Haemophilia Foundation Zambia - HFZ

Ministry of Health

ZAMBIA CHILDHOOD CANCER FOUNDATION
Enriching Lives Through Hope

ZAMBIAN NATIONAL GUIDELINES FOR THE MANAGEMENT OF HAEMOPHILIA

2020

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Professor Chifumbe Chintu
1935 – 2017

These guidelines are dedicated to the memory of Professor Chifumbe Chintu, who dedicated his life to improving the medical care and quality of life of patients with haemophilia and other blood disorders.

FOREWORD

These guidelines have been necessitated by the need to strengthen and streamline haemophilia care in Zambia. They provide comprehensive and latest information on haemophilia care in line with international standards and best clinical practice. The guidelines provide approaches to managing haemophilia in diverse settings which can be applied with ease in many settings within Zambia. They also emphasise the importance of home and community management of haemophilia.

Haemophilia is the oldest known and most clinically important inherited bleeding disorder. According to the Zambian haemophilia database, there are 194 patients diagnosed. It occurs at a rate of 1 in 10,000 male births and it is estimated that there are 1, 700 to 2, 000 haemophilia patients in the Zambian population, most of whom remain undiagnosed. If not well managed haemophilia is associated with severe, life threatening and long term debilitating complications.

These guidelines therefore come at an opportune time when our health care system is aiming to provide quality healthcare services as close to the family as possible, including persons living with haemophilia. These guidelines therefore are a great initiative and a starting point for strengthening structured haemophilia care in Zambia.

Last but not the least, I wish to thank the Zambia Childhood Cancer Foundation/Haemophilia Foundation Zambia (ZACCAF/HFZ), the World Federation of Hemophilia (WFH), the Haemophilia Guidelines Technical Working Group and all the collaborating partners for making it possible to produce this first edition of the Zambian guidelines for management of haemophilia. It is my sincere hope that these guidelines will be of great help to our health care providers for a long time to come and will continue to be updated with new emerging evidence and trends for optimal haemophilia care and better patient outcomes.

Dr Chitalu Chilufya, MP
MINISTER OF HEALTH

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CONTENTS

ABBREVIATIONS

APCC	Activated prothrombin complex concentrate
APTT	Activated Partial Thromboplastin Time
CMV	Cytomegalovirus
DDVAP	Desmopressin
FFP	Fresh Frozen Plasma
FVIII	Factor eight
FIX	Factor nine
HA	Haemophilia A
HA-I	Haemophilia A with inhibitors
HB	Haemophilia B
HB-I	Haemophilia B with inhibitors
HFZ	Haemophilia Foundation of Zambia
HTC	Haemophilia Treatment Centre
IEC	Information, Education & Communication
NMO	National Member Organisation
NSAIDs	Non-steroidal anti-inflammatory Drugs
PRICE	Protection Rest, Ice, Compression & Elevation
PT	Prothrombin Time
PLT	Platelets
PWH	People with Haemophilia
PWHA	People with Haemophilia A
VWD	von Willebrand Disease
WFH	World Federation of Haemophilia
ZACCAF	Zambia Childhood Cancer Foundation

CHAPTER ONE

1. OVERVIEW OF HAEMOPHILIA

1.1 Introduction

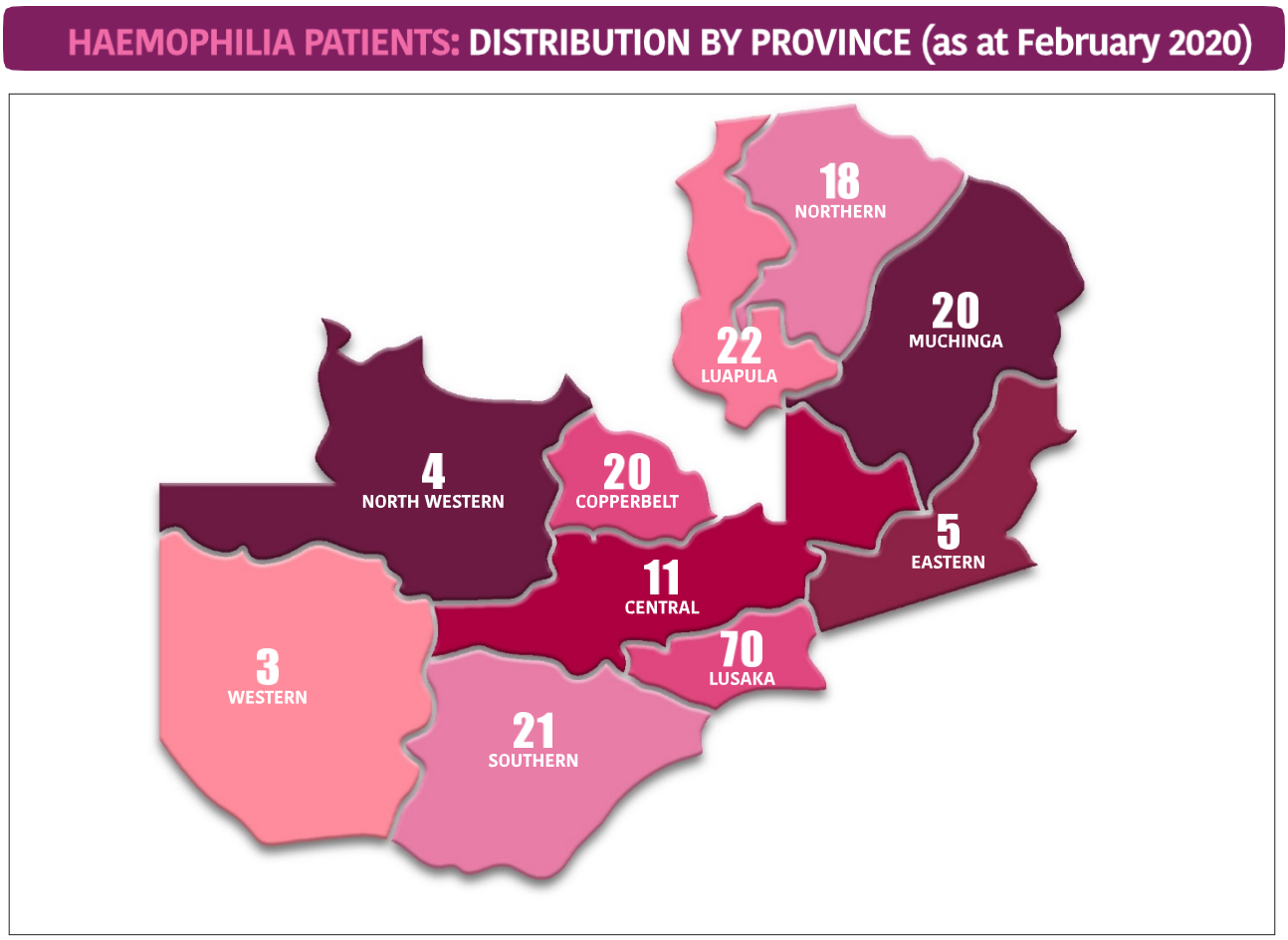
Haemophilia is a group of congenital bleeding disorders caused by deficiency of coagulation factor VIII (haemophilia A) or factor IX (haemophilia B) or rarely factor XI (haemophilia C). Haemophilia A and B are X-linked, whereas haemophilia C is autosomal recessive.[2]

The deficiency is due to a genetic mutation in the specific clotting factor gene. However, 30% of cases are non-hereditary resulting from spontaneous mutations without any family history of haemophilia.[4]

1.2 Epidemiology

Globally haemophilia A affects 1 in 5000 male births.[5] Haemophilia A is more common than haemophilia B, representing 80 to 85% of the total haemophilia population.[1,4] Following the advances in diagnosis, treatment and increased awareness, the number of known people living with haemophilia has been rising. Recently, a meta-analysis of registry data showed that the expected number of people living with Haemophilia (PLWH) world-wide is 1 125 000, a much higher figure than the previously known estimate of 400 000 patients.[6,7]

In Zambia, haemophilia data is limited. However, in the recent past, following the formation of the Haemophilia Foundation of Zambia (HFZ) in 2013 and its recognition as the National Member Organization (NMO) by the World Federation of Haemophilia (WFH) in 2014, there has been increased advocacy and awareness. The HFZ as an organisation was birthed out of a need for better patient care when the standard of care of haemophilia and other allied bleeding disorders was on-demand administration of blood and blood products. It is composed mainly of patients and parents as well as medical personnel. Even though the estimated number of PLWH in the Zambian population should be around 1700 to 2000, as of February 2020, the total number on the HFZ national register was 194.[8] Twenty have haemophilia B. The great variance between what is and what should be is because of the limited diagnostic capacity countrywide as well as inadequate awareness in the community. There are some epicentres around the country that have been identified in the northern and southern regions that are still being mapped. Most of the known patients are located in Lusaka province due to increased awareness and access to diagnostic and therapeutic facilities[8] as illustrated in the map below:



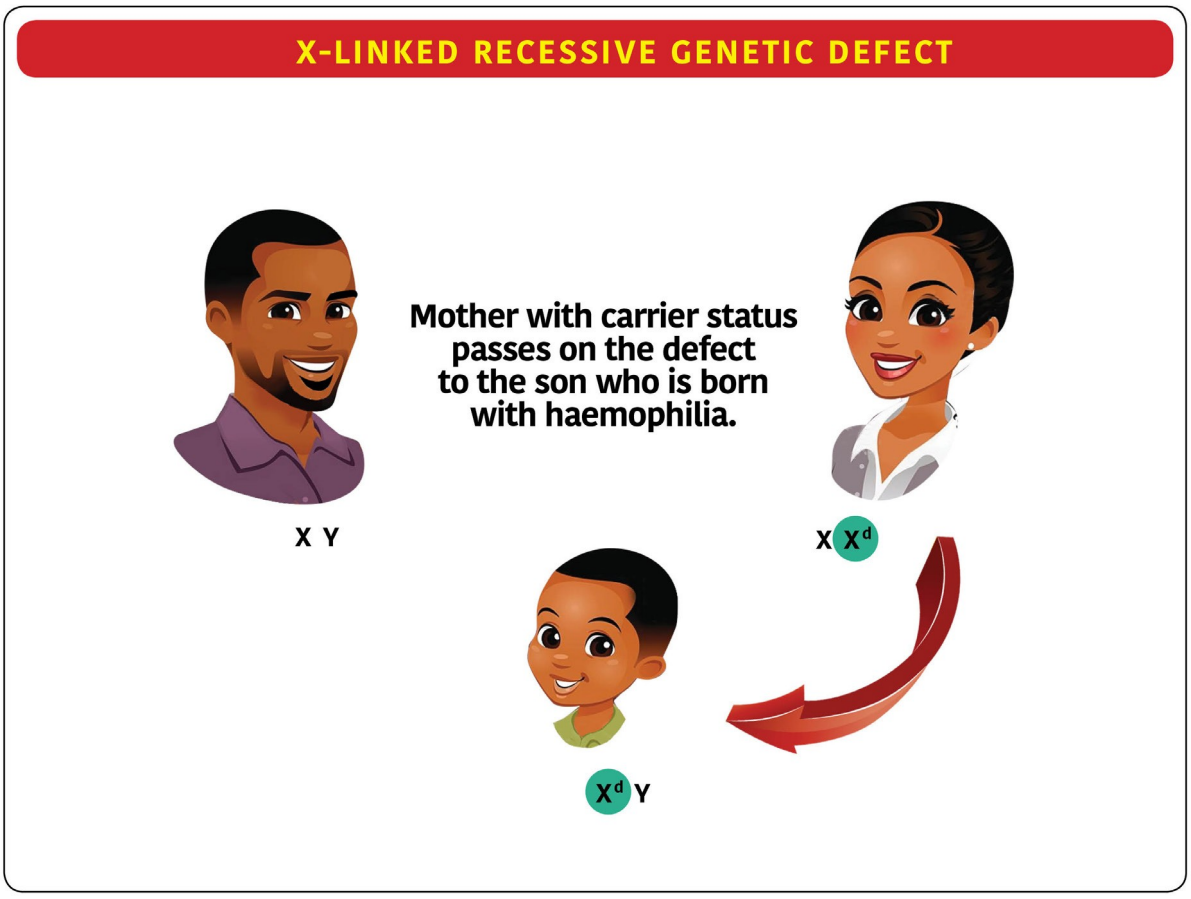
1.3 Pathophysiology

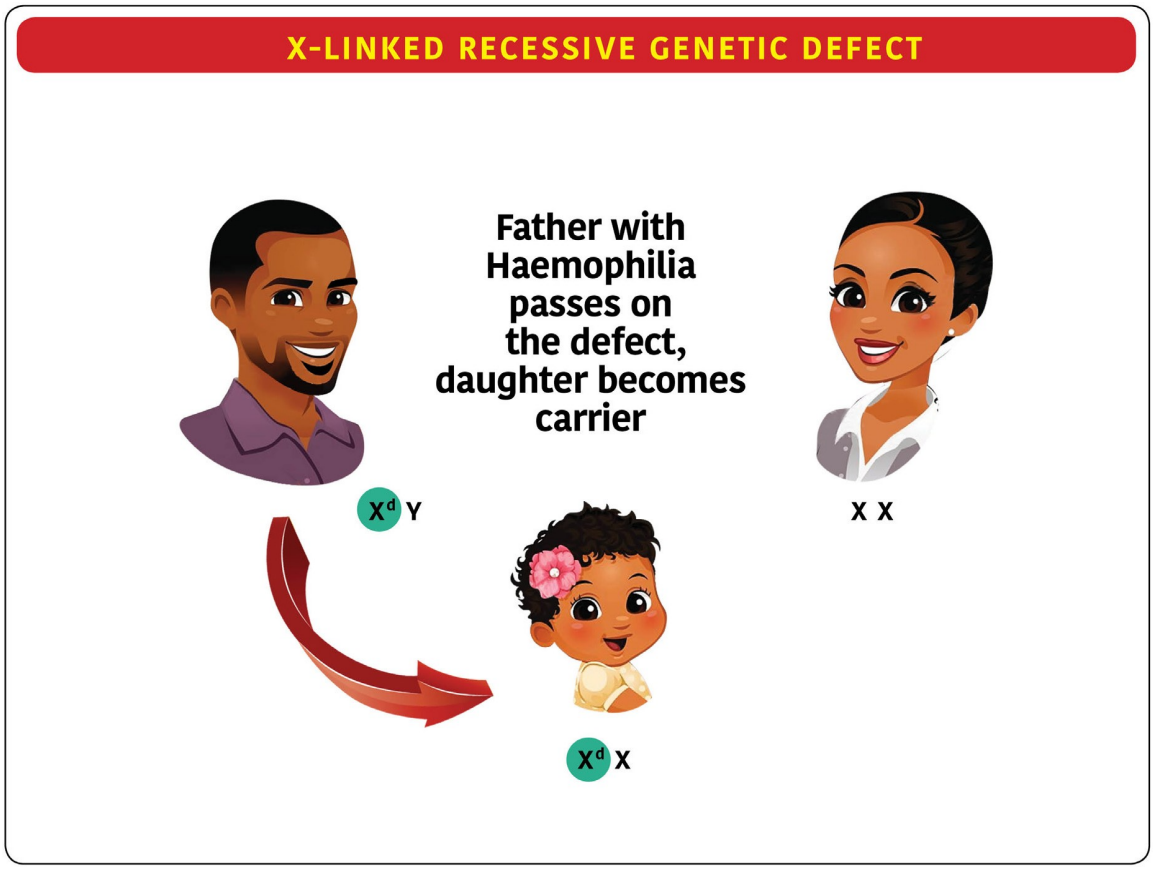
Bleeding from injuries resulting from activities of daily living is a common occurrence. When this occurs, the body has inherent mechanisms to stop the bleeding. This is done with the help of clotting factors of which Factors VIII and IX participate in conjunction with others. In patients with haemophilia, due to deficiency of factor VIII and/or IX, the clotting mechanism is impaired resulting in spontaneous, easy and prolonged bleeding.[4] Factor VIII as a co-factor to Factor IX is responsible for the activation of factor X which has a pivotal role in the coagulation cascade, in intrinsic pathways for formation of a stable fibrin clot to arrest haemorrhage.[4]

The haemophilia gene sits on the X-chromosome hence the mode of inheritance is X-linked.[1,2,4] This entails that only males are affected; they inherit the abnormal gene from their mothers. Affected fathers pass the gene to their daughters who become carriers as illustrated in figure 2 below.

For many years, people believed that only men could have symptoms of haemophilia and that women who "carry" the haemophilia gene do not experience symptoms themselves.
However, we now know that many carriers do experience symptoms of haemophilia.[9] As our knowledge about the disorder has increased, so has our understanding of why and how women can be affected. Some women live with their symptoms for years without being diagnosed or even suspecting they have a bleeding disorder.

In addition, syndromes such as Turner's may lead to a females being symptomatic due to a single X-chromosome and inactivation of the one X-chromosome (lyonisation).[2,4]


X-LINKED RECESSIVE GENETIC DEFECT
Mother with carrier status passes on the defect to the son who is born with haemophilia.
X Y
X X^d
X^d Y


X-LINKED RECESSIVE GENETIC DEFECT
Father with Haemophilia passes on the defect, daughter becomes carrier
X^d Y
X X
X^d X

1.4 Clinical features

The time of presentation varies with severity of the factor deficiency. However, most start to present as soon as they start ambulating and weight bearing through crawling and walking. Some may present early in life with muscular haemorrhages that result from intramuscular injection administration (such as vaccinations) and during neonatal circumcision for communities that practice it.[1,2,4]

The hallmark of haemophilia is bleeding tendency which varies depending on the severity of the factor deficiency. Those with mild disease may not bleed except following major trauma, whereas those with severe disease may bleed spontenously.[1,2,3] In our setting patients tend to be diagnosed late and this compromises treatment outcomes and quality of life. A high index of suspicion is therefore critical in early diagnosis of heamophilia.[3,4] Every patient who presents with the following should be suspected and further evaluated for haemophilia:

- A family history in which males tend to bleed easily
- A history of easy bruising even from what may seem to be insignificant trauma
- Spontaneous haemorrhage from anywhere which may include mucosal bleeds, subcutaneous, soft tissues and into major joints
- Prolonged and excessive bleeding following trauma or surgery[1,2,3,4]

Some patients present late with complications of recurrent bleeds into soft tissues and joints. Such complications include;

- Muscle atrophy
- Joint instability
- Contractures
- Joint axial deformities
- Joint crepitus
- Chronic pain
- Iron deficiency anaemia due to recurrent bleeding[1,2,3,4]

In the acute period of a severe bleed such as abdominal bleeding, or bleeding into major muscles such iliopsoas, patient may present with pain, severe anaemia or even in shock. Haemarthrosis remains by far the commonest presentation. Any patient presenting with joint swelling of sudden onset should be evaluated for haemophilia. Joint drainage is contraindicated before ruling out the possibility of haemophilia in such patients. Some patients have a tendency to bleed into a specific joint; when 3 or more bleeds occur in the same joint within 6 months, this is called a **target joint**. Special attention should be paid to such joints as the incidence of complications is high.[1,2,3,4]

Bleeding in haemophilia can be minor or major. Most patients with minor bleeds do not seek medical attention. Usually those who present to health facilities come with major bleeds, which could be classified as serious or life threatening.[1,2,]

Serious bleeding:

- Joints (haemarthrosis)
- Muscles, especially deep compartments (iliopsoas, calf, and forearm)
- Mucous membranes in the mouth, gums, nose, and genitourinary tract[1,2,3,]

Life threatening bleeding:

- Intracranial
- Neck/throat
- Gastrointestinal[1,3,4]

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CHAPTER TWO

2. GENERAL PRINCIPLES OF MANAGEMENT

Treatment of haemophilia requires a multi-disciplinary approach involving various categories of specialty. These may include: haematologists, orthopaedic surgeons, laboratory personnel, paediatricians, physiotherapists, physicians, pharmacists, nurses, clinical officers, counsellors and others. The principles of management are to:

- Prevent bleeding
- Treat acute bleeding
- Manage pain
- Prevent and treat complications
- Provide family counselling and psychosocial support

2.1 Prevent Bleeding

- The main aim of management is to prevent bleeding by prophylactic specific factor replacement therapy.
- Patients should avoid contact sports and activities that are likely to cause trauma
- Drugs such as acetylsalicylic acid (ASA), typical non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac, anticoagulants and fibrinolytic agents should be avoided
- Promote good oral hygiene to prevent periodontal disease and dental caries which may lead to gum bleeding

2.2 Treat Acute Bleeding

- Early symptoms of bleeding are usually recognized by patients even before the manifestation of physical signs. This is often described as a tingling sensation or “aura”.
- Treat bleeding with specific factor concentrate whenever possible.
- Treatment of acute bleeds should be initiated as quickly as possible, preferably within two hours.
- In an undiagnosed patient with clinical features suggestive of haemophilia with an acute bleed, treat.
- An assessment should be done during an episode of acute bleeding to identify the site of bleeding and managed appropriately
- For potentially life-threatening bleeds such as those in the head, neck, chest, and gastrointestinal tract, treatment with factor should be initiated immediately, even before diagnostic assessment is completed.
- In patients with mild and possibly moderate haemophilia A adjuvant therapy with desmopressin (DDAVP) is an option.
- In the absence of clotting factor concentrates, antifibrinolytic drugs such as tranexemic acid and Epsilon aminocaproic acid may be used for mucosal and dental bleeds
- In patients with joint and muscle bleeds, protection/splint, rest, ice, compression and elevation **(PRICE)** helps to reduce bleeding

2.3 Manage Pain

- Pain management is an essential component in the treatment of haemophilia patients
- Paracetamol and COX-2 inhibitors such as meloxicam and colecoxib are safe for analgesia
- Avoid other NSAIDs
- Physiotherapy and rehabilitation may be used in pain management and to control bleeding.
- **PRICE** can help to relieve pain resulting from joint and muscle bleeds

2.4 Prevent and Treat Complications

Complications may arise as sequelae of bleeding and/or treatment. They include joint and muscle damage, inhibitor development and the contraction of viral infections such as HIV, Hepatitis B and C and Cytomegalovirus (CMV) transmitted through blood products.

- Joint and muscle damage can be prevented by prompt management of acute bleeds, physiotherapy and where necessary, surgical intervention.
- Inhibitor development can be prevented by consistent optimal use of factor concentrates and adherence to management guidelines. For new patients, test for inhibitors after 50 exposures or after 6 – 12 months of consistent use. The use of other products such as cryoprecipitate and fresh frozen plasma (FFP) has been shown to increase risk of developing inhibitors and should be minimized whenever possible. Treat inhibitors according to the guidelines provided in chapter 8.
- Viral infection(s) transmitted through blood products can be prevented by limiting their use. Active screening for viral infections, hepatitis B vaccination and treatment where possible is essential.

2.5 Family Counselling and Psychosocial Support

Counselling and psychosocial support is essential and this should be done with the help of a psychosocial expert (preferably a social worker, or a psychologist) familiar with haemophilia and available community resources.

- Provide information, education and communication (IEC)
- Counselling of patient and their family
- Creating support linkages

2.6 Comprehensive Care

The wide-ranging needs of people with hemophilia and their families are best met through the coordinated delivery of comprehensive care by a multidisciplinary team of healthcare professionals from where a core team can be constituted.

Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality. Hemophilia is a rare disorder that is complex to diagnose and to manage. Optimal care of these patients, especially those with severe forms of the disease, requires more than the treatment of acute bleeding.

The core team should consist of the following members:

- A medical doctor – haematologist, paediatrician or a physician with or expertise in haemostasis
- A nurse coordinator - coordinates the provision of care, educates patients and their families, acts as the first contact for patients with an acute problem or who require follow-up and is able to assess patients and institute initial care where appropriate
- A musculoskeletal expert - physiotherapist, occupational therapist, physiatrist, orthopedist, rheumatologist who can address prevention as well as treatment of musculoskeletal concerns
- Laboratory specialist – important for the correct diagnosis and monitoring of disease
- Psychosocial expert (psychologist or social worker)

The roles assumed by core team members may differ, depending on the availability and expertise of trained staff and the organisation of services within the centre. All members of the core team should have expertise and experience in treating bleeding disorders and should be accessible to patients in a timely and convenient manner. Adequate emergency care should be available at all times.

For comprehensive care, the following support resources are necessary:

i) A laboratory with capability to perform precise and accurate coagulation function, factor assays and inhibitor testing.
ii) Clotting factor concentrates such as plasma-derived or recombinant, or extended-half life products and non-factor haemostatic agents where possible.
iii) Access to safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate, where clotting factor concentrates are not available.
iv) Casting and/or splinting for immobilization and mobility/support aids, to be accessible as needed.
v) Access to dental, obstetrics/gynaecology and infectious disease specialists as may be required

The comprehensive care team should be able to support family members by helping them to cope with risks and problems of everyday living, particularly with management of bleeding changes associated with different stages of the patient's growth and development (especially adolescence and aging). Issues regarding schooling and employment, risk of having another affected child and the options available are other areas of support. Establishing a long-term relationship between patients/families and members of the comprehensive care team promotes compliance.

Functions of a comprehensive care program

- To provide or coordinate inpatient (i.e. during hospital stays) and outpatient (clinic and other visits) care and services to patients and their families.
- Patients should be seen by all core team members at least yearly (children every six months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan.
- Referrals for other services can also be given during these visits.

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CHAPTER THREE

3.1 Pain Management in Haemophilia

Acute and chronic pain is common in patients with haemophilia. Adequate assessment of the cause of pain is essential for optimal management

Pain caused by venous access

- In general, no pain medication is indicated.
- In some children, application of a local anesthetic spray or cream at the site of venous access can be used to relieve the pain.

Pain caused by joint or muscle bleeding

- Drugs are often needed for pain control alongside efforts to stop the bleeding.
- Other measures include cold packs, immobilization, splints, and crutches.

Post-operative pain

- Intramuscular injection of analgesia should be avoided.
- Post-operative pain should be managed in coordination with the anesthesiologist.
- Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine and hydrocodone.
- With decreasing pain, paracetamol can be used.

Pain due to chronic haemophilic arthropathy

- Treatment includes functional training, adaptations, and adequate analgesia as suggested in flow chart 8.1 below. COX-2 inhibitors have a greater role here.
- Other NSAIDs should be avoided.
- In disabling pain, orthopedic surgery may be indicated.
- Refer patients with persisting pain to a specialized pain management team.

FLOWCHART 8.1: STRATEGIES FOR PAIN MANAGEMENT IN PATIENTS WITH HAEMOPHILIA

Notes:

- COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide, and others) OR Paracetamol plus codeine (3-4 times/day) or Paracetamol plus tramadol (3-4 times/day)
- Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times/day
- If for any reason medications have been stopped for a period of time, patients who have been taking and tolerating high-dose narcotic drugs should re-start the drug at a lower dose, or use a less powerful painkiller, under supervision.
- COX-2 inhibitors should be used with caution in patients with hypertension and renal dysfunction.

CHAPTER 4

4.1 Prophylaxis in Hemophilia

This refers to administration of a hemostatic agent/agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals. Traditionally, prophylaxis was mainly done by the administration of specific factor concentrates, but in recent times new non-factor therapeutic agents are now being introduced.

For patients with heamophilia A or B with severe phenotype (may include patients with moderate hemophilia), the WFH strongly recommends that such patients be on prohylaxis sufficient to prevent bleeds at all times. Prophylaxis should be tailored and adjusted for each individual patient.

TABLE 4.1: Factors that affect bleeding phenotype and contribute to interpatient phenotypic variability

Genetic differences	Non-genetic differences
• Hemophilic variants • Levels of other procoagulant and anticoagulant proteins • Inflammatory responses that might impact a person's susceptibility to joint damage from bleeding	• Levels and patterns of activity • Functional ability and physical coordination(i.e, strength, flexibility, balance, stability, mobility) • Risk-taking behaviours • Body build(i.e., muscle status) • Presence or absence of existing target joints or established hemophilic arthropathy • Occurrence of trauma

Regarding children, WFH recommends regular long term prophylaxis as a standard of care. When prophylaxis is not feasible, episodic (on demand) therapy is essential treatment for acute hemorrhages, but will not prevent long term joint damage. Early initiation of prophylaxis is recommended with clotting factor concentrates (standard or EHL FVIII/FIX) or other haemostatic agent(s) prior to the onset of joint disease and ideally before age 3years.

All forms of prophylaxis (high/intermediate/low-dose with CFCs or prophylaxis with non-factor replacement agents, such as emicizumab) provide superior benefits over episodic therapy.

There is increasing recognition and evidence that factor trough levels of 1-3 IU/dL(1-3%) are insufficient to totally prevent bleeds in all PLWH and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan. Most clinicians would prefer to target higher trough levels (>3% - 5%, or higher). Recent studies show that such trough levels achieve less bleeding. The use of extended half-life (EHL) clotting factor concentrates and non-factor therapies (Emicizumab) allows the achievement of better protection than simply a 1% factor level.

TABLE 4.2: Documented benefits of EHL CFCs

Benefit of lower infusion frequency	Benefits of higher factor trough levels
• Fewer clinic visits or home care nurse visits when commencing patients on prophylaxis, possibly leading to earlier start of prophylaxis • Less need for central venous access devices leading to some cost savings and reduced morbidity • Less burdensome infusion schedules(dosing days and times): • Few morning infusions • Few infusions on work/school days • Increased uptake of prophylaxis among patients not currently on prophylaxis	• More effective prophylaxis-higher level of prevention of bleeds(both clinically evident and sub-clinical micro-bleeds)while maintaining similar dosing schedules • Potentially greater level of sports participation(possibly including sports that have traditionally been discouraged) without incurring a substantially increased risk of bleeding

TABLE 4.3: DEFINITIONS OF FACTOR REPLACEMENT THERAPY PROTOCOLS

PROTOCOL	DEFINITION
Episodic	
On demand treatment	• Treatment given at the time of clinically evident **bleeding**
Continuou s	
Primary prophylaxis	• Regular continuous* treatment initiated before osteochondral joint disease determined by physical examination and/or imaging studies, and • Commenced prior to a second clinically evident large joint bleed** • initiated before age 3
Secondary prophylaxis	• Regular continuous* treatment commenced at the time of clinically evident bleeding after at least 2 bleeds into large joints** • commenced before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	• Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain X-rays of the affected joints
Intermittent ("periodic") Prophylaxis	• Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

* continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum a priory defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

**large joints = ankles, knees, hips, elbows and shoulders

NOTE: For children, primary prophylaxis given regularly over a long period of time is recommended

Administration and dosing schedules

The following protocol can be used:

The Utrecht protocol:

- 15-30 IU/kg per dose administered three times a week for those with hemophilia A, and twice a week for those with hemophilia B.
- In situations where there are greater constraints on supply of factor concentrates, prophylaxis may be initiated with lower doses of 10-20 IU/kg 2-3 times per week.
- The protocol should be individualized, based on age, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates.
- Very young children can start prophylaxis once a week and escalate depending on bleeding and venous access.
- Prophylaxis is best given in the morning to cover periods of activity and prior to engaging in activities with higher risk of injury.

4.2 Emicizumab

Emicizumab is a novel bispecific monoclonal antibody which mimics coagulation factor VIII and, therefore, is capable of promoting the activation of FX by FIXa, resulting in downstream haemostasis at the site of bleeding in patients with haemophilia A who have decreased or no circulating levels of FVIII

Indications

Emicizumab is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

Emicizumab is effective in prophylactic treatment among adult and paediatric patients, with or without inhibitors. For patients with severe phenotype haemophilia A without inhibitors, prophylaxis with emicizumab will prevent haemarthrosis, spontaneous, and breakthrough bleeding.

The priority for emicizumab and the WFH in Zambia is as follows:

1. Children under 12 years of age, diagnosed with inhibitors.
2. Patients with haemophilia 12 years and above diagnosed with inhibitors.
3. Children under 12 years of age, without inhibitors based on bleeding patterns

Dosage

The recommended dose is 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by 6 mg/kg once monthly (maintenance dose), administered as a subcutaneous injection.

Currently, administration of Emicizumab will only be done at the University Teaching Hospital- Children's Hospital Haemophilia Treatment Centre (HTC) in Lusaka.

Storage

Opened vials:

- Single use
- Discard any unused solution remaining after administering dose

Unopened vials

- Storage in refrigerator at 2- 8^{o}C in original carton to protect from direct light
- Do not freeze
- Do not shake
- If necessary, unopened vials may be stored at room temperature and then returned to refrigeration; temperature should not exceed 30^{o} C for up to 7 days.

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2. Guidelines for the management of haemophilia, World Federation of Hemophilia (WFH) second edition 2012. www.wfh. org

3. Johnny N Mahlangu and Anne Gilham, 2008. Guidelines for the treatment of Haemophilia in South Africa, SAMJ, Vol 99, No. 2

4. Manuel Carċao(2020 June) WFH guidelines for management of Hemophilia-Prophylaxis. Paper presented at WFH Virtual Summit

CHAPTER FIVE

5. LABORATORY DIAGNOSIS

5.1 Preanalytical Considerations

The correct diagnosis of a bleeding disorder is essential as it determines the appropriate intervention. The diagnosis of bleeding disorders requires a good laboratory service with systems that assure the quality of service, appropriate and well-maintained equipment, good supply of reagents and consumables and competent personnel.

The role of the laboratory for the diagnosis and management of bleeding disorders is critical and entails the following;

- Diagnosis of the disorder
- Classification of the disorder by type and severity
- Monitoring of therapy
- Testing for inhibitors

Tests for coagulation can adversely be affected by processes occurring prior to testing. It is preferred that specimens for coagulation studies are collected by laboratory staff with expertise in performing coagulation studies and close to the laboratory for prompt transportation. However, if this is not possible the following should be taken into consideration when collecting specimens for coagulation studies

- Correct practice of phlebotomy
  - Sample should be collected within one minute of tourniquet application
  - The blood draw should be clean and non-traumatic as tissue damage will activate the coagulation cascade
  - Blood should be collected in a plastic syringe or evacuated blood collection system such as the vacutainer® system
  - If using syringe and needle to collect blood, avoid frothing of blood

- Correct specimen bottle
  - The blood should be collected in citrate tubes (Light blue top)
  - If collecting multiple specimens, the order of blood draw is
    - Plain tube (No additive)
    - Citrate tube (Light blue top)
    - Clot activator gel tube (Red top with gel)
    - Lithium Heparin tube (Green or yellow top)
    - EDTA tube (Purple /Lilac top)
    - Fluoride tube (Grey top)
- Correct volume of blood
  - When using the evacuated system, allow the blood to flow freely into the tube until the blood stops flowing. The systems are designed to collect the correct amount of blood
  - If using a syringe and needle, ensure that the correct volume of blood is added to the tube. The volume of blood to be added may be indicated on the tube; some tubes will have a mark to indicate the level to which the tube ought to be filled.

- Correct specimen handling prior to delivery to the laboratory
  - samples should be delivered within 2hrs of collection
  - Specimens should be stored between 20 and 25°C prior to testing
  - **DO NOT STORE SPECIMENS IN FRIDGE.** (Fridge temperatures induce cold activation which adversely affects the test results)
- Specimen handling in laboratory prior to testing
  - Analysis of specimen should be within 4hrs after collection.
  - Samples that cannot be processed immediately should be spun and the plasma kept frozen at -30°C
  - Frozen plasma specimens should be thawed at 37°C rapidly to avoid formation of cryoprecipitate prior to testing
  - A platelet poor plasma(PPP) is ideal for testing

5.2 Interpretation of screening tests

Screening tests to be done include
1. Full blood count to establish the platelet count
2. Activated partial thromboplastin time (APTT) and Prothrombin time (PT)

See table 3.1 below

Table 3.1 I*nterpretation of screening tests*

Possible diagnosis	PT	APTT	PLT count
Normal	Normal	Normal	Normal
Hemophilia	Normal	Prolonged	Normal
VWD	Normal	Normal or prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

If the screening test results show prolonged APTT as is the case with Haemophilia, perform mixing/ correction studies to establish Factor deficiency or presence of inhibitors.

If there is correction, it indicates factor deficiency. No correction implies presence of inhibitors.

5.3 Classification of bleeding disorders by type

Perform factor deficiency testing to determine the types; Factor VIII deficiency is Hemophilia A; Factor IX deficiency is Hemophilia B and rarely Factor XI deficiency is hemophilia C. Correction studies using the deficient plasma can used to determine the defect. A 50:50 mix of the patient's sample and deficient plasma should be incubated and subjected to APTT test as shown in table 3.2 below:

Table 3.2: Interpretation of mixing/correction studies

Plasma defect	APTT	FVIII deficient Plasma	FIX deficient Plasma	Normal plasma
FVIII	Prolonged	No correction	Correction	Correction
FIX	Prolonged	Correction	No correction	Correction
FXI/FXII	Prolonged	Correction	Correction	Correction
Inhibitors	Prolonged	No correction	No correction	No correction

5.4 Definitive diagnosis and Severity

The severity is determined by performing Factor activity assay of the deficient factor.
Dilution of standard plasma and test samples are mixed with Factor deficient plasma. Comparisons of the APTT correction are made using a logarithmic or logarithm/linear scale graph paper.

Note: This plotting of graph is not necessary if test is done by automated analyser

Table 3.3: Classification of severity

Severity	Clotting factor level
Severe	<1IU/dl (<0.01 IU/ml) or <1% of normal
Moderate	1-5 IU/dl (0.01-0.05 IU/ml)or 1-5 of normal
Mild	5-40IU/dl(0.05-0.40IU/ml) or 5 - <40% of normal

5.5 Monitoring of therapy

This is achieved by continual performance of Factor activity assay

5.6 Testing for inhibitors

Perform mixing studies to screen for inhibitors
Perform Bethesda assay to quantify the inhibitors

Note: For more details on sample handling and procedures for all the tests, refer to the WFH laboratory manual for the diagnosis of hemophilia and other bleeding disorders

Reference

1. World Federation of Hemophilia. *Guidelines for the Management of Hemophilia.* Montreal: World Federation of Hemophilia, http://www1.wfh.org/publications/files/pdf-1472.pdf. (Accessed 31st October 2018)
2. World Federation of Hemophilia. *Diagnosis of Hemophilia and Other Bleeding Disorders A LABORATORY MANUAL Second Edition.* Montreal: World Federation of Hemophilia, http://www1.wfh.org/publications/files/pdf-1283.pdf. (Accessed 31st October 2018)
3. Clinical and Laboratory Standards Institute. Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays: Approved Guideline– 5/ed. CLSI H21-A5, Wayne PA, Clinical and Laboratory Standards Institute 2008.
4. 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. *Semin Thromb Hemost;*35(8):786-93.

CHAPTER SIX

6. HEMOSTATIC AGENTS

6.1 Clotting factor concentrates

Product selection should consider purity of product and viral inactivation/elimination. All products should be stored under optimum conditions as specified by manufacturer. Ideal preparation should have an extended half-life. Products that can be stored under room temperature or higher are better suited for our setting.

FVIII concentrates (plasma derived FVIII; recombinant FVIII; extended half-life FVIII)

FVIII concentrates are the treatment of choice for hemophilia A.

Dosage and administration

- Vials of factor concentrates are available in dosages ranging from approximately 250 IU to 4000IU each.
- In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2 IU/dl. The half-life of FVIII is approximately 8-12 hours.
- The patient's factor level should be measured 15 minutes after the infusion to verify the calculated dose.
- The dose is calculated by multiplying the patient's weight in kilograms by the desired rise in factor level in IU/dl, multiplied by 0.5. Example: 50 kg × 40 (IU/dl desired rise in level) × 0.5 = 1,000 units of FVIII. Refer to Tables 6.1 and 6.2 for suggested factor level and duration of replacement required based on type of hemorrhage.
- FVIII should be infused by slow IV injection at a rate not to exceed 3 ml per minute in adults and 100 units per minute in young children, or as specified in the product information leaflet.
- Subsequent doses should be based on the half-life of FVIII and on the recovery in an individual patient for a particular product.
- It is best to use the entire vial of FVIII once reconstituted.

NOTE: Continuous infusion avoids peaks and troughs and is convenient and should be used where possible. Dose for continuous infusion is adjusted based on frequent factor assays and calculation of clearance. Since FVIII concentrates of very high purity are stable in intravenous solutions for at least 24-48 hours at room temperature with less than 10% loss of potency, continuous infusion for a similar number of hours is possible.

FIX concentrates for treatment of Haemophilia B

FIX concentrates fall into two classes:

- Pure FIX concentrates, which may be plasma derived or recombinant.
- FIX concentrates that also contain factors II, VII, IX, and X, also known as activated prothrombin complex concentrates (aPCC), are only rarely used.

- Whenever possible, the use of pure FIX concentrates is preferable for the treatment of HB as opposed to aPCC.

Dosage and administration

- Vials of FIX concentrates are available in doses ranging from approximately 250 to 2000 units each.
- In the absence of an inhibitor, each unit of FIX per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1 IU/dl.
- The half-life is approximately 18–24 hours with slight variation depending on the product
- The patient's FIX level should be measured approximately 15 minutes after infusion to verify calculated doses.
- Recombinant FIX (rFIX) has a lower recovery than plasma-derived products, such that each unit of FIX per kg body weight infused will raise the FIX activity by approximately 0.8 IU/dl in adults and 0.7 IU/dl in children under 15 years of age.
- Dosage: Patient's weight in kilograms multiplied by the desired rise in factor level in IU/dl. Example: 50 kg × 40 (IU/dl desired rise in level) = 2000 units of plasma-derived FIX. For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 × 1.25) = 2500 units for adults, and 2000 ÷ 0.7 (or 2000 × 1.43)
  = 2860 units for children.

Refer to Tables 9.1 and 9.2 below for suggested factor level and duration of therapy based on type of hemorrhage.

- FIX concentrates should be infused by slow or continuous IV injection at a rate not to exceed a volume of 3 ml per minute in adults and 100 units per minute in young children, or as recommended in the product information leaflet.
- In case of allergic reactions cover patients with a steroid like hydrocortisone or change the brand of clotting factor concentrate.

6.2 Other plasma products

Fresh frozen plasma (FFP)

If avoidable, the use of FFP is not recommended due to safety and quality concerns restrict the use of FFP to HB patients where FIX product concentrates are not available. One ml of fresh frozen plasma contains 1 unit of factor activity. Start with a dose of 15−20 ml/kg.

Cryoprecipitate

Due to concerns about quality and safety, the use of cryoprecipitate should be limited to situations where clotting factor concentrates are not available. Cryoprecipitate contains significant quantities of FVIII (about 3-5 IU/ml), VWF, fibrinogen, and FXIII but not FIX or FXI.A bag of cryoprecipitate made from one unit of FFP (200-250ml) may contain 70–80 units of FVIII in a volume of 30–40 ml.

6.3 Non- factor Therapy

The approved non-factor is Emicizumab for prophylaxis of HA and HA-I (details of dosage is found in chapter 4)

6.4 Adjuvant Therapies

Therapeutic agent	Use	Dose
Desmopressin (DDVAP)	• Treatment of moderate or mild haemophilia A; releases stored factor VIII and vWF into the circulation • Particularly useful in the treatment or prevention of bleeding in carriers of hemophilia. • Contraindicated in individuals with atherosclerotic cardiovascular disease or high blood pressure • May be associated with syndrome of inappropriate ADH secretion so fluid restriction and monitoring of weight, urea and electrolytes is important	• Desmopressin may be administered subcutaneously, intravenously or intranasally • Give 0.3 µg/kg IV in 50 ml of 0.9% saline over >30 minutes • 0.4 µg/kg SC
Tranexemic acid (Cyclokapron)	• Antifibrinolytic – prevents clot breakdown • Indicated for mucous membrane bleeding • Contraindicated in haematuria or with concurrent use of either factor IX complex or activated prothrombin complex concentrate (e.g. FEIBA®). • Can be used in conjunction with recombinant factor VIIa (NovoSeven® • Used for skin or mucosal bleeds (e.g. oral bleeding, epistaxis, menorrhagia). • Useful in dental surgery for control of oral bleeding associated with	• Given PO or by IV or as a mouthwash • 15 - 25 mg/kg/dose PO every 6 or 8 hours

	eruption or shedding of teeth.	
Epsilon aminocaproic acid (EACA)	• Similar to tranexamic acid but is less widely used; has a shorter plasma half-life, is less potent, and is more toxic	• PO or IV every four to six hours up to a maximum of 24 g/day • Can cause reversible myopathy
Fibrin glue	• Has haemostatic, sealing and healing properties • Can be used for dental extraction and to stop bleeding from mucous membranes	

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Table 6.1 PLASMA FACTOR PEAK LEVEL AND DURATION OF ADMINISTRATION (High dosage practice pattern)

HEMOPHILIA A			HEMOPHILIA B	
TYPE OF HEMORRHAGE	DESIRED LEVEL (IU/DL)	DURATION (DAYS)	DESIRED LEVEL (IU/DL)	DURATION (DAYS)
Joint	40–60	1–2, may be longer if response is inadequate	40–60	1–2, may be longer if response is Inadequate
Superficial muscle/no NV compromise (except iliopsoas)	40–60	2–3, sometimes longer if response is inadequate	40–60	2–3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
■ Initial	80–100	1–2	60–80	1–2
■ maintenance	30–60	3–5, sometimes longer as secondary prophylaxis during physiotherapy	30–60	3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
■ initial	80–100	1–7	60–80	1–7
■ maintenance	50	8–21	30	8–21
Throat and neck				
■ initial	80–100	1–7	60–80	1–7
■ maintenance	50	8–14	30	8–14
Gastrointestinal				
■ initial	80–100	7–14	60–80	7–14
■ maintenance	50		30	
Renal	50	3–5	40	3–5
Deep laceration	50	5–7	40	5–7
Surgery (major)				
■ Pre-op	80–100		60–80	
■ Post-op	60–80	1–3	40–60	1–3
	40–60	4–6	30–50	4–6
	30–50	7–14	20–40	7–14
Surgery (minor)				
■ Pre-op	50–80		50–80	
■ Post-op	30–80	1-5, depending on type of procedure	30–80	1–5, depending on type of procedure
■ Pre-op	50–80		50–80	
■ Post-op	30–80	1-5, depending on type of procedure	30–80	1–5, depending on type of procedure

TABLE 6.2: PLASMA FACTOR PEAK LEVEL AND DURATION OF ADMINISTRATION (Lower dose practice pattern)

HEMOPHILIA A			HEMOPHILIA B	
TYPE OF HEMORRHAGE	DESIRED LEVEL (IU/DL)	DURATION (DAYS)	DESIRED LEVEL (IU/DL)	DURATION (DAYS)
Joint	10–20	1–2 may be longer if response is inadequate	10–20	1–2, may be longer if response is inadequate
Superficial muscle/no NV compromise (except iliopsoas)	10–20	2–3, sometimes longer if response is inadequate	10–20	2–3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss				
■ Initial	20–40		15–30	
■ Maintenance	10–20	3–5, sometimes longer as secondary prophylaxis during physiotherapy	10–20	3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head				
■ Initial	50–80	1–3	50–80	1–3
■ Maintenance	30–50			
20–40	4–7			
8–14	30–50			
20–40	4–7			
8–14				
Throat and neck				
■ Initial	30–50	1–3	30–50	1–3
■ Maintenance	10–20	4–7	10–20	4–7
Gastrointestinal				
■ Initial	30–50	1–3	30–50	1–3
■ Maintenance	10–20	4–7	10–20	4–7
Renal	20–40	3–5	15–30	3–5
Deep laceration	20–40	5–7	15–30	5–7
Surgery (major)				
■ Pre-op	60–80		50–70	
■ Post-op	30–40			
20–30				
10–20	1–3			
4–6				
7–14	30–40			
20–30				
10–20	1–3			
4–6				
7–14				
Surgery (minor)				
■ Pre-op	40–80		40–80	
■ Post-op	20–50	1–5, depending on type of procedure	20–50	1–5, depending on type of procedure

References

1. Hemophilia of Georgia. Protocols for the treatment of hemophilia and von willebrand disease. Hemophilia of Georgia, 2012. http://www.hog.org/publications/page/ protocols-for-the-treatment- of-hemophilia-and-vonwillebrand-disease-2 (Accessed June 6 2012).
2. World Federation of Haemophilia, 2012. Guidelines for the management of haemophilia, 2nd edition, *Blackwell publishing Ltd,* DOI: 10.1111/j.1365-2516.2012.02909.
3. Steve Pipe: (2020 June) WFH guidelines for management of Hemophilia-Prophylaxis. Paper presented at WFH Virtual Summit 2020
4. Mahlangu J and Gilham A (2008) Guideline for the treatment of haemophilia in South Africa, *S Afri Med J* 98 (125-140)

CHAPTER SEVEN

7. MANAGEMENT OF SPECIFIC HAEMORRHAGES AND COMPLICATIONS

Bleeding in PLH can occur at different sites resulting in different complications. Each site requires specific management modalities. External bleeds occur in the skin (cuts), in the mouth, lips, tongue or nose (epistaxis). Internal bleeds such as occur in the muscles, joints (knee, ankle, elbow, hip), can result in serious complications such as haemodynamic instability and chronic arthropathies. Haemorrhages such as intracranial bleeds, abdominal cavity bleeds, neck/throat as well as bleeds due to severe trauma can be life-threatening. Management of major bleeding episodes in a patient with inhibitors should be managed in consultation with an HTC.

7.1 Joint bleeds (Haemarthroses)

Commonly affected joints in order of occurrence:

- Knee
- Elbow
- Ankle
- Shoulder
- Wrist
- Hip
- Other joints

Clinical features

- Clinical features include: Tingling sensation or aura at the onset, loss of range of motion, pain, warmth over the joint and swelling of a joint. Some symptoms such as loss of range of motion, swelling and pain at rest worsen as the bleeding progresses.
- A target joint is a joint in which 3 or more bleeds have occurred within a period of 6 months.

Treatment

- **PRICE** protocol can be initiated at home. Involves the following:
  1. **P**rotection. immobilisation of affected limb/joint in a splint until pain resolves.
  2. **R**esting the affected limb. Non-weight bearing.
  3. **I**ce application. Apply pack for 15-20 min every 4 to 6 hours.
  4. **C**ompression. Application of compression bandage to reduce bleeding.
  5. **E**levation of affected limb.
- Administer appropriate dose of factor concentrate
  1. Haemophilia A: 20 - 40 IU/kg FVIII if minor bleed or 40 - 50 IU/kg IV if major bleed given twice a day.
  2. Haemophilia B: 20 - 40 IU/kg FIX if minor bleed or 60 - 80 IU/kg IV if major bleed IV daily.
- **Give analgesia** -paracetamol, or propoxyphene, buprenorphine or tramadol
  - For pain not settling after factor infusion if bleed is major.
- Start rehabilitative exercises under factor cover as soon as symptoms disappear to facilitate return to Pre-bleed structure and function.

  If bleeding does not stop- repeat half loading dose of factors
  - Consider presence of inhibitors

  Arthrocentesis – removal of blood from a joint under aseptic condition
  - should be done under factor level above 30-50IU/dl for 48-72hrs

Indications

1. Tense painful haemarthrosis not improving 24hours of conservative treatment.
2. Evidence of neurovascular compromise in the affected limb
3. To rule out septic arthritis

7.2 Muscle and tissue bleeds

An episode of bleeding into muscle should be confirmed by clinical examination and/ imaging.

Causes include a direct blow, sudden stretch, intra muscular injection or even spontaneous onset

Muscles commonly affected

- Iliopsoas
- Forearm muscles
- Calf muscles
- Quadriceps femoris

Clinical features

- Aching in the affected compartment
- Pain
- Numbness
- Muscle tightness
- Swelling – usually unilateral
- Warm to touch
- Tender
- Bruising
- Altered sensation

Treatment

- Admit to hospital
- Bed rest
- Analgesia – based on severity of pain. (visual analog score)
  -Avoid COX I inhibitors
- Administer FVIII /FIX until symptoms subside
- Monitor response to therapy

Imaging

Ultrasound and or CT/MRI scan

Surgical decompression

Fasciotomy done as a surgical emergency to release compartment syndrome

Physiotherapy

- Start immediately even before pain subsides (PRICE)
- Progress gradually to rehabilitation

Iliopsoas Hemorrhage

- Bleeding into iliopsoas muscle
- May manifest with atypical clinical features
- Poses challenge in diagnosis
- Considered as major bleed

Clinical Features

- Pain: lower abdomen, groin and lower back
- Tenderness on extension of the ipsilateral hip joint
- Paresthesia on the medial aspect of the thigh
- Reduced power in the extensors of ipsilateral knee
- Reduced or loss of patellar reflex

Treatment

- Admit
- Strict bed rest. Do not allow the patient to ambulate with crutches
- Factor concentrate FVIII /FIX
- Physiotherapy -careful, supervised.

Imaging

- Confirm diagnosis with Ultrasound and/or MRI scan
- Monitor size of haematoma with serial ultrasound scans

Differential diagnosis

- Appendicitis
- Septic arthritis of hip joint. Hip joint abducted and externally rotated in septic arthritis.

7.3 Gastrointestinal and abdominal bleeding

Gastrointestinal bleeding or haemorrhage and abdominal bleeding are classified as major bleeding episodes. These bleeds may result into death. Treatment should be instituted immediately by a doctor trained in haemophilia management. Hospitalization is usually required for appropriate urgent factor replacement.

Sites of bleeding

- Anywhere along the gastrointestinal tract from mouth to rectum
- Angiodysplasia (vascular malformations of the GIT)
- Bleeding peptic and duodenal ulcers
- Bleeding haemorrhoids or varices
- Peritoneal

Clinical features depend on severity and site of bleeding

- Melaena stools i.e. altered blood in stool in upper GIT bleeding
- Haematochezia (fresh blood mixed with stool) for lower GIT bleeds
- Haematemesis (vomiting blood) for upper GIT bleeds
- Abdominal pain
- Chronic GIT bleeds may present with features of iron deficiency anaemia

Treatment

- Initial treatment may focus on resuscitation that may include intravenous fluids and blood transfusion.
- The treatment goal is to raise factor level to 80-100% in at least 6 days
- Plasma factor levels should be monitored and maintained
- Haemophilia A: Give 40-50U/kg FVIII 12 hourly intravenously for 1- 6 days.

Continue maintenance treatment to keep FVIII levels above 50% for 7-14 days

- Haemophilia B: Give 60-80U/kg FIX 12 hourly intravenously for 1-6 days. Continue maintenance treatment to keep FIX levels above 30% for 7-14 days.

- Oral Tranexamic acid should be given concomitantly at 1g 8-hourly
- Lower and upper GIT endoscopy may be done under factor cover to establish the cause of the bleed
- Abdominal Ultrasound Scan or CT scan should be done for suspected intra-abdominal bleed.

7.4 Epistaxis

Refers to bleeding from the nose. It can be anterior (most common) or posterior. Epistaxis is classified as a minor bleeding episode.

Common causes include the following

- Arteriovenous malformations
- Nasal polyp
- Allergic and non-allergic rhinitis
- Trauma
- Hypertension
- Drugs e.g. NSAIDs,Warfarin,Clopidogrel
- Spontaneous

Treatment
Can be pharmacological and non-pharmacological

Non-Pharmacological

- Tilting head forward so that any blood will come out of the nares and not down the back of the throat.
- Applying firm pressure to the entire side of the nose that is bleeding for 15 minutes. Pharmacological
- Treatment goal is to raise plasma factor level to 20-40 % with FVIII or FIX concentrate
- Haemophilia A:Give 20-40U/kg FVIII 12 hourly intravenously
- Haemophilia B:Give 20-40U/kg FIX 12 hourly intravenously
- Oral Tranexamic acid should be given concomitantly at 1g 8-hourly 3-8 days
- Aminocaproic acid at 3-5g 6 hourly 3-10 days

If bleeding is persistent or recurrent, ENT consult may be required for rhinoscopy and further management
Treat underlying cause where possible

7.5 Genito- Urinary Bleed

Usually spontaneous, if persistent or recurrent should be investigated further.
Signs and symptoms

- May have renal angle tenderness
- Red or dark urine
- Usually no dysuria or features of urinary tract infection

Treatment

- Increase fluid intake
- Raise plasma factor level to 40 - 50% in haemophilia A and 50% in haemophilia B for 3 -5 days.
- Ensure that there is no clot formation causing urinary tract obstruction.
- Do not use tranexamic acid – it is contraindicated in proximal urinary bleeds.
- Give 20 - 25 IU/kg FVIII twice daily for 3 days or 30 -50 IU/kg FIX intravenously daily for 3 days and then review.
- Increase fluid intake by 2 - 3 liters per day.
- Painless haematuria should be treated with complete bed rest and vigorous hydration (3 litres/m^2 body surface area) for 48 hours.
- Desmopressin should be avoided when hydrating intensively.
- Look for and treat any possible infection with appropriate antibiotics.

7.6 Head injury and central nervous system bleeds

- All CNS bleeds and head injuries are medical emergencies and warrant immediate admission.
- Patient must receive treatment with factor concentrate even before further investigations are undertaken.
- CNS bleeds can be life-threatening or result in permanent neurological damage.

Clinical features

- Headaches, usually persistent despite analgesia
- Nausea, vomiting, neck stiffness and photophobia (features of raised intracranial pressure)
- Visual and hearing impairment, dizziness, loss of balance, ataxia
- Altered mental state (Lethargy, drowsiness, Loss of consciousness, confusion, irritability)
- vertigo, seizures
- Focal neurological deficits (muscle weakness, paralysis.)

Management goals

- Raise factor level to 80 - 100% for haemophilia A and 60 - 80% for haemophilia B for 7 days.
- Maintain plasma factor level at 50% for haemophilia A and 30% for haemophilia B for a further 14 days.

Treatment

- Admit
- administer factor replacement immediately to limit bleeding
- Haemophilia A: give 40 - 50 IU/kg FVIII intravenously 12-hourly for 7 days.
- Haemophilia B: give 60 - 80 IU/kg FIX intravenously daily for 7 days.
- Involve neurosurgical and haematological expertise early.
- Urgent CT or MRI scans after factor replacement
- Anti-epileptic medication to control seizures or as soon as bleed is confirmed even without active seizures.
- Monitor factor level pre- and post-infusion.
- Factor concentrate may be administered as continuous infusion or as bolus injection.

7.7 Oral bleeding

Common sites

- Gingival and buccal mucosa
- Dental caries
- Bitten tongue
- Torn lip.

Clinical features

- Haematemesis
- Cuts or lacerations in the mouth bleeding profusely
- Gingivitis
- Oral infection.

Management goal

- Raise factor plasma level to 20 - 40% with FVIII or FIX concentrate.
- Use adjuvant therapy in addition to factor to stop bleeding.

Treatment

- Haemophilia A: give 20 - 40 IU/kg FVIII 12-hourly intravenously.
- Haemophilia B: give 20 - 40 IU/kg FIX daily intravenously.
- Tranexamic acid solution: give 5 - 10 ml (500 mg/5 ml) 6-hourly, holding in mouth for 2 minutes before swallowing. Tranexamic acid tablets can also be crushed in warm water before swallowing.
- Continue factor infusion and tranexamic acid until bleeding stops.
- May need local measures to stop bleeding.
- Check haemoglobin level if bleeding is excessive and patient symptomatic.

CHAPTER EIGHT

8. COMPLICATIONS

8.1 Musculoskeletal Complications

Synovitis

- Inflammation of synovium following acute haemarthrosis.
- Synovium is inflamed, friable and hyperemic

Clinical features: presents with pain and swelling of joint
Imaging: MRI, ultra sound and x-ray.
Treatment: to stop inflammatory process (COX 2)

- Preserve joint function
- PRICE
- Factor concentrate replacement to prevent recurrent bleeds

Chronic synovitis

- Results from repeated acute haemarthrosis.
- Inflammation of joint synovium for over 3 months.
-
- Characterized by hypertrophy of the synovial membrane and new blood vessel formation.

These vessels are prone to bleeding resulting in worsening synovitis and bleeding.

Clinical features

- Painless joint swelling
- Spontaneous joint bleeds
- Recurrent bleeds not responsive to factor replacement
- Warm to touch
- Atrophy of muscles around the affected joint
- Reduced range of motion

Investigations

- FBC
- Factor VIII/IX assays
- X-ray- periarticular soft tissue swelling
- Ultrasound - synovial thickening
- MRI – synovial thickening and early cartilage degeneration

Treatment

- Prevent bleeds by raising factor levels above 5%
- Physiotherapy
- Functional bracing
- Anti-inflammatory drugs – COX2

Surgical treatment

Deactivating /removal of synovial membrane

Indication – persistent bleeding in chronic synovitis not controlled by other means.

- Synovectomy – open or arthroscopic
  -requires large supply of clotting factor
  - must be performed by experienced team

- considered when less invasive procedures fail

- Radioisotopic synovectomy
  - Procedure of choice
  - Few side effects
  - Done in outpatient setting
  - Single dose of clotting factor
- Chemical synoviorthesis
  -Use sclerosing agents: rifampicin or oxytetracycline chlorhydrate
  -Weekly injections until synovitis is controlled
  - Painful injection.

Administer local anesthesia, oral analgesia and clotting factor before sclerosing agent

Chronic haemophilic arthropathy

Chronic haemophilic arthropathy can develop at any time from the second decade of life (and sometimes earlier), depending on the severity and frequency of bleeding and its treatment.
The process is set in motion by the immediate effects of blood on the articular cartilage during haemarthrosis. It is reinforced by persistent chronic synovitis and recurrent haemarthrosis, resulting in irreversible damage. With advancing cartilage loss, a progressive arthritic condition develops that includes:

- secondary soft tissue contractures
- muscle atrophy
- Angular deformities.

Deformity can be enhanced by contracture following muscle bleeds or neuropathy.

- Loss of motion is common, with flexion contractures causing the most significant functional loss.
- Joint motion and weight bearing can be extremely painful.
- As the joint deteriorates, swelling usually subsides due to progressive fibrosis of the synovium and the capsule.
- If the joint becomes ankylosed, pain may diminish or disappear.

The radiographic features of chronic haemophilic arthropathy depend on the stage of involvement:

- Radiographs will show only late osteochondral changes
- Ultrasound or MRI examination will show early soft tissue and osteochondral changes
- Bone erosions and subchondral bone cysts will develop, causing collapse of articular surfaces, which can lead to angular deformities
- Fibrous or bone ankylosis may be present.

The goals of treatment are to improve joint function, relieve pain and assist the patient to continue or resume normal activities of daily living.

Treatment options for chronic haemophilic arthropathy depend on:

- Stage
- Symptoms
- Impact on patient's lifestyle and functional abilities.

Treatment

- Patients with chronic haemophilic arthropathy should ideally be reviewed by a multidisciplinary team that includes a physiotherapist and a musculoskeletal medical specialist.

- Pain should be controlled with appropriate analgesics. Certain COX-2 inhibitors may be used to relieve arthritic pain (refer to chapter 2 and 6)
- Supervised physiotherapy aiming to preserve muscle strength and functional ability is an important part of management at this stage.
- Secondary prophylaxis may be necessary if recurrent bleeding occurs, and may be timed with physiotherapy to optimise outcomes.

Other conservative management techniques include:

- Serial casting to assist in correcting deformities
- Bracing and orthotics to support painful and unstable joints
- Walking or mobility aids to decrease stress on weight-bearing joints
- Adaptation to home, school or work environment to allow participation in community activities and employment, and to facilitate activities of daily living.

If these conservative measures fail to provide satisfactory relief of pain and improved functioning, surgical intervention may be considered. Surgical procedures, depending on the specific condition needing correction, may include:

- extra-articular soft tissue release to treat contractures
- osteotomy to correct angular deformity
- prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder or elbow)

CHAPTER NINE

9. SURGERY

9.1 Management of patients undergoing surgery and invasive procedures.

May be required for haemophilia-related complications or unrelated disease.

Should be done at or in close consultation with an HTC

Monitoring of clotting factor level and inhibitors should be done before surgery

Type of surgical intervention

- Classify surgical intervention According to perceived risk of bleeding
  1. Minor surgery; endoscopy, skin biopsy lumbar puncture, etc.
  2. Major surgery; laparotomy, arthroplasty, etc.

Preoperative assessment and preparation

- Consultation among surgeon, anesthesiologist, hematologist and blood bank.
- Investigations: FBC, Liver function, kidney function, inhibitor level and factor level.
- Prepare a written treatment plan and communicate with all stakeholders.
- Adequate factor cover before and after surgery.

Management goals

- Raise factor levels to 50-80% for minor surgery and 80-100% in major surgery.
- Maintain factor level at 50% for major surgery for at least 7-14 days after surgery.
- Minimize intraoperative and postoperative blood loss.

Treatment

Hemophilia A: for major surgery give 40-50IU/kg FVIII and minor surgery 20-40IU/kg, 30min before surgery, 6hrs postoperatively and then 12 hourly thereafter.

Hemophilia B: major surgery, give 60-80IU/kg FIX and for minor surgery 20-40IU/kg 30min before surgery. Repeat same dose 6 hours postoperatively and then daily thereafter.

- Factor infusion should continue for 7-14 days after major surgery
- Maintain factor levels above 50% until healing starts.
- Use elastic stockings as DVT prophylaxis in high risk patients
- Use of antibiotics postoperatively is mandatory.
- Patient should receive adequate analgesia

In case of emergency surgery, if factor concentrates are not available adequate blood bank support for plasma concentrates is needed.

9.2 Circumcision

- Surgical removal of the covering of glans penis (foreskin)
- People who commonly conduct this procedure are diverse and include
- Medical practitioner/surgeon
- Allied medical practitioners
- Religious practitioners
- Cultural practitioners
- Ethnic practitioners

Non-medical practitioners of circumcision pose a major risk as they may not adhere to guidelines.

- Techniques are non-standardized and diverse
- Traditional scissors
- Unicirc instrument
- Diathermy knife
- Circumcision would be considered minor surgical procedure. However, in haemophilia, this procedure requires the same degree of due diligence and care as any other major surgery.
- Indication and benefits vs risks must be carefully weighed and balanced. Critical factors to consider before conducting circumcision:
- first principle: do no harm
- Patient factors - Inhibitor risk, venous access and wound care
- Access to replacement clotting factor concentrate
- Experience in haemophilia management
- Capacity and ability to manage complications

Principles of perioperative haemostatic

management Pre-surgery assessments

- Individualised pharmacokinetic assessment
- Inhibitor measurement

Dosing to target FVIII/FIX

- 80-100% day of surgery
- >50% for day 1-3 after surgery
- Treatment may need to go beyond day 5 for patients who continue to bleed and may require further evaluation

Appropriate management of complications

- Effective treatment of bleeding: including factor replacement and adjunct therapies
- Effective treatment of infection: broad spectrum antibiotics
- Effective treatment of pain: certain COX 2 inhibitors and paracetamol

CHAPTER TEN

10. SPECIAL CONSIDERATIONS

10.1 MANAGEMENT OF HAEMOPHILIA CARRIER AND PREGNANCY

Females who are heterozygous for a haemophilia gene mutation are known as carriers. A heterozygous female can be a carrier of haemophilia without having symptoms, as she has another X- chromosome to produce FVIII and FIX. Carrier detection and prenatal diagnosis are important in high risk females with a family history of haemophilia and those with suggestive clinical features
such as heavy menstruation or prolonged bleeding. Carriers can therefore make an informed decision on whether or not they will risk having a baby with haemophilia as they have a 50% chance of having a son with haemophilia or a daughter who is also a carrier.

Management approach

- Confirmation of carrier status by molecular/genetic analysis (where possible)
- Check haemophilia carrier baseline factor level.
- Symptomatic carriers are managed according to severity of symptoms
- May be treated with DDAVP, Tranexamic acid or Factor replacement
- Level of factor should be done to establish bleeding risk before pregnancy or going into labour.
- Symptomatic carriers should wear medical emergency bracelets
- Menorrhagia can be controlled using hormonal, haemostatic or surgical methods

a. Pre-pregnancy

- Provide pre-pregnancy genetic counseling to all carriers
- Establish the mutation/gene abnormality

b. At pregnancy

- Take family and personal bleeding history
- Plan management with obstetrician and haematologist
- Measure factor level at 28 and 34 weeks
- If bleeding do not use DDAVP, use clotting factor instead

c. At delivery

- Plan for vaginal delivery.
- Avoid scalp monitoring.
- Avoid instrumental delivery.
- If labour is prolonged, perform caesarean section – follow major surgery protocol (refer to chapter 5)
- Take blood from umbilical cord for urgent FVIII/FIX assay.
- Avoid heel pricks for coagulation assays.
- FIX assay can be unreliable in a newborn.
- Give the baby oral vitamin K or intravenously if not available. Avoid intramuscular injection.
- Watch for bleeding in mother and child. If either the mother or baby is bleeding excessively, use clotting factor replacement.

d. 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 warranted.
- Factor levels fall to baseline in first week
- Females who are carriers or high -risk can then be managed appropriately for bleeding complications
- Females who are non-carriers or at low risk would be at very low risk of bleeding complications

Prenatal counseling and testing

Females who are shown to be carriers or high risk should be offered genetic counseling when they reach child-bearing age to discuss their risks and options for prenatal testing and pregnancy management .

Genetic testing

- May be done by direct mutation analysis or gene tracking (linked marker) analysis.
- May require blood samples from a number of family members (including unaffected individuals)
- Consult with a genetic centre to determine from which family members samples are required.

10.2 MANAGING PATIENTS WITH INHIBITORS

The most serious current complication of factor replacement therapy for haemophilia patients is the development of Inhibitors. 'Inhibitors' in haemophilia are IgG antibodies that the body produces; they neutralize the procoagulant abilities of replacement factor products and make it more difficult to stop a bleeding episode. Therefore, PwHA that fail to respond clinically to clotting factor therapy (and they have been responsive previously) may have inhibitors. Managing patients with inhibitors is more challenging; it results in more serious bleeding complications, allergic reactions, greater treatment costs and high rates of morbidity and mortality.[15, 16]

Inhibitor occurrence is more likely in people of African descent, in HA more than HB, more so in those with severe deficiency. Up to 33% of patients with severe HA and 1% to 6% of those with HB will develop inhibitors at some point in their lives.[1,2,15] Additionally, there is a high rate of concordance in family members and people who are genetically related. The earlier the age at start of treatment, the less likely the development of inhibitors. Patients that have undergone surgery and receive large amounts of factor replacement over a short period of time are also more susceptible to the development of inhibitors.

Managing patients with inhibitors should be done in consultation with a Haemophilia Treatment Centre (HTC). Confirmation of the presence of inhibitors, and the quantification thereof, is done by measuring inhibitor titres in Bethesda Units (BU) and the Nijmegen modified Bethesda Assay is preferred to the ordinary Bethesda Assay.[3] If a Bethesda Assay cannot be done, the presence of an inhibitor can be verified using APTT-based mixing studies[4] – when a patient's serum is mixed with normal serum, APPT must correct. If it does not, the patient more likely has inhibitors. However this method will not quantitate the activity of the inhibitors. Test results of 5BU or lower are called "low titre" inhibitors whereas test results that are greater than 5BU are called "high titre" inhibitors.

People diagnosed with low titre inhibitors are more likely to have transient titres and more successful inhibitor treatment than those with high titre inhibitors.[5]

Anamnestic response: this is the exaggerated response in inhibitor titres after further exposure to factor concentrates. In "low responders - LR" the titres don't rise much but in "high responders - HR" the titres rise in three to five days before thy fall back to baseline.

When to test for inhibitors

1. When clinical and laboratory response to factor replacement therapy is sub-optimal
2. All patients planned for surgery.[6]
3. Monitor all paediatric patients with severe HA every 6 to 12 months after initial exposure, then annually.
4. Monitor all patients with HA and HB as well as von Willebrands type 3 at least once per year.[7]
5. When recovery assays (APTT) are not as expected
6. All PwH who have been intensively treated with factor replacement therapy for more than 5 days (within 4 weeks of last exposure)
7. PwH switching to a new factor product should be monitored for inhibitor development.[8,9]

Treatment of haemophilia A with inhibitors

The choice of a treatment product should be based on the titre of inhibitor (LR versus HR), records of clinical response to product and site and nature of bleed. From the outset, it is important to determine the objective of treatment; whether it is to stop an active bleed in a patient with inhibitors or to eradicate inhibitors.

- **High-Dose Clotting Factor Concentrates:** PwHA with low titer inhibitors who are bleeding may be treated with higher amounts of factor to neutralise the inhibitor and yet have enough left over to stop the bleeding. Factor VIII is given at a dose 2 to 3 times the normal to achieve haemostasis. If there is poor response or the inhibitor levels rise, treat with bypassing agents.
- **Bypassing Agents:** Bypassing agents are special blood products that are used to treat bleeding episodes for patients with high titer inhibitors. Instead of replacing the missing factor, they go around (or bypass) the factors that are blocked by the inhibitor to help the body form a normal clot. Close monitoring of patients taking bypassing agents is important to ensure that their blood is not clotting too much or clotting in the wrong places in the body. aPCC (FEIBA®): Give at 50 - 100 IU/kg IV 12-hourly for 3 days. Do not exceed a maximum dose of 200 IU/kg and do not give concurrently with antifibrinolytic drugs, because of increased risk of thrombosis rFVIIa (NovoSeven®): Give dose of 90 - 120 µg/kg IV every 2 - 3 hours as bolus or 20 IU/kg/hour as continuous infusion. [10] Sequential by-passing therapy is indicated when conventional single bypass therapy fails. This is done by alternating rFVIIa and aPCC. This must be done in conjuction with an HTC.
- **Non-factor Therapy:** Emicizumab is a product that works by restoring the function of activated factor VIII without being affected by inhibitors, and can be used to treat and prevent bleeding episodes in people with hemophilia A. Emicizumab is given by subcutaneous injection once a week, providing a more desirable alternative route of administration.[11] Ensure to discontinue the administration of aPCC (FEIBA) atleast 24 hours prior to the administration of Emicizumab is initiated. This is because there is increased risk of thrombotic microangiopathy and thromboembolism when aPCC and Emicizumab are co-administered. The recommended dose is 3mg/kg SC once weekly for the first four weeks followed by 1.5mg/kg once weekly (or 3mg/kg once in two weeks or 6mg/kg once a month)[12, 13]. Emicizumab prophylaxis is recommended over rFVIIa in ITI-

refractory or ITI-naïve patients. There are other non-factor therapies still in early phase trials.

- Immune Tolerance Induction (ITI) Therapy: The goal of ITI therapy is to eradicate the inhibitor and to teach the body to accept factor as a normal part of blood again. With ITI therapy, people receive large amounts of factor (100 iu/kg) every day for many weeks or months.[11]
- Immunosuppressive (IS) agents: cyclophosphamide, rituximab and steroids have been used to eradicate inhibitors with varying response rates varying between 33 and 63% according to various case reports and case series studies.15 Randomized trials are required to fully explore the effects of IS agents.

Managing haemophilia B with inhibitors

rFVIIa and aPCC are effective for treatment of an acute bleed in patients with high titre and/or high responder to FIX. Patients receiving aPCC are at risk of anaphylaxis and anamnestic reaction; hence rFVIIa is the preferred bypass agent that does not contain FIX. Although there are no known tolerisation procedures for haemophilia B patients with inhibitors, Plasma-derived FIX may be used with careful monitoring of anaphylactic reactions.

NOTE: Laboratory monitoring of patients during treatment by measuring FVIII or FIX activity (in LR) or by performing thromboelastography (in HR) is ideal. Where this is not possible the performance of APTT-based mixing studies is indicated.

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CHAPTER ELEVEN

11. NURSING CARE, IMMUNISATION AND HOME MANAGEMENT

11.1 NURSING CARE

Planned nursing care is a critical component of managing haemophilia patients.

• A patient with Haemophilia will have prolonged bleeding even from the most innocuous ofinjuries, so care needs to be taken to avoid intramuscular injections unless absolutely necessary.

• Butterfly cannulas are preferred if available for venous access but any small gauge needle from 24G-27G can be used for both adults and children

• No invasive procedures should be done without replacing missing factor. Ensure that pre op procedures or checklists include factor administration for all known haemophilia patients. All procedures that have a bleeding risk must be conducted after prophylactic factor has been provided.

• Apply pressure for 3-5 minutes post venipuncture

• Follow the 'Factor first, treat first and investigate later' principle. For bleeding patients, when in doubt administer factor and investigate later

• Assess for pain and/or swelling. Do this by asking the patient for the location of pain. Inspect and palpate gently to confirm and rate the swelling or pain.

• Assess for range of motion.

• Assess for family coping methods. Look for cues of adaptive and maladaptive coping methods and engage the family and patient. Give information and encourage positive coping and help to alleviate anxiety

11.2 IMMUNISATIONS

• Haemophilia patients, young and old, should receive recommended immunisations.

• Subcutaneous vaccines are generally safer and more acceptable.

• Where necessary, intramuscular vaccines should be given using a small needle such as 24G (or smaller) in a larger muscle.

• It may be necessary to administer factor before immunizing a known Haemophilia patient.

• The best is to schedule vaccination at or around the same time as the factor dose for patients on prophylactic factor therapy.

• After immunization, apply gentle pressure and treat with ice to reduce bleeding

• Always warn about the risk of hematoma

• Provide pain relief; Paracetamol is the drug of choice

11.3 HOME MANAGEMENT

Haemophilia is a chronic and lifelong condition whose management extends beyond hospital care.

Home Therapy

• Home therapy may include administration of factor in the home by the patient or care giver as routine prophylaxis or the management of minor complication such as the sudden development of a minor bleed.

• The patients can be trained to administer factor at home. The training is targeted at care givers and older children and must be as comprehensive as possible and include information on dosing and infection prevention.

• where resources allow training, camps are recommended on an annual basis as fora for enhanced education and psychosocial support

• Give adequate information on recognizing bleeds and other danger signs

- Patients should be reviewed by trained personnel for assessment at least once per quarter if there are no complications
- On demand therapy or review by trained personnel is indicated when there is a complication.
- Teach the caregiver and/or older child to recognize danger signs.

Lower Level Facility Care-

Where there are challenges with the patient ability to either store factor at home or inability to administer it themselves, care can be monitored via a non Haemophilia Treatment Centre including health posts. The facility should;

- Stock and administer factor as required by the patient.
- Assess the patient routinely and in emergency situations
- Refer patients in need of specialized care or laboratory investigation that the facility may not have
- Ensure that the Haemophilia patients are reviewed at least once per quarter by trained personnel if there are no complications but always emphasis is to be made that care is readily available as and when the patient needs it.

Home Visits and Outreach Services

Home visits and outreach activities should be conducted by a team of trained healthcare providers at scheduled intervals. During these visits:

- Patients receive their specific factor dose
- Routine patient Screening
- Physical examination
- Physiotherapy sessions: this must include education on what household tools can be used for home physiotherapy sessions and safe areas within the household
- Counselling of the patient and his family
- Health talks targeting the larger community
- School visits for orientation and introduction of patient to ensure care is extended to all levels of interaction
- Ensure prior permissions and agreement with patients in respect of confidentiality and privacy

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HAEMOPHILIA MEDICAL CARD

Ministry of Health

Haemophilia Foundation Zambia - HFZ

ZACCAF
ZAMBIA CHILDHOOD CANCER FOUNDATION

Passport size photo

The bearer of this card has a bleeding disorder.

They may be carrying medication.

Please afford them any assistance that may be necessary.

PERSONAL DETAILS

Name: .....

Address: .....

Cell: .....

E-mail: .....

PERSONAL INFORMATION

Diagnosis: .....

Factor Deficiency/Level: .....

Treatment: .....

Date: .....

After injury, repeat doses may be necessary.