Consensus Statement of the Indian Academy of Pediatrics in Diagnosis and Management of Hemophilia

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Justification: Despite having standard principles of management of hemophilia, treatment differs in various countries depending on available resources. Guideline for management of hemophilia in Indian setting is essential.

Process: Indian Academy of Pediatrics conducted a consultative meeting on Hemophilia on 18th September, 2016 in New Delhi, which was attended by experts in the field working across India. Scientific literature was reviewed, and guidelines were drafted. All expert committee members reviewed the final manuscript.

Objective: To bring out consensus guidelines in diagnosis and management of Hemophilia in India.

Recommendations: Specific factor assays confirm diagnosis and classify hemophilia according to residual factor activity (mild 5-40%, moderate 1-5%, severe <1%). Genetic testing helps in identifying carriers, and providing genetic counseling and prenatal diagnosis. Patients with hemophilia should be managed by multi-specialty team approach. Continuous primary prophylaxis (at least low-dose regimen of 10-20 IU/kg twice or thrice per week) is recommended in severe hemophilia with dose tailored as per response. Factor replacement remains the mainstay of treating acute bleeds (dose and duration depends on body weight, site and severity of bleed). Factor concentrates (plasma derived or recombinant), if available, are preferred over blood components. Other supportive measures (rest, ice, compression, and elevation) should be instantly initiated. Long-term complications include musculoskeletal problems, development of inhibitors and transfusion-transmitted infections, which need monitoring. Adequate vaccination of children with hemophilia (with precautions) is emphasized.

Keywords: *Coagulation, Factor VIII deficiency, Prophylaxis, Treatment*.

Hemophilia (A or B) is an inherited (X-linked recessive) bleeding disorder caused by deficiency of coagulation factors VIII or IX, respectively. Males are affected and females are asymptomatic or mildly affected carriers. Deficiency of either of these factors results in defective intrinsic coagulation pathway (decreased and delayed generation of thrombin, defective clot formation, and hemorrhagic diathesis). Globally, the prevalence is around 1 in 5000 male births for hemophilia A and 1 in 30,000 male births for hemophilia B [1]. World Federation of Hemophilia (WFH) report on the annual global survey 2015, which covered 91% of world population, identified nearly 190,000 hemophilia patients (nearly 150,000 (80%) with hemophilia A) [2]. There were around 17,500 hemophilia patients (83% hemophilia A) identified from India in this survey [2], which should be an under-estimate. Even if the principles of management remain same, treatment differs in various countries based on the available resources. Hence, an indigenous guideline that fits management of hemophilia in Indian setting is essential.

Accompanying Editorial: Pages 559-60

Experts in Hemophilia were invited from all over the country, and a one-day consultative meeting was convened under the aegis of Indian Academy of Pediatrics on 18th September, 2016 at New Delhi. Based on the discussion of experts and review of scientific literature, a manuscript was prepared and was circulated to all authors. Their suggestions were reviewed and incorporated in the final document. We aimed to provide recommendations regarding the diagnosis and management of hemophilia in Indian setting, including prophylaxis, treatment of acute bleeds and management of specific complications.

DIAGNOSIS

When to Suspect Hemophilia?

One-third of cases are due to spontaneous mutations with no prior family history. Ideally, the remaining two-thirds should be diagnosed antenatally or at birth because of family history. However, in the Indian setting, the first clinical presentation is often a post-traumatic bleed, usually hemarthrosis or skin bleed [3]. Clinical suspicion of hemophilia should arise in any child with joint bleeds, easy bruising, unprovoked deep-seated bleeds or prolonged/ excess bleeds following surgery or trauma. Intracranial haemorrhage in neonate might be the earliest and devastating manifestation seen in 2-4% of cases [4]. Other neonatal presentations include subgaleal bleeds and cephalhematoma. Most of these may be associated with traumatic deliveries (like forceps or vacuum extraction), and underlying hemophilia should not be missed [4]. Prolonged bleeding after circumcision and muscle hematoma following vaccination in an infant are other early manifestations. Although hemophilia patients can bleed anywhere, the hallmark is deep bleeding into joints and muscles. In infants and toddlers, ankle is the most common site followed by knees. In older children, knees and elbows are frequently involved. The most common joint involved in patients not taking prophylaxis is knee, followed by elbow, ankle, shoulder and wrist. In those on prophylaxis, ankle is commonly involved.

Occasionally, mucosal bleeds (epistaxis, gums, gastrointestinal, genitourinary) might be the presenting features. Central nervous system (CNS) bleed may occur at any age, insidiously or following mild trauma. A suspected intracranial bleed in a diagnosed hemophilia patient must be first treated with factor concentrates even before confirmation by neuroimaging.

The bleeding phenotype differs based on the factor level and accordingly hemophilia is classified into mild (5-40%), moderate (1-5%) and severe (<1%). Severe hemophilia presents with spontaneous bleeds, especially from CNS, muscle, joints, etc. Nearly 50% with severe hemophilia manifest by 6-8 months of age (with increase in physical activity). Moderate hemophilia has heterogeneous manifestations. People with mild hemophilia usually bleed only after major surgery or trauma. Female carriers of hemophilia too can present with bleeding in form of menorrhagia, skin bruising and post-surgical or peri-partum hemorrhage [5].

How to Diagnose Hemophilia?

Initial screening blood investigations (with reference ranges) for any child with suspected bleeding disorder include: platelet count (150-450 × 10^3/µL); prothrombin time (PT) (11-15 seconds), and activated partial thromboplastin time (aPTT) (29-35 seconds). In hemophilia, screening tests reveal a prolonged aPTT with a normal PT and platelet count [6]. The other inherited conditions with similar screening results include von Willebrand disease (certain types), factors XI, XII, high molecular weight kininogen and prekallikrein deficiencies. Mixing study is a simple test performed by mixing plasma from the patient with pooled normal plasma in 1:1 proportion and repeating aPTT after incubating for 30-60 minutes. Correction of aPTT after mixing suggests deficiency in any of the factors in intrinsic pathway. Prolonged aPTT may not get corrected with mixing study in case of presence of antibodies to factor VIII or IX, lupus anticoagulant or heparinized sample [6]. Specific factor assays for factor VIII or IX should be done for specific diagnosis and ascertaining its severity.

All female carriers in the family should get their factor level tested as they can have levels ranging from normal to borderline (40-60%). Those with borderline levels can have increased bleeding tendency, especially during pregnancy, invasive procedures and trauma [5]. They might also require factor replacement during such conditions. Menorrhagia is frequently noted in such carriers, which may respond to anti-fibrinolytics or oral contraceptives. Rarely, females can have hemophilia (factor level <40%). The Mini Report 1 of Annual Global Survey published by WFH in April 2017 has identified nearly 4000 females with Hemophilia A and 1300 females with Hemophilia B.

How to avoid erroneous laboratory results?: There should not be any strenuous exercise or intake of drugs like aspirin prior to sample collection. Samples should be stored at 20-25ºC and processed within 4 hours of collection (preferably collected nearby a laboratory), as delayed processing gives erroneous results [7]. If the transport time to laboratory is >4 hours, centrifuge the sample immediately to separate platelet poor plasma and transport frozen plasma in dry ice. Specimens can be stored at –20ºC for up to 2 weeks or at –70ºC for up to 6 months. There should not be contamination with heparin (avoid collection from central catheters). While collecting blood sample in a citrate vial, blood:citrate ratio of 9:1 should be maintained. Blood should be collected till the mark provided. Any abnormal result may be reconfirmed in a standard laboratory along with above precautions.

The diagnosis of hemophilia B in neonatal period and infancy may be challenging as the normal factor IX level is low in neonatal period, and age-specific cut-off levels should be used. While a diagnosis of moderate and severe cases is still possible, a suspected mild hemophilia B requires confirmation at 3-6 months of age.

Genetic Diagnosis

Genetic analysis is recommended, wherever feasible, not only for the affected male, but also for all the at-risk female family members to identify carriers. It helps in genetic counselling for the family and provides prenatal diagnosis. During pregnancy of carrier females, it is advisable to perform chorionic villous sampling at 11-14 weeks of gestation. Identification of mutation also helps in preimplantation genetic diagnosis (PGD) that is legal in India if carried out under strict conditions and criteria. In case the fetus is affected, the family is counselled regarding the diagnosis and options of continuing the pregnancy or medical termination. In patients with severe hemophilia A, inversions of intron 22 (reported in 40–45%) and intron 1 (reported in 1–6%) of factor VIII gene are the most common mutations [8,9]. If these two variations are not identified, Sanger sequencing of the gene identifies other mutations. In Hemophilia B, majority are point mutations (commonly missense mutations).

Specific gene defects are thought to contribute to about 40% risk of inhibitor formation. Large deletions and nonsense mutations carry the highest risk, whereas missense and splicing mutations carry the lowest risk for inhibitor formation [10]. There are more than 2000 identified mutations in hemophilia A and more than 1000 in hemophilia B. Mutation may not be identifiable in a small proportion of hemophilia patients.

TREATMENT OF HEMOPHILIA

The aim of treatment is to prevent and treat acute bleeds, thereby preventing and minimizing long-term morbidity. Specific treatment should be initiated in acute bleeds as soon as possible. Patients recognize an aura (usually a tingling sensation) even before bleed becomes obvious. In life-threatening situations, it is better to treat even if doubtful, and even before a formal investigation has been done. Children with hemophilia are best managed in a comprehensive manner by multi-specialty team (parents, pediatric hematologist, laboratory hematologist, orthopedic surgeon, pain management expert, physiotherapist, dedicated nurse, dentist and social worker).

Lifestyle Measures

Regular physical activity (non-contact sports like walking, swimming, cycling, yoga, table tennis) to help build a strong musculoskeletal system and fitness is required [7]. However, activities prone to trauma (like football, hockey) are to be avoided. Braces, helmets and splints should be applied when required, to protect the injury-prone area before engaging in contact sports. Elastic, neoprene, splints and arch supports may be used to support a joint and some adjacent muscles. These devices help protect the joint; however, some can restrict joint movement. Activities should be withheld during acute bleeds and restarted gradually to avoid re-bleeds. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that affect platelet function should be avoided. Paracetamol is safe. Oral hygiene is essential as caries predispose to gum bleeds. A hemophilia patient should always carry an identity card containing information about his diagnosis, severity, prophylaxis regimen, inhibitor status and emergency contact details [7]. Veins are lifelines for hemophilia patients and should be handled with care.

Prophylaxis

As compared to severe hemophilia, moderate hemophilia (>1% factor activity) patients seldom experience spontaneous bleeding with preserved joint function. The concept of prophylaxis aims to maintain nadir factor activity >1% in severe hemophilia by regular factor VIII injections. Prophylaxis has been found beneficial even when nadir factor levels are not maintained >1% at all times [11]. The objective of prophylaxis is to prevent bleeding and joint destruction, thereby preserving normal musculoskeletal function [12]. Prophylaxis can be episodic, continuous or periodic. Episodic is the term used when factor replacement is given only during evident bleeding. Continuous prophylaxis is termed for children who receive replacement of factor at least >85% of the year. Depending upon the time of start of prophylaxis, they are categorized into primary (before 2nd episode of joint bleed), secondary (after 2 or more joint bleeds and before developing any joint disease) and tertiary prophylaxis (after the onset of joint disease). Various doses for prophylaxis have been studied like Malmo protocol (25-40 IU/kg/dose) and Utrecht protocol (15-30 IU/kg/dose) [7]. While higher doses of Factor VIII prophylaxis would help limit morbidity and disability, cost precludes its use in our country. There is now data from resource-poor settings to demonstrate that lower doses of Factor VIII used for prophylaxis would also limit the number of acute bleeds, and hence the long-term joint morbidity [13-16]. However, episodic prophylaxis has not been found to be useful. MUSFIH (Musculo Skeletal Function in Hemophilia) study concluded that episodic factor replacement did not alter the natural course of the joint disease [17].

The group recommends a continuous primary prophylaxis (at least low-dose regimen of 10–20 IU/kg twice or thrice per week) in severe hemophilia. This should be a starting dose with further modifications made as per intercurrent/breakthrough bleeding frequency. In young

infants and children, even a weekly dose can be initiated with dose titrated as per response. Preferable time for administering prophylaxis doses is in morning and/or just before undertaking activities at-risk for trauma (to effectively cover these activities). Central venous lines may facilitate home-based factor therapy, but comes with a risk of infection and thrombosis. Home-based treatment is feasible for mild to moderate bleeds, if caretakers are trained properly. Home therapy allows immediate access to factors and hence decreases the complications secondary to bleeding. Patient and the family members should be educated regarding the disease, signs and symptoms of bleeding, dosage of factor concentrates and performing venepuncture.

Treatment of Acute Bleeding

As soon as patient perceives a joint bleed, provide initial management [Rest, Ice, Compression and Elevation (RICE)] wherever the patient is. Ice pack should not be in direct skin contact, and applied for 20 minutes once in 4-6 hours. Factor replacement should be started immediately (as soon as possible). The dose and duration of factor therapy depends on body weight, site and severity of bleed (***Table* I**). Arthrocentesis should be considered only in the extremely rare scenarios (evidence of septic arthritis, neurovascular compromise, tense painful joint not responding to factor therapy, especially hip joint), after maintaining a factor level of around 50%. Joint movements should be initiated as soon as pain and swelling start to subside and gradually increased. ***Table* I** shows the desired rise in factor level in various sites of bleeds in different resource settings. We recommend administering (at least) the doses suggested in resource-constrained settings (but may need to be escalated if clinical response is unsatisfactory).

Epistaxis is a common problem in children. Patient should be trained to sit in upright position and pinch the nose with thumb and index finger for 10 to 15 minutes while breathing through mouth. If the bleeding still continues, the procedure can be repeated once more. Local anti-fibrinolytics may be used. Factor replacement is often not necessary until the bleeding is very severe or recurrent.

The details of Hemophilia Treatment Centers in India where Anti Hemophilic Factor is available free of cost is

TABLE I WORLD FEDERATOION OF HEMOPHILIA RECOMMENDATIONS FOR DESIRED FACTOR LEVEL AND DURATION IN VARIOUS BLEEDS

Site of bleed	*Hemophilia A*		*Hemophilia B*	
	No resource constraints	*Resource constrained*	*No resource constraints*	*Resource constrained*
Joints	40-60% for 2 days	10-20% for 2 days	40-60% for 2 days	10-20% for 2 days
Superficial muscles	40-60% for 2-3 days	10-20% for2-3 days	40-60% for 2-3 days	10-20% for 2-3 days
Iliopsoas/deep muscles; Neurovascular compromise; significant blood loss	80-100 % (days 1-2), 30-60 % for days 3-5 or longer	20-40 % initially, then 10-20 % for days 3-5 or longer	60-80 % (days 1-2), 30-60 % for days 3-5 or longer	15-30 % initially, then 10-20 % for days 3-5 or longer
Brain, spine, head	80-100 % (days 1-7); 50 % (days 8-21)	50-80% (day 1-3); 30-50% (day 4-7); 20-40% (day 8-14)	60-80 % (days 1-7); 30 % (days 8-21)	50-80% (day 1-3); 30-50% (day 4-7); 20-40% (day 8-14)
Throat and neck	80-100 % (days 1-7); 50 % (days 8-14)	30-50% (day 1-3); 10-20% (day 4-7)	60-80 % (days -7); 30 % (days-14)	30-50% (day 1-3); 10-20% (day 4-7)
Gastrointestinal	80-100 % initially, then 50 % (total 7-14 days)	30-50% (day 1-3); 10-20% (day 4-7)	60-80 % initially, then 30 % (total 7-14 days)	30-50% (day 1-3); 10-20% (day 4-7)
Renal	50% for 3-5 days	20-40 % for 3-5 days	40% for 3-5 days	20-40 % for 3-5 days
Deep laceration	50% for 5-7 days	20-40 % for 5-7 days	40% for 5-7 days	20-40 % for 5-7 days
Major surgery	80-100% pre-operatively; 60-80% (post-op day 1-3); 40-60% (day 4-6); 30-50% (day 7-14)	60-80% pre-operatively; 30-40% (post-op day 1-3); 20-30% (day 4-6); 10-20% (day 7-14)	60-80% pre-operatively; 40-60% (post-op day 1-3); 30-50% (day 4-6); 20-40% (day 7-14)	50-70% pre-operatively; 30-40% (post-op day 1-3); 20-30% (day 4-6); 10-20% (day 7-14)
Minor surgery	50-80% pre-operatively; 30-80% 1-5 post-op days (as required)	40-80 % pre-operatively; 20-50% 1-5 post-op days (as required)	50-80% pre-operatively; 30-80% 1-5 post-op days (as required)	40-80 % pre-operatively; 20-50% 1-5 post-op days (as required)

available from *http://www.hemophilia.in/index.php/hemophilia-treatment-centers*. Currently, 74% of the country is covered under complete, parital or free factor support. Awareness about these centers near the patient's locality should be explored to utilize these resources.

Calculation of dose of factors: Calculation of the doses in individual episodes for different patients to achieve a desired factor level is based on the formulae given below:

- Factor VIII (IU per dose) = U/dL desired rise (%) × Body weight (kg) × 0.5;

(1 U/kg of factor VIII increases the body level by 2%; half-life of factor VIII is 8-12 hours)

- Factor IX (IU per dose) = U/dL desired rise (%) × Body weight (kg);

(1 U/kg of factor IX increases the body level by 1%; half-life of factor VIII is 18-24 hours). Because recovery of recombinant factor IX activity is less than that of therapeutic plasma-derived factor IX, 1.2 to 1.5 times the dose should be administered if using recombinant factor IX [18,19].

The frequency of doses should be 12-hourly in hemophilia A and 24-hourly in hemophilia B. For example, if a 25 kg severe hemophilia A patient had a hemarthrosis and the targeted factor level is 20% (in view of resource constraints), requirement of factor VIII (IU per dose) = 20 × 25 × 0.5 = 250 IU per dose. The child should receive 250 IU of factor VIII as a slow intravenous injection every 12 hourly till the desired duration (say 2 days in this case). In case of hemophilia B, the same dose of factor IX is given every 24 hourly. It is a good practice to carefully round off the dose to nearest vial strength without any treatment compromise in order to avoid wastage of factors.

Continuous infusion is preferable in life-threatening bleeds. It avoids peaks and troughs. It may lead to reduction in total factors consumed (cost-effective). Factor levels should be monitored and doses adjusted accordingly. Pump failure is a concern and should be monitored.

Choice of factor replacement products: In the 1950s and 1960s, bleeding episodes were treated with fresh frozen plasma (FFP). Modern treatment started in 1965 with identification of the cryoprecipitate fraction. Subsequently, plasma-derived factor VIII and IX concentrates were introduced. The recombinant factor VIII and recombinant factor IX were introduced in 1992 and 1997 respectively [9]. The salient features of various products containing Factor VIII are compared in ***Table* II**.

Various studies have been conducted to know whether the incidence of inhibitor formation more in recombinant factor concentrates compared to plasma

TABLE II CHARACTERISTICS OF VARIOUS PRODUCTS CONTAINING FACTOR VIII

Feature	*Plasma derived factor concentrates*	*Recombinant factor concentrates*	*Cryoprecipitate*	*Fresh frozen plasma*
Contents	Factor VIII and vWF	Factor VIII only	Factor VIII, vWF, Fibrinogen, Factor XIII	All coagulation factors
Risk for TTI	Screened for TTIs.Viral inactivation (Heat / Solvent) done. Risk of prion mediated diseases exists.	No risk for TTIs (free of viral contamination)	Screened for TTIs, but viral inactivation not done	Screened for TTIs, but viral inactivation not done
Risk of allergic reactions	More with lower purity preparations	Rare	Commoner than factor concentrates	Commoner than factor concentrates
Uses	Hemophilia A,vWD [24]	Hemophilia A	Used only if specific factor concentrates not available (Hemophilia A, vWD, factor XIII deficiency, Not in Hemophilia B	Used in DIC, Cogulopathy of unkown cause, liver failure. Used in factor deficiencies (including Hypofibrinogenemia) Hemophilia B), only if factor concentrates not available
Strengths	Vials: 250 IU, 500 IU, 1000 IU, 1700 IU.	Vials: 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU.	1 bag = 70-80 IU of factor VIII	1 mL = 1% factor activity

TTI - transfusion transmitted infections; vWF – von Willebrand Factor; vWD – von Willebrand Disease.

derived products. SIPPET trial was one such prospective trial which reported that early replacement therapy with plasma-derived factor VIII (23.2%) was associated with a lower incidence of inhibitor development than with recombinant factor VIII (37.3%) [20]. However, other studies have found much lower incidences of inhibitor formation with recombinant factors concentrates. We recommend the use of factor concentrates (either plasma-derived or recombinant) in preference to cryoprecipitate or FFP due to concerns about their quality and safety.

Desmopressin acetate: In mild to moderate forms of hemophilia A and in carriers, the synthetic vasopressin analogue Desmopressin acetate (given IV, SC or intranasal) can be used to increase plasma concentrations of factor VIII and VWF. It does not increase factor IX levels. A single dose (0.3 µg/kg IV infusion/SC) increases factor VIII levels by 3-to 6-folds. IV Desmopressin is available in 40 µg/10 mL vials. A trial to assess response is essential prior to use in acute bleeds. The intranasal desmopressin is given at a dose of 150 µg for children weighing <50 kg and 300 µg for those weighing >50 kg. The peak effect is seen 60-90 minutes after administration and generally depends on the patient's baseline factor VIII activity. Repeated doses may result in tachyphylaxis, water retention and hyponatremia. Availability of only low concentration sprays (10-20 µg/puff) in India prevents its use in hemophilia.

Antifibrinolytics: Tranexemic acid (25 mg/kg oral or 10 mg/kg IV every 6-8h) is useful, especially for bleeds in areas rich in fibrinolytic activity (especially in oral, nasal cavity). Swish and swallow technique can be applied in oral bleeds. It is contraindicated in hematuria and those receiving activated prothrombin complex concentrates (aPCC) due to risk of thrombosis.

Pain management: Pain is a common symptom in patients with hemophilia. The cause of pain may vary from acute pain caused by venipuncture or bleed to chronic arthropathy. Paracetamol is the preferred analgesic. In cases of severe chronic arthropathy, COX-2 inhibitors or opioids might be required.

Vaccination in Hemophilia: Subcutaneous (SC) administration of vaccines is preferred over intramuscular (IM) or intradermal. Vaccines that are routinely given IM (including hepatitis A, hepatitis B, and influenza) can be given SC in children with hemophilia, with no compromise in efficacy and immunogenicity. Use a thin needle (25-27 gauge) and apply prolonged pressure for 5 minutes. Avoid factor replacement close to vaccinations, as vaccination induces an inflammatory reaction and thus may increase the chance of developing inhibitors, which is a serious complication.

Long-term Complications in Hemophilia

Chronic Arthropathy

Recurrent hemorrhages lead to target joints which progress to chronic arthropathy with functional impairment and pain. Synovitis stage should be managed with compression bandages and splints along with analgesics and factor replacement. Restricted joint movement may result in muscle wasting and weakness, and thus an active strengthening program is necessary to maintain normal strength. Management includes acute treatment of hemarthrosis followed by at least a short course of secondary prophylaxis (6-8 weeks) along with physiotherapy.

Physiotherapy programs should be encouraged. It includes superficial thermotherapy, joint traction, passive muscle stretching, isometric and resisted exercise, exercises for mobility and pain management, proprioceptive exercises, etc. This produces significant improvements in pain perception, joint range of motion and muscle strength. Various randomized studies have shown the safety of physiotherapy interventions. The frequency of bleeding was reduced. The chronic pain improved with physiotherapy. Finally, educational physiotherapy improves the perception of pain and the quality of patients with haemophilia [21].

If the synovitis persists or fails to respond to the above measures, synovectomy may be considered. Options for synovectomy include chemical, radio isotopic, arthroscopic or open surgical synovectomy. Further, in patients with permanent joint damage with signs of chronic arthropathy the management includes surgical procedures like tissue release, synovectomy, osteotomy, joint replacement or arthrodesis. Surgery and joint replacement is not needed in those who have been adequately managed and do not have inhibitors. Hence, factor replacement is recommended and is cost saving in the long-term [22].

Development of Inhibitors

Approximately 33% patients with severe Hemophilia A, 13% with mild–moderate hemophilia A and 3% with Hemophilia B develop neutralizing alloantibodies (inhibitors) directed against factor VIII or IX [23]. In mild to moderate hemophilia, inhibitor formation is common with intense immune stimulation with high doses of factors in a short period (like in post-operative cases). In a recent study of 1285 Indian patients with hemophilia A, 6% had inhibitors, with incidence being higher in patients from Southern India (13%) and highest in Chennai (21%) [24]. Severe allergic reactions are known to occur in patients with inhibitors, especially in

hemophilia B. Risk factors include early age at exposure, presence of the common inversion mutation, large deletions of *FVIII* gene, and a sibling with hemophilia and an inhibitor. Majority of inhibitors develop early in the treatment trajectory (after a median exposure of 10 exposure days and less common after 150 exposure days) [25]. Initially, if feasible, inhibitor screen should be performed once in every 5 exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, at least two times a year until 150 exposure days, and later annually [25]. Later, inhibitor should be screened in the following situations: (*i*) prior to and after any surgery or invasive procedure: (*ii*) before and after a switch of products; and (*iii*) whenever clinically indicated (bleeding episodes while on prophylaxis, response to factor therapy in acute bleeds is sub-optimal).

Screening is done by mixing studies, where a failure to correct aPTT with mixing in a known hemophilia B patient indicates factor IX inhibitors. However, in hemophilia A, factor VIII inhibitors are characteristically time-dependent. Immediate mixing results show correction of aPTT, which is lost when the same 1:1 mix is incubated for 2 hours at 37°C. A difference of >5 seconds between immediate mix and incubated mix indicates factor VIII inhibitors. If the inhibitor screen is positive, Nijmegen Bethesda assay is used to quantify inhibitors. One Bethesda unit (BU) is the amount of antibody that neutralizes 50% of factor activity. High titer inhibitors have ≥5 BU/mL and low titers have 0.6 to <5 BU/mL. Low titer patients who have rapid anamnestic response upon exposure to factors are termed high-responders and those without anamnestic response are low-responders.

Prevention and treatment of acute bleeding in patients with inhibitors: In patients with high titer inhibitors, bypassing agents (Activated Prothrombin Complex Concentrates (FEIBA) or recombinant Factor VIIa) should be used for treatment of bleeding in patients with inhibitors and may be given as prophylaxis as shown in ***Table* III**. However, the cost of these drugs is exorbitant, precluding their routine use in our country. Low titer low responders are amenable to treatment with factors if having serious bleed and bypassing agents are not available. Low titer high responders should receive only bypassing agent similar to high titer patients.

Eradicating inhibitors: Immune Tolerance Induction (ITI) remains the mainstay of treatment to eradicate the inhibitors. ITI refers to regular, frequent, and prolonged exposure of the patient to specific factor concentrates thereby inducing peripheral tolerance. Various regimens with regard to dosage and duration of factor exposure are available and are beyond the scope of this guideline. Again, high cost involved in this treatment precludes its routine use. Bleeding episodes need treatment with bypassing agents for patients on ITI (especially with titers >10 BU).

ITI should be continued until inhibitor titers are negative. Overall, ITI is successful in 70% of hemophilia A and in 30% of hemophilia B patients with inhibitors [23]. ITI failure is defined as less than 20% reduction in inhibitor titer over a period of 6 months or lack of tolerance by 33 months [26]. When successful, factor concentrates can be restarted for prophylaxis and treatment.

If ITI alone fails, it can be tried again in combination with various drugs like Rituximab, Cyclophosphamide and IVIG [26]. In a phase II trial, Rituximab for the treatment of Inhibitors in Congenital Hemophilia A (RICH) study, Rituximab monotherapy (375 mg/m^2/dose weekly for 4 weeks) was administered to 16 hemophilia A patients with inhibitor level >5 BU. Three patients (18.8%) had a major response (*i.e.* inhibitor level <5 BU) [27]. The role of Rituximab monotherapy needs further investigation.

We recommend the use of ITI, if practically feasible.

Transfusion-transmitted Infections (TTI)

Use of plasma-derived product (with efficient viral inactivation) and recombinant factors have significantly decreased TTIs in developed countries. In our part of the world, TTIs pose a challenge, as blood products are still used in hemophilia management due to lack of access to

TABLE III BYPASSING AGENTS USED IN INHIBITOR MANAGEMENT [23]

	Recombinant FVIIa	*aPCC (FEIBA)*
Mechanism of action	Activates FX on the surface of platelets	Action of FXa and FII
Half-life	2-3 hours	8-12 hours
Dosing and frequency		
Acute bleeding	90-120µg/kg every 2-3 hourly	50-100 U/kg 2-3 times daily [Max. dose is 200 U/kg/day]
Prophylaxis	90 µg/kg/day	85 U/kg three times/week

factor concentrates. We recommend vaccination against hepatitis B in all children diagnosed with hemophilia. Screening of HIV, hepatitis B and HCV should be performed in all hemophilia patients.

CONCLUSIONS

These advances are likely to improved the management of hemophilia in coming times. Newer products with extended half-life and action through different mechanism are under study. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody, that bridges activated factor IX and factor X to restore the function of missing activated factor VIII, which is needed for effective hemostasis [28]. It is administered as a once-weekly subcutaneous injection. In a recent phase III trial, emicizumab significantly reduced bleeding episodes in hemophilia A patients with inhibitors with few adverse effects.

Factor concentrates (plasma derived and recombinant) have revolutionized the management of hemophilia in the recent decades. The government initiatives have increased the supply of factor concentrates and safer products are available for use. Insured patients are routinely being given prophylaxis and have excellent musculoskeletal functions in the long term. However, implementation of prophylaxis programs is not routine. Complications are rampant in India, adding to the suffering of patients and financial burden. Government allocation of resources and strategies to implement home care, increase availability and distribution of factor concentrates are needed to fulfil the goal of prophylaxis.

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Summary of IAP Consensus Statement for Hemophilia

- Clinical suspicion should arise in any child with easy bruising, unprovoked deep seated bleeds or prolonged/ excess bleeds with surgery or trauma.
- Screening tests reveal a prolonged aPTT with a normal PT and platelet count.
- Correction of aPTT after mixing suggests factor deficiency in intrinsic pathway. Specific factor assays for factor VIII or IX should be done for specific diagnosis.
- Specific precautions should be taken to avoid erroneous laboratory results.
- Genetic analysis is recommended for identifying carriers in family, genetic counselling and prenatal diagnosis.
- All female carriers in the family should get their factor level tested as they can have increased bleeding tendency, especially during pregnancy, invasive procedures and trauma.
- Children with hemophilia are best managed in a comprehensive manner by multi-specialty team.
- Continuous primary prophylaxis is recommended in children with severe hemophilia [at least low-dose regimen of 10–20 IU/kg twice or thrice per week] to prevent acute bleeds and preserve musculoskeletal function.
- Initial management [Rest, Ice, Compression and Elevation (RICE)] should be provided as soon as a patient perceives a joint bleed.
- Factor replacement should be started immediately (as soon as possible). Home therapy is advocated if possible. The dose and duration of factor therapy depends on bodyweight, site and severity of bleed.
- Administer doses (at least) as suggested in resource-constrained settings (but may need to escalate if no satisfactory clinical response).
- Factor concentrates (either plasma-derived or recombinant) should be used in preference to cryoprecipitate or FFP.
- Children with hemophilia should be vaccinated as per IAP schedule with special precautions.
- Long-term complications of hemophilia include chronic arthropathy, development of inhibitors and transfusion-transmitted infections.
- Hemophilia Treatment Centers in various parts of India provide free factors to manage acute bleeding episodes. Further resource allocation with strategic implementation of prophylaxis and prevention programs by the government is the need of the hour.

Available from: *https://www1.wfh.org/publication/files/pdf-1669.pdf*. Accessed February 14, 2018.
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ANNEXURE

PARTICIPANTS OF THE CONSULTATIVE MEET

Chairperson and Convener: Anupam Sachdeva

Experts (In alphabetical order): Amita Mahajan (Delhi), Anand Prakash (Bangalore), Arun Singh Danewa (Delhi), Atish Bakane (Delhi), Jasmita Dass (Delhi), Jyoti Kotwal (Delhi), Kapil Garg (Jaipur), Manas Kalra (Delhi), Neha Rastogi (Delhi), Neha Singh (Delhi), Nita Radhakrishnan (Delhi), Payal Malhotra (Delhi), Prachi Jain (Delhi), Ramya HN (Delhi), Ruchira Mishra (Delhi), Sanjeev Digri (Jammu), Satya Prakash Yadav (Delhi), Shirali Agarwal (Delhi), Satyaranjan Das (Delhi), Sirisha Rani S (Hyderabad), Sudhir Sapkota (Delhi), Tulika Seth (Delhi), Vinod Gunasekaran (Delhi).