MINISTRY OF HEALTH

KENYA NATIONAL CLINICAL GUIDELINES *for the* Management *of* Haemophilia

Kenya Haemophilia Association

MINISTRY OF HEALTH

Kenya National Clinical Guidelines for the Management of Haemophilia

KENYA NATIONAL CLINICAL GUIDELINES
FOR THE MANAGEMENT OF HAEMOPHILIA
MANAGEMENT

Developed by the Department of Non-Communicable Diseases - Ministry of Health

Department of Non-communicable Diseases, Ministry of Health
P.O. Box 30016 – 00100 Nairobi, Kenya
Telephone: +254 202717077/+254202722599
Email: dghealth2019@gmail.com
Website: www.health.go.ke

Kenya Haemophilia Association

TABLE OF CONTENTS

Foreword	ii
Acknowledgement	iv
Executive summary	vi
CHAPTER 1: INTRODUCTION	**12**
Types of Haemophilia	12
Severity	12
Rationale	12
Genetics of Haemophilia	13
CHAPTER 2: DIAGNOSIS	**14**
Genetic counseling and testing	14
Bleeding manifestations in Haemophilia	14
Laboratory diagnosis	14
Sample Collection	15
Sample preparation for transportation	15
Sample Storage:	15
Laboratory Testing	15
Important points to consider	15
CHAPTER 3: MANAGEMENT OF HAEMOPHILIA	**26**
3.1 Types of bleeds in haemophilia	9
3.1.1 Major bleeding	9
3.1.2 Minor bleeding	9
3.2.1 Joint bleed (haemathrosis)	10
3.2.2 Soft tissues (Muscles, ligaments, tendons, subcutaneous space)	11
3.2.3 Head injury/Central Nervous System (CNS) bleed.	12
3.2.4 Oral bleeding	13
3.2.5 Gastrointestinal bleeding	14
3.2.6 Genito- urinary bleed	14
3.3 Factor replacement dosing regimens	15
3.4 Physical therapy	16
3.4.1 Acute joint bleeds	16
3.4.2 Management of acute muscle bleeds	17
General physical activity considerations	17
3.4.3 Exercises	18
3.4.4 Sports risk rating	18
Category 1	18
Category 2	18
Category 3	18

3.5 Prophylaxis using clotting factor concentrates 19
3.6 Management of pain in haemophilia 20

CHAPTER 4: MANAGEMENT OF COMPLICATIONS IN HAEMOPHILIA 26
Management of Acute bleeding episodes 22
4.1.4 Measures to eradicate inhibitors: 24
4.2.2 Physical therapy in management of chronic synovitis 25

CHAPTER 5: SPECIAL CIRCUMSTANCES IN MANAGEMENT OF HAEMOPHILIA 28
5.1 Management of patients undergoing surgery/ invasive procedures 26
5.1.1 Preoperative assessment and preparation 26
5.1.2 Treatment approach/Hemostatic plan 26
At pregnancy 28
At delivery 29
Post-partum 29

CHAPTER 6: SPECIAL CIRCUMSTANCES IN MANAGEMENT OF HAEMOPHILIA 31
Referral system 31
Kenya Health Information System 34

REFERENCES 36

LIST OF FIGURES
Figure 1: Genetics of haemophilia 4
Figure 2: National referral structure 35

LIST OF TABLES
Table 1: Type of bleed vs factor deficient 15
Table 2: Type of blood product vs FVIII or FIX contained per bag 16
Table 3: Type of prophylaxis 19
Table 4: Prophylaxis intensity of haemophilia A and haemophilia B 19
Table 5: National Referral System 31

FOREWORD

Haemophilia is a rare bleeding disorder in which blood doesn't clot normally due to lack of sufficient blood-clotting proteins (clotting factors). If you have haemophilia, you may bleed for a longer time after an injury than you would if your blood clotted normally. It is an inherited, sex-linked, lifelong bleeding disorder which affects males almost exclusively. Although rare, females can be affected too. It most frequently presents itself through joint and muscle bleeds. The disease affects about 1 out of every 10,000 persons in the population and with a global population of 7.7 billion, it is therefore estimated that there are about 770,000 haemophiliacs globally. In Kenya, it is estimated that about 5,000 persons are living with this condition.

Haemophilia is associated with significant morbidity and mortality while its management requires a technical multi-disciplinary approach. It is envisaged that the Ministry of Health and Kenya Haemophilia Association will continue partnering with all stakeholders in cascading care to all levels in order to minimize complications while providing easy access to treatment and care. Efforts will be pursued to train all health care cadres involved in the management of haemophilia in Kenya for both congenital and acquired types using these guidelines.

I am greatly pleased to witness the end of this long journey of the development of Kenya's first Haemophilia National Management Guidelines. The process has been a learning experience and was highly consultative based on scientific evidence and high impact intervention protocols from across the world. These guidelines are aligned to the Constitution of Kenya 2010, Vision 2030, the Health Sector Policy 2014-2030, Kenya Health Sector Strategic Plan 2018-2023 and the Ministry of Healths vision and mission which recognize Kenyans right to the highest standard of health.

The key areas covered in these guidelines are presented in a simplified manner using a public health approach for haemophilia control and Management. As Kenya rolls out one of its 'Big Four Agenda' on Universal Health Coverage, these guidelines shall be crucial in creating an enabling environment for management of haemophilia which is one of the chronic conditions needing life-long care. Blood and blood product transfusion services will face increasing pressure as patients with haemophilia are significant recipients of emergency transfusions. With improved care haemophilia patients will live longer thus requiring more blood transfusions, clotting factor concentrates and other supplies.

Levels of service delivery for patients with Haemophilia have been aligned to the Kenya Essential Package for Health (KEPH) levels. These guidelines articulate the requisite guidance for standardized management of haemophilia at all levels of service delivery. The guidelines have addressed care from psychosocial counselling, diagnosis, management and appropriate referral. They provide a guide on the continuum of care required throughout the life course of these patients. These guidelines shall be used by all healthcare personnel responsible for the management of this condition as well as teaching institutions from both the public and private sectors. All healthcare providers are therefore urged to use these guidelines for early and effective management of patients with haemophilia for better outcomes to ensure that patients enjoy a quality life and contribute to the economic development of Kenya.

SEN. MUTAHI KAGWE, EGH
THE CABINET SECRETARY
MINISTRY OF HEALTH

ACKNOWLEDGEMENT

The Kenya National Guidelines for the Management of Haemophilia treatment were developed by experts from various fields brought together by the Ministry of Health in conjunction with the Kenya Haemophilia Association (KHA). The main objective of these guidelines is to provide the clinicians with evidence-based recommendations in the management of haemophilia. It was a journey achieved through efforts by the Haemophilia Technical working group under the leadership and guidance of the KHA Medical Advisory Committee (MAC), which is mandated to ensure appropriate and ethical practices are enhanced in managing patients with haemophilia in Kenya.

It is envisaged that the use of these guidelines will be cascaded to all levels of health service provision to facilitate smooth management of haemophilia and associated complications in Kenya.

Special thanks go to the Novo Nordisk Haemophilia Foundation (NNHF) that funded and supported the development of these guidelines, Novo Nordisk Foundation (NNF), the Kenya Haemophilia Association MAC, the University of Nairobi, Kenyatta National Hospital, Moi University, Moi Teaching and Referral Hospital/ AMPATH patient and parent groups, Muranga County Referral hospital (MCRH), Coast General Teaching and Referral Hospital (CGTRH) and the World Federation of Haemophilia (WFH), for their contributions towards the development of these guidelines.

Ministry of Health further recognizes the effort of the following TWG members in the finalization of these guidelines: Ministry of health: Dr Fridah Govedi, Dr Nduku Kilonzo, Dr Waqo Ejersa, Dr Ephantus Maree, Dr Gladwell Gathecha, Dr Oren Ombiro, Scolastica Mwende, Christine Yegon; Dr. Kibet Peter Shikuku (UoN), Dr Pauline Nganga (UoN), KNH: Dr Matilda Ongondi, Dr Victoria Kithinji, Roseanne Anguche, Agripina Matasyio, Anastacia Khasiani; MTRH; Dr Jacob Injere, Dr Mwaniki Christopher, Dr Festus Njuguna, Dr Carole Kilach, Phyllis Bartilol, and Cyrus Njuguna. Others include Irene Chami (WFH), Prof. Johnny Mahlangu, Prof Karanja Njoroge (Board chair KHA), James Kago (KHA patient rep), Edwin Adol (KHA), Carlos Maube (KHA), Betty Mbogho (CGTRH) and Jane Mugacha (MCRH).

The Ministry of Health remains committed to work with all stakeholders to reduce the burden on haemophilia in the country.

SUSAN N. MOCHACHE, CBS
PRINCIPAL SECRETARY
MINISTRY OF HEALTH

EXECUTIVE SUMMARY

The executive summary has focused majorly on key areas on haemophilia care and management. The introduction has given an elaborate understanding of haemophilia by essentially stating the definition of the disease, explains the rationale warranting the establishment of this guidelines, the global epidemiology of haemophilia, the pathophysiology of the disease which is majorly sex-linked though occasionally a few cases may be acquired and finally characteristic uncontrollable bleeding into joints and other tissues that have been associated with mild, moderate or severe complications that may be fatal. Haemophilia is a sex-linked disease that mainly affects men but carrier mothers are just as much affected by uncontrollable bleeds as their sons which requires a fresher look and attention at all levels of care in Kenya. When the disease is appropriately managed, a normalized individual with an improved quality of life is achieved. To obtain this, early diagnosis of the disease is essential with the provision of replacement factor concentrates as a means to correct the missing clotting factor. Patients presenting with cardinal signs and symptoms require specific and specialized testing capabilities to ensure adequate and appropriate characterization of the disease that has a major bearing on the extent and modality of care to be provided.

As a country, we recognize the chronicity associated with haemophilia and its complications. The disease requires continuous and intense psychosocial support to the patients, parents and the community at large. Patients require planned care that includes prophylaxis for both acute and chronic bleeds, pain management, physiotherapy to rehabilitate affected tissues as well as home therapy to manage and control acute bleeds. These patients require special considerations during surgical procedures such as circumcision, dental extractions and manipulations, vaccinations and immunizations in general as well as special preparations for carrier women during birth to avoid unnecessary blood loss leading to severe postpartum haemorrhage.

Haemophilia patients may develop antibodies against products used for care besides having deformities associated with haemophilic joint arthropathies. This requires a multidisciplinary approach with specialized interventions, which can be costly and risky to the patient. All efforts will be put in place to ensure optimal patient care is provided through a stratified process. This guideline recommends three levels of care with comprehensive clinical care being provided at approved referral facilities while other treatment centres will be capacitated to provide basic care for all bleeders. Availability of the factor concentrates at levels of patient care will guarantee control of bleeds and subsequent improvement of the quality of life for patients with bleeding disorders.

DR PATRICK AMOTH, EBS
Ag. DIRECTOR GENERAL
MINISTRY OF HEALTH

ACRONYMS

APCC	Activated Prothrombin Complex Concentrates
AMPATH	Academic Model Providing Access to Healthcare
APTT	Activated Partial Thromboplastin Time
BU	Bethesda Units
CFCs	lotting Factor Concentrates
CGTRH	Cost General Teaching and Referral Hospital
CT scan	Computerized Tomograph
DDAVP	Desmopressin
EACA	Epsilon Aminocaproic Acid
FEIBA	Factor Eight Inhibitor Bypass Activity
FFP	Fresh Frozen Plasma
HCCC	Haemophilia Comprehensive Care Clinic
HTC	Hemophilia Treatment Centre
INR	International Normalized Ratio
IU	International Units
KHA	Kenya Haemophilia Association
KEPH	Kenya Essential Package for Health
MAC	Medical Advisory Committee
MCRH	Muranga County Referral hospital
MRI	Magnetic Resonance Imaging
MTRH	Moi Teaching and Referral Hospital
NCD	Non-Communicable Diseases
NNHF	Novo Nordisk Hemophilia Foundation
PLWH	People Living with Hemophilia
PGD	Pre-Implantation Genetic Diagnosis
PND	Prenatal Diagnosis
PNP	Pooled Normal Plasma
PRICE	Protection, Rest, Ice and Elevation
PTT	Prothrombin Time Test
rFVIIa	Recombinant Activated Factor Seven
SOPs	Standard Operating Procedures
TENS	Transcutaneous electrical nerve stimulation
TT	Thrombin Time
UoN	University of Nairobi
vWF	von Willebrand factor
WFH	World Federation of Hemophilia

Chapter 1:

INTRODUCTION

Haemophilia is an inherited, X-linked, lifelong bleeding disorder which affects males almost exclusively. Although rare, females can be affected too. It most frequently presents itself through joint and muscle bleeds. The disease affects about 1 out of every 5,000 males for haemophilia A, and 1 in every 20,000 males, for haemophilia B. There are, however, a few cases of acquired haemophilia.

Haemophilia is diagnosed by characteristic bleeding history and confirmed by laboratory testing, that reveals a prolonged Activated Partial Thromboplastin Time (APTT) and low factor VIII/IX levels.

Haemophilia A is more common than haemophilia B. Haemophilia A is estimated to account for 80%-85% of all haemophilia cases while haemophilia B is estimated to account for 15%-20% of all haemophilia cases. Estimated prevalence at birth is 24.6 cases per 100 000 males for all severities of haemophilia A (9.5 cases for severe haemophilia A) and 5.0 cases per 100 000 males for all severities of haemophilia B (1.5 cases for severe haemophilia B). (Srivastava et al., 2020)

Types of haemophilia

haemophilia a is the most common type and is due to a deficiency of clotting Factor VIII.
Haemophilia B is due to a deficiency of clotting Factor IX.
haemophilia C is due to deficiency of factor XI and is very rare.

Severity

Haemophilia is classified as severe, moderate, or mild, according to the levels of circulating Factors VIII or IX, which determine the expected frequency of bleeding:

- Severe: Factor VIII or IX is in less than 1%, with patients experiencing frequent spontaneous bleeds
- Moderate: Factor VIII or IX is between 1-5%, and patients exhibit less frequent bleeds, which usually come after either trauma, surgery or dental procedures.
- Mild: Factor VIII or IX is greater than 5 but less than 40% with occasional bleeding following severe trauma or surgery.
- The recommendation is to treat by replacement of the deficient clotting factor besides other medical interventions.

Rationale

According to the Annual Global Survey conducted by the World Federation of Haemophilia in 2019;115 countries were surveyed globally. There were 324,648 patients identified with various congenital bleeding disorders. 195,263 people living with haemophilia were identified and out of this number 157,517 had haemophilia A and 31,997 had haemophilia B. There were 5749 patients with their haemophilia type unknown and finally 80,302 were identified to have Von Willebrand disease.

In relation to factor distribution per region 82% of the total FVIII IUs are used by 29% of the population. In the global factor distribution based on the gross national income; 92% of the total FVIII IUs are used in high income and upper-middle-income countries, that comprise 41% of the population.(WFH, 2020)

In Africa, there are 6,387 identified out of 83,725 which is 8% identification rate. In Kenya, there are 650 people living with haemophilia

(PLWH) identified out of the expected 5,520 which is a 12% identification rate. This identification rate is much higher in Europe, United Kingdom, Canada, Australia and the United States America. This creates huge disparities in PLWH in Africa compared to those in the high resource countries, while those in Africa are grappling with joint deformities from early years in life due to late diagnosis and lack of treatment.

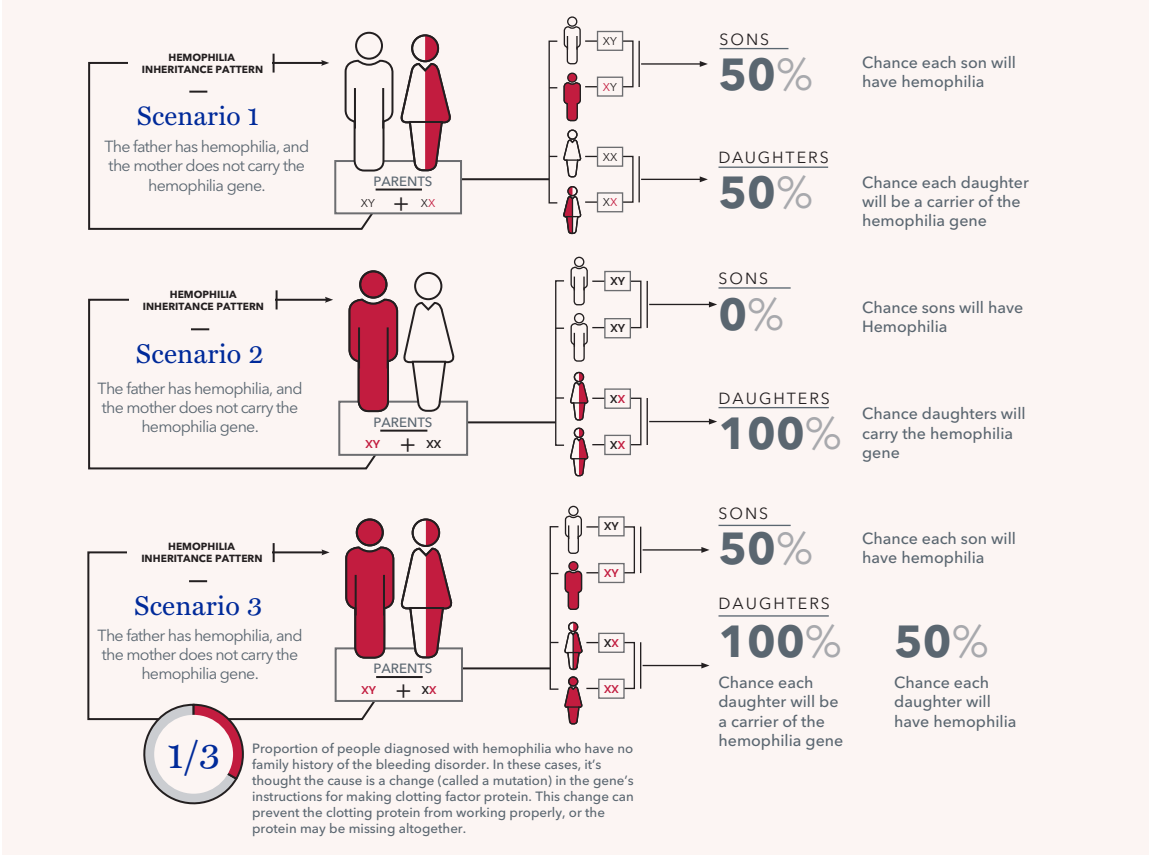
The recommended International Unit (IU)per capita per patient for minimal survival is 1 IU per capita but the current rate in Kenya is 0.107IU per capita. Currently, the treatment products are solely donated by the World Federation of Haemophilia. (WFH, 2020)

There is lack of awareness among healthcare workers and limited resources to support haemophilia in Non-Communicable Diseases (NCD) resulting in the need to increase awareness to healthcare workers and the general public.

This guidelines are meant to assist the clinical team in providing care using available resources in their jurisdictions. The least amount of factor that can be prescribed for a non fatal bleed is 40% but when treatment products are available, then the suggested treatment amounts should be administered. More so, provide as much optimal care as possible to a bleeder with the understanding that the disease requires a multidisciplinary approach as recommended in the guidelines.

Genetics of haemophilia

Haemophilia is an x-linked disease that commonly affects men. Women have two X chromosomes and are, therefore, rarely affected. Not unless both chromosomes are defective. Women who have only one defective X-chromosome are called carriers. The diagrams below summarize the possible outcomes of children born to affected parents. All daughters of males with haemophilia are obligate carriers.



Chapter 2:

DIAGNOSIS

Due to the clinical presentation of the haemophilia condition, good clinical family history is essential, since over two-thirds of the patients have a positive family history. A definitive laboratory diagnosis is mandatory to determine the type and level of factor deficiency.

GENETIC COUNSELING AND TESTING

Genetic counselling for people with haemophilia and their families is an essential requirement prior to genetic testing. This includes obtaining informed consent from the patient, parent, or legal guardian, requiring both permission to carry out testing as well as education to ensure that they fully understand the testing procedure, the benefits and limitations of the test, and possible consequences of the test results. Genetic counselling should also provide information and advice about prenatal diagnosis (PND), management of pregnancy and delivery in haemophilia carriers, and pre-implantation genetic diagnosis (PGD). It is important to be aware of and follow the relevant laws governing these procedures in Kenya. (Srivastava et al., 2020)

Genetic testing will not always identify the underlying variant associated with the haemophilia phenotype. Genetic counselling should highlight this possibility to the individual referred for genetic testing. Genetic diagnostic laboratories should adhere to strict protocols and standard operating procedures. (Srivastava et al., 2020)

This test though is not readily available in our country but samples can be obtained and sent for testing in external laboratories. Liaise with the haemophilia comprehensive centre closest to you for further advise and guidance.

Bleeding manifestations in Haemophilia:

The characteristic phenotype in haemophilia is a bleeding tendency. While the history of bleeding is usually life long, some children with severe haemophilia may not have bleeding symptoms until later when they start walking or running. Patients with mild haemophilia may not bleed excessively until they experience trauma or surgery. The severity of bleeding in haemophilia is generally correlated with the clotting factor level as indicated above. Some of the notable symptoms include:

- Umbilical stump bleeds
- Easy bruising
- Spontaneous bleeding
- Excessive bleeding following trauma or surgery
- Joint bleeds (haemarthrosis)
- Gastrointestinal bleeds
- Central Nervous System bleeds
- Muscular bleeds
- Epistaxis
- Hematuria
- Heavy menstrual bleeds in haemophilia carriers

LABORATORY DIAGNOSIS:

This is a very important part of care since the treatment is usually guided by the type and level of factor deficiency.

Sample Collection:

NB: Please liaise with the testing laboratory before sample acquisition for further guidance

- Before sample collection, the patient drug history should be known, and strenuous physical activities avoided because this

elevates von Willebrand factor (vWF) and FVIII in circulation. There is the physiological elevation of FVIII and vWF in pregnancy.

- A venous sample should be drawn according to the standard operating procedures for collecting a blood sample, for coagulation testing. Pay attention to the ratio of blood volume to anticoagulant. Blood should be collected in sodium citrate (blue top) vacutainer.
- Blood from an indwelling catheter should be avoided for coagulation testing.
- Hemolyzed samples should not be analyzed.

SAMPLE PREPARATION FOR TRANSPORTATION:

For blood samples drawn outside the location of the testing laboratories, sample preparation should be as follows:

- Centrifuge the correctly drawn citrated blood sample within 30 minutes to 2 hours of collection, at 3000rpm for 10-15minutes at room temperature.
- Transfer the citrated platelet-poor plasma (less than 10x109/l) into a capped plastic tube that is clearly labelled with patient name, gender and file number.
- Place it in a plastic biohazard marked zipper bag including the request form in the separate pocket and ship it on dry ice if available; if not, pack icepacks tightly in a cool box and place the sample in the centre using triple packaging for safety and preservation of the sample integrity. Transport immediately using the fastest means of transport available or at night if it is during the hot season to reduce the probability of sample thawing during transportation.
- If transportation will be done, it should be within 24 hours of sample collection. The sample should be stored at -200C.

SAMPLE STORAGE:

- For plasma samples that will not be analyzed within 4 hours, then they should be either stored at -20OC for 3 weeks or -80OC for long term storage.

LABORATORY TESTING:

- Before testing, frozen samples should be thawed rapidly for 4-5 minutes at 370C to avoid the formation of cryoprecipitate.
- Equipment being used for coagulation testing should be validated and calibrated as required.
- Reagent storage and use should follow the manufacturer's instructions to maintain potency/stability.
- The testing will involve basic screening tests i.e. Prothrombin Time Test (PTT), activated Partial Thromboplastin Time (aPTT) and Thrombin Time (TT). All testing procedures should follow Standard Operating Procedures (SOPs).
- Then followed by confirmatory/second level testing: mixing tests, factor assays and inhibitor testing (where necessary) which can be done at haemophilia comprehensive care centres' laboratories.
- Confirmatory diagnostic tests will be done in the tertiary comprehensive care centres while basic coagulation testing will be available in the secondary treatment centres.

NB: CORRECTION TESTS

Abnormal screening tests may be further investigated using correction or mixing studies.
Correction or mixing studies using pooled normal plasma (PNP) may help to define whether prolonged coagulation times are due to factor deficiency, circulating anticoagulants or inhibitors.
The APTT of a patient/normal plasma mix may initially be normal and then progressively prolonged on incubation in the presence of a time-dependent inhibitor (e.g., many acquired autoantibodies against FVIII), although this pattern can be variable in cases with complex kinetics. (Srivastava et al., 2020)

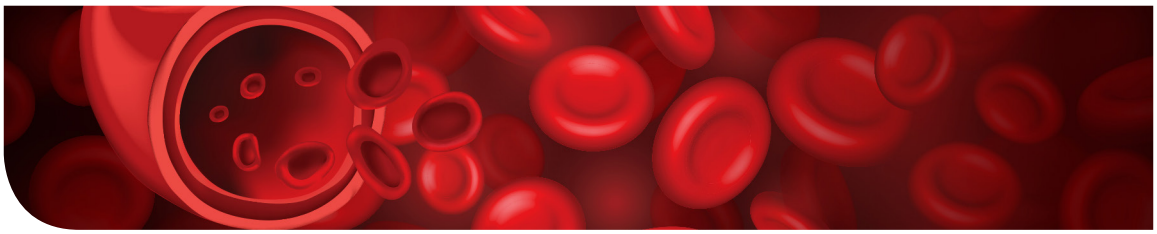
IMPORTANT POINTS TO CONSIDER:

- Quality assurance is of utmost importance at every stage of coagulation testing, starting from the collection of the sample, transportation (where necessary), the analysis and release of the results back to the requesting clinician.
- Any abnormal screening test results require confirmatory testing.
- All testing laboratories should have their internal quality control in place and participate in an external quality control program and review each performance.
- Trained personnel with a high standard of knowledge in hemostasis should perform the testing in the laboratory.
- Performance of PTT or International Normalized Ratio (INR) does not exclude a bleeding disorder especially haemophilia.
- When testing patients who are on emicizumab (Hemlibra) take note that it affects the APTT making it considerably shortened (within or below the normal range)
- It is advisable to use chromogenic FVIII assays of bovine origin (containing bovine Factor X) and not human. This applies to both factor level and inhibitor assay testing.
- Use specific emicizumab calibrators when setting up assays(Srivastava et al., 2020)

	Severe	Moderate	Mild
Factor level	<1%	1% to <5%	5% to <40%
Age at presentation	Birth to 3 years	Birth to 10 years	5 to >21 years
Presentation	• Family history (prenatal or postnatal • screening) • Neonatal bleeding (circumcision, heel • sticks) • Bruising (<1 year) • Vaccine-related bleed • Mucosal bleed • Joint bleed	• Family history (prenatal orpostnatal screening) • Neonatal bleeding (less likely than in severe cases) • Vaccine-related bleed • Mucosal bleed • Joint bleed	• Post-traumatic bleed • Postsurgical bleed
Risk for inhibitor development	• ~25% in FVIII • ~5% in FIX	~1% to 2%	Very rare
Risk for hemophilic arthropathy	Universal without prophylaxis	Very common without prophylaxis	Rare

Chapter 3:

MANAGEMENT OF HAEMOPHILIA



The major management of haemophilia is by replacement of the missing clotting factor protein or by activating the coagulation system using alternative means.

There are two main approaches in management of haemophilia;

- Prophylaxis- Prophylaxis in haemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding. Prophylaxis is the recommended mode of management.
- On demand therapy - This is the administration of coagulation agents when bleeds occur.

3.1 TYPES OF BLEEDS IN HAEMOPHILIA

Bleeding can be classified as either major or minor.

3.1.1 MAJOR BLEEDING

These bleeds are life threatening or may cause deformity. Appropriate factor replacement should be initiated urgently. Advice should be sought from a Haemophilia Comprehensive Care Clinic (HCCC). If the patient has an inhibitor, the HCCC must be consulted for optimum haemostatic care.

Body areas which may be associated with major bleeds include:

- Central nervous system
- Gastrointestinal tract
- Neck/ throat
- Hip or iliopsoas
- Advanced joint/ muscle
- Compartment syndrome.
- Also in severe injury

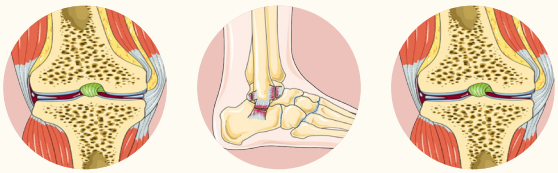
3.1.2 MINOR BLEEDING

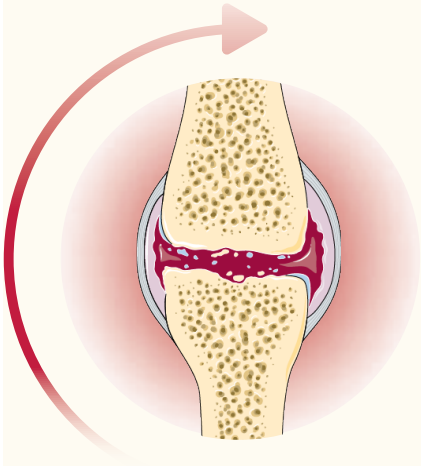
These bleeds do not impose an immediate danger to the person. However, if they are prolonged, they may cause complications and therefore should be treated early. They include:

- Joint (early).
- Muscle/ soft tissue (early)
- Oral.
- Epistaxis.
- Painless hematuria.

3.2 MANAGEMENT OF SPECIFIC BLEEDS

In major bleeds, aim at replacing the factor deficiency by 80-100% while 40-60% in minor episodes.





3.2.1 JOINT BLEED (HAEMATHROSIS)

This is the most common presentation in persons living with haemophilia that affect hinge joints (knee, elbow and ankle) and less commonly, the ball and socket joints (shoulder and hip). Any other joint can be affected. After one or several haemathrosis with synovitis, the joint may become targeted for recurrent bleeding and damage (target joint). Those patients with target joints should be referred to the HCCC for further management.

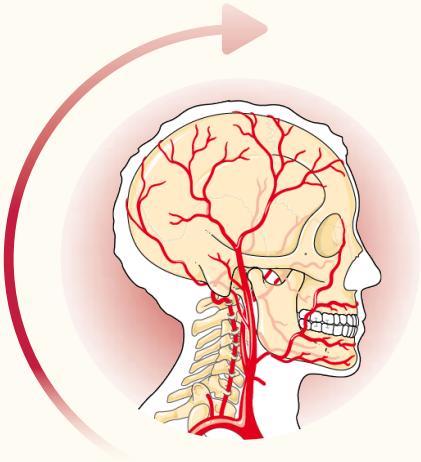
Signs and symptoms of joint bleeds

- Tingling sensation/Aura (early)
- Pain
- Warmth and tenderness on touch
- Swelling
- Limited range of motion
- Limping or inability to use the affected limb
- Stiffness

TREATMENT OUTLINE

Do not delay treatment. Early bleeding can be felt by the patient before signs are apparent. Obvious joint swelling is a late sign of bleeding. Interventions include:

- Joint Protection, Rest, Ice, Compression and Elevation (PRICE) that should be initiated as soon as possible.
- Replace the deficient factor
- No circumferential casting use back slab if indicated.
- DO NOT PERFORM NEEDLE ASPIRATE on the swollen joint unless an infection is suspected.
- Ultrasound of the joint
- X-ray usually not indicated unless fracture is suspected.
- Physiotherapy after pain has subsided.
- Red cell transfusion if necessary (whole or Packed)



3.2.3 HEAD INJURY/CENTRAL NERVOUS SYSTEM (CNS) BLEED.

This medical emergency and can occur with or without recognizable trauma especially in children. Patients with suspected head injury must be given factor infusions as soon as possible even before confirmation with imaging.

SIGNS & SYMPTOMS

Note that onset may be delayed.

- Headache
- Vomiting
- Sudden back pain
- Irritability
- Convulsions
- Lethargy/ drowsiness
- Vision disturbance
- Focal neurologic deficits e.g. weakness
- Loss of consciousness
- Paralysis

MANAGEMENT OUTLINE:

If a CNS bleed is suspected, Initiate factor replacement and then do head imaging (CT scan/MRI)

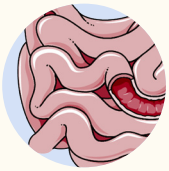
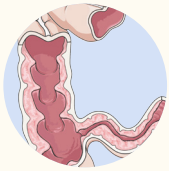
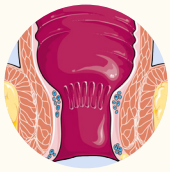
- Urgent factor replacement to levels between 80 – 100% for a minimum of 7 days. Then maintain plasma factor level at 50% for haemophilia A and 30% for haemophilia B, for a further 14 days (Total 21 days from initiation of treatment)
- Immediate medical evaluation and Hospitalization
- Consult with a HCCC
- Imaging with CT-Scan or MRI
- Obtain neurosurgical review/consult if necessary
- Red cell transfusion if necessary (whole or Packed)

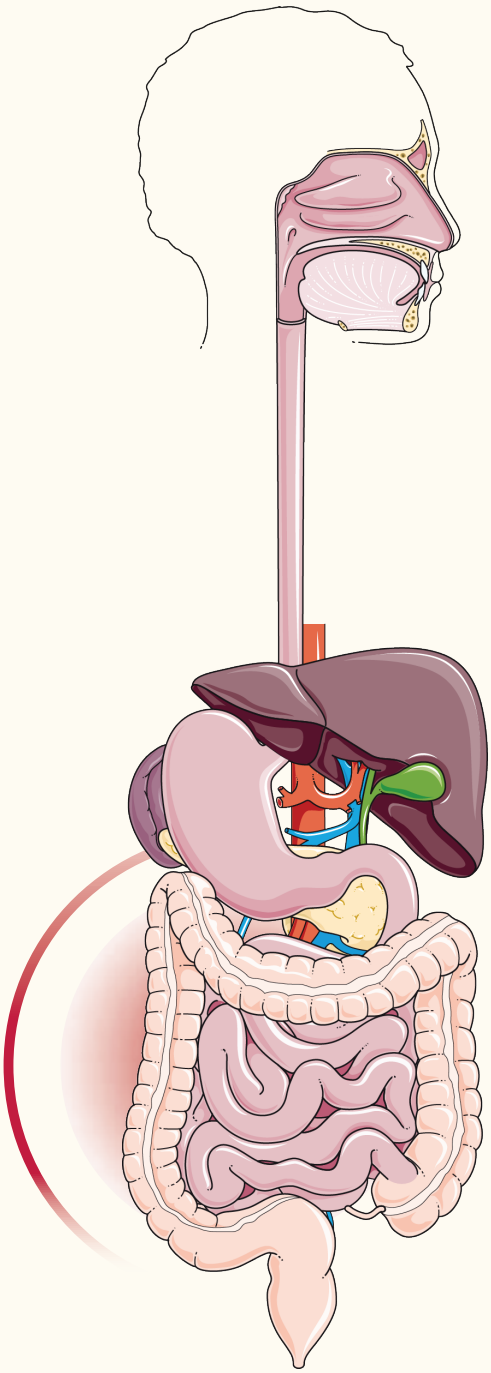
3.2.4 ORAL BLEEDING

Dental/ gum bleeding/ tongue lacerations.

- Bleeding can be profuse
- Swallowing blood may lead to dark tarry stools.

NOTE: *Torn frenulum and upper lip bleeding are common in young children. Dental procedures require prior therapy to raise factor levels.*



3.2.5 Gastrointestinal bleeding

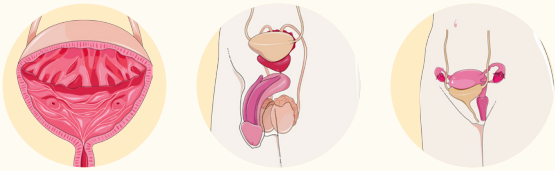
This is an emergency:

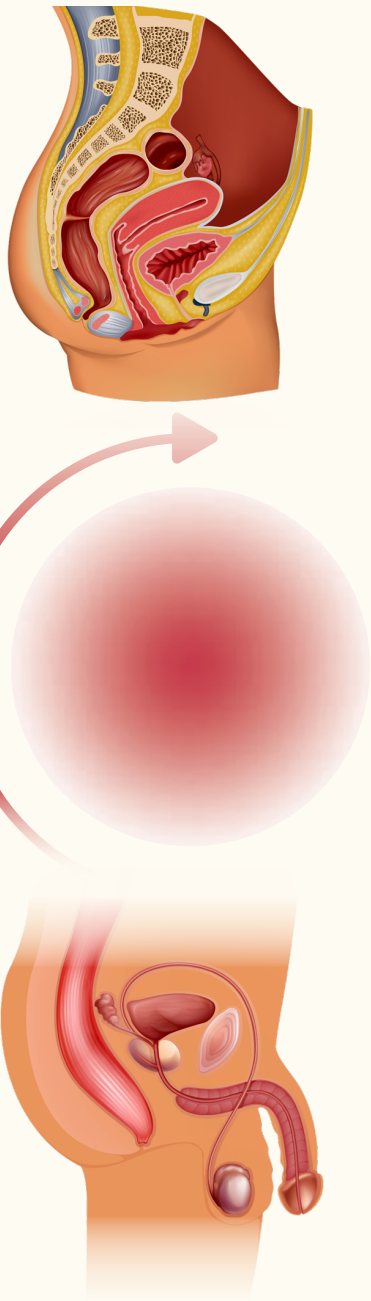
- Bleeding can be profuse
- Blood/ fresh or coffee ground vomiting
- Dark/ tarry stool

Abdominal pain – examine to rule out a GIT bleed and if suspected, factor should be infused then investigate for possible bleed. An acute abdominal (including retroperitoneal) hemorrhage can present with abdominal pain and distension and can be mistaken for a number of infectious or surgical conditions. It may also present as a paralytic ileus.

Treatment Outline:

- Immediate factor replacement.
- Check vitals, full blood count (Monitor Hb levels regularly)
- Immediate evaluation and hospitalisation to allow infusion of factor to levels above 80% and monitor and replace any ongoing blood loss.
- Consult HCCC.
- Concomitant antifibrinolytics (tranexamic acid therapy
- Investigate for site of bleeding as appropriate.





3.2.6 Genito-urinary bleed

Spontaneous, persistent or recurrent hematuria should be investigated.

Signs and symptoms

- May have renal angle tenderness
- Red or dark urine
- Usually no dysuria

Treatment Outline:

- Increase fluid intake.
- Bed rest
- If not resolved within 24 hours of onset, treat with factor replacement,
- Continue to increase fluids and bed rest for 7 days
- If the bleeding persists, consult a urologist.
- Anti-fibrinolytic agents like tranexamic acid are contraindicated as it may lead to blood clots and urine retention.

3.3 Factor replacement dosing regimens

Bleeding episodes are best treated with factor concentrates that may be either plasma derived, or recombinant

Table 1 Type of Bleed vs Factor Deficient

Types of bleed/Factor Deficient	FVIII	FIX
Major 80 – 100%	40 – 50 IU/Kg	80 – 100 IU/kg
Minor 40 – 60%	20 – 30IU/Kg	40 – 60IU/ kg

- Expected response: 1 IU/kg = 2% rise in Factor VIII level
- Expected response: 1 IU/kg = 1% rise in Factor IX level
- Always check the half-life of the product you are using. The traditional factor IX concentrates have a half-life of about 18-24 hours.
- Most traditional factor VIII concentrates have a half-life of 8-12 hours. The new recombinant products have an extended half-life.
- If there is no response to appropriate replacement therapy, consult the HCCC and consider, testing for inhibitors.
- Repeat doses may be required depending on the severity of bleeding. There are new emerging products including monoclonal antibodies e.g emicizumab that are available in the market.
- Round off dose to the nearest vial: do not discard excess Factor VIII but rather infuse the whole vial.

Use of blood products

In the absence of factor concentrates, minor bleeds can be treated using Fresh Frozen Plasma and Cryoprecipitate with inferior outcomes to factor concentrates. Fresh frozen plasma is recommended for both FVIII and FIX deficient patients while cryoprecipitate is best applicable in management of FVIII deficiency.

Table 2: Type of blood product vs FVII or FIX contained per bag

Type of blood product	FVIII or FIX contained per bag
FFPs	200IU of either FVIII or FIX per unit/bag
Cryoprecipitate	100IU of FVIII per unit/bag

Safe factor infusion

Factor infusion is a clean procedure therefore hygiene should always be observed. Below is an outline to prepare and infuse factor products:

- Wash your hands
- Prepare the medication as per manufacturer's insert
- Find a comfortable position, choose a vein, and fix the cannula
- Secure the cannula in in place
- Remove tourniquet, ensure there is back flow and infuse factor slowly over 3-5 minutes.

- Once you are done, remove the cannula and dispose appropriately and hold pressure with your finger using a dry cotton swab on the site for at least 5 minutes.

3.4 PHYSICAL THERAPY

Physical therapy is a very crucial component of haemophilia care in restoring and maintaining musculoskeletal health. It is useful for managing both acute and chronic musculoskeletal complications. It helps improve the quality of life for people living with haemophilia.

3.4.1 Acute joint bleeds:

During acute bleeds, no physical therapy should be done without adequate factor coverage.

The following measures are useful and can be done even before factor infusion:

- **PRICE (Protect, Rest, Ice, Compression, Elevation)** should be implemented to minimize bleeding, pain and swelling;

1. Protect/Rest: This can be done using a slings and splints. Walkers and crutches are used to promote non-weight bearing activity of the affected lower extremity.
2. Ice: Apply wrapped ice around the affected joint intermittently. Apply 5 mins on and 10 mins off, repeat 3-4times. This can be repeated every 2 hours until the pain subsides. If ice is unavailable use a cloth soaked in cold water and repeat as above.
3. Compression: Compress the joint that is affected using crepe bandages or tubular sleeves. Never use compression on muscle bleeds since it can compromise blood flow.
4. Elevation: This means putting the affected area at a level higher than the heart. You can use pillows, folded blankets, clothes or adjustable beds.

3.4.2 MANAGEMENT OF ACUTE MUSCLE BLEEDS

- Rest the affected area
- Start soft tissue mobilization after pain has subsided.
- Progress to mobilization exercises.

GENERAL PHYSICAL ACTIVITY CONSIDERATIONS

- Consider all these aspects of the person's general health condition, in activity selection.
    1. Target joints.
    2. Bleeding history.
    3. Severity of haemophilia.
    4. Safety equipment.
    5. Joint condition.
- Encourage participation in regular physical activity. Prophylactic factor infusion is recommended for continuous physical therapy.
- After bleeding episode resume activity only when motion, strength coordination are restored
- Resuming activity too soon may result in rebleeding.
- Encourage use of protective gears e.g. helmet when cycling and when riding motorcycles.
- Advise to maintain appropriate body weight

3.4.3 EXERCISES:

Depending on the individual, sub maximal isometric exercises may be initiated after factor infusion and pain has subsided. This should however be discontinued if it causes pain in the affected area.

These Basic principles apply to exercises after an acute bleed:

- Start with isometric exercises.
- Progress to pain free isotonic exercises.
- Wean splints and slings as appropriate.
- Implement progressive weight bearing and gait training.

- Add isotonic/resistive strengthening exercises
- The exercises are supervised by a trained physiotherapist who also gives a home-based program.
- After full pain free range of motion has been achieved:
- Include all muscle groups surrounding joint
- Include proprioceptive training.

3.4.4 SPORTS RISK RATING

All types of sports can be divided into these categories:

Category 1

- Most individuals with haemophilia can safely participate in the following sports: swimming, golf, hiking, cycling a static bicycle.

Category 2

- Physical, social and psychological benefits of these sports outweigh the risks. The patients should be advised to infuse factor and be cautious while participating in them.
- Majority of sports fall into this category e.g. basketball, baseball, gymnastics, bowling and skiing

Category 3

- The risks of these sports outweigh the benefits
- Examples are football, wrestling, hockey and rugby

3.5 PROPHYLAXIS USING CLOTTING FACTOR CONCENTRATES

Prophylaxis is the preferred standard of care as opposed to on demand therapy. It helps to prevent occurrence of bleeds and thereby the chronic complications like arthropathy. It can be primary, secondary or tertiary as shown in the table below.

Conventional factor prophylaxis for haemophilia A and B defined according to when prophylaxis is initiated.

Table 3: Type of ProphylaxisType of Prophylaxis

	Description
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 the onset of documented joint disease
Tertiary prophylaxis	Typically applies to prophylaxis commenced in adulthood

Primary and secondary prophylaxis are associated with better long-term musculoskeletal functions. The dosing and frequency of prophylaxis is dependent on the factor deficiency and the type of product used (Conventional or Extended Half-Life). Extended half-life products require less infusion frequency. Conventional factor prophylaxis with standard half- life clotting factor defined according to its intensity

The regimen for prophylaxis depends on the type of factor concentrate available: whether short acting or extended half-life products. Prophylaxis is best used when parents/ patients have learnt self-infusion.

3.5.1 PROPHYLAXIS USING NON-FACTOR PRODUCTS

Emicizumab is approved for prophylaxis for FVI-II deficient patients with or without inhibitors. Prophylaxis dosing with emicizumab consists

Table 4: Prophylaxis Intensity of Haemophilia A and Haemophilia B

Prophylaxis intensity	Haemophilia A	Haemophilia 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)

of an induction period of 3.0 mg/kg/week for 4 weeks by subcutaneous injection. This is followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.

3.6 MANAGEMENT OF PAIN IN HAEMOPHILIA

Pain in haemophilia may be caused by:

- Joint capsule stretching as a result of haemathrosis
- Pressure due to bleeding in a closed compartment (muscle, brain etc.)

The most effective pain management is early and appropriate factor replacement. This should aim to relieve pain without increasing the risk of bleeding. Analgesics can be given orally, parenterally or through skin patches. Avoid intramuscular injections. Use the oral route unless patient is unable to swallow or tolerate oral medication.

For mild pain, oral paracetamol is recommended, while for moderate pain, paracetamol in combination with weak opioids (e.g. Tramadol, dihydrocodeine) should be used. Strong opioids (e.g. morphine, fentanyl) should be given for severe pain in combination with paracetamol. Adjuvant pain medication (lorazepam, amitriptyline) may be used with any degree of pain. Other non pharmacological methods are applicable.

Non-steroidal analgesics should be avoided e.g. Brufen, Aspirin, Diclofenac, Indomethacin, e.tc. as they increase the risk of bleeding due to their antiplatelet effects.

3.7 MENTAL HEALTH AND HAEMOPHILIA

Haemophilia as chronic condition that puts a lot of psychological and emotional stress to both persons living with haemophilia and caregivers. As such, healthcare workers should always be on the lookout for their mental wellbeing. Mental health interventions include peers support groups participation, psychological counselling and when need be, referral to a mental health professional. Psychosocial counsellors should be part of the comprehensive care team to support in care of persons living with haemophilia and their caregivers.

3.8 PATIENT/CAREGIVER EDUCATION

People with haemophilia and family/primary caregivers must receive comprehensive education on haemophilia care, particularly on the prevention and treatment of bleeds. Education components should focus on musculoskeletal complications, and training on essential skills for self-management, including bleed recognition, self-treatment, record-keeping, dental care, and risk management.

NOTE: *Patients should be encouraged to attend a comprehensive care clinic at least once a year or more often if clinically indicated.*

Chapter 4:

MANAGEMENT OF COMPLICATIONS IN HAEMOPHILIA

Several complications may develop in people living with haemophilia the most concerning being development of inhibitors and chronic synovitis.

4.1 INHIBITORS IN HAEMOPHILIA

Inhibitors" in haemophilia are IgG alloantibodies to exogenous clotting factor VIII (FVIII) or factor IX (FIX) that neutralize the function of infused clotting factor concentrates (CFCs). The presence of a new inhibitor should be suspected in any patient with haemophilia who fails to respond clinically to CFC replacement therapy, particularly in previously responsive patients. Inhibitors may develop in upto 25% of persons with haemophilia A, but are much less common in haemophilia B (1 -3%).

4.1.1 Risk Factors for the development of inhibitors:

- Severe haemophilia,
- Family history of inhibitor development
- More cumulative infusions of clotting factor
- Race (Predominantly those of African descent)
- Genetic variant
- Type of products used (Plasma vs Recombinant Factors)
- Individuals develop inhibitors usually within the first 50 exposure days after starting Factor VIII replacement therapy
- Inhibitors titers are measured in Bethesda units (BU);
- Low responders: titer remains below < 5BU
- High responders: titer above > 5BU. The level may increase markedly and rapidly after Factor infusion (may have rapid anamnestic response)

4.1.2 TREATMENT:

- Management of patients with inhibitors is complex and should be done in a HCCC. The management involves treatment of acute bleeds and measures to eradicate the inhibitors:
- Management of Acute bleeding episodes
- Low responding inhibitor titers (<5 BU):
- Give factor concentrate at 200-300% correction
- Monitor response clinically.
- Frequent monitoring of factor recovery levels

High responding (> 5 BU):

- *Both Activated Prothrombin Complex Concentrates (APCC) [example Factor Eight Inhibitor Bypass Activity (FEIBA)] and recombinant activated factor seven (rFVIIa) [e.g. NOVOSEVEN] are effective for treatment of acute bleeding episodes in patients with Factor VIII and IX inhibitors*
- *Activated Prothrombin Complex Concentrate – APCC (FEIBA):*
- *FEIBA contains already activated factors II, IX, and X.*
- *Dose 50 – 100 U/kg every 12 -24hr until clinical improvement.*
- *DO NOT exceed a single daily dose of 200 U/kg.*

- *DO NOT infuse antifibrinolytic drugs (e.g. Tranexamic acid) concurrently because of the risk of thromboembolism*

Recombinant Factor VIIa /rFVIIa (NOVOSEVEN):

- *Factor VIIa activates Factor X and leads to the formation of a hemostatic plug.*
- *90 µg/kg every 2 – 3 hourly or by adjusted-dose continuous infusion (at 2µg/kg/hr.).*
- *Single dose of 270µg/kg may be used until clinical improvement.*
- *•Tranexamic acid 10mg/kg/dose PO /IV 6hrly may be used concurrently with recombinant factor VIIa.*

Emicizumab

Emicizumab has been licensed for bleed prevention in patients with haemophilia A with and without inhibitors. Prophylaxis dosing with emicizumab consists of an induction period of 3.0 mg/kg/week for 4 weeks by subcutaneous injection. This is followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.

4.1.4 MEASURES TO ERADICATE INHIBITORS:

Immune tolerance induction (ITI):

- It should be initiated at a Comprehensive Haemophilia Treatment Centre
- Successful therapy (eliminating the inhibitor) may take months
- The process involves infusing high doses of factor concentrates(> 200% correction) and giving immunosuppressant.
- Monitor all patient every 3-6months for the development of inhibitors,
- Test for inhibitors incases of poor response to appropriate factor replacement therapy.

4.2 CHRONIC SYNOVITIS

Following acute hemarthrosis, the synovium becomes inflamed, hyperemic, and friable. This acute synovitis can take several weeks to resolve. Failure to manage acute synovitis results in recurrent hemarthroses and subclinical bleeds. The synovium becomes chronically inflamed and hypertrophic, and the joint becomes prone to further bleeding. A vicious cycle of bleeding, loss of joint motion, and inflammation can ensue which ultimately leads to irreversible cartilage and bone damage and impaired joint function. If this process exceeds 3 months, it is defined as chronic synovitis. Even with rehabilitation, the synovium never returns to its original state. Given that clinical signs do not always adequately represent the actual situation, ultrasound evaluation is advised.

4.2.1 TREATMENT OF CHRONIC SYNOVITIS

The goal of chronic synovitis treatment is to suppress synovial activation and reduce inflammation to preserve joint integrity and function. Non invasive options include

- Tertiary Prophylaxis (for those not on regular prophylaxis)
- Physical therapy
- Selective COX-2 inhibitors to reduce inflammation.
- Invasive management include:
- Synovectomy
- Synoviothresis (Ablation of the synovium may be done through surgery, radioisotopes or medication).
- Joint replacement when indicated

4.2.2 PHYSICAL THERAPY IN MANAGEMENT OF CHRONIC SYNOVITIS

These measures help improve joint function in those with chronic synovitis

- Splinting
- Bracing.
- Strengthening and range of motion exercises which are progressive
- Teaching balance and coordination
- Transcutaneous electrical nerve stimulation. (TENS)
- Activity modification.
- Adaptive equipment.
- Bracing/orthotic devices

Chapter 5:

SPECIAL CIRCUMSTANCES IN MANAGEMENT OF HAEMOPHILIA

People with haemophilia and their families may experience a number of health- or haemophilia-related conditions or management issues over the course of their lives. These include bleeding and reproductive complications that may affect carriers, specific requirements for surgery and other invasive procedures, psychosocial matters, a range of comorbidities due to lifestyle and aging, and other issues.

5.1 Management of patients undergoing surgery/ invasive procedures

This protocol should be followed any time an invasive/ surgical procedure is to be done on a person living with haemophilia.

5.1.1 Preoperative assessment and preparation

- There should be consultation between the surgical team and the Haemophilia treatment team. Ensure the type of haemophilia is clear and enough factor concentrate is available.
- Always check for inhibitor levels. If inhibitors are present, the patient should be referred to a HCCC for further management
- Ensure availability of blood products
- Prepare a written hemostatic management plan and communicate this to all teams involved in the care of the patient.
- Try to have the surgery done early in the week and early in the day (Monday or Tuesday) to allow for proper immediate post-operative care.

5.1.2 Treatment approach/ hemostatic plan

- Raise factor level to 50-80% for at least 3 days for minor surgery, and 80-100% for major surgery, and maintain factor level above 50% for 7-14 days (Confirm the half-life of the product and adjust the intervals accordingly)
- Adjunct therapy include antifibrinolytic that is available before and after the operation and continue six hourly for at least 7 days post operation.
- Monitor intraoperative and postoperative blood loss and transfuse red cells if necessary.
- Avoid NSAIDs and intramuscular analgesics
- Do not anticoagulate
- Introduce postoperative rehabilitation and mobilization gradually under factor coverage.
- Use of antibiotics postoperatively is mandatory.
- Ensure that patient receives adequate pain management.
- Cover the operation site with petroleum jelly gauze or other non-stick dressing and avoid using force during removal of the dressing.

- The patient should be monitored frequently for bleeding and signs of infection e.g. formation of pus.
- If the patient is bleeding despite administration of adequate factor dosage, re-evaluate for inhibitors or bleeding from a blood vessel.
- Instruct the patient to avoid strenuous activities during the healing period.

5.2 DENTAL PROCEDURES

Maintaining good oral health and preventing dental problems is of great importance in people with haemophilia to prevent oral diseases and conditions such as gingivitis, dental caries, and periodontal diseases, which may cause serious gum bleeding, especially in those with severe/ moderate haemophilia, and to avoid the need for major dental surgery.

- Administer factor products before the procedure to a level of 50 – 80% correction depending on the type of procedure required and maintain the levels for a period of 1-3 days.
- Adjunct therapy with antifibrinolytic should be given before and after and continue six hourly for at least 7 days post the procedure.
- Antibiotics should be prescribed if clinically indicated for management of infections.

5.3 CIRCUMCISION IN HAEMOPHILIA

Circumcision is a widely practiced surgical procedure in African communities, In haemophilia, circumcision is associated with a number of complications including prolonged bleeding, infection, delayed skin healing/increased morbidity, gangrene, risk of inhibitor development, psychosocial scarring, and risk of mortality. The key considerations for circumcision in patients with haemophilia include individual patient factors such as inhibitor development, venous access, and wound care, as well as the expertise and resources at the hospital/treatment centre.

5.3.1 SURGICAL CONSIDERATIONS INCLUDE:

- A qualified healthcare worker should perform the circumcision procedure in conjunction with the hematology team with access to clotting factor concentrates.
- Plasma factor level should be raised to 80-100% just prior to the procedure. Continue clotting factor replacement with the goal to maintain factor levels above 50% for the first 3 days, and above 30% for the subsequent 4-8 days.
- Adjunct therapy with antifibrinolytic should be given before and after and continue six hourly for at least 10 days post the procedure.
- Antibiotics should be prescribed if clinically indicated for management of infections.
- Intraoperative care should be taken to cauterize all bleeding vessels.
- Use of topical fibrin sealant or paraffin gauze as an adjunctive therapy.
- • Inhibitor measurements should be repeated if there is intractable bleeding that is poorly responsive to replacement therapy and local hemostatic measures.
- Use of dissolvable stitches is recommended.

5.3 VACCINATIONS

Vaccination against communicable diseases is crucial for disease prevention. People with haemophilia should receive all immunizations recommended for their age group. Factor infusion should be done prior to administration of all intramuscular vaccines. An ice pack should be applied 5 minutes before the injection. Use the smallest gauge of needle available and apply pressure at the injection site for at least 10 minutes.

5.4 Haemophilia carriers and pregnancy

Mothers of children with haemophilia carry the haemophilia gene and are at an increased risk of reproductive related bleeding.

5.4.1 Treatment plan for Carriers

- Provide pre-pregnancy genetic counseling to all carriers.
- Check the carrier baseline factor level.
- Symptomatic carriers should be managed according to severity of symptoms
- Treat with DDAVP, Tranexamic acid or Factor replacement when indicated
- Symptomatic carriers should wear medical emergency bracelets if available.
- Menorrhagia can be controlled using hormonal, hemostatic or surgical methods
- At pregnancy
- Management should be planned with obstetrician and hematologist
- If bleeding do not use DDAVP, use clotting factor instead
- At delivery
- Plan for vaginal delivery
- Avoid scalp monitor, vacuum and forceps delivery methods.
- Take cord blood for factor levels assay.
- Avoid heel pricks on male babies and give oral Vitamin K.
- Watch for bleeding in the mother and the child.
- If the mother is bleeding excessively, use clotting Factor replacement.
- Post-partum
- Watch for post-partum bleeding and manage as per obstetrics protocols.
- Treat with factor replacement, tranexamic acid or DDAVP, and blood transfusion as needed.Factor levels fall to baseline within the first week of delivery.

5.5 Comorbidities

A range of new challenges accompanies the increase in life expectancy for people with haemophilia due to major advances in haemophilia care, including the availability of safe and effective CFCs. An increasing number of people with haemophilia develop significant comorbidities, such as cardiovascular and metabolic diseases, renal disease, and cancer/malignancies. In general, the comorbidities occurring in older patients with haemophilia should be treated in consultation with relevant specialists as they would in the unaffected population of the same age, but treatment should be adapted when the risk of bleeding is increased by the use of invasive procedures or medications that may cause bleeding.

Chapter 6:

SPECIAL CIRCUMSTANCES IN MANAGEMENT OF HAEMOPHILIA

Following promulgation of the Kenyan constitution in 2010, health care is now a devolved function in 47 counties. Based on the Health Act 2017 and the Kenya Health Policy 2014-2030, there are six levels of health care as shown in the table below.

The primary and secondary health facilities are under the management of the county governments while tertiary facilities are under the national government. The primary care facilities comprise the dispensaries and health centres while the secondary health facilities are the sub-county and county referral hospitals. Tertiary facilities are the National Referral Centers.

Table 5: National Referral System

Level of Health	Human Resources	Function/ Responsibility
Level 1 (Community Health Services)	•Community Health Volunteers •Community Health Assistants	• Awareness creation • Identification of potential patients • Referral to primary health facilities • Rehabilitative post-treatment • Psychosocial support.
Level 2-3 (Primary Facility)	Nurses and Clinical Officers, Lab Technicians/ Technologists	• Awareness creation • Basic haemophilia care like infusion of factor for known haemophilia patients • Referral for potential Haemophilia patients to secondary and tertiary facilities • Pain management • Rehabilitative post-treatment and infusion of factors • Psychosocial support.

Level 4-5 (Secondary Facility)	• Specialists (Physicians, paediatricians, surgeons, gynaecologists, family physicians, ENT surgeons, psychiatrists, orthopaedic surgeons etc.) • Dentists • Medical Officers • Clinical Officers • Nurses • Physiotherapist • Laboratory Technician/ Technologist	• Physical Therapy and rehabilitation after joint bleeds • Management of comorbidities • Dental care • Quality-of-life assessments and psychosocial support • Ongoing patient/family caregiver education and support. • Provision of clotting factor concentrates (CFCs), either virus-Inactivated plasma-derived or recombinant, as well as other hemostatic agents such as desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid [EACA]) where available • Provision of safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate if adequately screened, tested, and/or virus-inactivated where CFCs are not available • Casting and/or splinting and mobility/support aids, as needed • Refer severe Haemophilia cases for management to tertiary level • Surgeries, including minor procedures e.g. circumcision, should be done from this level.
Level 6 (Tertiary Facilities	Human resources in level 5 plus: • Sub-specialists e.g. Hematologists, neurosurgeons, vascular surgeons etc.	Serve as the Haemophilia Comprehensive Care Centres with the following Capabilities: • Coagulation laboratory services with the capacity to perform clotting factor assays and inhibitor testing • Genetic Testing • The HCCCs should have a Haemophilia multi-disciplinary team that meets regularly. • Prevention of bleeding and joint damage; • Prompt management of bleeding episodes • Physical Therapy and rehabilitation after joint bleeds

Level 6 (Tertiary Facilities (continued)		• Pain management • Management of musculoskeletal complications • Prevention and management of inhibitors • Management of comorbidities • Dental care • Quality-of-life assessments and psychosocial support • Genetic counselling and diagnosis • Ongoing patient/family caregiver education and support • Provision of clotting factor concentrates (CFCs), either virus-Inactivated plasma-derived or recombinant, as well as other hemostatic agents such as desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid [EACA]) where available • Provision of safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate if adequately screened, tested, and/or virus-inactivated where CFCs are not available • Casting and/or splinting and mobility/support aids, as needed.

REFERRAL SYSTEMS:

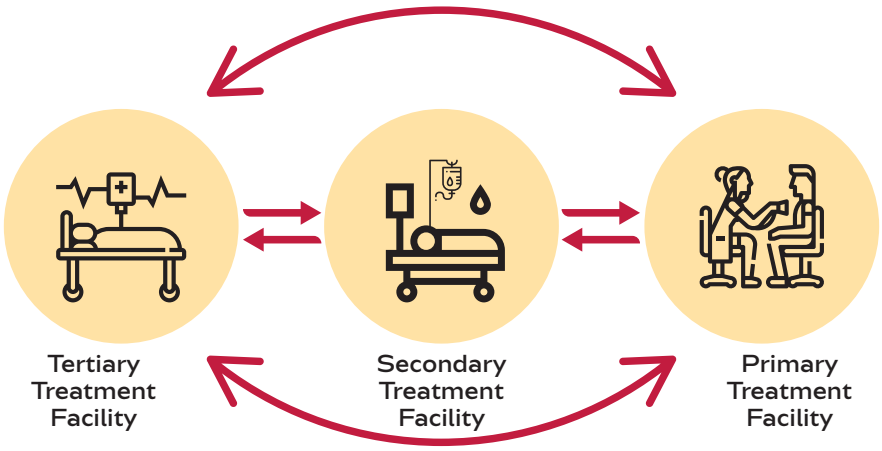
There are two types of possible referral systems for patients living with haemophilia and other bleeding disorder patients in Kenya. These are: 'upward and downward' referral systems.

Upward referral system involves patient flow from the primary, secondary to tertiary treatment facilities while downward referral system involves the movement of patients from tertiary to secondary treatment to primary care facilities. As a country, due to different capabilities in the treatment facilities, patients in the primary level facilities may be referred directly to the tertiary facilities for full diagnostic workup and determination of a treatment plan. Those referred to the secondary treatment facilities may be worked up partially; treatment initiated but shall require referral to a tertiary facility for comprehensive care. All patients should be seen at the tertiary facility at least once a year for comprehensive care assessment and follow-up. However, select county referral facilities may be upgraded to haemophilia comprehensive care centres if they meet the requisite criteria.

Considerations for the establishment of haemophilia treatment centres and haemophilia comprehensive care centres shall include:

- Number of people with haemophilia and other bleeding disorders
- Presence of human resources (to form part of the multidisciplinary team)
- Geographical area for equal distribution of treatment centres
- Availability of existing infrastructure
- Availability of financial resources and referral structures

Figure 2: National Referral Structure



DATA MANAGEMENT

Proper documentation and data management is key to planning for care of haemophilia patients. Data management shall be though the following:
Haemophilia Registry:

- The National Haemophilia Registry will provide an online platform for a network of HTCs around the country to collect uniform and standardized data to track treatment and management of patients, monitor patient outcomes, and guide clinical practice.
- The Registry will be used to collect accurate data on people with haemophilia in terms of their treatment and outcomes including disease severity, type of treatment, bleeding episodes, adverse events, joint status, inhibitor status, comorbidities, and quality of life.
- Registry data will allow analysis of standards of care and can be used as a tool for auditing clinical and laboratory services; this, in turn, can support the development of better quality of care and facilitate resource planning and allocation.
- The registry will help to advance understanding of the variations in haemophilia treatment; describe care patterns, including appropriateness and disparities in the delivery and quality of care; indicate factors that influence prognosis and quality of life; and provide evidence on resource utilization.
- Adequate provision must be made for data privacy, confidentiality and respect for human rights in compliance with national regulations and best ethical practices.
- It is important to ensure that the patient and/or the parent or legal guardian (in the case of minors) understands a registry's purpose and uses and provides informed written consent for the collection and sharing of data related to the patient's care.
- The registry will be integrated into existing electronic medical records and other patient information management systems.

KENYA HEALTH INFORMATION SYSTEM

Haemophilia key performance indicators from service delivery data shall be integrated into the KHIS. HTCs shall ensure timely reporting on these indicators, conduct periodic data reviews and use this data for decision making for clinical services delivery to improve patient care . Haemophilia services shall be integrated into routine data quality audits, mentorship and support supervision.

References

ASTERMARK, J., ALTISENT, C., BATOROVA, A., DINIZ, M. J., GRINGERI, A., HOLME, P. A., KARAFOULIDOU, A., LOPEZ-FERNÁNDEZ, M. F., REIPERT, B. M., ROCINO, A., SCHIAVONI, M., Von DEPKA, M., WINDYGA, J., & FIJNVANDRAAT, K. (2010). Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report. Haemophilia, 16(5), 747–766. https://doi.org/10.1111/j.1365-2516.2010.02231.x

Blanchette, V. S., Key, N. S., Ljung, L. R., Manco-Johnson, M. J., van den Berg, H. M., & Srivastava, A. (2014). Definitions in hemophilia: communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis, 12(11), 1935–1939. https://doi.org/10.1111/jth.12672

Bush, M. T., & Roy, N. (1995). Hemophilia emergencies. Journal of Emergency Nursing, 21(6), 531–540. https://doi.org/10.1016/s0099-1767(05)80270-3

BYAMS, V. R., KOUIDES, P. A., KULKARNI, R., BAKER, J. R., BROWN, D. L., GILL, J. C., GRANT, A. M., JAMES, A. H., KONKLE, B. A., MAAHS, J., DUMAS, M. M., McALISTER, S., NANCE, D., NUGENT, D., PHILIPP, C. S., SOUCIE, J. M., & STANG, E. (2011). Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres. Haemophilia, 17, 6–13. https://doi.org/10.1111/j.1365-2516.2011.02558.x

CHI, C., LEE, C. A., SHILTAGH, N., KHAN, A., POLLARD, D., & KADIR, R. A. (2007). Pregnancy in carriers of haemophilia. Haemophilia, 0(0), 071018054549001-??? https://doi.org/10.1111/j.1365-2516.2007.01561.x

Dunkley, S., Curtin, J. A., Marren, A. J., Heavener, R. P., McRae, S., & Curnow, J. L. (2019). Updated Australian consensus statement on management of inherited bleeding disorders in pregnancy. Medical Journal of Australia, 210(7), 326–332. https://doi.org/10.5694/mja2.50123

Elalfy, M. S., Elbarbary, N. S., Eldebeiky, M. S., & El Danasoury, A. S. (2012). Risk of Bleeding and Inhibitor Development After Circumcision of Previously Untreated or Minimally Treated Severe Hemophilia A Children. Pediatric Hematology and Oncology, 29(5), 485–493. https://doi.org/10.3109/08880018.2012.704624

Haghpanah, S., Ardeshiri, R., Zahedi, Z., Golzadeh, M. H., Silavizadeh, S., & Karimi, M. (2013). Attitudes and practices with regard to circumcision in haemophilia patients in Southern Iran. Haemophilia, 19(3), e177–e178. https://doi.org/10.1111/hae.12120

Hermans, C., & Kulkarni, R. (2018). Women with bleeding disorders. Haemophilia, 24, 29–36. https://doi.org/10.1111/hae.13502

Kadir, R. A., Davies, J., Winikoff, R., Pollard, D., Peyvandi, F., Garagiola, I., Pabinger, I., & Federici, A. B. (2013). Pregnancy complications and obstetric care in women with inherited bleeding disorders. Haemophilia, 19, 1–10. https://doi.org/10.1111/hae.12269

Kearney, S., Sharathkumar, A., Rodriguez, V., Chitlur, M., Valentino, L., Boggio, L., & Gill, J. (2014). Neonatal circumcision in severe haemophilia: a survey of paediatric haematologists at United States Hemophilia Treatment Centers. Haemophilia, 21(1), 52–57. https://doi.org/10.1111/hae.12528

Kletzel, M. (1989). Postdelivery Head Bleeding in Hemophilic Neonates. American Journal of Diseases of Children, 143(9), 1107. https://doi.org/10.1001/archpedi.1989.02150210143035

Kulkarni, R., Presley, R. J., Lusher, J. M., Shapiro, A. D., Gill, J. C., Manco-Johnson, M., Koerper, M. A., Abshire, T. C., DiMichele, D., Hoots, W. K., Mathew, P., Nugent, D. J., Geraghty, S., Evatt, B. L.,

& Soucie, J. M. (2016). Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. Haemophilia, 23(2), 207–214. https://doi.org/10.1111/hae.13081

Lambert, C., Meité, N. '. D., Sanogo, I., Lobet, S., Adjambri, E., Eeckhoudt, S., & Hermans, C. (2019). Hemophilia carrier's awareness, diagnosis, and management in emerging countries: a cross-sectional study in Côte d'Ivoire (Ivory Coast). Orphanet Journal of Rare Diseases, 14(1), 26. https://doi.org/10.1186/s13023-019-1005-9

Ljung, R., & Tedgård, U. (2003). Genetic Counseling of Hemophilia Carriers. Seminars in Thrombosis and Hemostasis, 29(1), 031–036. https://doi.org/10.1055/s-2003-37937

Mannucci, P. M., Schutgens, R. E. G., Santagostino, E., & Mauser-Bunschoten, E. P. (2009). How I treat age-related morbidities in elderly persons with hemophilia. Blood, 114(26), 5256–5263. https://doi.org/10.1182/blood-2009-07-215665

Meijer, P., & Verbruggen, B. (2009). The between-Laboratory Variation of Factor VIII Inhibitor Testing: The Experience of the External Quality Assessment Program of the ECAT Foundation. Seminars in Thrombosis and Hemostasis, 35(08), 786–793. https://doi.org/10.1055/s-0029-1245111

Miller, C. H. (2018). Laboratory testing for factor VIII and IX inhibitors in haemophilia: A review. Haemophilia, 24(2), 186–197. https://doi.org/10.1111/hae.13424

MILLER, R. I. V. A. (1999). Counselling about diagnosis and inheritance of genetic bleeding disorders: haemophilia A and B. Haemophilia, 5(2), 77–83. https://doi.org/10.1046/j.1365-2516.1999.00288.x

O'Hara, J., Hughes, D., Camp, C., Burke, T., Carroll, L., & Diego, D.-A. G. (2017). The cost of severe haemophilia in Europe: the CHESS study. Orphanet Journal of Rare Diseases, 12(1), 106. https://doi.org/10.1186/s13023-017-0660-y

Pai, M., Chan, A., & Barr, R. (2013). How I manage heavy menstrual bleeding. British Journal of Haematology, 162(6), 721–729. https://doi.org/10.1111/bjh.12447

Peyvandi, F., Mannucci, P. M., Garagiola, I., El-Beshlawy, A., Elalfy, M., Ramanan, V., Eshghi, P., Hanagavadi, S., Varadarajan, R., Karimi, M., Manglani, M. V., Ross, C., Young, G., Seth, T., Apte, S., Nayak, D. M., Santagostino, E., Mancuso, M. E., Sandoval Gonzalez, A. C., … Rosendaal, F. R. (2016). A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. New England Journal of Medicine, 374(21), 2054–2064. https://doi.org/10.1056/nejmoa1516437

Plug, I., Mauser-Bunschoten, E. P., Bröcker-Vriends, A. H. J. T., van Amstel, H. K. P., van der Bom, J. G., van Diemen-Homan, J. E. M., Willemse, J.´ ., & Rosendaal, F. R. (2006). Bleeding in carriers of hemophilia. Blood, 108(1), 52–56. https://doi.org/10.1182/blood-2005-09-3879

RAGNI, M. V., OJEIFO, O., FENG, J., YAN, J., HILL, K. A., SOMMER, S. S., TRUCCO, M. N., & BRAMBILLA, D. J. (2009). Risk factors for inhibitor formation in haemophilia: a prevalent case-control study. Haemophilia, 15(5), 1074–1082. https://doi.org/10.1111/j.1365-2516.2009.02058.x

Srivastava, A., Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S. W., Carcao, M., Mahlangu, J., Ragni, M. V., Windyga, J., Llinás, A., Goddard, N. J., Mohan, R., Poonnoose, P. M., Feldman, B. M., Lewis, S. Z., Berg, H. M., & Pierce, G. F. (2020). WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia, 26(S6), 1–158. https://doi.org/10.1111/hae.14046

Seck, M., Sagna, A., Guéye, M. S., Faye, B. F., Sy, D., Touré, S. A., Sall, A., Touré, A. O., & Diop, S. (2017). Circumcision in hemophilia using low quantity of factor concentrates: experience from Dakar, Senegal. BMC Hematology, 17(1), 8. https://doi.org/10.1186/s12878-017-0080-1

Singleton, T., Kruse-Jarres, R., & Leissinger, C. (2010). Emergency Department Care for Patients

with Hemophilia and Von Willebrand Disease. The Journal of Emergency Medicine, 39(2), 158–165. https://doi.org/10.1016/j.jemermed.2007.12.024

van den Berg, H. M., Fischer, K., Carcao, M., Chambost, H., Kenet, G., Kurnik, K., Königs, C., Male, C., Santagostino, E., & Ljung, R. (2019). Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. Blood, 134(3), 317–320. https://doi.org/10.1182/blood.2019000658

Verbruggen, B., van Heerde, W., & Laros-van Gorkom, B. (2009). Improvements in Factor VIII Inhibitor Detection: From Bethesda to Nijmegen. Seminars in Thrombosis and Hemostasis, 35(08), 752–759. https://doi.org/10.1055/s-0029-1245107

WFH. (2020). WORLD FEDERATION OF HEMOPHILIA REPORT. Retrieved from www.wfh.org

Zimmermann, R., Staritz, P., & Huth-Kühne, A. (2014). Challenges in treating elderly patients with haemophilia: A focus on cardiology. Thrombosis Research, 134, S48–S52. https://doi.org/10.1016/j.thromres.2013.10.023

ABOUT KENYA HAEMOPHILIA ASSOCIATION

Kenya Haemophilia Association

About Kenya Haemophilia Association

The Kenya Haemophilia Association (KHA) was established in Nairobi in 1979. In 1992, it was recognized as a National Member Organisation (NMO) by the World Federation of Hemophilia (WFH). With this status, it is the official Kenyan patient organisation in charge of representing the rights of all patients living with Haemophilia and allied bleeding disorders in Kenya.

Vision

To achieve the highest standard of care for people living with Haemophilia and other bleeding disorders in Kenya.

Mission

To work together with other stakeholders for the social good and greater benefit of all people living with Haemophilia and other bleeding disorders in Kenya.

Main Objectives:

- To provide clinical support, management and care for people living with haemophilia and other bleeding disorders in Kenya;
- To lobby the government, agencies and institutions concerned to provide a conducive environment for the holistic management of haemophilia and other bleeding disorders in Kenya;
- To create awareness to the general public on haemophilia and other bleeding disorders
- To engage in resource mobilisation activities that will facilitate the activities of the Association;
- To promote research and education through dissemination of information on haemophilia and other bleeding disorders
- To train and build the capacity of care givers involved in management of haemophilia and other bleeding disorders.

MINISTRY OF HEALTH

KENYA NATIONAL CLINICAL GUIDELINES *for the* Management *of* Haemophilia

Kenya Haemophilia Association