-40		15-30	
• maintenance	10-20	3-5, sometimes longer as secondary prophylaxis during physiotherapy	10-20	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
• initial	50-80	1-3	50-80	1-3
• maintenance	30-50	4-7	30-50	4-7
	20-40	8-14	20-40	8-14
Throat and neck				
• initial	30-50	1-3	30-50	1-3
• maintenance	10-20	4-7	10-20	4-7
Gastrointestinal				
• initial	30-50	1-3	30-50	1-3
• maintenance	10-20	4-7	10-20	4-7
Renal	20-40	3-5	15-30	3-5
Deep laceration	20-40	5-7	15-30	5-7
Surgery (major)				
• Pre-op	60-80		50-70	
• Post-op	30-40	1-3	30-40	1-3
	20-30	4-6	20-30	4-6
	10-20	7-14	10-20	7-14
Surgery (minor)				
• Pre-op	40-80		40-80	
• Post-op	20-50	1-5, depending on type of procedure	20-50	1-5, depending on type of procedure

Third- generation (Turoctocog Alfa)

No animal or human plasma- derived proteins are used during production in cell culture or during stabilisation process.

TUROCTOCOG ALFA (FIGURE 7)

It is a B domain truncated third generation recombinant analogue of factor VIII(rDNA) prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation thereby bringing down the risk of infection to the greatest extent. It has been approved for use in the treatment of bleeding in all age groups and for long term prophylaxis in severe haemophilia A.

Novo Eight undergoes a 5 step purification process that includes solvent detergent treatment and nanofiltration with 20 nm membranes as recommended by WFH.

CONCLUSION

Management of haemophilia is a multimodality comprehensive health care approach which includes first aid measures, factor replacement preferably recombinant factor concentrates, pharmacotherapy, pain management prevention of disabilities, rehabilitation by physiotherapy and psychological counselling for patients as well as family. Prophylactic factor replacement therapy is advisable in the long term because it eliminates high cost associated with management of diseased joints and

Table 7: Supportive Strategies for Haemophilia Management	
Antifibrinolytic drug (e.g. tranexamic acid, epsilon aminocaproic acid)[1]	Adjunctive treatment for mucosal bleeds and dental extractions. Contraindications to the use of antifibrinolytic drugs include upper urinary tract bleeding (due to risk of clot retention in the ureter and bladder) and subarachnoid bleeding (due to risk of vasospasm and ischaemic stroke)
Certain COX-2 inhibitors[1]	Used judiciously for joint inflammation after an acute bleed and in chronic arthritis
First aid measures[1]	Protection (splint), rest, ice, compression and elevation (PRICE) as adjunctive management for bleeding in muscles and joints
Physiotherapy[22, 23]	To manage recovery after a muscle or joint bleed; prevent future bleeding episodes or support recovery from surgical procedures
Analgesics[1]	To control arthropathic pain
Conservative management: serial casting, bracing, orthotics[1]	To correct deformities or support painful and unstable joints
Elective orthopaedic surgery[1]	Synovectomy to reduce bleeding frequency Extra-articular soft tissue release to correct contractures Arthroscopy to diagnose and correct adhesions or impingements within joint Arthrodesis for surgical immobilization of a damaged joint Prosthetic joint replacement for treatment of severely affected major joints

Table 8: Strategies for pain management	
1	Paracetamol/acetaminophen If not effective ↓
2	COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide, and others) OR Paracetamol/acetaminophen plus codeine (3-4 times/day) OR Paracetamol/acetaminophen plus tramadol (3-4 times/day)
3	Morphine: Use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times/day

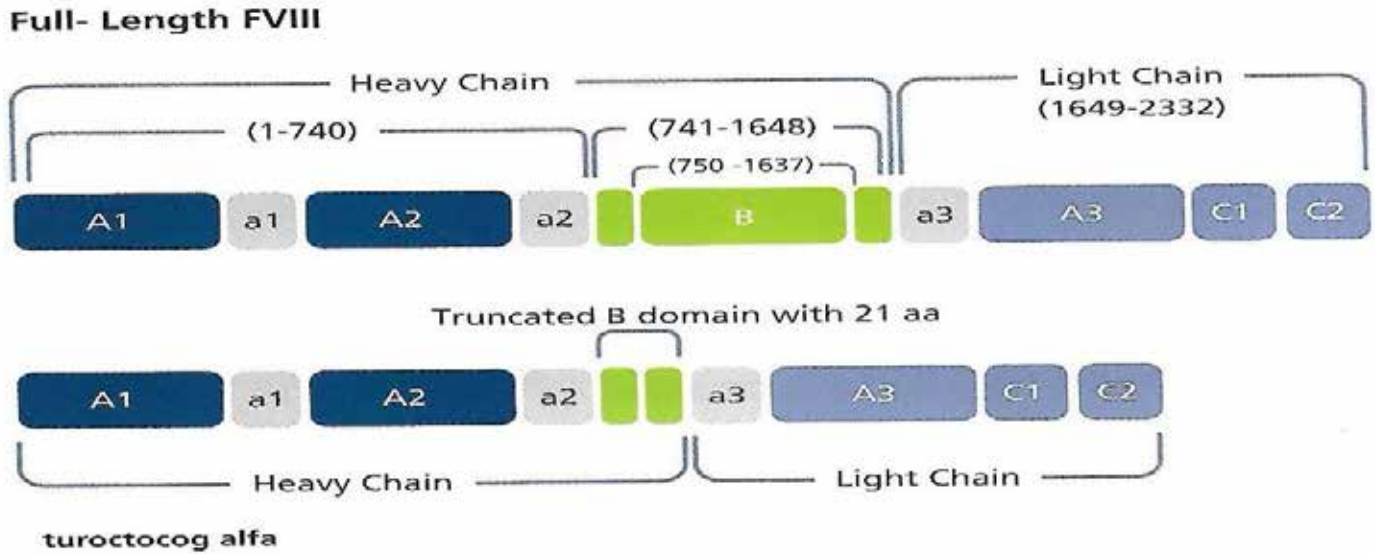


Fig. 7: Structural Comparison between Full Length FVIII and Turoctocog Alfa

Table 9: Management of Patients with High-Titre Inhibitors

Bypassing agents	Immune tolerance induction to eradicate the inhibitor	Other treatment modalities[1,33]
• Examples are activated prothrombin complex concentrates (aPCCs) and recombinant activated Factor VII (rFVIIa) • Studies suggest improved efficacy for rFVIIa (81-91%) than for aPCC (64-80%) when used for on demand treatment of bleeding episodes in haemophilia patients with inhibitors.[34]	• Immune tolerance induction (ITI) is an immune system "desensitization" technique to eradicate an alloantibody inhibitor to FVIII • High doses of FVIII concentrates (recombinant or plasma-derived) are administered regularly per protocol over months • The success of ITI approaches 90% usually over approximately 6-12 months for allo-FVIII antibody inhibitors.[35] • The success of ITI is eradicating FIX inhibitors in haemophilia B is reported to be as low as 13-31%.[36-38]	• Immunosuppressive agents can be given as co-adjuvants during ITI

improves the quality of life. Gene therapy may offer a potential cure for haemophilia in the near future.

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