Review Article

A Review on Hemophilia in Children

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Introduction:
The hemophilias are the commonest inherited bleeding disorder which can lead to chronic disorder and life long disabilities if not properly managed[1]. Although medical literature supports the existence of life long bleeding disorders along with their familial occurrence since tenth century, physicians were the helpless witness of the exsanguinating bleeders of the hemophiliacs[2]. Understanding of the patho-physiology has long been delayed due to complexity of clotting mechanism. Due to advancement in protein chemistry and recombinant DNA technology a comprehensive account of normal coagulation and molecular genetics of hemophilia have been explored. Application of restriction fragment length polymorphism (RFLP) for carrier detection has revolutionized lab process [3]. In the past decades, hemophilia has moved from the status and fatal heredity disorder to that of a defined group of disorder in a molecular basis for which safe and effective treatment is available [4]. And hemophilia is likely to be first common severe genetic disorder to be cured by gene therapy until then main challenge remains to overcome the development of inhibitor and managing patient with inhibitors and in fact it is also a great challenge for the society to provide proper management to four fifth of hemophilia, who are living in developing countries [4].

Definition and Types: Hemophilias are the hereditary bleeding disorder due to absence or deficiency of plasma clotting factors, resulting in prolong and uncontrolled bleeding either spontaneously or following trauma [4]. Two most common forms of hemophilia are Hemophilia A (HA) and Hemophilia B (HB) and are caused by deficiency of factors VIII and IX respectively. HA accounts for 80-85% of cases and HB in 15-20% of cases [5, 6]. Both types are inherited as X linked recessive pattern characterized by prolonged bleeding and hemorrhages typically in joints and soft tissues[5].

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An uncommon type, Hemophilia C is an autosomal recessive defect that results in deficiency of factors XI and is characterized by bleeding in mucous membrane, the pattern of bleeding similar to Von Willebrand disease rather that hemophilia A and B [6, 7]. This review will focus on Hemophilia A and Hemophilia B.

Epidemiology: Hemophilia is prevalent worldwide and occurs in all racial and socioeconomic groups [5]. The incidence of HA and HB is about 15-20 per 100 000 male born world wide. HA is also known as 'Classical hemophilia' and account about 80% of cases of hemophilia and occurs 1 in 10,000 male births [8]. HB also known as 'Christmas disease' occurs in about 1 in 25,000 male births. According to the Report of the annual global survey 2009, the 11th survey by World federation of Hemophilia (WFH) with a participating 105 countries, total number of hemophiliac is 153,253 of which 115,209 is HA and 24,038 is HB[9]. Number of HA and HB patients with clinically identified inhibitors was 5013 & 363, Reported number of Hemophiliacs infected with HIV and HCV was 5,665 & 24,340 [9]. However, these figures are an underestimate than actual ones. Because as per estimation of WFH, with a prevalence of HA and HB of 135 per million male child (world population being 6 billion), there would have been 399,000 hemophilia worldwide. So majority of the patients remains under diagnosed and it is true that most of them are living in the developing countries[10].

Genetics: HA and HB are transmitted by X linked recessive fashion. Genes for HA and HB are located on tip of the long arm of X chromosomes in band Xq28 & Xq27 respectively[1]. So there is 50% chance that son of a female carrier will inherit the disorder. Male with hemophilia will not transmit this disease to his son but all his daughters will be carrier. Female carriers usually don't have symptoms of hemophilia but hey may have lower than usual level of clotting factors [8]. Genes encoding factor VIII is large and complex (186 kb). HA can result from many genetic errors like- a large variety of point mutation, gene deletion, stop

codon abnormality, frame shift mutation and inversion mutation.These knowledge help in carrier identification by DNA analysis and correction of gene defect to prevent inhibitor development[1].

Early studies identified genetic defect in nearly all patients who had mild to moderate hemophilia but only 50% of cases of severe hemophilia. Recent works showed that a novel "FLIP TIP" inversion at the end of X chromosome is responsible for the 50% cases of hemophilia. Here, a small gene of unknown mutation termed F8A is inserted within a non coding region of large FVIII resulting division and inactivation of FVIII gene. This mutation facilitates testing DNA for carrier identification.

The gene for FIX is 34 KB long and the nature of the protein is vitamin K dependent serine protease composed of 415 amino acids synthesized in the liver [1]. Gene deletion and point mutation are seen in HB gene. FIX is synthesized in liver and requires vitamin K for gamma carboxylation. Plasma concentration is 50 times more than FVIII and it has a half life of 24 hours which accounts for a milder phenotype of HB[11].

Hemostasis and the role of factor VIII and IX: Bleeding occurs in hemophilia due to failure of secondary hemostasis. Primary hemostasis is the formation of the platelet plug that occurs normally but the stabilization of the fibrin is defective because inadequate amount of fibrin are generated. Factor VIII and IX are known to be central to the process of blood coagulation and for the adequate generation of thrombin [5]. Following an injury cryptic tissue factors (TF) on the TF bearing cells activates FVII to factor VIIa in order to from a *TF-VIIa complex*, which in turn activates FX to FXa and some FIX to FIXa. This actvated FXa form complex with plasma derived FV to form *FXa /FVa (prothrombinase) complex* on the TF bearing cells which converts a small amount of prothrombin to thrombin. *This priming dose of thrombin, formed in the initiation phase, is not sufficient to generate large amounts of fibrin*. It binds to platelets and initiates several reactions on the platelet surface. It releases FVIII from VWF and activates it to FVIIIa, activates platelet FV to FVa, and FXI to XIa that converts plasma FIX to IXa and reactivates the platelet. This is called the *amplification phase*. In the final or propagation phase, the FIXa

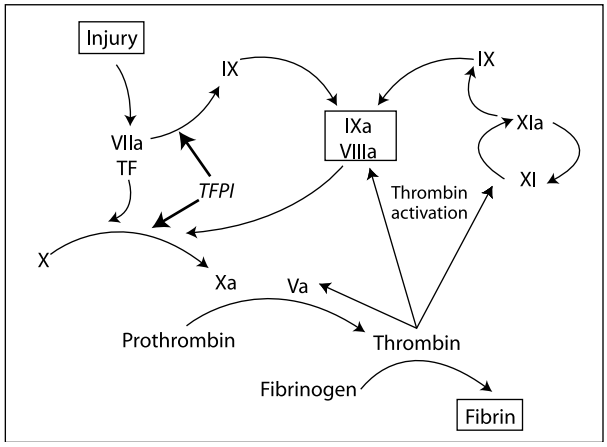

Figure: *Schematic model of coagulation in vivo* Abbreviations: TFPI-Tissue factor pathway inhibitor.

(derived from FVIIa as well as FXIa activation) forms a tenase complex with FVIIIa and results in activation of large amounts of *FXa–FVa complex (prothrombinase)* that leads to generation of large amounts of thrombin (or **thrombin burst**) that converts large amounts of fibrinogen to fibrin resulting in a clot. In hemophilia, thrombin is not generated on the platelet surface due to lack of FVIII or IX (lack of tenase formation). Thus there is no thrombin burst or generation of large amounts of thrombin [5].

Clinical manifestation: The Clinical manifestation of HA and HB are identical, however HB is relatively milder disease so often diagnosed relatively in later life [6]. Hemophiliacs have the heterogenous phenotypic presentation depending upon its severity described in the table [12, 13].

Table I

Relationship of factor level to the severity of clinical presentation in hemophilia

Types	% of FVIII & FIX	Type of hemorrhage
Severe	<1	Spontaneous; hemarthroses and deep tissue hemorrhages
Moderate	1-5	Gross bleeding following mild to moderate trauma,; some hemarthroses; seldom spontaneous hemorrhages
Mild	>5-<40	Severe hemorrhages only following moderate to severe trauma, spontaneous bleeding is rare

Table-II
Common sites of hemorrhage in hemophilia.

Hemarthrosis	Retropharyngel
Intrmuscular hematoma hematuria	Retroperitoneal
Mucous membrane hemorrhage:	Hemorrhage causing compartmental
Mouth	syndrome/nerve compression
Dental	Femoral (ilispoas),
Epistaxis	Sciatic (buttock),
High risk hemorrhage	Tibial (calf muscle),
Central nervous system	Perineal (anterior compartment of leg),
Intracranial extracranial	Median and Ulnar nerve (flexor muscles of fore arm)

Severe hemophilia usually present in neonatal period and early infancy, while moderate hemophilia in toddlers and mild hemophilia in late childhood or adolescent and adult often incidental or following major trauma [13]. Bleeding is the hallmark of hemophilia, sites and pattern of bleeding varies over life time[8]. Table shows the common site of hemorrhage in hemophilia **[13]**.

In neonatal period and infancy: Newborns with hemophilia have distinctive different pattern of as compared with older children and adult[11]. And it could be misdiagnosed especially in the setting of negative family history[14]. Though hemarthrosis is rare, iatrogenic and cranial bleeding is common [15]. According to US HTC surveillence study on a large sample of 864 hemophiliacs of 0-2 years of age, 73% of the severe hemophilia was diagnosed within first month of life, however among these cases only 28.8% cases were diagnosed due to bleeding. Among the rest 47.2% cases of carrier mother, 23.2% due to family history. Bleeding from circumcision was the most common hemorrhagic complication in 45% cases followed by head bleeds in 17.7% cases. Most common first bleeding sites are shown table [15].

Table-III
Sites of bleeding episodes in 278 newborn with hemophilia[15]

Sites of bleeding	Frequency	Percentage
Circumcission	126	45.49
Head (ICH)	49(16)	17.69 (32.6)
Heal stick	41	14.8
Venepuncture	10	3.6
Intramuscular injection	9	3.25
Soft tissue	7	2.53
Oral mucosa	3	1.08
Joint	1	0.36
others	22	7.94
Unknown	9	3.25

Similar pattern of bleeding is also reported by another large hospital based retrospective study in 399 newborn [16, 17].Intracranial hemorrhage (ICH), though rare, is the serious complication often misdiagnosed in neonatal period because of vague presentation especially with negative family history. High index of suspicions are necessary to pick these cases. The reported incidence of ICH (3.5-4%), though higher than general population is misleading and may be higher if one consider asymptomatic ICH [15]. The Hemophilia Growth and Development study found abnormal MRI in 20% of children with hemophilia and 50% of them had silent ICH[18]. In the UDC data, 3.47% newborn had an ICH associated with delivery and the incidence was more with vaginal delivery. The most common sites for ICH were subdural (68.2%), intracere34al (13.6%), cerebellar (9%), and 4.6% each of subarachnoid and ventrcular [18].

Beyond neonatal period most hemophilic seldom have bleeding episode requiring treatment unless accidental injury occurs. Beginning around 1 year of age when the child learns to walk has frequent fall or bumps into the furniture, acute hemarthrosis may occur. Soft tissue bruising and laceration is common in this age group and in a family with unaware of the disease status, he or she might have been suspected as child abuse. Tongue and mouth laceration may occur around this time[1].

Older children and adolescent: Hemarthrosis is the leading bleeding symptoms in older children and adolescent. Recurrent bleedings causes pathological changes leading to 'target joint' and eventually further bleeding into the joint occur without trauma, overtime this cycle of bleeding causes erosion of joint cartilage resulting in arthritis and the crippling deformities of hemophilic arthropathy [1,8]. Radiological joint damage

might appear by 6 years in subjects with no or minimal episode of hemarthrosis[19]. Eighty percent of bleeding occurs in knee, ankles, and elbow; however involvement of other joints is not unusual. Karim et al in their study in Bangladeshi children shows 82% children present with joint symptoms and knee joint involvement was the most common (68%) followed by ankle joint (44%) and elbow joint in 14% cases[20]. Hemarthrosis as the predominant presentation with most affected joint being knee joints were also found in Korean study [21]. However many other studies conducted in Netherlands, France and Spain showed ankle joint as mostly affected joints[22, 23, 24].

Muscular hemorrhage: Muscular bleeding occurs in 10-25% of all bleeds in severe hemophilia and bleeding may become limb threatening, recovery and rehabilitation may be protracted [25]. In contrast to hemarthrosis, muscle bleeds are mostly associated with trauma[25]. Affected muscles become swollen, painful and stiff. There may be bruising on overlying skin if the bleeding occurs in superficial muscle. Deeper muscle bleeding causes pressure on nerves leading to numbness and tingling sensation and if not properly treated by factor replacement leads to compartmental syndrome[4] and insufficiently treated muscle bleed may also result in several other complications like irreversible damage to muscle, reduce range of movement, loss of function, myositis ossificans and damage to tendon (Volksmann's ischemic contractures). Iliopsoas bleeding might be life threatening as large volume of blood is accumulated causing shock. Signs of iliopsoas bleeding include upward flexion and discomfort on passive extension of thigh, tendeness on palpation on the lower quadrant and paresthesias just below the inguinal ligament from femoral nerve compression[1, 25].

Intracranial hemorrhage: Intracranial hemorrhage is the serious complication of hemophilia with a significant cause of disability and long term neurological sequelae as many as 60-75% cases [16,17]. Prevalence of symptomatic ICH in all ages varies from 3-12% with a substantial proportion occurring in children [26]. Severity of the disease, trauma to head, mode delivery and presence of inhibitor are the risk factors for developing ICH [27]. Beyond neonatal period, ICH is 20-50 times more frequent in hemophiliac than general population and trauma appears the risk factors in 22-53% cases[16, 26]. In children <2 years of age most frequent first documented symptom were apathy and or unusual tears (20.7%), Vomiting (17.2%) and coma (13.8%). In those e"2 years most frequent symptoms were headache (46.9%), coma (21%) and vomiting (12.3%) and Irrespective of age coma was observed during the course of ICH in 2/3rd of the cases[5].

Hematuria: Hematuria usually results from blow to the flank, renal calculi and rarely, it may be spontaneous and asymptomatic. It is an infrequent occurrence before 12 years of age. Every patient with haemophilia will present at least one episode of haematuria in his lifetime. There is a greater incidence in spring and autumn. In general, haematuria episodes have a short duration and do not cause any severe sequelae, except in patients with high titer inhibitors and in HIV patients with bone marrow hypoplasia [28].

Diagnosis of hemophilia [29]: At birth: Hemophilia is diagnosed either due to known family history or after presentation with bleeding. **Collection of blood sample:** Arrangement of collection of blood sample from fetal side of placenta should be done if there is possible family history or mother of a male fetus is known or possible carrier. If any newborn /child presents with unusual / prolonged bleeding is subjected for basic screening test. **Screening tests:** Complete blood count- remains normal other than anemia. Bleeding time: remains normal. ***Prothrombin time (PT)****:* also normal in hemophilia. ***Activated partial thromboplastin time (APTT)****:* usually increased by one and half fold to more than 2 fold. Normal hemogram, bleeding time and PT with prolonged APTT leads to the suspicion of hemophilia which warrants specific factor analysis.

Specific study: Correction study with deficient plasma might identify the types of hemophilia and with normal plasma might suggest presence of inhibitors. Quantitative assay of FVIII, FIX helps in identify the types of hemophilia and its severity. *Molecular genetic testing: a.* Sequence analysis, b. Targeted sequence analysis, c. Deletion and duplication analysis and Linkage analysis for a) Tracking an unidentified mutation, b) Identifying the origin of de novo mutation

Carrier detection: a) Factor assay- usually lower than normal b) DNA analysis- identifies the genetic abnormality.

Antenatal diagnosis: by collecting sample of chorionic villous (CVS) in10-12 weeks of pregnancy and amniotic fluid (amniocentesis) in 16-20 weeks of pregnancy for molecular genetic testing.

Management of hemophilia: Hemophilia is managed through a combination of education, clotting factor replacement and comprehensive care. Proper exercise and nutrition help control bleeding and maintain health[8]. Primary aims are- Prevention of bleeding and treatment of acute bleeding, Provide comprehensive care by multidisciplinary care team, Home therapy, Attention for psychosocial health and Rehabilitation[30].

Treatment of acute bleeding: Factor replacement and other pharmaceutical therapy.

Factor replacement: Replacement therapy is the break through in the treatment of hemophilia which started with fractionated human plasma (FFP) in 1930's [8] which reduces mortality and gave hope for the unfortunate hemophiliacs and to the treating physicians as well. But because of low content of factors large volume is needed for replacement. However it is still in use in acute bleeding where specific cause is not identified and also in resource poor country where availability of clotting factors are limited. **Cryoprecipitate**, first available in 1960's provide concentrated FVIII (100 unit in 5-15 ml bag). It is also in use in many countries because of its availability and low cost. Unfortunately both the FFP and cryoprecipitate are not heat treated and not recommended for specific therapy as they contain many other factors and they must be kept frozen until use [8]**. FVIII and FIX concentrate** developed during 1960's and 1970's, by additional purification technique, provides specific replacement therapy for specific hemophilia. Plasma derived concentrate are made from as many as 20000-30000 donors and risk of transmission of blood born diseases like hepatitis and HIV was improved by donor screening and viral inactivation and purification process. **Recombinant factor VIII** developed in 1984 through sequencing of human factor VIII gene by genetically modified cells and is purified by MAB (monoclonal antibody) chromatography technique that render the potential of unlimited supply and virtually devoid of risk of blood born infectious agents. Only disadvantage is its high cost.

Principles for factor replacement [30]

- Factor replacement in acute bleeding should be prompt and within 2 hours and if in doubt about the bleeding treatment should be started before assessment is complete.
- Whenever possible specific deficiency should be corrected by specific factors
- Adjuvant therapy can be used to control bleeding in the absence of clotting factor concentrate
- If bleeding does not resolve despite adequate treatment, clotting factor should be assayed and inhibitors should be assayed if the clotting factors level are unexpectedly low
- Home therapy can be encouraged in case of mild to moderate bleeding.

Table-IV

Facts regarding factor replacement are shown in table IV[5]

Facts	FVIII	FIX
Normal level of activity (%)	50-100%	50-100%
Rise of factor level by infusion of 1 unit	2%	1%
Half life	8-12 hours	18-24 hours
Haemostatic level		
Mild to moderate hemorrhage	30-50%	25-30%
Severe life threatening hemorrhage	100%	100%

Calculation of dose of recombinant FVIII and FIX is as follows [13:] Dose of FVIII= % desired of factor x Body weight (kg) x 0.5, Dose of FIX= % desired of factor x Body weight (kg) x 1.4

Table-V

Types of products currently in use for replacement are shown in table-V [31]

Hemophilia A
High purity plasma derived FVIII concentrates
Full length recombinant FVIII concentrates
b domain deleted recombinant FVIII concentrates
Hemophilia B:
High purity plasma derived FIX concentrates
Recombinant IX concentrates

For effective treatment factor level should be raised to haemostatic level depending upon types of bleeding and should be maintained satisfactorily for a sufficient period of time. Table-VI summarizes recommended factor replacement by WHF for some common types of hemorrhage in a patient with hemophilia when are is no significant resource constraint; however WFH also recommended factor replacement schedule when there is significant resource constraint[30].

Table-VI

Suggested plasma factor peak level and duration of administration (when there is no significant resource constraint)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level (IU dL^{-1})	Duration (days)	Desired level (IU dL^{-1})	Duration (days)
Joint (Hemarthrosis)	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 N-V 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

Other pharmaceutical option for treatment of bleeding: Desmopressin: [30, 32]: Desmopressin (1-deamino 8 D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of vasopressin that boost plasma level of FVIII and VWF by releasing VWF, FVIII: C and other clotting factors from vascular endothelial cells. It is useful in mild to moderate hemophilia A and can be used by intravenous, subcutaneous and intranasal route. However its use is limited by tachyphylaxis and lack of effectivity in some patients. A single dose of 0.3 µg/kg DDAVP, either by IV or SC route, could raise FVIII by 2- 10 folds (average, 3 folds). Highly concentrated intranasal spray formulation is ideal for home uses.

Tranexamic acid[30]: It is an anti fibrinolytic agent that competitively inhibits activation of plasminogen to plasmin. It promotes clot stability and it is useful as an adjunctive therapy in hemophilia especially bleeding in skin and mucosal surfaces like oral bleeding, epistaxis etc. It is especially used in dental surgery and may be used to control oral bleeding associated with eruption and shedding of teeth[30].

Epsilon aminocaproic acid: It is similar to tranexamic acid but less widely used as it has shorter plasma half life less potent and more toxic. It is administered orally 4-6 hours interval. GI upset is common complication. Myopathy is a rare adverse reaction often partial and associated with raised creatinine kinase and even myoglobinuria[30].

Surgical management: Surgery should be performed in person with hemophilia in a well organized hemophilia care setting with appropriate communication and planning between the medical staffs, surgeons and coagulation technologists. The patient's inhibitor status must be known before hand. Whenever possible, initial bolus dose of desired clotting factors should be followed by continuous infusion of factors. This will prevent hazardously low trough level of clotting factors caused by delay in infusion of follow up doses.[32].

Management of inhibitors: Inhibitors are the alloantibodies develop against infused coagulation factors occurring mainly in severe hemophilia and commonly in hemophilia A[11]. Inhibitor development is the most significant complication and remains the biggest challenge in hemophilia care today [33]. Antibodies inactivates the pro coagulant activities of FVIII [5,33] and inhibits patients response to replacement

therapy [33]. Incidence of inhibitors development is approximately 30% in hemophilia A and 3% in hemophilia B and inhibitors tends to develops early in the course of replacement therapy and develops relatively early in childhood and within 50 exposure to FVIII (median 10-11 exposures)[4,33,34].Debates continue on risk of development of inhibitors. Severity of the disease, genetic factor, family history, non Caucasian is the major risk factors for inhibitor development. Gene deletion, frame shift mutations are the genetic defects plays major role. On the other hand, polymorphism within the immune system affecting IL-10, TNFá and Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA-4) also affects the risk of inhibitor development. Other factors includes the type of factor replacement products, schedule in which it is administered and patients status at the time of factor replacement [34]. Inhibitors should be suspected in any patient who fails to respond clinically to clotting factors, particularly if he has been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished and these patients must be subjected for detection of inhibitor. Inhibitors are quantitated using the Bethesda assay and clinically are classified as Low responder <5 Bethesda unit (BU) or high responder e" 5BU[5,13]. Very low level of 0.08 BU can be detected by using NIjmegen modification of Bethesdamethods [35].

Low responder inhibitors: Approximately half of patients with inhibitors are low responders and, of these, approximately half will have transient inhibitors. These patients do not exhibit anamnesis upon repeated exposure to FVIII; 1 BU neutralizes 50% of factor VIII/IX activity. In patient with very low titer inhibitors generally treated with a higher dose of FVIII results in disappearance of inhibitors in some cases, other remains with low titer while other cases becomes high titer inhibitor overtime[4]. In serious limb or life-threatening bleeding, a bolus infusion of 100 units/kg of FVIII is administered; a repeat dose of 100 units / kg is administered at 12 hour intervals[13]. Alternatively, the level is maintained with a continuous infusion rate based on the inhibitor titer and recovery and survival studies which estimate half-life of the factor. FVIII assay should be obtained 1 hour after the bolus infusion and trough or steady-state FVIII levels should be followed at least daily thereafter[30].

High responder inhibitors: Treatment of an acute bleeding by the use of bypassing agents (activated prothrombin complex concentrate [aPCC] and recombinant FVIIa [rVIIa]) and inhibitor eradication is achieved through immune tolerance.

Life-threatening bleeding: *If the inhibitor titer is <20 BU:* High-dose continuous infusion of FVIII with the adjustment of dose based on recovery and survival studies. *If a factor VIII level is not attainable or the antibody level is greater than 20 BU:* By-passing agents to initiate hemostasis independent of FVIII, such as treatment with activated prothrombin complex concentrates (aPCC) or rFVIIa. There is no demonstrated difference in the efficacy of either product.

Immune tolerance induction (ITI): The goal of ITI is the permanent eradication of inhibitors with restoration of normal pharmacokinetics defined as plasma FVIII recovery >66% and a half life >6 hours determined following a 72 hours FVIII exposure free period. Mechanism of ITI and the best means to achieve tolerance still unknown, despite development of multiple ITI protocol since its inception in the 1970's[36]. Table-VIII Immune-tolerance induction protocols[36]

Table-VII

Recommendations for Replacement Therapy for Treatment of Bleeding in Patients with FVIII Inhibitor[13]

Type of Patient	Type of Bleed	Recommended Treatment
Low responder (<5 BU)	Minor or major bleed	Factor VIII infusions using adequate amounts of factor VIII to achieve a circulating hemostatic level
High responder with low inhibitor level (<5 BU)	Minor/major bleed Life threatening bleed	PCC, aPCC or rVIIa infusions Factor VIII infusions until anamnestic response occurs, then aPCC or rVIIa infusions
High responder with high inhibitor level (>5 BU)	Minor bleed Major bleed	PCC, aPCC or rVIIa infusions PCC, aPCC or rVIIa infusions

Abbreviations: BU, Bethesda units; PCC, prothrombin complex concentrates. Activated PCC, e.g., Autoplex (Hyland) and FEIBA (factor VIII inhibitor bypassing activity).

Table-VIII
Immune tolerance protoclo

Bonn protocol[37]	Malmo protocol[38]	Van Creveld[39]
fVIII 100 U/kg BID	Immunoadsorption using protein A column if inhibitor titer >10 BU/mL	Factor VIII 25-50 IU/kg
FEIBA 100 U/kg BID	Cyclophosphamide 12-15 mg/kg IV daily × 2 days then 2-3 mg/kg PO daily × 8-10 days	BID for 1-2 weeks, then 25 IU/kg every other day
	FVIII is given to achieve a 40%-100% fVIII level followed by fVIII infusion every 8-12 hours to achieve 30%-80% level	
	IVIG 2.5-5 g IV immediately after the first fVIII infusion followed by 0.4 g/kg daily days 4-8	

Proposed mechanism of tolerance development includes clonal deletion, energy, and induction of suppressor T cells and synthesis of anti idiotic antibodies[36].

Types of product to be use are not beyond debate. Some have observed a higher success rate when fVIII products containing VWF are used. In most study used rFVIII or FVIII of high purity. However some patient responded to intermediate purity FVIII after failing to response to rFVIII or FVIII of high purity product [36].Immune tolerance can be achieved in approximately 70% of patients who receive regular and prolonged infusion of FVIII with or without immune modulation[36]. It is less likely to be achieved in patients with a long standing inhibitors or a historical inhibitor titer more than 200BU/ml. Failure of ITI is yet to define. In most Immune Tolerance Trial, failure is defined as a lack of a 20% decrease in the inhibitor titer over a 6-month period or a lack of tolerance by 33 months; however it needs to be individually and some physicians favor continuing ITI in patients who achieve a detectable fVIII level and/or a favorable clinical response (decreased bleeding frequency) despite a persistently positive inhibitor titer or abnormal recovery [36]. Immune modulation: Since the development of alloantibodies depends on the immune system, it has been postulated that modulation of the immune system can improve response rates to ITI. Intravenous immunoglobulin, cyclophosphamide, corticosteroids, and immunoadsorption are used early. More recently, the combination of rituximab and ITI has been reported to be successful in several patients who had previously failed ITI alone[36,40].

Prophylactic therapy: Prophylactic therapy is the regular infusion of exogenous coagulation factors in a person with hemophilia in order to prevent spontaneous bleeding. Prophylactic infusion of factor concentrate of FVIII and FIX is widely accepted as gold standard treatment in children with severe hemophilia[41]. Prophylaxis prevents bleeding and joint destruction and should be the goal to preserve normal musculoskeletal function[42,43]. Several studies has clearly documented that long term prophylaxis had proven effective in reducing bleeds in preventing hemophilic arthropathy and even delayed prophylaxis is able to reduce the frequency of bleeding as well as patients physical and psychological restrictions[31]. The aim of prophylaxis is to convert the severe hemophilia to a milder form by maintaining the trough level of factors essentially >1% of normal[31]. Prophylaxis with FVIII and FIX bypassing FVII is also effective in patient with high titer of inhibitors. Definition of prophylaxis as given in table is recommended by WFH and WHO since 1994[30].

Table-IX

Definitions of factor replacement therapy protocols for prophylaxis[30]

Continuous prophylaxis

Primary prophylaxis: Regular continuous treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years.

Secondary prophylaxis: Regular continuous treatment started after 2 or more bleeds into large joints and before the onset of joint disease documented by physical examination and imaging studies.

Tertiary prophylaxis: Regular continuous treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints

Intermittent (periodic) prophylaxis

Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

Although there is general agreement among the investigators that early initiation of prophylaxis <2 years of age is ideal, there is still debate about its intensity of treatment regimen and how to initiate prophylaxis (table X) shows the different regimens followed in different countries[31]**.**

Table-X

Prophylaxis regimen in hemophilia[31].

High dose regimen (Sweden, Germany , UK, Italy)		
Hemophilia A	25-40 IU/Kg	Three times weekly or every other day
Escalating dose regimen		500 IU once weekly, rapidly increased to twice or three times weekly on the basis of venous access (Sweden)
Hemophilia B	25-40 IU /Kg	Two to three times weekly
Intermediate dose regimens (The Netherlands)		
Hemophilia A	15-25 IU/Kg	Two to three times weekly
Hemophilia B	30-500 IU /Kg	once to twice weekly

Although the cost of prophylaxis is very high, cost benefit study showed that the ultimate expenses may not be greater than those for treatment on demand[41]. However, universal implementation of primary prophylaxis in children is challenging in developing countries where only resource for minimal on demand treatment is available.

Comprehensive care: Comprehensive care for the person with hemophilia has been defined as the continuing supervision of all medical and psychosocial factors affecting them and their family[44]. The model of comprehensive care first developed in USA in response to the development of plasma derivatives as treatment for hemophilia afterwards has been followed worldwide. The model include establishing prophylaxis and other treatment protocols, development of psychosocial, education and research programme, maintenance of a patient registry, genetic and reference diagnostic services and coordination and management of a wide variety of multidisciplinary interventions[31].The core team at a hemophilia comprehensive treatment center (HCTC) includes hematologists, laboratory staff, nurses, physiotherapists and social workers. It should also involve the collaboration of several other allied specialists. Genetic counseling for patients and their families, and advice about prenatal diagnosis and management of pregnancy and delivery in hemophilia carriers should be offered [31]. Comprehensive care model has normalized life for patients with hemophilia in countries of the developed world with a life expectancy is close to healthy persons without the treat of transmission of serious blood-borne infections by concentrates since 1990, and joint disease

produced by bleeding episodes is non-existent in children under the age of 15 years[45,46,48,49]. Individuals with hemophilia pursue life with the vigor of any normal population [44]. Most centers practicing this model of care are based in developed countries and can meet costs for plentiful treatment products through government or insurance-company funding. Unfortunately, hemophiliacs in developing countries are far away to entertain these facilities, where major problems remains regarding diagnosis and treatment [44].

Gene therapy: Through the introduction of a functional gene into a target cell, gene therapy aims to restore, modify or enhance cellular functions[49]. Hemophiliacs are monogenic disorder and were felt an ideal target for gene therapy because only a small rise in factor concentrations to more than 1–2% of normal would achieve the goals of prophylaxis without regular infusions of concentrate and would ensure a substantial improvement in lifestyle for severe hemophilia[5].

The ultimate target of gene therapy for hemophiliacs A and B would be direct correction of the molecular defect in the mutated gene. Though such direct gene modification has been demonstrated, [50,51] but for haemophilias A and B this approach remains far reaching in the future. So, gene therapy for hemophiliacs relies on addition of normal factor VIII or IX genes. With present technology, gene therapy can offer the prospect of a true cure for hemophilia in animal models, but this is not currently realizable in human beings[5].

More than 25 patients with hemophilia have now been treated in phase I gene-therapy protocols. However, no study has conclusively shown that therapeutic concentrations of factors VIII and IX can be reliably obtained5. Hemophilia still remains a prime target for gene therapy. However, hemophilia is no longer a life-threatening disease with current therapy that is both safe and effective. A balance between the benefits and theoretical risks must be taken into account when gene-based approaches to therapy are being considered[52, 53].

Management of hemophilia in developing countries: It is estimated that 80% patients live in developing country[54] and nearly 70% of the hemophiliacs are under diagnosed and remained untreated [10]. In contrast to the developing countries, where life expectancy of the hemophiliacs is close to normal healthy persons due to improved care and access to the clotting factors, most of the hemophiliacs in developing countries are still facing problem related to uncontrolled bleeds, hemarthroses and poor quality of life [10, 54].

Management of hemophilia in developing countries poses great challenges. Government and family monetary resources are usually inadequate, knowledge and awareness about hemophilia and its management often nonexistent, with often no access to proper diagnostic testing, and therapeutic material is inadequate not only in quantity but in terms of its viral safety. In addition, there are variations in populations with regard to income, education, and motivation levels. It is estimated that less than 5% of the population in developing countries would be able to provide a level of treatment for a hemophiliac son like that available in developed countries [55].

Hemophilia care in developing countries targets with – a. Establishing regional HTCs at suitable place in the country with a goal to provide comprehensive care and making liaison with WFH, b. Capacity building with trained manpower and diagnostic facilities by making regional cooperation with established centers nearby, c. Making provision of adequate supply of factors replacement primarily by using available resources like FFP, cryoprecipitate by strengthening transfusion services and procurement of costly factors depending upon the available fund and encouragement for using of adjuvant modalities of treatment, d. Build up national hemophilia registry for actual identification of the hemophiliacs and e. Awareness about hemophilia and carrier detection with an aim for prevention hemophilia.

Bangladesh perspectives: Bangladesh being a developing country has been working hard to improve its common problem of malnutrition, infectious and communicable diseases and rightly progress to achieving MDG goal by reducing maternal mortality, perinatal mortality, infant mortality and child mortality rate. So, non communicable disease like hemophilia is getting more concern.

National registry for hemophilia yet to be developed hence unavailability of reliable data regarding various parameters of the disease. Hemophiliacs are still taken care of by the general physicians and got special care in a handful number of specialized center mostly in the tertiary care hospitals in the capital city. Patients are usually diagnosed only after bleeding episode and some times the episode are serious causing serious

consequences. Study on hemophilia is also scarce. Hospital based studies did not report any case detected in newborn period reflecting inadequacy of knowledge and attitude of the treating physician towards hemophilia[20].

Like many other developing countries, Bangladesh is also lacking in comprehensive care for hemophiliacs. As per report of the annual global survey 2009 by WFH, only three hemophilia treatment centers are existing in Bangladesh [9]. However these centers are not well equipped with diagnostic facilities and adequate trained manpower. Under detection of the hemophiliacs: As there is no geographic, ethnic or racial variation in the incidence of hemophilia, given the prevalence of hemophilia A of 105 per million and of hemophilia B of 28 per million, Bangladesh (population 160 millions) would have 10800 hemophiliacs. But reported cases are only 424 (367 Hemophilia A and 57 hemophilia B) and there is no reported inhibitors[54, 9]. Among the reported cases, only 9 cases are under 5 years of age[9].

Inadequate diagnostic facility for categorization of the cases of hemophilia is alarming. This is reflected by the detection of small percentage of severe hemophilia in hospital based studies [20]. In addition these facilities are located in the capital cities. There is no facility for genetic study or carrier detection right now.

Coagulation factors: Not widely available throughout the country and throughout the year. No provision of supply of factors by the government. Only some private pharmacies mainly in the capital city procure by themselves and are selling with high prices. Alternative for factor like fresh frozen plasma, cryoprecipitate are available in a few old government medical college hospitals on demand. Hopefully blood bank facilities are expanding though out the country in government medical college hospitals and these alternative products could be ensured in near future for the poor fellows of hemophilia who can not procure costly factors. Trained manpower: Shortage of expert and trained manpower for caring hemophilia is also another issue in our country. Good news is that Department of pediatric hematology and oncology has been expanded in eight Medical Colleges with pediatric hematology specialist, where care of regional hemophiliacs might be arranged in near future.

The role of World Federation of Hemophilia in the management of hemophilia: The World Federation of Haemophilia (WFH) is a global not-for-profit organization devoted to care of hemophilia and related disorders. It started its journey Founded in 1963 in Montréal. Over the last 40 years; it has grown tremendously and now has 107 National Member Organizations and has been recognized by the World Health Organization. The WFH is working with the mission of to introduce, improve, and maintain care for patients with hemophilia and related disorders. The WFH organizes regular educational workshops on key aspects of hemophilia care. It offers fellowship to approximately 30 healthcare professionals each year that provide funding for a period of study of up to 8 weeks at an International Hemophilia Training Center of their choice. The WFH runs twinning program to help emerging hemophilia treatment centers to develop partnerships with well-established centers. As the ultimate goal of the WFH is to promote sustainable hemophilia treatment in developing countries, donations of concentrate are regularly made through the Humanitarian Aid program[56].

WFH also publishes several useful publications, such as the WFH register of coagulation factor concentrates, the WFH laboratory manual, Guideline on management of hemophilia, Report of the annual global surveys on a regular basis [56].

Future prospects:

Recombinant DNA technology and protein engineering are creating hope. Technological advances to improve the half-life of recombinant clotting factors for hemophilia replacement therapy is closer to reality. Other major aspects of research and development in pipeline toward the new therapeutic agents for hemophilia are: (1) lower cost factor concentrates, (2) non-protein therapies, (2) novel bypassing agents for hemostatic control of inhibitors.[31,57].

Conclusion:

The hemophilias are the commonest inherited bleeding disorder which can lead to chronic disorder and life long disabilities if not properly managed.

Over the past decades, its management has improved markedly and the life expectancy of a newborn with hemophilia would be close to normal healthy child and the hemophiliacs could pursue life with vigor of any normal population. But this is materialized only for those who live in developed countries where dedicated comprehensive care for hemophiliacs are available. Vast majority of hemophiliacs, living in developing countries with poor to nonexistent services

of hemophilia care, are still facing the problem of bleeding along with its complications and poor quality of life.

WFH with its mission and vision is trying to minimize the gap through expanding its different program. However successful management of the hemophiliacs in developing countries will largely depend primarily on the attitude of the participating countries. With the success of gene therapy and availability of the new bioengineered products the prospect of the hemophiliacs will be brighter in near future.

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