GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA IN EGYPT

SECOND EDITION

Developed by an Egyptian Expert Panel

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CONTENTS

Background

The second edition of Egyptian Guidelines have been developed by an expert panel of hemophilia treaters to support the appropriate management of people with hemophilia in Egypt. Although the guidelines are based primarily on the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, Third Edition(1), they aim to address unmet needs and local requirements in Egyptian healthcare settings. The second edition of these guidelines also provide guidance on the novel therapeutics newly introduced since the previous edition.

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Introduction

The healthcare system in Egypt is complex owing to the large number of public entities involved in the management, financing, and provision of care.(2) The World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia are widely recognized as the gold-standard document for informing healthcare professionals on the comprehensive management of patients with hemophilia.(1) The guidelines proposed here have been developed to address important issues related to the management of hemophilia in Egypt, including circumcision and hepatitis C virus (HCV) management. It is important to note that these guidelines should be used as a supplement to the WFH recommendations.

1. General care and management of hemophilia

1.1 What is hemophilia?

Hemophilia is an X-linked congenital bleeding disorder, caused by a deficiency of coagulation factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B). Hemophilia has an estimated incidence of approximately one in 10,000 births.(3) According to 2020 WFH Annual Global Survey, the number of registered patients with hemophilia B is one-fifth of registered patients with hemophilia A, suggesting a prevalence of one case in 50,000 population. (4)

Hemophilia A is more prevalent than hemophilia B, representing 80–85% of the total hemophilia population. According to the WFH Annual Global Survey, there were an estimated 6,233 people with hemophilia (PWH) in Egypt in 2020.(4)

The characteristic phenotype in hemophilia is the bleeding tendency. Its severity is generally correlated with the clotting factor level. Patients with a FVIII/IX level below 1% activity have severe disease characterized by spontaneous bleeding. Those with a level of 1–5% activity have a moderate bleeding phenotype, characterized by traumatic bleeding episodes with occasional spontaneous bleeds. Patients with a level of 5–40% activity will only suffer traumatic and surgical bleeding.(4) Hemophilia should be suspected in patients presenting with excessive bleeding following minor surgery, such as circumcision. Definitive diagnosis should be confirmed through factor assay to demonstrate deficiency of FVIII or FIX.

While bleeding tendency is life-long, PWH may not present with bleeding symptoms until later in life; for example, when they begin walking or running.

1.2 PRINCIPLES OF CARE

Management of hemophilia has several aims, which include prevention and treatment of bleeding, prevention of long-term joint damage, physical therapy, dental care, vaccinations, nutritional support, genetic counseling, and psychological support.

For optimal care, PWH should be treated within a comprehensive care setting. A patient's core management team should include a hematologist, nurse coordinator, laboratory specialist, musculoskeletal specialist, physical therapist, orthopedic surgeon, and psychologist. The patient should also have access to a chronic pain specialist, dentist, geneticist, hepatologist, infectious disease specialist, immunologist, gynecologist/obstetrician, and vocational counselor, if possible.

The primary aim of care is to prevent and treat bleeding with the deficient clotting factor. Whenever possible, factor deficiency should be treated with factor concentrate (see section 6.2 Product selection). WFH guidelines recommend prophylaxis with clotting factor concentrates (CFCs) or non-replacement therapy as a standard of care for prevention, as well as early treatment of bleeds. In order to achieve this goal, both availability of products and education of patients on home therapy are mandatory.

1.3 HOME THERAPY

Early treatment of bleeds minimizes the amount of blood in affected joints, improving short- and long-term outcomes, such as reduced pain and swelling, as well as reduced joint damage. Home therapy provides the patient with immediate access to clotting factor, which enables early treatment to stop bleeding and reduce resultant long-term damage. Besides the increase of factor level with clotting factor concentrates (or desmopressin in mild hemophilia A), management of muscle and joint bleeds can be achieved through first-aid measures such as PRICE: splints (**P**rotection), **R**est, apply **I**ce in the bleeding location, **C**ompression, **E**valuation. In case of mucosal bleeds or dental extractions, antifibrinolytic drugs (i.e., tranexamic acid, epsilon-aminocaproic acid) can be an effective adjunctive treatment. Home therapy is necessary for effective use of prophylactic treatment.

Where home therapy programs are available, there is a reduction in clinic visits and hospital admissions, easing the burden on public health facilities. Nevertheless, it is important to ensure a regular clinic visit (every 3 months) for follow-up. Training and education are very important for both parents and patients, particularly in relation to the following aspects of care:

- How to self-infuse
- How to keep bleeding records
- How to transport, store, and use factor
- How to dispose needles and used product containers
- How to handle blood spills
- How to manage complications of therapy

RECOMMENDATIONS

Home therapy should be encouraged for effective management of bleeding and prophylactic therapy; however, it is important that regular clinic visits continue to ensure good management of hemophilia. First aid measures and antifibrinolytic agents are encouraged as adjuvant therapy. Parents and patients should be educated on all the steps underlying home therapy to build confidence, ensure safety and promote home therapy as an option for the management of hemophilia.

1.4 PHYSIOTHERAPY

Physiotherapy is important in the management of hemophilia to prevent and treat musculoskeletal damage.(3) In addition to clotting factor concentrates, usually prescribed by the hematologist, management of acute hemarthrosis and chronic arthropathy requires close collaboration between the orthopedic surgeon and physiotherapist. This collaboration, which should also involve a coagulation and musculoskeletal specialist, is key to effectively prevent hemarthrosis, manage acute joint bleeding episodes, assess joint function, and actively treat chronic arthropathy.(5) Physiotherapy should be initiated as soon as the pain subsides and should be continued to gradually restore full muscle length, strength, and function.

The evaluation of joint status and progression of arthropathy, including its impact on quality of life, represents an integral part of the consultation. A short and easy scoring system can be used to support the evaluation of joint health and should be adopted to monitor patient outcomes.(5)

RECOMMENDATIONS

It is recommended that the hemophilia treater talks directly with the local physiotherapist to provide education on the special needs of treating someone with hemophilia, specifically regarding the use of factor replacement therapy prior to the physiotherapy session. Physiotherapy maneuvers are best carried out immediately after factor infusion. A short and easy scoring system, such as the Hemophilia Joint Health Score (HJHS) should be adopted to evaluate joint health.

1.5 NUTRITION AND VACCINATION

It is important for PWH to maintain good nutrition, particularly in ensuring adequate absorption of key nutrients such as calcium, iron, and vitamins C and D.

Management of patients who are overweight or obese is challenging and costly, requiring constant follow-up of the patient's nutrition, lifestyle, weight, and physical activity levels. Adequate weight management should be encouraged.

Immunization against hepatitis A and hepatitis B viruses (HAV and HBV) is mandatory for all PWH. Routine HAV vaccination should be performed in all patients >1 year of age.(2) Patients >5 years of age should be screened for HBV and revaccinated if they test negative. Vaccinations should be subcutaneous, rather than intramuscular or intradermal.

RECOMMENDATIONS

Appropriate healthcare should be provided to all PWH, including nutritional advice and follow-up – calcium, iron supplements (guided by iron level), and vitamins C and D. Routine HAV vaccination in all PWH >1 year of age is mandatory. HBV screening is essential for PWH >5 years of age, and it is important to revaccinate those who test negative.

1.6 ROUTINE MONITORING IN PWH

The WFH Guidelines for the Management of Hemophilia (3rd edition) note that "in the management of hemophilia, outcome assessment refers to the use of specific tools designed to monitor an individual's disease course and to measure the consequences of the disease and its treatment (i.e., the effectiveness of hemostatic therapy and associated complications)."(1)

Based on the suggestions detailed in the WFH Guidelines for the Management of Hemophilia (2nd edition),(3) we recommend the following for patient monitoring:

- Regular standardized evaluation should be performed and documented at least every 12 months in adults and at least every 6 months in children, to enable longitudinal assessment of individual patients and identify new or potential problems in their early stages, so that treatment plans can be modified
- After every severe bleeding episode PWH should be evaluated by the multidisciplinary care team

Monitoring/outcome assessment in hemophilia should cover two aspects:(1, 3)

1. Disease-related outcomes
    - Bleeding events
    - Pain
    - Musculoskeletal status monitoring
    - Protocol and type of CFCs or non-CFC products used and the response to them
    - Overall psychosocial status
    - Dental/oral health
2. Therapy-related outcomes
    - Testing for inhibitor development
    - Monitoring for less common complications of CFC and non-CFC therapy, including thrombosis and allergic/anaphylactic reactions
    - Monitoring for transfusion-transmitted infections: commonly human immunodeficiency virus (HIV), HCV and HBV, and others if indicated
    - Issues related to venous access
    - Issues related to compliance and adherence

MONITORING FOR BLEEDING EVENTS

According to the WFH Guidelines for the Management of Hemophilia (3rd edition) "the most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes."(1) Frequency of bleeding is assessed by estimation of annualized bleeding rate (ABR) and annualized joint bleeding rate (AJBR), calculated as the number of reported bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12.(6)

Other aspects of bleeding events that should be documented are:(3, 6, 7)

- Site and duration of each bleed
- Target joint or non-target joint bleed
- Provoked (i.e., traumatic) or spontaneous bleed
- Dose, number, interval, and response to factor administration
- Need for hospitalization and duration

RECOMMENDATIONS

It is recommended that the frequency of all bleeds is documented in real time by patients/caregivers and reviewed together by the hemophilia treatment center at least annually, with particular reference to intra-articular, intramuscular, and central nervous system bleeds, including their recovery status.

MONITORING FOR PAIN

Acute and chronic pain are common in PWH. Acute pain may be caused by venous access, joint or muscle bleeds, postoperative pain, and dental pain. Patients with hemophilic arthropathy can suffer long-term adverse effects due to chronic pain, disability, and reduced quality of life.(8) Monitoring for pain and its causes is essential to guide proper management.(1, 9)

Pain assessment can be done using:

- Qualitative pain scale: the Wong-Baker FACES Pain Rating Scale can be used in children over the age of 3 years and in adults;(10) the Face, Legs, Activity, Cry, Consolability (FLACC) pain scale was developed to assess the level of pain in children who are too young to cooperate verbally, and can also be used in adults who are unable to communicate(11)

- Quantitative pain scales such as the numerical rating pain scale designed to be used by those over the age of 9 years(12)

Pain can also be scored through subscales within quality-of-life questionnaires and within specific joint assessment instruments such as the HJHS.(1, 13)

RECOMMENDATIONS

Pain is best assessed and addressed in the context of a comprehensive care setting.

MUSCULOSKELETAL STATUS MONITORING AND OUTCOME ASSESSMENT

In PWH, the impact of bleeding on the musculoskeletal and other systems can be measured across several domains. This includes assessment of bleeding on body structure and function, activity levels, participation levels and health-related quality of life (HRQoL) as per the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF).(1, 14) All of these domains may be affected by contextual factors including environmental, personal, and economic characteristics.(15)

RECOMMENDATIONS

Assessment and documentation of the musculoskeletal and overall health of each patient should be done at least annually in adults and every 6 months in children.(1) Standard definitions and validated tools should be used.(1, 3, 16)

Musculoskeletal status monitoring should include the following assessments:(1, 3, 6)

- Body structure and function
    - Clinical assessment of joints is performed using:
        - The HJHS in children and young adults(13, 17)
        - The Gilbert score in adults and children with established arthropathy(17)
    - Radiological joint assessment:
        - Early structural changes in joints are assessed using ultrasound(18) or magnetic resonance imaging (MRI) when feasible(19)
        - Late osteochondral changes are assessed on plain radiographs (Pettersson score)(20)
- Functional activity levels should be assessed using the most appropriate option available for that individual, such as:
    - Haemophilia Activities List (HAL)(21)
    - Haemophilia Activities List for children (PedHAL)(22)
    - Functional Independence Score in Hemophilia (FISH)(16)
- HRQoL tools aim to evaluate the various dimensions in the ICF model of health(15)
    - A number of hemophilia-specific HRQoL questionnaires have been developed and used successfully in clinical studies, including:
        - The Haem-A-QoL for adults(23)

    - The Haemo-QoL for children and adolescents(24)
    - The Canadian Haemophilia Outcomes–Kids Life Assessment (CHO-KLAT)(25)
  - They should be used only in combination with the other domains of the WHO ICF

- Patient-reported outcomes (PROs) provide a report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. These included:
  - Generic instruments such as the five-level EuroQol five dimensions (EQ-5D-5L) or Short Form 36 Health Survey v2 (SF-36v2)(26)
  - Disease-specific instruments such as the HAL and PedHAL(20, 21)

2. LABORATORY DIAGNOSIS AND TESTING

2.1 PRINCIPLES OF DIAGNOSIS

Early diagnosis is important for the effective management of hemophilia. A correct diagnosis is essential to ensure that a patient receives the appropriate treatment, particularly considering that different bleeding disorders may have very similar symptoms.(2)

An accurate diagnosis can only be made with the support of a comprehensive and accurate laboratory service. Screening tests should be used to identify the potential cause of bleeding; for example, platelet count, bleeding time (in select situations) or other platelet function screening tests, prothrombin time (in select situations), and activated partial thromboplastin time (APTT).(3) Diagnosis should be confirmed by factor assays and other appropriate specific investigations. A central laboratory to confirm factor level is mandatory. Genotyping is essential; however, genetic testing services are currently limited in Egypt.

RECOMMENDATIONS
Specific WFH guidelines on laboratory practices for the diagnosis of hemophilia should be followed.

2.2 DETECTION OF INHIBITORS

"Inhibitors" in hemophilia refer to immunoglobulin G (IgG) antibodies that neutralize or limit the effectiveness of clotting factor concentrates.(3) Depending on the potency of inhibitors present, treatment may be rendered partly or completely ineffective, resulting in increased morbidity.(27, 28) Inhibitor development is multifactorial, with genetic and non-genetic risk factors involved.

The cumulative incidence of inhibitory antibody development in previously untreated people with hemophilia A is approximately 30%, of which 79% of cases occur within the first 20 exposures to FVIII concentrates and the remaining 21% within the first 75 exposures.(29). Early inhibitor detection is essential for initiating appropriate treatment.(1) Although inhibitors usually occur within the first 50 to 100 exposure days, a low risk of inhibitor development remains throughout a patient's life.(30, 31) The impact of treatment-related factors on inhibitor development in previously untreated patients (PUPs) with hemophilia A is still debated.(32)

Development of inhibitors in PWH is one of the most serious complications of hemophilia management today(2) and monitoring for inhibitor development in PWH treated with CFCs is mandatory. The 2nd edition of the WFH Guidelines for the Management of Hemophilia suggested inhibitor monitoring be scheduled on the basis of days of CFC exposure,(3) while the 3rd edition suggested less frequent monitoring (Table 1).(1)

Immune tolerance induction and immunomodulatory therapy are not used in patients in Egypt, as no patient or medical authority can cover the cost of the factor concentrate. Bypassing agents, such as NovoSeven® (eptacog alfa [activated]), and more recently, activated prothrombin complex concentrate (APCC), and Hemlibra® (emicizumab-kxwh), are valid options for hemophilia patients with inhibitors.

Table 1: Indications for inhibitor testing(1, 3)

WFH Guidelines for the Management of Hemophilia, 2nd edition(3)	**WFH Guidelines for the Management of Hemophilia, 3rd edition(1)**
• For children, inhibitors should be screened once every 5 exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least twice a year until 150 exposure days • For adults with more than 150 exposure days, apart from a 6–12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor	• After initial factor exposure • For patients with newly diagnosed hemophilia A, the WFH recommends regular inhibitor screening at least every 6–12 months, and then annually* o REMARK: In general, more frequent screening should be considered for recurrent bleeds or target joints that occur despite standard factor replacement • After intensive factor exposure – e.g., daily exposure for more than 5 days** • For failure to respond to adequate CFC replacement therapy • For lower than expected factor recovery or half-life after CFC replacement therapy • For suboptimal clinical or laboratory response to CFC replacement therapy • Before surgery • For suboptimal post-operative response to CFC replacement therapy
* While some references advocate more frequent screening,(33) this remains controversial with few data	

**Screening should be performed in any patient, regardless of age or disease severity, who is intensively treated (i.e., for more than 5 consecutive days) and within 4 weeks of the last infusion(1, 3)

RECOMMENDATIONS

Specific WFH guidelines on the detection of inhibitors should be followed.

3. SPECIAL MANAGEMENT ISSUES

3.1 VIRAL HEPATITIS IN EGYPT

Egypt has the highest prevalence of HCV infection in the world, with 14.7% of people aged 15–59 years affected.(34) The high prevalence of HCV is thought to have resulted from its transmission during parenteral antischistosomal therapy (PAT) mass-treatment.(35) Current risk of transmission of HCV through the healthcare community setting is still considered to be substantial.(35)

Knowledge about the viral load distributions in different stages of HCV infection is essential to compare the efficacy of serologic screening and nucleic acid testing in preventing transfusion transmission risk. Studies have been conducted on the HCV-RNA levels in Egyptian blood donors in the pre-seroconversion window period and in later anti-HCV-positive stages of infection.(36) These studies found that individual donor nucleic acid testing (ID-NAT) for HCV-RNA was efficacious, and concluded that serologic testing provides minimal incremental safety following the introduction of ID-NAT. The findings indicate that ID-NAT could potentially be a more cost-effective measure for evaluation of blood safety.(36)

A recent national health survey and national programs to control viral hepatitis reported reduction of prevalence to 4.6%. The impact of the national program to treat hepatitis C using direct-acting antiviral drugs has further improved prevalence, but this has not been reported yet. The prevalence of HBV infection is currently 1.3%–1.5%, having declined after the national immunization program. HAV and hepatitis E Virus (HEV) infections still represent a challenge due to high rates of community infection and lack of blood screening programs for the two viruses.(37)

Current management of viral hepatitis for PWH in Egypt includes compulsory HBV vaccination, mass treatment of patients and carriers of HCV, an improved blood safety program, and improved programs of hospital infection control. There is a need to recommend mandatory vaccination against HAV in patients with hemophilia. The use of virally inactivated plasma-derived CFCs, recombinant CFCs, non-replacement novel agents and virally inactivated blood components such as solvent and detergent (S/D) cryoprecipitate and S/D plasma should be recommended to avoid transfusion-transmitted viral infections.

RECOMMENDATIONS

Prevention of HCV transmission in PWH is a priority of care in Egypt and regular screening is important, even in asymptomatic patients. Patients should be educated on the potential risks underlying the use of blood products and stricter policies are needed to protect them. For PWH with active HCV or HBV infection, specific antiviral therapy should be provided. Mandatory vaccination against HBV and HAV is recommended. Regular screening for HIV should also be recommended and antiviral agents must be provided

3.2 PSYCHOSOCIAL ISSUES

Psychosocial factors have a significant impact on the quality of life of patients with chronic diseases such as hemophilia. Interventions to support the psychosocial needs of patients and their carers, including providing information and assistance, clarifying doubts, and teaching coping strategies to minimize the impact of the associated disabilities, may help to maximize patient outcomes and improve the quality of life of their families.(38, 39)

Programs and studies have shown positive results from providing psychological support to parents following the diagnosis of hemophilia. Parents who participated in a program of monthly psychological support and counseling showed significant improvement in pre- and post-study psychological test results by displaying greater use of problem-focused coping strategies (recognition that a situation can change), and reduced use of emotion-focused strategies (indicative of no change).(40)

RECOMMENDATIONS

PWH and their families should be provided with access to psychological and social support. A specialized psychosocial specialist should focus on patient and family education and addressing the emotional burden of the disease on the patient. Increased awareness of hemophilia is also needed among healthcare providers and the general population; for example, through medical caravans and the media.

3.3 CIRCUMCISION

In Egypt, circumcision is an important cultural practice and must be considered for PWH. Modern hemophilia treatment aims to integrate PWH into society, while acknowledging and respecting their culture and beliefs.

Such an approach is vital in order to succeed in hemophilia management in Egypt.

Despite the high costs of the procedure and the risks of developing inhibitors, social demand for circumcision of boys with hemophilia is significant.

Since the risks of developing inhibitors is higher during the neonatal period, postponing circumcision until after 6 months of age is advisable. Conducting the procedure between 6–18 months of age is preferred.(41) This age recommendation was based on an early prophylaxis in children and so, by this age, they might have passed 20 exposure days and consequently the risk of inhibitor development is reduced. As primary and secondary prophylaxis is still not the standard of care in Egypt, postponing circumcision to 6–18 months may still be the first exposure to CFCs.

An Egyptian-Center case-controlled study of PUPs or minimally treated patients (MTPs) with hemophilia A who underwent circumcision with minimal CFC replacement had comparable inhibitor development to an age-matched cohort of PWH without circumcision. The study concluded that performing circumcision in PUPs with hemophilia A using minimal CFC perioperative prophylaxis does not represent an increased risk factor for inhibitor development. It also concluded that an early-age control of bleeding with minimal CFC perioperative prophylaxis is more efficient than at an older age.(42)

RECOMMENDATIONS

CIRCUMCISION AT AN EARLY AGE CAN BE CONDUCTED WITH MINIMAL PERIOPERATIVE CFC PROPHYLAXIS.

In PWH with family history of development of inhibitors, it is recommended to perform the circumcision after 20–50 exposure days. In these patients, screening for inhibitors should be done 4–12 weeks after surgery to identify if they will develop inhibitors.

3.4 DENTAL CARE

In Egypt, children with hemophilia have generally received suboptimal dental care, but their oral health requires thorough assessment. Oral health education, plaque control, and access to dental care are essential to improve the oral health of these pediatric patients.(43)

GENERAL MEASURES

Good oral hygiene for PWH should be encouraged to prevent the need for dental work and oral diseases such as gingivitis, dental caries, and periodontal disease, which may cause serious gum bleeding. Teeth should be brushed at least twice daily for plaque control, using a soft or medium textured toothbrush and fluoridated toothpaste.

DENTAL SURGERY AND INVASIVE PROCEDURES

The WFH Guidelines for the Management of Hemophilia (3rd edition) recommendations for dental surgery and invasive procedures include:(1)

- Before any dental surgery or other invasive procedure within the oral cavity, hemostasis management should be individually planned under the advisement of a hematologist
- Systemic or topical antifibrinolytics (i.e., tranexamic acid or epsilon-aminocaproic acid) are effective as adjunct treatment in the management of dental interventions pre- and postoperatively and have the potential to reduce the need for factor replacement therapy
- Antibiotics should only be prescribed if clinically indicated for management of infection
- [Additional Egyptian Guidelines]: Antibiotic prophylaxis should be administered to patients with prosthetic joint replacement

Any swelling, difficulty swallowing (dysphagia), hoarseness or prolonged bleeding after dental surgery must be reported to the dentist/hematologist immediately.

The WFH Guidelines for the Management of Hemophilia make the following recommendations for anesthesia during dental procedures:(1)

- For many dental procedures, adequate local anesthesia is necessary, and most dental injections can be delivered safely

- Higher-risk intramuscular oral injections may require systemic hemostatic measures. These measures should be established preoperatively under advisement of a hematologist
- Alternative low-risk routes of delivery such as intraligamentary single-tooth anesthesia or buccal infiltration injections are effective alternatives to inferior alveolar nerve blocks

Specific treatment guidelines for treatment management of patients undergoing dental interventions are summarized in Table 2

TABLE 2: Guidelines for people with moderate-to-severe hemophilia requiring outpatient/inpatient surgical dental treatment

Procedure	FVIII/IX levels required	Pre-, peri- and postoperative schedule
Restorative procedures	Can generally be performed without raising factor levels If nerve blocks are needed, first raise factor level to ≥50% F VIII: 25–30 IU/kg/dose FIX: 50 IU/kg/dose	Tranexamic acid PO 25 mg/kg every 6 h for 24 h before surgery (adult 500–1000 mg) Continue for 3–7 days (postoperative) Avoid acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory drugs Local measures to control/prevent bleeding should be used
Dental extraction Dento-alveolar or periodontal surgery	Raise factor level to 50–60% Continue factor coverage for 1–2 days (postoperative) if needed FVIII: 25–30 IU/kg/dose FIX: 50 IU/kg/dose Non-absorbable sutures preferred	Extensive procedures may require hospitalization Tranexamic acid IV 10 mg/kg 1 h before surgery or PO 25 mg/kg/6 h and continue for 7–10 days after procedure Soft diet for 7 days Local measures (tranexamic acid mouth rinse) to control/prevent bleeding should be used Careful brushing around wound site for minimum of 3–5 days postoperatively to avoid disturbing clot and wound healing Antibiotic prophylaxis (in case of bacteremia and possible pre-surgical infection); oral course for 7 days Smoking should be avoided
Major surgery Maxillofacial surgery	*Preoperative* Raise factor level to 100% FVIII: 50 IU/kg/dose FIX: 100 IU/kg/dose *Postoperative* Factor level 50% for 7 days FVIII: 25 IU/kg/dose FIX: 50 IU/kg/dose	As above Inpatient for 7–10 days
Endodontic treatment	None in moderate hemophilia Raise factor level to 50–60% in severe hemophilia FVIII: 25–30 IU/kg/dose FIX: 50 IU/kg/dose	As above

RECOMMENDATIONS

Good oral hygiene should be encouraged in PWH. Hemostasis management (including systemic and/or topical antifibrinolytics) should be individually planned with advice from a hematologist before any dental work is undertaken. Patients with prosthetic joint replacement need antibiotic prophylaxis. Any problems after dental surgery (swelling, difficulty swallowing, hoarseness, prolonged bleeding) must be reported immediately. Most dental injections can be delivered safely in PWH.

3.5 OBESITY IN PEOPLE WITH HEMOPHILIA

An increasing number of PWH are living to an older age thanks to improvements in hemophilia management, brought about by the routine access to replacement coagulation factors. As a result, PWH are at risk of age-related diseases, such as obesity and type 2 diabetes.(44)

Increased prevalence of obesity has been observed in both adult and pediatric hemophilia populations, similarly to trends described for the global population. However, over 10 years an approximate 20% increase in obesity was reported in adults, and approximate 40% increase was observed in children.(45)

3.5.1 CLINICAL IMPACT OF OBESITY IN PEOPLE WITH HEMOPHILIA

DOSING AND ADMINISTRATION OF FACTOR REPLACEMENT

The dose of intravenous replacement coagulation factor products is determined based on the patient's body weight. However, owing to the reduced plasma volume in adipose tissue, the pharmacokinetics of the administered dose of coagulation factor must be considered in PWH who are overweight/obese.(46) Additionally, dosing according to 'ideal body weight' for height may allow for a significant reduction in factor consumption in people who are overweight/obese, which could reduce the cost of prophylaxis while maintaining the safety of patients.(47)

There is also evidence that being overweight/obese can impact the administration of coagulation factor. A study evaluating a population of 10,814 male PWH A and B found that those who were overweight/obese were less likely to administer home-infusion or self-infusion of factor concentrate (prophylactic), compared with individuals of normal weight, potentially due to the greater difficulty in obtaining venous access to administer treatment.(48) Consequently, PWH who are overweight/obese may be unable to obtain all of the benefits associated with home treatment, including better quality of life and reduced pain, disability, and time spent in hospital.(48)

MUSCULOSKELETAL HEALTH

Spontaneous joint bleeds account for up to 80% of all bleeding episodes in PWH. For individuals with severe hemophilia, recurrent bleeding into the joints causes intra-articular changes, which can lead to restricted movement, structural damage and hemophilic arthropathy. Muscle hematomas are another frequent complication that can lead to inflammation, infections, muscle dysfunction or a decreased range of motion, further contributing towards long-term damage.(49)

Several studies have evaluated the clinical impact of being overweight/obese on musculoskeletal health in PWH. One study conducted on PWH from the USA demonstrated a link between excess adiposity and a reduced range of motion in weight-bearing joints and a faster loss of joint mobility(45). Similar findings have been described for European PWH. A study of pediatric PWH observed significant reductions in the active range of flexion of the knees and elbows among individuals who were overweight or obese.(50) Analysis of a cohort of Dutch hemophilia patients also reported that being overweight/obese was associated with an increased number of joint bleeds and lower limb function, (51) An association between obesity and the frequency of chronic pain has also been described.(52)

Severe hemophilia may give rise to sarcopenia and decrease maximal muscle strength, possibly as a consequence of these patients reducing their levels of physical activity in order to prevent bleeds and preserve joint health.(53) Moreover, people with severe hemophilic arthropathy typically have reduced mobility and loss of muscle function, leading to inactivity and subsequent muscle atrophy, which may increase their risk of weight gain.

The association between low bone mineral density, increased hemophilic arthropathy, reduced mobility and muscle atrophy highlights the need to assess bone health and to take into account the impact of overweight/obesity on bone mineral density among PWH.(3)

PSYCHOLOGICAL IMPACT

Among PWH, the high prevalence of depression and the psychological impact of their condition must also be considered. A survey of 307 PWH A in the UK found that 32% of patients reported experiencing depression or anxiety. The stigma associated with having a bleeding disorder or contracting HIV or HCV infection through contaminated blood products were identified as major concerns by the respondents.(54)

3.5.2 SCREENING TOOLS FOR IDENTIFICATION OF OVERWEIGHT /OBESE PEOPLE WITH HEMOPHILIA

As with the general population, measurement of body mass index (BMI) is one of the most frequently utilized methods for diagnosing overweight/obesity in PWH.(55) Measurement of waist circumference is a strong predictor of visceral obesity and has been shown to be more accurate than BMI for determining health risks associated with obesity. Another potential option is the waist-to-height ratio – which has been shown to have a higher level of accuracy as a predictor of whole body fat percentage and visceral adipose tissue than BMI – waist circumference, or waist-to-hip ratio.(56)

3.5.3 APPLICATION OF GENERAL GUIDELINES FOR WEIGHT MANAGEMENT IN HEMOPHILIA

Given the multiple causes and potential complications of obesity, it is important to follow an optimal approach to weight management, which incorporates careful clinical decision-making and individualized care. Although no specific guidelines exist for weight management in PWH, the existing general guidelines for children and adults are still applicable to the management of patients with underlying disorders. Specific treatment approaches, such as suitable physical activities/exercise and bariatric surgery may need careful consideration in PWH. It is important to involve and consult the multi-disciplinary hemophilia treatment center (HTC) team when applying general weight management guidelines.(57)

Comprehensive lifestyle modification forms the basis of interventions to prevent weight gain or promote weight loss and incorporates steps to reduce calorie intake, increase physical activity, and also establish behavioral changes, which help to increase patient adherence to these changes in diet and exercise. More intensive approaches for weight loss, such as pharmacotherapy and bariatric surgery, are recommended for people with obesity-related comorbid conditions and/or higher body weight, particularly individuals with severe obesity and in cases where behavioral therapy alone has not been successful to achieve clinically meaningful weight loss. It may be helpful to consult with an obesity medicine specialist in order to determine whether drug therapy or bariatric surgery is necessary. In the case of PWH, appropriate hemostatic coverage during surgery should be administered in the perioperative setting under the direction of the HTC.(58)

DECREASING CALORIC INTAKE

Reduced caloric intake should be the major component of any weight loss intervention, and can be achieved by targeting a specific caloric target (1200–1500 kcal/day for women and 1500–1800 kcal/day for men) or energy deficit (500 or 750 kcal/day), or restricting intake of specific foods or food groups.(59)

There is a lack of evidence that calorie-neutral changes in the macronutrient composition of meals have a direct impact on weight loss. However, controlling macronutrient consumption may help to optimize dietary adherence or manage cardiovascular risk factors, such as hypertension or cardiovascular disease. Individualizing the patient's reduced calorie diet based on their personal preferences as well as any cultural, geographic, or financial barriers, is important for implementing an effective weight loss program.(60)

INCREASING PHYSICAL ACTIVITY

Physical activity is a key component of weight loss interventions, particularly for maintaining weight loss. The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) has published evidence-based clinical practice guidelines for the management of obesity, which support the following individualized exercise regimens: aerobic activity (150 minutes or more of moderate exercise per week, distributed across three to five daily sessions), resistance training (2–3 times a week) and active leisure activity.(59) However, for PWH, it is essential to carefully consider the person's risk of bleeding, level of pain and functional impairment when devising an exercise regimen. A review article on the topic of managing hemophilia in PWH and obesity identified the following steps to allow regular activity in this patient population: low-impact aerobic activities such as swimming, walking or cardiovascular training using an elliptical machine or stationary bike; reducing the intensity of resistance exercises; incorporating a stretching routine; and recognizing and managing the risk of activity-related pain or bleeding.(61)

The hemophilia care team is responsible for advising PWH on physical activities to participate in, and how to adjust their treatment regimens when undertaking exercise and how to manage potential bleeding events that might result from physical activity. The National Hemophilia Foundation has published a general guideline with information on determining the types of activities appropriate for PWH at different ages.(62) However, any exercise regimen should also broadly consider personal preferences, history of activity-related bleeding and specific functional limitations.

ESTABLISHING BEHAVIORAL CHANGE

Behavioral therapy is the third component of comprehensive lifestyle intervention, and includes several personalized interventions, including weight and behavioral self-monitoring, goal-setting, education, psychological counseling, stress reduction and mobilization of social support.(61)

RECOMMENDATIONS

The basis of interventions to prevent weight gain or promote weight loss is comprehensive lifestyle modification. A reduction in caloric intake should be the main component of any weight loss intervention. This may be achieved by targeting a specific caloric target (1200–1500 kcal/day for women and 1500–1800 kcal/day for men) or energy deficit (500–750 kcal/day), or by restricting consumption of particular foods or food groups. Recommendations for increasing physical activity should take account of an individual's risk of bleeding and level of pain and functional impairment. Behavioural interventions to promote adherence to these changes may include weight and behavioural self-monitoring, goal-setting, education, psychological counseling, stress reduction and mobilization of social support. General recommendations for weight loss for children and adolescents include similar lifestyle modification such as reduction of energy intake, increased physical activity and adoption of dietary habits to reduce calorie intake.(63)

4. HEMOSTATIC AGENTS AND DOSING REGIMENS

4.1 CLOTTING FACTOR CONCENTRATES

There are two categories of FVIII and FIX concentrate for the treatment of hemophilia A and B, respectively: plasma-derived and recombinant. Plasma-derived clotting factor is manufactured from large pools of human plasma, and undergoes various processes that aim to inactivate and eliminate known blood-borne viruses.

Recombinant clotting factor concentrates are manufactured from genetically engineered cell lines and undergo multiple purification steps, which are specific to each product manufacturer.

4.2 PRODUCT SELECTION

Currently CFCs for the management of hemophilia are highly effective; the main treatment choice considerations are product safety and cost.

At a global scale, in the 1970s and 1980s, large numbers of PWH became infected with blood-borne viruses due to contaminated plasma-derived FVIII and FIX concentrates.(64) Careful selection of blood donors, screening of plasma, and advances in manufacturing of clotting factor concentrates have led to the almost complete elimination of the risk of known viral transmissions. However, despite the advances in prevention of transmission of known lipid-enveloped blood-borne viruses, blood can never be considered completely sterile as there are transitory or permanently circulating viruses that are not currently screened for, such as HEV, Epstein–Barr virus, parvoviruses, cytomegaloviruses and Torque teno virus.(65) Additionally, non-lipid-enveloped pathogens may survive current viral inactivation processes, and emerging viral and non-viral pathogens, such as prions, should also be considered.(66)

The risk of prion-mediated disease through plasma-derived products is higher in the absence of a reliable screening test for variant Creutzfeldt-Jakob disease (vCJD), and when there are no established manufacturing steps to inactivate the vCJD prion.

For patients with hemophilia A, it is also important to identify persistence of inhibitors against FVIII, as this is a potential risk factor that increases physical disability.(67) However, the development of neutralizing anti-FVIII inhibitors is not solely dependent on the specific type of concentrate product used.(68)

RECOMMENDATIONS

Recombinant clotting factor concentrates are considered the gold-standard therapy and are the recommended treatment of choice for PWH in Egypt. If resources are limited, virally inactivated plasma-derived concentrates can be used. Due to the high prevalence of HCV in Egypt, cryoprecipitate, fresh frozen plasma, and solvent and detergent filtration cryoprecipitate should only be used in emergency situations when no alternatives are available.

4.3 CRYOPRECIPITATE

In Egypt, due to cost and resource constraints, both virally inactivated cryoprecipitate by the solvent and detergent (S/D) method and virally inactivated plasma by the S/D method are used for the management of patients with hemophilia.

Data have shown that S/D filtration cryoprecipitate FVIII "can be safely used for the control of acute and chronic bleeding episodes in hemophilia A patients"(69) but the WFH Guidelines recommend it should only be used in "situations where clotting factor concentrates are not available".(1)

Regarding dosage, the WFH Guidelines highlights that "a bag of cryoprecipitate made from 1 unit of fresh frozen plasma (200–250 ml) may contain 70–80 units of FVIII in a volume of 30–40 ml".(1)

4.4 FRESH FROZEN PLASMA

Fresh frozen plasma is a limited option to treat hemophilia A as it is generally difficult to achieve FVIII levels higher than 30 IU/dl.(1)

Although fresh frozen plasma can be used for the treatment of hemophilia B in countries with limited resources to afford plasma-derived FIX concentrates, the WFH Guidelines do not recommend its use due to its safety and quality concerns.(1)

4.5 PROPHYLAXIS VS ON-DEMAND THERAPY

The WFH Guidelines state that "prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability."(1) Prophylaxis has been characterized according to when it is initiated (Table 3). These definitions apply to both hemophilia A and B.(1)

Prophylaxis is the standard of care in children with hemophilia and has evolved over the past 50 years.(70) Compared with on-demand treatment, prophylaxis in children with severe hemophilia:(71-73)

- Reduces the risk of bleeding episodes
- Minimizes joint damage
- Optimizes functional outcomes

Many different protocols are followed for prophylaxis (Table 4), and the optimal regimen remains to be defined. Prophylaxis should be tailored to individual patients, and evidence shows that favorable

treatment outcomes can be achieved using lower doses of CFC without compromising patient safety.(74) Low-dose prophylaxis may suit countries with budget constraints. A low-dose regimen comprises 10–15 IU/kg/dose, 2–3 times per week.(1)

With effective prophylaxis, treatment objectives have moved from resolution of bleeding to prevention of bleeding and arthropathy.(71)

Table 3: Conventional factor prophylaxis for hemophilia A and B defined according to when prophylaxis is initiated(1)

Protocol	Definition
Primary prophylaxis	Regular continuous prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and 3 years of age
Secondary prophylaxis	Regular continuous prophylaxis initiated after two or more joint bleeds but before the onset of joint disease; this is usually initiated at 3 or more years of age
Tertiary prophylaxis	Regular continuous prophylaxis initiated after the onset of documented joint disease. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood

Table 4: Conventional factor prophylaxis with standard half-life clotting factor defined according to its intensity(1)

Prophylaxis intensity	Hemophilia A	Hemophilia B
High-dose prophylaxis	25–40 IU FVIII/kg every 2 days (>4000 IU/kg per year)	40–60 IU FIX/kg twice per week (>4000 IU/kg per year)
Intermediate-dose prophylaxis	15–25 IU FVIII/kg 3 days per week (1500–4000 IU/kg per year)	20–40 IU FIX/kg twice per week (2000–4000 IU/kg per year)
Low-dose prophylaxis (with escalation of dose intensity, as needed)	10–15 IU FVIII/kg 2–3 days per week (1000–1500 IU/kg per year)	10–15 IU FIX/kg 2 days per week (1000–1500 IU/kg per year)

RECOMMENDATIONS

Prophylaxis is the preferred treatment approach for all PWH to preserve musculoskeletal function, as it helps to prevent bleeding and joint damage and improves quality of life. Low-dose (recombinant third-generation products: 10–15 IU/kg) prophylaxis 2 to 3 times per week is an effective option, but should be individualized according to age, venous access, bleeding phenotype, activity levels, and availability of clotting factor concentrates. For the treatment of very young children, one option is to start prophylaxis once a week and escalate the frequency depending on bleeding and venous access.

5. COMPLICATIONS OF HEMOPHILIA

5.1 SYNOVECTOMY

Approximately 80–90% of bleeding episodes in hemophilia occur in the musculoskeletal system, especially in the large synovial joints (elbows, knees, ankles, hips, and shoulders).(3) Chronic hemophilic synovitis is characterized by persistent joint swelling and proliferative synovitis.(75)

A reduction of the hypertrophied synovium is the key to preventing recurrent intra-articular hemorrhages.(75) The vicious cycle of hemarthrosis–synovitis–hemarthrosis secondary to recurrent hemarthroses must be interrupted as soon as possible to avoid the development of hemophilic arthropathy.(75)

Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding and it is not possible to be controlled by other means.(2) If a radioisotope is not available for radioactive synovectomy, chemical synovectomy with rifampicin is an appropriate alternative;(2) however, chemical synovectomy can be more painful than radioactive synovectomy.(76)

A combined prospective study comparing chemical (rifampicin) vs radioactive (^{90}Y) synovectomy showed both methods have similar results.(76)

RECOMMENDATIONS

Guided by ultrasound, non-surgical synovectomy is the procedure of choice. Chemical synovectomy should be used when appropriate and available. Rifampicin is highly effective, has few side effects, and can be administered in an outpatient setting, when preceded and followed by factor infusion, analgesic use and bed rest.

5.2 CNS BLEEDING

Central nervous system (CNS) bleeding is the most common emergent bleeding event encountered among PWH.(77) It includes bleeding inside the skull (intracranial hemorrhage [ICH]), which can be subdural, epidural or intra-parenchymal in location), or the spinal canal (spinal hematoma).(78, 79)

INTRACRANIAL HEMORRHAGE

ICH results in high rates of mortality and disability among PWH.(76) Mortality from ICH is around 20%,(80) and is higher in younger children and in developing countries.(81) The prevalence of ICH in the pediatric (non-neonatal) hemophilia population is about 12%, with 50% of cases being clinically silent.(82)

Trauma is the leading cause of this devastating complication in childhood and adolescence.(80) However, a history of head trauma may be difficult to determine, particularly in children with severe hemophilia.(79)

Predisposing risk factors for spontaneous ICH include severe disease, infections (HCV and HIV), the presence of inhibitors, age <5 or >50 years, a previous ICH episode,(83) thrombocytopenia, hypertension(80, 84) and the absence of prophylaxis.(85) Even in patients with non-severe hemophilia, spontaneous ICH has been reported with no additional risk factors.(83)

ICH should be suspected in any hemophilia patient with or without a history of head trauma if any of the following signs or symptoms are present: headache; blurred vision; nausea or vomiting; mood or personality changes; drowsiness; loss of balance or coordination; weakness or clumsiness; stiffness of the neck; loss of consciousness; seizures or localizing signs. However, a significant number of patients may be asymptomatic at the time of initial evaluation. Delayed onset of symptoms is usually associated with a subdural bleed.(86) Any patient aged 3–18 years with moderate or severe hemophilia who presents with a history of a persistent or unexplained headache should be considered to have CNS bleeding until proven otherwise and should be thoroughly evaluated.(87)

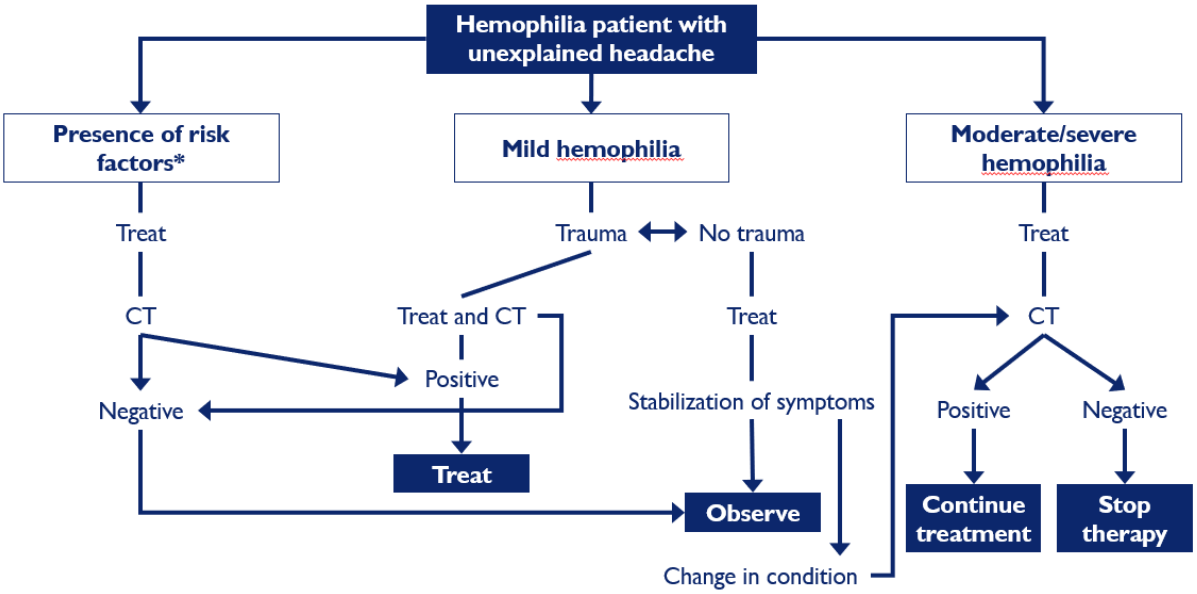
It is critical to immediately increase clotting factor level to at least 100%, even before the bleeding is identified by brain imaging studies.(77) Neurosurgical intervention for evacuation may be warranted, particularly in surgically approachable sites (especially subdural hematomas).(88) Additionally, clotting factor replacement, neurosurgery, and airway management are necessary for patients who are comatose or incapacitated, and also in cases where intracranial pressure is increased.(89)

RECOMMENDATIONS

Any head trauma in PWH must be considered non-trivial until proven otherwise, and immediate treatment is recommended. Any unexplained or persistent headache in PWH aged 3–18 years should be evaluated and managed according to the proposed algorithm, even in absence of history of head trauma (Figure 1).(87)

Figure 1: Suggested algorithm for management of unexplained or persistent headache in

children (3–18 years of age)(90)



*Risk factors: presence of HIV, HCV or inhibitors; age <3 years, hypertension, decreased platelets. MRI is recommended as the ideal radiologic investigation, if easily accessible

ICH IN NEONATES

ICH is the leading cause of morbidity and mortality in newborns with hemophilia. ICH incidence in neonates with hemophilia (3.4–4.0%) is substantially higher (40–80 times) than in neonates without congenital bleeding disorders. Nearly half of these ICH episodes occur in the first days of life and are frequently related to the delivery.(90) Prolonged labor (>24 hours), operative vaginal delivery (i.e., with the assistance of vacuum or forceps) and severe disease are the most important risk factors for ICH. Signs and symptoms of neonatal ICH can often be vague and may be mistaken for other entities. Anemia, lethargy, hypotension and shock are common symptoms of ICH, and neurologic manifestations include seizures and a bulging fontanel.(91)

Hemophilia is not a contraindication to vaginal delivery, either for female hemophilia carriers or for affected fetuses. If there is no obstetric contraindication to vaginal delivery, an attempt at vaginal delivery can be planned with careful monitoring. If an assisted birth is a possibility, this plan should be abandoned early in favor of a caesarean section. Invasive fetal monitoring, such as placement of intrapartum fetal scalp electrodes and fetal scalp blood testing, should be avoided.(92)

Suspicion of ICH calls for an immediate cranial ultrasound.(77) However, cranial ultrasound is limited in its capacity to detect subdural or subarachnoid hemorrhages, especially at the convexity of the brain; hence, a computed tomography (CT) scan is preferred after traumatic delivery following CFC administration.(93) Because almost one-third of new cases of severe hemophilia A present with no family history, it has been recommended that all male newborns presenting with ICH should have an APTT test performed immediately after birth and that FVIII and FIX assays should also be conducted as soon as possible.(94) Furthermore, in neonates with moderate or severe hemophilia prophylaxis should be started as soon as possible to reduce the risk of ICH, which is particularly high among pediatric patients

aged ≤2 years.(95)

RECOMMENDATIONS

Delivery of a fetus with suspected hemophilia should take place in a hemophilia treatment center under the supervision of a hemophilia expert. The delivery plan should be reviewed, and availability of CFC should be ensured. Sensible safety precautions along with primary prophylaxis are recommended for children with severe hemophilia.

SPINAL HEMATOMA

Sudden severe pain in the back, with or without a history of trauma to the back, is the usual manifestation of spinal hematoma. Decompression surgery by laminectomy may be needed at any age to relieve spinal cord compression and to reduce the risk of paralysis, especially if pressure is not relieved with CFC during the first critical hours. However, early identification of spinal hematomas and administration of CFC replacement therapy to achieve normal physiologic levels may prevent the requirement for neurosurgery.(96)

MANAGEMENT CONSIDERATIONS

For head traumas or suspected CNS bleedings in PWH, if the patient is on home therapy, the product may be administered before leaving home or on route to the facility (preferably a hemophilia treatment center), provided the bleeding is not life-threatening and this does not result in delays. In life-threatening circumstances, emergency medical transport should be called and the product administered on route.(78)

Hospital admission is mandatory for CNS bleeding in PWH, and urgent hematological and early neurosurgical consultation must be sought. Rapid clinical assessment, airway maintenance and intravenous access should be performed. Treatment with CFC must be given immediately in the emergency department, even before admission to hospital; it must NOT be delayed until radiologic investigations confirm bleeding or laboratory tests have been obtained. In other words: treat first, evaluate second, and plan further therapy after weighing up all relevant issues.(77) The maximum time between arrival at the hospital and clinical assessment should not exceed 15 minutes, and the maximum time to CFC replacement should not exceed 30 minutes.(97) The importance of urgently giving CFC outweighs considerations of what specific factor preparation is administered – the available product should be given.

Sufficient CFC should be infused to ensure a normal physiologic level initially (at least 100% within the normal range). If neurosurgery is needed, subsequent doses should be given much sooner because of high factor clearance during surgery.(77) Further doses will depend on imaging results; maintaining factor levels until etiology is defined is essential. Continuous infusion shortly after the bolus dose is appropriate. A dose of 4 IU/kg/h of standard half-life FVIII concentrate and 6 IU/kg/h of standard half-life FIX concentrate for hemophilia A and B, respectively, will often maintain the factor level initially achieved by the bolus infusion.(98) Alternatively, repeated doses can be given according to CFC availability (Table 5).(99) If possible, circulating factor levels should be maintained above 50% at all times for up to 3 weeks following a CNS bleed to minimize the risk of a re-bleed. A longer duration may be needed if an

extensive neurosurgical procedure was required.

Table 5: Suggested peak plasma factor levels and duration of administration in patients with CNS bleeding (with and without significant resource constraint)(99)

Therapy	Hemophilia A		Hemophilia B	
	Desired level (IU/dl)	Duration (days)	Desired level (IU/dl)	Duration (days)
No significant resource constraint				
Initial	80–100	1–7	60–80	1–7
Maintenance	50	8–21	30	8–21
Significant resource constraint				
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

RECOMMENDATIONS

An MRI scan of the brain is the preferred method of evaluation; if this is not feasible, a CT scan can be used.(100) The factor level should initially be raised to100% and maintained appropriately for at least 14 days. Lifelong or long-term secondary prophylaxis is mandatory after CNS bleeding.

MANAGEMENT OF INHIBITORS

PWH who are known to have inhibitors and develop an acute CNS bleed should be treated with a bypassing agent, such as recombinant FVIIa (rFVIIa), rather than higher doses of FVIII or FIX. Treatment should start with ≥120 mcg/kg rFVIIa at least every 2 hours. Once hemostasis is achieved, further dosing and lengthening of the interval can be based on the patient's clinical situation.(100) The duration of treatment can be up to 14 days.(101)

RECOMMENDATIONS

For patients with inhibitors, treatment should be with large doses of bypassing agent and lifelong secondary bypassing agent prophylaxis.

6. BLEEDING IN FEMALES

6.1 HEMOPHILIA CARRIER ANALYSIS

A hemophilia carrier state may be an important differential diagnosis in a girl or young woman who is bleeding and has an increased bleeding score compared with control. A carrier state should be suspected in a girl with abnormal bleeding and a positive family history of hemophilia; for example, the daughter of a PWH should be considered an obligate carrier.

6.2 MULTIMODAL APPROACH TO TREATMENT AND CARE

Normal coagulation FVIIII and FIX levels in the general healthy population range between 0.50–1.50 IU/ml.(102) Female carriers of a *F8* or *F9* gene mutation on one X chromosome typically have FVIII or FIX levels approximately 50% under these levels (0.5 IU/ml), although a wide range of factor levels are seen in these patients.(102)

Many carriers are asymptomatic because their other X chromosome contains a functioning copy of the gene to produce factor levels within the lower limit of the normal range, which may be adequate to maintain hemostasis.(1) However, ~30% hemophilia carriers display low clotting factor levels, and even mildly reduced levels of 0.41 and 0.60 IU/mL have been associated with bleeding (103, 104). In addition, some hemophilia carriers may also experience abnormal bleeding episodes despite having normal factor levels.(100)

Heterogeneity of symptoms in female carriers could occur due several variables that lead to low factor levels, including inactivation of one of the X chromosomes (known as Lyonization); ABO blood group; mutations in the genes encoding von Willebrand factor; compound heterozygosity, or homozygosity.(100)

Bleeding in female carriers is mostly mucocutaneous bleeding and may include epistaxis, menorrhagia, bleeding with interventional procedures, and postpartum hemorrhage.(100, 103) Iron deficiency is a common complication in adolescent girls due to mismanaged menorrhagia.(103, 105) It has been shown that between 14–19% of hemophilia A carriers report hemarthrosis.(106) Furthermore, studies have shown an association between FVIII or FIX deficiencies among hemophilia carriers and reduced range of motion in joints. Some carriers also show pathologic and radiologic evidence of structural joint damage.(103, 105, 107)

Pedigree analysis and FVIII or FIX levels are not sufficient to ascertain diagnosis of hemophilia carrier state.(107, 108) The gold standard for identification of female carriers is DNA mutation analysis; however, the causative mutation may not always be detectable and genetic testing may not be available in Egypt except in a limited number of specialized centers.(109,110,111)

For girls or women diagnosed with an isolated FVIII or FIX deficiency, carriership of hemophilia should also be ruled out via genetic tests, even if there is no familial history of hemophilia.(112)

RECOMMENDATIONS

Immediate female relatives (mother, sisters and daughters) of a person with hemophilia should have their clotting factor level checked, especially before any invasive intervention, before childbirth or if any symptoms occur. Girls and women in families with hemophilia are not just carriers; they are PWH too and should be recognized as such. They can be safely cared for at hemophilia treatment centers. Birth control pills and antifibrinolytic agents are useful in controlling symptoms of menorrhagia. Carriers should be treated with a multimodal approach that enhances patient education and awareness, with an emphasis on self-report of symptoms and communication with healthcare providers.

7. TRANSITIONAL AND ADULT HEMOPHILIA CARE

7.1 IMPLEMENTATION OF TRANSITIONAL CARE

GOAL, CHALLENGES AND KEY OUTCOME INDICATORS

*"The **goal of transition** is to provide healthcare that is uninterrupted, coordinated, developmentally appropriate and psychologically sound prior to and throughout transfer into the adult system."(113, 114)*

The main barrier to transition is the continuity of medical care.(113)

Challenges during transition to adulthood medical care include:

- Severing of relationships with the long-term pediatric care provider
- Adaptation to an unfamiliar environment
- New responsibilities of self-management
- Miscommunications between the existing pediatric care provider and the new environment of care with the adult hemophilia care team
- Incomplete medical records and transfer of data
- Barriers to availability of replacement factors and the budget for comprehensive care of adult hemophilia patients
- Other areas of care that are limited due to lack of financial coverage
- Hemophilia treatment centers (HTCs) not being currently available to treat adults with hemophilia in Egypt

Key outcome indicators and process in transitional care for adolescents with hemophilia and rare bleeding disorders (RBDs) include:

- Measurement of treatment adherence
- Change in bleeding rate
- Self-efficacy skills
- Hemophilia knowledge
- Patient and caregiver satisfaction
- Time gap between last pediatric and first adult clinic
- Number of emergency room visits

- Number of hospital admissions

GUIDELINES FOR TRANSITIONAL CARE

Transition guidelines could be used by the teams who are involved in providing care for patients with hemophilia/RBDs patients. These include all the multidisciplinary teams working together to provide comprehensive care for these patients, such as parents, nurses, psychologists, physicians, hematologists, other subspecialties and physical therapists.(115)

Transition guidelines consist of the following components:

1. Self-advocacy
2. Independent healthcare behavior
3. Sexual health
4. Social support
5. Educational/vocational/financial planning
6. Health and lifestyle behavior
7. Communication and HTC/team support

Procedures to implement the transition guidelines:(116)

1. Each patient needs an individualized plan for transition of care taking into account factors including: age range, clinic visits, parent visits, home visits and schooling conditions
2. The people who need such a plan are hemophilia patients, carriers and patients with other RBDs
3. All care team members are responsible for the transition plan; the team includes physicians, nurses, social workers, physical therapists, genetic counselors and health advocates
4. One staff member will be the liaison between all team members and all the parties on the pediatric and adult medicine sides

Our experience of implementing transitional care consisted of the following:

- An MD liaison from pediatrics and MD partner from internal medicine should coordinate the process of transition
- Combined clinics in pediatric hospital set-up, which was attended by hematologists from Pediatrics and Internal Medicine Departments
- Newly developed outpatient clinic in the Internal Medicine Department
- Hard copy of patient medical records provided by the Pediatric Clinic was handed to the Internal Medicine Hematologist attending the joint clinic to continue medical record compiling on the adult side (Internal Medicine)

7.2 OPTIMIZING CARE OF ADULT PATIENTS

EXISTING CHALLENGES (117)

Developing countries, such as Egypt, are faced with numerous challenges and barriers for the provision of care for patients with hemophilia and other RBDs, which are listed below:

- Lack of proper healthcare infrastructure
- Lack of human resources trained for hemophilia care
- Competing healthcare priorities of the government
- Lack of effective roles of medical insurance in health population
- Lower visibility of hemophilia patients in the healthcare system
- Low awareness across medical professionals, general population, policy makers, families and patients
- Non-availability of factor concentrates
- Inadequate pain management
- Viral hepatitis
- Lack of comprehensive care and HTCs
- Lack of highly specialized staff and those needed in specific subspecialities
- Lack of research and publications
- Limitations to early therapy of bleeding disorders
- **Educational barriers:** lack of awareness among patients and their families regarding the bleeding signs and early replacement therapy; education of caregivers at schools
- **Financial problems** related to the cost of clotting factor products, insurance coverage, insurance caps and out-of-pocket costs
- **Distance to the treatment centers:** remote area patients from upper Egypt and countryside
- Problems related to **venous access**
- Problems related to **home care** and **home infusion**
- Multiple **psychological barriers** can prevent adherence to treatment regimens
- **Unavailability of HCC/HTC**
- Unavailability of **subspecialists** to handle multi-problematic and complicated cases
- Inadequate **prophylaxis protocols** leading to adult hemophilia patients with musculoskeletal disorder and resulting disabilities
- Limited job opportunities, and limited education in schools and university for adults with hemophilia
- Inadequate **physiotherapy** or inadequate replacement factors required by physiotherapy
- Complications are common in adults; **hemophilic pseudotumors** are more common in Egypt because of inadequate replacement therapy
- Major problem of **HCV and HBV**

- Lack of resources to treat **patients with inhibitors**; no financial support to implement immune tolerance induction
- Financial limitations hindering the provision of new medications such as Hemlibra (emicizumab)
- No programs to include patients in gene therapy protocols
- **The cost of elective surgery due to the need for factor replacement therapy**
    - Readiness of hospitals and unavailability of **interested surgeons** to treat hemophilia patients
    - Critical situation and inappropriate readiness for **emergency medical care** such as fractures or acute abdominal conditions

GAP CLOSURE TO OVERCOME BARRIERS AND CHALLENGES

Despite the aforementioned barriers and challenges, our hospital has taken steps to address some of these issues in order to improve care of adult PWH in Egypt. A summary of these initiatives is provided below.

COMPREHENSIVE CARE SYSTEM

The existing set-up of hemophilia treatment centers in Egypt is not ideal for treating adults. The age policy for transition varies depending on the healthcare provider. Adult age is considered to be ≥18 years in some medical facilities and ≥14 years in others.

As there is no HTC care system for adults in Egypt, we aimed to resolve this issue by coordinating with different specialties and subspecialities to assemble a multidisciplinary team for comprehensive care of adult PWH.

The team includes:

- Clinical hematologists
- Pediatricians
- Trained residents
- Associate lecturers
- General surgeons
- Vascular surgeons
- Plastic surgeons
- Orthopedic surgeons
- Rheumatologists with experience in invasive procedures such as ultrasound studies and interventions
- Clinical pathologists
- Laboratory services
- Blood banking services

- Radiology services
- On-demand services such as cardiology, nephrology, endocrinology, hepatology, infectious diseases specialist and intensive care services

Nursing orientation and training is in place; however, committed nursing staff are needed for the implementation of this initiative (118)

Even if the personnel and specialists are available, they are not always accessible. Also, it is difficult to find qualified personnel to handle the multifaceted problems of hemophilia care.

Another challenge was to obtain an assigned location and to organize the logistics for the multidisciplinary team to meet and work together. This was resolved by preparing a special clinic to be part of the readiness for transitional care.

It was difficult to coordinate a regular fixed time to gather all these parties together. However, our IT department helped to arrange gatherings through cellular communication to hold multidisciplinary meetings and reach a final consensus regarding patient management plans and treatment.

This was the situation in Cairo University Hospital, but unfortunately the minimum requirements are absent in rural or remote areas, such as upper Egypt low socioeconomic districts.

ADDRESSING THE COST OF CARE (118, 119)

Citizens on average or above average earnings cannot afford the cost of hemophilia care. For example, the cost of non-medical and logistic aspects of treatment such as transportation and accommodation for those individuals who travel to access medical services in big cities is excessive for most PWH. The consequences of school absence and difficulty of working with a disability exacerbate the problem. Over 90% of our adult patients have musculoskeletal disorders and present wide-ranging levels of disability.

University hospital, insurance hospital and governmental hospital staff are not paid for their time or expertise. Most of the medical cost falls under factor replacement alongside the costs of laboratory services and support specialties such as radiology and blood banking.

Possible solutions include:

- Provision of medical care for less cost by universities
- Medical insurance sponsored by a governmental entity – the Ministry of Health (MOH)
- Special medical insurance by private companies
    - The private medical insurance companies do not cover congenital diseases except by special arrangement with the patient or his spouse
- MOH coverage of medical care by the General Health Council (Commission)
    - This needs a medical report to be prepared by three MDs
    - The general medical commission provides a minimal amount of funding that can cover only the price of one or two bottles of replacement factor
- Personal donations by individuals and businessmen in the community

- Donations by non-governmental organizations (NGOs)

7.3 Awareness and education

Until recently, many people, families, social groups and some primary care physicians were not aware of hemophilia or other RBDs.

Circumcision of males and its associated complications often represent the first encounter with hemophilia, and usually it is a disappointing occasion for a family who were happy to have baby boy and then discover have a newborn with a disease.

Patient and family awareness represents the cornerstone to train the adult patient and his parents and caregivers about home therapy. Home therapy includes having access to trained caregivers who can handle emergency situations of mild to moderate musculoskeletal disorder, and being trained to use factor replacement at home. For being able to use factor replacement at home, it is important to have a good mechanism to monitor the procedure and guarantee that the patient is receiving the factor, and to be trained to follow up on any complications that could happen. Some cases need dosage modification of the factor and a trained caregiver to be involved in its administration.

Social awareness will encourage donations by environmental people, authorities, and NGOs.

Awareness by physicians in the front-line of care will save the patient's limbs and life by appropriate referral to any of the centers capable of managing hemophilia and RBDs. Primary care physicians can start treatment by basic care of trauma, such as cold compresses, immobilization and diagnosis of the problem, depending on the available services in each facility. An important duty of the primary care physician is to refer the patient to a specialized center or nearby medical facility able to handle patients with hemophilia and other RBDs. With the appropriate referrals made, real differences in the outcome of care and quality of care will be visible.

Another key issue for physicians treating hemophilia is education regarding the use of plasma and cryoprecipitate due to the unavailability of replacement factor.

7.4 Hemophilia management: Summary of key recommendations

Conservative management of hemarthrosis(117, 119)

- Splints, rest, ice, compression, elevation (PRICE) in case of trauma
- Immobilization of the injured joint
- Adequate pain management
- Management of chronic synovitis
- Successful role of ultrasonography, which is performed by rheumatologists. This can be diagnostic or therapeutic by intervention modalities
- Use of antifibrinolytic in different ways with appropriate dose

- Use of prosthetics and orthotics by an expert to avoid side effects
- Physical therapy by a hemophilia-experienced physical therapist to choose the right modality and the appropriate plan. Factor should be infused before the physiotherapy session to avoid aggravation of bleeding
- All previously mentioned options can reduce factor usage or can play a role in the management of hemarthrosis until factor is available for administration

PAIN MANAGEMENT IN HEMOPHILIA AND RBDS(119)

- Avoid non-steroidal anti-inflammatory drugs (NSAIDs), which are the mainstay of pain therapy in PWH; however, COX-2 inhibitors have been found to be relatively safe
- Paracetamol is the medicine of choice but does not have a very strong analgesic effect; however, it is more effective if used regularly rather than as required, or when combined with an opioid such as codeine or dextropropoxyphene
- Narcotic analgesics are used, but they can be very addictive
- Morphine is less addictive than pethidine
- Fentanyl skin patches can be used

Most of these medications have limitations associated with their use, and they are not easily available or accessible.

JOINT INJECTIONS IN HEMOPHILIA PATIENTS(119, 120)

Chronic synovitis is an uncommon problem. Regular factor replacement with intense physiotherapy and secondary prophylaxis with physiotherapy are costly in Egypt and developing countries.

SYNOVECTOMY(117, 120)

Open orthoscopic synovectomy is rarely done in adult patients at our center. It is highly costly with a guarded outcome, as it requires four or five sessions of treatment.(117)

Medical Chemical synovectomy is the injection of intra-articular rifampicin or tetracycline, neither of which is available in Egypt.

Radioactive synovectomy is currently not available in Egypt, but we are trying to make it available as it makes a significant contribution to decreasing factor replacement. This treatment requires only one session of intra-articular injection of radioactive material, which is expensive and unavailable in Egypt. Only one or two doses of factor replacement is needed to complete the procedure.

SURGERY IN HEMOPHILIA

In our experience, most surgeries in PWH are done on an emergency basis. Procedures are needed for orthopedic problems, acute abdominal catastrophes and cases of hemophilia pseudotumors. All these procedures will require a large amount of factor replacement that needs huge financial resources. The

cost and availability of replacement factor is a real challenge as it impacts the outcome.

The role of trained surgeons is indispensable. The decision of the surgeons to intervene or not is a real challenge, which affects patient outcomes and the cost of factor replacement. Talented, experienced surgeons are needed to practice safe surgery with adequate hemostasis.

PROBLEMS WITH VENOUS ACCESS(119)

Venous access problems are a significant barrier for hemophilia home care. Central venous access is an option for some outpatients. Complications such as infections are a major challenge. Insertion and removal of a permcath is another challenge that needs good coverage by factor replacement. Infective endocarditis is a possible complication with infected permcaths.

Newer medications such as Hemlibra (emicizumab) will be very popular due to the subcutaneous mode of administration. Cost is a factor that may limit its usage.(119, 120)

CHRONIC LIVER DISEASE(117)

Many patients receive plasma cryoprecipitates, which are blood-derived products and are potential sources of viral infections such as HCV, HBV and HIV. A taskforce was formulated among our team to treat hemophilia patients with hepatitis C within the Egyptian National Program of Hepatitis C Treatment.

ACQUIRED HEMOPHILIA(119, 121)

Acquired hemophilia is a rare autoimmune disorder, which is caused by the production of inhibiting antibodies against a coagulation factor, most commonly FVIII. It can occur in both males and females with no previous history of abnormal bleeding events. The severity of bleeding can vary ranging from no or mild bleeding to life-threatening bleeding events. Patients with acquired hemophilia typically present with subcutaneous bruising and mucosal and deep soft tissue bleeding. Uncontrolled bleeding following surgical intervention or trauma is also frequent in undiagnosed patients, but unlike in congenital hemophilia, hemarthrosis is rare.

Acquired hemophilia can occur in patients of all ages, but is more common in the elderly. It is also often associated with other underlying autoimmune disorders (e.g., rheumatoid arthritis, lupus), pregnancy and dermatological disorders.

The main treatment goals for patients with acquired hemophilia include the control of acute bleeding, removal of the inhibitory autoantibody, protection of patients against trauma and avoidance of non-essential invasive procedures that may cause acute bleeding events.

An algorithm for the diagnosis of acquired hemophilia is shown in Figure 2. International treatment recommendations for bleeding patients with acquired hemophilia include the administration of bypassing agents, including recombinant FVII, APCC, or recombinant porcine FVIIII. Furthermore, the removal of autoantibodies can be achieved with immunosuppressive therapy, including corticosteroids, cyclophosphamide and rituximab, or combinations of these agents (Figure 3).

Figure 2: Diagnostic algorithm for acquired hemophilia(115)

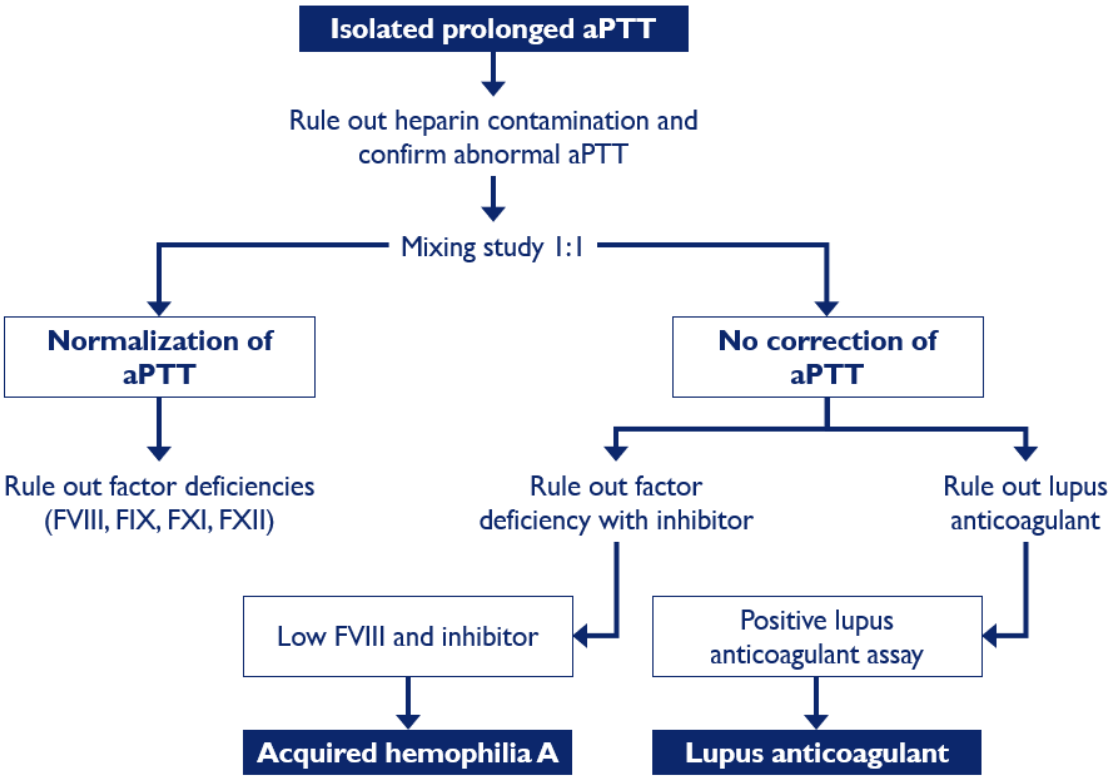
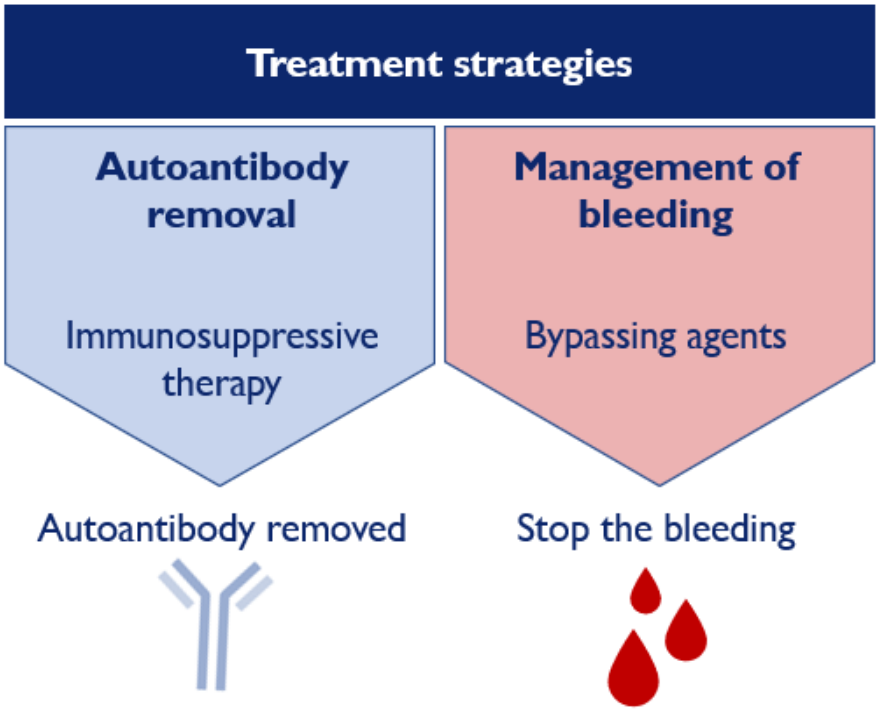


Figure 3: Treatment strategy for acquired hemophilia(119)



8. EGYPTIAN SOCIETY OF HEMOPHILIA AND FUTURE STRATEGIC OBJECTIVES

8.1 INTRODUCTION TO THE EGYPTIAN SOCIETY OF HEMOPHILIA (ESH)

The regular management of hemophilia in Egypt started through the establishment of a Diagnostic Unit of Inherited Bleeding Disorders (IBD) in the Central Health Laboratories of the Ministry of Health (MoH) and a Hemophilia Treatment Center in the National Institute of Diabetes, in 1968. Three years later, Dr Bothaina El Shenawy, together with a group of interested hematologists and PWH, founded the Egyptian Society of Hemophilia (ESH). The role of ESH is summarized in Figure 4.

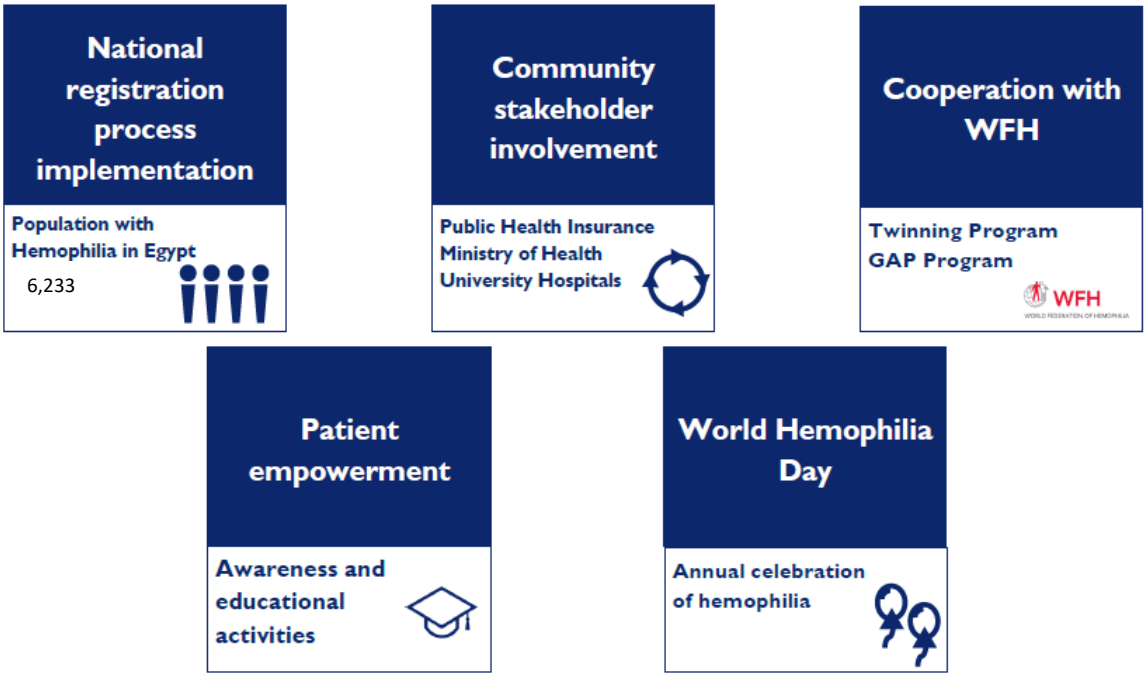
The ESH objectives are to:

1. Accurately identify IBD through the provided MoH laboratories and blood research departments
2. Establish and maintain a national registry to accurately determine the epidemiological data of IBD and improve decision-making on adequate 'patient' treatments
3. Increase public awareness about IBD and advocate for the rights of PWH in accessing appropriate healthcare and integration in society through:
    - Free education
    - Exemption from military service
    - Employment rights similar to other impairment disorders
4. Scientific research in the field of IBD
5. Cooperation with other national and international organizations that can help to improve the care of patients with IBD

8.2 NATIONAL CARE PROGRAM FOR IBD

As a result of the work by the ESH there are now about 21 hemophilia treatment centers across the country, IBDs are among government priorities, and allocated budget is progressively increasing.

Figure 4: Role of the Egyptian Society of Hemophilia



8.3 Patient Advocacy

Introduction to patient advocacy

Patient advocacy has been defined as an area of specialization in healthcare dealing with advocacy for patients, survivors and caregivers. Patient advocates can be made up by individuals or represented by a larger organization. Healthcare advocates work closely with patients, their loved ones and other professionals working in the facility, focusing on health conditions, healthcare resources and the needs of patients and the public.

Patient advocacy groups have several roles in the field of rare diseases including:

- Education of stakeholders (patients, physicians, caregivers and payers) about diseases
- Campaign for improvements in diagnosis/treatment of specific diseases
- Raise awareness of diseases in the medical community with a view of funding research and development
- Promote universal patient access to effective therapies
- Foster research collaborations, including obtaining funding for clinical trials

Challenges in hemophilia management

A review article identified the following challenges for the management of hemophilia patients in developing countries:(117)

- Lack of proper healthcare infrastructures and human resources suitable for hemophilia care
- Competing healthcare priorities of the government.

- Lack of penetrance of medical insurance in the population (except students)
- Low visibility of hemophilia patients in the healthcare system
- Low awareness of the condition among the medical profession, population and policy makers
- Non-availability of factor concentrates
- Inadequate utilization of knowledge for reducing factor concentrate use
- Inadequate pain relief
- Challenges due to inhibitor development
- Viral hepatitis
- Lack of publications relevant to the country

One of the major solutions to the challenges faced by PWH is the presence of an active patient advocacy organization aiming to:

- Link individual patients with caregiving organizations (hospitals) and doctors
- Ensure that patients receive evidence-based information and up-to-date treatment and are protected from transfusion-transmitted infections
- Advise government and other bodies on the management options in hemophilia
- Act as a sounding board for adopting advanced treatment options
- Interact with other similar non-governmental organizations to mobilize funds and other expertise to materially improve the physical, social and economic wellbeing of PWH

The presence of the ESH, and its links with the WFH, is an important step in establishing a strong advocacy program targeting government, doctors and opinion makers to solve many of the above challenges. The WFH Advocacy Program was launched in 2006 to help national patient organizations to bring about change through advocacy and to strengthen the voice of people around the world who are affected by inherited bleeding disorders. This program provides hands-on training, coaching and tools to encourage and empower national member organizations (NMOs) to implement successful advocacy projects and activities.

HOW TO BOOST PATIENT ADVOCACY

The WFH provides the following recommendations for improving patient advocacy for PWH:(122)

1. **Establishing a National Hemophilia Committee (NHC)**
   This should include the key clinicians, the hemophilia organization, the MoH and, in many cases, the paying authority, and it can be a very progressive step in improving hemophilia care. Involvement of the NHC in the decision-making process is the optimum way to organize care, regardless of where the country stands in the development of its hemophilia program. It increases the influence of the NMO, the opportunity for a coordinated approach to be taken by the NMO and clinicians, and the amount of personal contact between the NMO and the key health and government officials who make the policy allocation decisions on health budgets. It can raise the profile of hemophilia with the key officials

2. **Standards and guidelines**
   These can be tremendously helpful and can be used as an advocacy tool when seeking access to a better level of hemophilia care
3. **Broadening the community**
   There is strength in numbers. Hemophilia is a rare disease, and governments may look at a hemophilia society and realize that it represents one person in 10,000, or 0.01% of the population. We can increase that percentage by expanding our membership to include people with von Willebrand disease and rare bleeding disorders, carriers of hemophilia, women with bleeding disorders and others who share many of the same goals. By including these other groups, we strengthen the society, we bring in new members, we have more lobbying power, and we can call for greater resources to be spent in this area

8.4 ESH VISION AND STRATEGIC PLAN UNTIL 2025

01 PUBLIC AWARENESS

There is interest in increasing knowledge about IBD among healthcare professionals and the community, particularly through governmental support

02 PRODUCT AVAILABILITY

Increase the availability of FVIII from 0.36 IU/capita to 0.86 IU/capita

03 NATIONAL GUIDELINES

Establish National management guidelines and ensure regular reviews and updates

04 DIAGNOSIS

Introduction of a national screening program for inhibitors to FVIII and FIX

05 NATIONAL REGISTRATION

Introduce regular evaluation of management outcome and establish a national registry

06 COMMUNITY SUPPORT

Increase governmental support for rehabilitation of patients with IBD

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10. APPENDIX

10.1 FISH/CLINICAL SCORING SYSTEM

The FISH (Functional Independence Score for patients with Hemophilia) has been developed as a measure of disability in PWH.(51) According to the developers of this assessment tool, the FISH is intended to measure what the person with disability *actually does*, and not what he ought to be able to do, or might be able to do if circumstances were different. It can be used to evaluate change in functional independence over time, or after a therapeutic intervention.(51) By incorporating items that are perceived as important by PWH, the FISH is performance-based and is relatively safe to perform. The FISH is intended to complement other measurement scores of body structure and function, clinical joint evaluation score and the radiological score. Several activities are not specifically evaluated by the FISH, and therefore it may be necessary to complement this assessment tool with other self-rated scores.(51) The major advantage of the FISH is that it can be used with illiterate patients and in different language settings, as it is an objective, performance-based instrument. It has good face and content validity and internal consistency (Cronbach's alpha of 0.83). It correlates well with other self-rated activities such as the Stanford Health Assessment Questionnaire (HAQ) (0.90), and has a reasonable correlation with the clinical score (-0.68) and radiological score (-0.44).(52)

RECOMMENDATION

Any trained therapist or clinician can administer the FISH. It is advised that one reads the complete instructions before scoring the activity and that one performs the test as instructed, without any modifications. It is also necessary to score the activity only after observing the subject performing the task. One should not score the item based on the person's subjective ability.

FUNCTIONAL INDEPENDENCE SCORE IN HEMOPHILIA (FISH)

Performance-based instrument

Patient Name:	**Patient Code:**							
	Today (dd/mm/yyyy):___/___/___.							
A. Self Care								
1. Eating and grooming	1		2		3		4	
2. Bathing	1		2		3		4	
3. Dressing	1		2		3		4	
B. Transfers								
4. Chair	1		2		3		4	
5. Squatting	1		2		3		4	

C. Locomotion								
6. Walking	1		2		3		4	
7. Stairs (12–14 steps)	1		2		3		4	
8. Running	1		2		3		4	
Total Score								
Scores range from 1 to 4 depending on the degree of independence (see scoring key).								
Comments:								

LEVELS OF FUNCTION AND THEIR SCORES (FOR INPUT INTO THE FISH SCORING SHEET)

4. The subject is able to perform the activity without any difficulty like other healthy peers
3. The subject is able to perform the activity without aids or assistance, but with slight discomfort. He is unable to perform the activity like his healthy peers
2. The subject needs partial assistance / aids / modified instruments / modified environment to perform the activity
1. The subject is unable to perform the activity, or needs complete assistance to perform the activity

EATING AND GROOMING

(A) EATING

Activity

Serve the meal with appropriate utensils and implements and observe the subject's ability to mix and lift the food to his mouth using hands or implements.

Scoring

Score 4 if the subject:

- has no difficulty in performing the activity

Score 3 if the subject:

- has to lean over unnaturally to reach his food due to limitation of flexion of the elbow
- has to take several breaks in between due to pain

Score 2 if the subject:

- uses implements that are not commonly used in his community – e.g., spoon or a fork in a community where other members use their hands
- is a right-handed individual, but has to eat with his left hand due to problems with the right upper limb

Score 1 if the subject:

- is unable to feed himself

(B) GROOMING

Grooming includes oral care, hair grooming, and washing hands and face.

Scoring

Score 4 if:

- the subject has no difficult in grooming
- the child needs assistance only to apply the toothpaste on the brush

Score 3 if the subject:

- adopts abnormal postures to comb the back of his head / shave / wash his face
- experiences pain or discomfort while grooming (as assessed by the observer)
- takes an unnaturally long time to perform the activity

Score 2 if the subject:

- is not able to comb hair in all areas of the head – the back / side of the head (is not able to perform the activity completely)

Score 1 if the subject:

- is unable to do the activity because of problems with reach

BATHING

Activity

This activity assesses the ability to wash, soap and dry different parts of the body – including the perineal region and feet – except the back. It is essential to assess the reach on **both** sides of the body, using **both** hands.

Scoring

Score 4 if the subject:

- has no difficulty in bathing

Score 3 if the subject:

- adopts unusual postures while bathing – e.g., places feet on a stool to apply soap
- is in discomfort while performing the activity

Score 2 if the subject:

- has to use instruments to reach any part of the body (except the back)

Score 1 if the subject:

- requires a bed bath, or is unable to perform most of the activity of bathing / drying

DRESSING

This activity assesses the ability to get dressed – wearing a shirt / T-shirt / vest / trouser / dhoti / tie / socks.

Scoring

Score 4 if the subject:

- is able to get dressed without discomfort and without assistance

Score 3 if the subject:

- experiences discomfort during the activity (assess the activity using an open shirt with buttons, **and** a T-shirt or vest)

Score 2 if the subject:

- requires help to wear the trouser

Score 1 if the subject:

- requires help in >50% of the activity

CHAIR TRANSFER

Activity

This activity assesses the ability to get up from a chair. Place a chair with armrests of an appropriate height in front of the subject (i.e., the patient sits comfortably with hips and knees flexed to 95 degrees, with feet on the ground – 18 inches for adults).

Scoring

Score 4 if the subject:

- has no difficulty in performing the above activity

Score 3 if the subject:

- leans excessively forward in order to get up
- sits with one or both knee joints slightly extended, but does not require support to get up

Score 2 if the subject:

- requires a lot of support from the armrest to get up
- requires the use of crutches to get up

Score 1 if the subject:

- is not able to get up from the chair

SQUATTING

Activity

This assesses the ability to squat on the floor and rise to an erect posture.

Scoring

Score 4 if the subject:

- has no difficulty in performing the activity

Score 3 if the subject:

- is able to squat to a height of 8–12 inches (6–10 inches for children)
- is able to squat to a height of 8 inches, with one leg in extension (6 inches for children)
- is able to squat to a height of 8–12 inches (6–10 inches for children) using momentary support from the side / floor

Score 2 if the subject:

- is able to squat to a height of 8–12 inches (6–10 inches for children) with maximum support from a chair / grab-rail

Score 1 if the subject:

- is not able to squat to a height of 12 inches with support from the side (10 inches for children)

WALKING PATTERN

Activity

Walking is to be assessed over a distance of **10 meters**.

Scoring

Score 4 if the subject:

- has an apparently normal gait

Score 3 if the subject:

- has a stiff knee gait / limp or if stance phase in a limb is reduced due to pain

Score 2 if the subject:

- uses a cane / walking stick
- uses a knee / ankle brace

Score 1 if the subject:

- is unable to walk 10 meters

STAIR CLIMBING

Activity

Place the subject in front of a flight of stairs with banisters/side rails. There should be at least 14 steps, each of approximately 8 inches in height.

Scoring

Score 4 if the subject:

- is able to climb up / down the stairs without a limp or aid with an alternating stepping pattern

Score 3 if the subject:

- has a limp / discomfort while climbing the steps
- uses the rails for occasional minimal support – he should be able to climb up / down the steps within 14 seconds (in either direction)
- climbs up the stairs taking one step at a time
- climbs down the stairs taking one step at a time

Score 2 if the subject:

- takes more than 14 seconds to climb up / down the stairs using the aid of the rails or crutches / assistance of a helper (in either direction)

Score 1 if the subject:

- is unable to climb 14 steps

RUNNING

Activity

Running is to be assessed over a distance of 25 meters for children and 50 meters for adults (age 15 years and above).

Scoring

Score 4 if the subject:

- has no difficulty / discomfort while running

Score 3 if the subject:

- has pain / discomfort while running
- is able to run only part of the distance

Score 2 if the subject:

- is not able to run, but is able to walk briskly (>70 meters/min for children and >100 meters/min for adults)

Score 1 if the subject:

- is not able to walk briskly (<70 meters/min for children and <100 meters/min for adults)