Treatment Guidelines for Haemophilia in South Africa

These guidelines have been compiled by the South African Haemophilia Foundation Medical Advisory Committee (SAHFMAC) to facilitate the appropriate management of people with haemophilia (PWH).

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Note to Healthcare Personnel

This booklet is intended as a guide for healthcare personnel who might not be familiar with haemophilia. Individuals with haemophilia and their physicians should be advised by a Comprehensive Haemophilia Treatment Centre staffed by a multidisciplinary team skilled in the care of this uncommon chronic bleeding disorder.

Parents of patients with severe haemophilia are usually trained in home infusion of the clotting factor when their child is about four years old and self infusion is normally accomplished by 12 - 14 years of age. However, infants and boys with mild haemophilia must rely on a Haemophilia Centre or other medical facility for clotting factor infusions.

Please contact Sr Anne Gillham or Sr Mirriam Mokwena (phone 011-787 6710; or cell phone 083 225 9850 or 082 896 3833) or your nearest Haemophilia Treatment Centre if you have any uncertainty regarding management.

Comprehensive Haemophilia Treatment Centres

TOWN	HOSPITAL	PHYSICIAN	PHONE
Bloemfontein	Universitas	D. Stones	051-405 3293
Cape Town	Red Cross Childrens	P. Hartley	021-658 5297
Durban	King Edward VIII	F. Bassa	031-260 4375
Johannesburg	Johannesburg	R. Schwyzer	011-488 3294
Pietersburg	Pietersburg	C. Sutton	015-297 3163
Port Elizabeth	Livingstone	Mrs A. Agherdien	041-451 3317

Telephone numbers of other Haemophilia Treatment Centres in South Africa are listed on page 17.

HAEMOPHILIA OVERVIEW

Haemophilia is an inherited, x-linked, lifelong bleeding disorder which affects males almost exclusively. Most frequently haemorrhage involves joints or muscles. Bleeding patterns differ with age: infants usually bleed into soft tissues or from the mouth but as the boy grows, characteristic joint bleeding becomes more common.

Haemophilia A is the most common form of haemophilia and is due to a deficiency of clotting factor VIII.

Haemophilia B is due to a deficiency of clotting factor IX.

Severity

Haemophilia is classified as severe, moderate, or mild according to the levels of circulating factor VIII or IX and indicates the expected frequency of bleeding:

- ***Severe:***
  factor VIII or IX < 2%
  Factor VIII or IX replacement is needed several times per month for traumatic or apparently spontaneous bleeding.
- ***Moderate:***
  factor VIII or IX 2 - 5%
  Less frequent bleeding which usually follows trauma, surgery or dental work.
- ***Mild:***
  factor VIII or IX 5 - 25%
  Occasional bleeding, usually only after severe trauma or surgery.

Factor VIII Inhibitors in Haemophilia

Inhibitors may develop in 15 - 35% of persons with haemophilia A but are much less common in haemophilia B.

Risk factors for the development of inhibitors:

- severe haemophilia
- family history of inhibitor development
- more frequent in black patients

If a child is going to develop an inhibitor, this usually happens within a few months after starting factor VIII replacement therapy.

Inhibitors titres are measured in Bethesda units (BU)

Low Responders: titre remains below 5 BU

High Responders: titre above 5 - 10 BU. The level may increase markedly and rapidly after factor VIII infusion (may have rapid anamnestic response in 3 days)

Rules for Inhibitor Management

1. **Monitor all patients every 3 - 6 months for the development of inhibitors. This is particularly important and should be done more frequently in newly diagnosed black children with severe haemophilia A, who are at greater risk.**

2. **Never undertake a surgical procedure or joint aspiration in a person with haemophilia without checking for inhibitors.**

3. **If there is no response to appropriate replacement therapy, test for inhibitors.**

4. **Call a Haemophilia Treatment Centre for advice on patient management.**

Refer to page 13 for factor VIII inhibitor management options.

TYPES OF BLEEDING IN HAEMOPHILIA

Major bleeding episodes

- Central nervous system
- Gastrointestinal
- Neck/throat
- Severe injury
- Hip or iliopsoas
- Advanced joint/muscle
- Forearm compartment

Important

- May cause death or crippling. Advice should be sought from a Haemophilia Treatment Centre physician.
- Start appropriate factor replacement urgently. Hospitalisation is usually required to maintain adequate factor levels.
- If the patient has an **inhibitor,** the Haemophilia Treatment Centre must be consulted for major bleeding problems.

Minor bleeding episodes

- Joint (early)
- Muscle/soft tissue
- Mouth/gums
- Epistaxis
- Painless haematuria

Important

- Although considered minor bleeds, complications may occur. If there are uncertainties about medical management, consult a Haemophilia Treatment Centre.
- Treat early to avoid long term complications.

Haemarthrosis

Commonly affected joints

Knees, elbows, ankles, (shoulder, hip and other joint bleeds are rare).

- After one or several haemarthrosis with synovitis, a joint may become 'targeted' for recurrent bleeding and damage.
- These patients should be referred for synovectomy

Symptoms & Signs

- Tingling sensation (early)
- Stiffness
- Pain
- Limited range of motion
- Swelling
- Limp or refusal to use limb

- **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.

Treatment Guidelines

Replace missing factor see:
page 11 haemophilia A
page 12 haemophilia B

Rest the affected joint/limb

- posterior splint
- sling for arm
- no weight bearing

- Treat **early.**
- **Repeat infusions** in 12 to 24 hours.
- Ice packs may reduce bleeding:
  Apply 5 minutes on 10 minutes off.
- No circumferential casting.
- X-ray **not** indicated - only if fracture is suspected.

Muscle & Soft Tissue Bleeding

Dangerous Areas

- Forearm compartment
- Neck/throat
- Iliopsoas/retroperitoneal
- Popliteal

- Aggressive treatment may be indicated. Consult a Haemophilia Treatment Centre for advice.
- Hospitalisation may be required.

Symptoms & Signs

- Muscle tightness (early)
- Pain
- Swelling
- Limited range of motion
- Bruising
- Warmth
- Refusal to use limb (young child)

- **Bruising may be absent with deep muscle bleeding.**
- **Muscle compartment** bleeding (calf, forearm) may cause nerve damage or vascular compromise.
- **Asymmetry** of use or motion in the young child.

Treatment

Replace missing factor refer to:
page 11 haemophilia A
page 12 haemophilia B

Rest affected joint/limb

- posterior splint
- sling
- no weight bearing

- Treat **early.**
- **Repeat infusions** in 12 to 24 hours.
- Ice packs 5 minutes on, 10 minutes off.
- No circumferential casting.

Head Injury - a Medical Emergency

History

Minor head trauma can lead to CNS bleeding.

Unrecognised trauma is common in children.

"Spontaneous" bleeds can occur.

- **Toddlers** and young children are prone to head injury.

Symptoms & Signs

(onset may be delayed)

- Headache
- Vomiting
- Irritability/convulsions
- Lethargy/drowsiness
- Vision disturbance
- Focal neurologic deficits
- Ataxia

Any of these with or without a history of trauma is highly suggestive of CNS bleeding. These are **late** features secondary to mass effect or brain irritation.

NB: Symptoms may mimic a viral infection.

Treatment

1. **Urgent factor replacement** - measure level and maintain above 50%. Refer to:

   page 11 haemophilia A

   page 12 haemophilia B

2. **CT scan of head**
3. **Call a Haemophilia Treatment Centre**

- **If in doubt - treat**
- Factor replacement for possible subarachnoid bleeding is indicated even with a normal CT scan.
- For proven intracranial bleeding treatment is required for 10 -14 days.

Dental / Gum Bleeding / Epistaxis / Tongue

- Bleeding can be profuse
- Swallowing blood:
  vomiting blood
  dark tarry stools
- May need Hb and HCT

- **Torn frenumlum** (upper lip) bleeding is problematic in the young child.
- **Dental** injection or extraction requires prior infusion to raise factor levels.

Treatment

Replace missing factor refer to:

page 11 haemophilia A

page 12 haemophilia B

- Local pressure.
- Ice 5 minutes on, 10 minutes off.
- If tooth extracted use deep silk or Vicryl suture.
- Tranexamic acid may be useful (Refer to page 15).
- Red cell transfusion if necessary.

- Cool, soft, or liquid diet following gum bleeding or dental extraction.

Gastrointestinal Bleeding

Potential emergency

- Bleeding can be profuse
- Blood/coffee-ground emesis
- Dark/tarry stools

- **Abdominal pain -** regard as a bleed until proven otherwise: infuse factor first, then investigate as for all GIT bleeds.

Treatment

- Immediate factor replacement refer to:
  page 11 haemophilia A
  page 12 haemophilia B
- Consult a Haemophilia Treatment Centre.
- Check BP, Hb & HCT.

- Hospitalise to maintain factor level and monitor ongoing blood loss.
- Investigate for site of bleeding.
- May need red cell transfusion.

Genito-urinary Bleed

- Usually spontaneous

- Persistent or recurrent haematuria should be investigated

Signs & Symptoms

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

Treatment

- Increase fluid intake (1 glass/hour)
- Bed rest
- If not resolved in 24 hours treat with factor replacement

- Tranexamic acid is contraindicated

Refer to:
page 11 haemophilia A
Page 12 haemophilia B

- Continue to increase fluids and bed rest for 7 days

TREATMENT OF BLEEDING EPISODES

Factor VIII Treatment Guidelines

Refer to page 16 for the products available in South Africa

- **Always refer to the Haemophilia Treatment Centre physician's instructions**
- **Treatment products may change: always read the package insert**
- **Patients with inhibitors require special treatment**

Factor VIII replacement for Haemophilia A, no inhibitor

Dose depends on bleeding severity

Minor bleed: 15-25 IU/kg

Major bleed: 40 IU/kg

Expected response: 1 IU/kg = 2% rise in factor VIII level

Half life Factor VIII: 8-12 hr

For serious bleeding **factor VIII assay** may be required to monitor the response to the infusion.

If there is no response to appropriate replacement therapy, test for inhibitors.

- **The Haemophilia Treatment Centre** physician chooses the most suitable product for each patient. Please follow these recommendations.
- **Plasma-derived factor VIII** is treated with heat or solvent/detergent to inactivate viruses.
- **Round off** dose to the nearest vial; do not discard excess factor VIII but rather infuse it.
- **Repeat doses** may be required depending upon the severity of bleeding: Always needed for major bleeds every 12 - 24 hours.

Factor IX Treatment Guidelines

Refer to page 16 for the products available in South Africa

- **Always refer to the Haemophilia Treatment Centre physician's instructions**
- **Treatment products may change: always read the package insert**
- **Patients with inhibitors require special treatment**

Factor IX replacement for Haemophilia B, no inhibitor

Dose depends on bleeding severity

Minor bleed: 15-20 IU/kg

Major bleed: 40 IU/kg

Expected response: 1 IU/kg = 1.5% rise in factor IX level

Half life Factor IX: 16-24 hr

For serious bleeding **factor IX assay** may be required to monitor the response to the infusion.

If there is no response appropriate replacement therapy, test for inhibitors.

- **The Haemophilia Treatment Centre** physician chooses the most suitable product for each patient. Please follow these recommendations.
- **Plasma-derived factor IX** concentrates are treated with solvent/ detergent to inactivate viruses.
- **Factor IX Complex [Prothrombin complex concentrate (PCC)]** also contains factors II, VII and X (can reverse the effects of warfarin).
- NB: thrombosis or disseminated intravascular coagulation may occur with frequent or large doses of PCC.

Factor VIII Inhibitor Management Options

Refer to page 16 for the products available in South Africa

1. Acute bleeding episodes

Ice/cold pack - 5 minutes on, 10 minutes off
Immobilise joint with a splint

Low Responder (< 5 BU)

- Give factor VIII at 2 - 3 times the normal dose
- Monitor response clinically

High Responder (> 5 - 10 BU)

- **Activated Prothromibin Complex Concentrate (APCC)**
  Dose: 50 - 100 IU/kg q12 - 24h
  Infuse at 2 IU/kg/h
  Do not exceed a single dose of 200 IU/kg
  - **Do not** use antifibrinolytic drugs (eg. Tranexamic acid) concurrently because of the risk of thromboembolism
- **Recombinant factor VIIa**
  90 μg per kg q2 - 3 h or by continuous infusion (at 20 μg/kg/hr) until clinical improvement. Factor VIIa activates factor X and leads to the formation of a haemostatic plug.
  Tranexamic acid 15 - 25 mg/kg/dose po q6- 8h may be used concurrently with recombinant factor VIIa.

2. Long term

Management - Immune tolerance (IT)

- IT should be initiated at a Haemophilia Treatment Centre.
- Successful therapy (eliminating the inhibitor) may take months. Several regimens are effective - the Dutch regime (25 IU factor VIII/kg 3 times per week) is the most affordable.

Rehabilitation Exercises After Joint or Muscle Bleeds

Rehabilitation after a bleed is essential to maintain strength and range of motion.

When to start rehabilitation exercises?	As soon as the pain is gone.
What exercises?	1. Static excercise. 2. 3 days after resolution of the bleed: free active excercises where the only resistance is gravity. 3. 10 days after the resolution of the bleed: weight bearing excercises to build up muscle strength and bulk.

Hepatitis

- Any PWH may have transfusion acquired infection.
  - Test regularly for HAV, HBV, HCV.
  - Antibody/antigen negative patients should be immunised.
  - Active infection should be excluded in positive patients.
  - Patients with chronic active hepatitis should be referred to a hepatologist for management.

NB: Patients with hepatic dysfunction may have other factor deficiencies (test PI or INR) or a low platelet count.

Treatment Guidelines for Other Products

Do not give aspirin	• Aspirin impairs platelet function which may compound exisiting bleeding disorder.
Tranexamic acid **(Cyclokapron®)** (see package insert) 15-25 mg/kg/dose po q6 or 8 hr.	• Antifibrinolytic - prevents clot breakdown. • Indicated for mucous membrane bleeding. • Contraindicated in haematuria or with concurrent use of factor IX complex, or activated PCC.
DDAVP (Desmopressin) 0.3 μg/kg IV in normal saline over 20-30 minutes 0.4 μg/kg SC Intra nasal DDAVP (nasal spray 150 μg/ml) 1 spray per nostril - total dose 300 μg	• Moderate or mild haemophilia A and von Willebrand disease. • Releases stored factor VIII and vWF into circulation. • Less effective with lower baseline factor VIII level. • Tachyphylaxis may occur with repeat doses. NB: Beware of fluid retention and syndrome of inappropriate ADH secreation Monitor weight and baseline U+E Restrict fluid as necessary
Childhood Immunisation Following the injections: press on area > 5 min. Apply ice.	• Avoid other intramuscular injections in haemophilia.

Haemophilia Treatment Products Available in South Africa

Product Name	Company	Contact Details
Factor VIII Products Haemosolvate Factor VIII	Natal Bioproducts Institute	Ronnie Ramphal 031 719 6789 083 229 5339
Virally Inactivated Factor VIII	Western Province Blood Transfusion Service	021 507 6300
Factor IX Complex Products (Prothrombin Complex Concentrates [PCC]) Haemosolvex Factor IX	Natal Bioproducts Institute	Ronnie Ramphal 031 719 6789 083 229 5339
Activated Prothrombin Complex Concentrates (APCC) FEIBA	Adcock Ingram Critical Care	011 494 8000 082 901 1213
Recombinant Factor VIIa NovoSeven	Novo Nordisk	Ntsoaki Motebang 011 807 0794 083 255 8305
DDAVP (Desmopressin) Octastim	Ferring	Elaine Cross 011 392 4651 082 412 6251

HAEMOPHILIA INFORMATION

Haemophilia Treatment Centres and Treaters

Johannesburg		
Dr D Brittain	Johannesburg	082 808 7535
Dr R Schwyzer	Johannesburg	011 488 3294
Dr S Field	Johannesburg	011 761 9000 082 450 4798
Sr B Mbele	Johannesburg	011 488 3294
Sr A Gillham	Johannesburg	011 787 6710 083 225 9850
Sr M Mokwena	Johannesburg	011 787 6710 082 896 3833
Ms F Semple (Physiotherapy)	Johannesburg	011 488 4202
Dr A Krause (Genetics)	Johannesburg	011 489 9219
Dr E Hartman	Chris Hani Baragwanath	011 933 1530
Dr M Patel	Chris Hani Baragwanath	011 933 8000
Cape Town		
Prof P Hartley	Red Cross Children's	021 658 5185
Sr F Douglas	Red Cross Children's	021 658 5185
Dr A Bird	WPBTS	021 507 6300
Dr C du Toit	Groote Schuur	021 404 3084
Prof G Wessels	Tygerberg	021 938 9224
Tygerberg Clinic	Tygerberg	021 938 5648
Sr R Olivier	Red Cross Children's	083 258 6163
Sr AL Cruickshank	Groote Schuur	082 788 1038
Port Elizabeth		
Mrs A Agherdien	Livingstone	041 451 3317 083 244 3634
East London		
Dr P Knox	SA National Blood Service	043 704 8200 082 807 3362
Sr S Sogcwe	Frere	043 709 1111 x 2370 043 763 7568

Haemophilia Treatment Centres and Treaters cont.

Contact person	Hospital	Phone
Durban		
Dr R Thejpal	King Edward VIII	031 260 4375
		082 562 4491
Sr D Nkosi	King Edward VIII	031 360 3680
		083 265 5248
Dr F Bassa	King Edward VIII	031 260 4375
Pretoria		
Dr J C Opperman	Pretoria Academic	012 354 1466
Dr O N Beck	Pretoria Academic	012 319 2449
Sr K Bester	Pretoria Academic	012 354 2251
Mrs E Remmers (Physiotherapy)	Pretoria Academic	012 354 1652
Bloemfontein		
Prof D Stones	Universitas	051 405 3293
		083 444 7233
Dr M Coetzee	Universitas	051 405 3116
		082 550 1968
Sr A Booyens	Universitas	051 405 3069
		082 475 2738
Polokwane		
Dr C Sutton	Polokwane Provincial	015 287 5000
		083 635 0535
Sr P Adolf	Polokwane Provincial	015 287 5000
Dr N Shipalana	Mankweng	015 267 0330
		083 659 0243
Sr F Kgopa	Mankweng	015 267 0330
		082 701 6465

S A Haemophilia Foundations

Foundations	Phone
Johannesburg Sheila Scott	011 849 1733
Durban John Schimper	031 710 6911 (w) 082 800 7812
Port Elizabeth Mark Morris	082 800 9477
Bloemfontein Steve Swanepoel	051 433 2882 (w) 051 436 6954 (h)
Pretoria Marchaine Wright	012 547 0827
Cape Town Bradley Rayner	021 781 0915 (h) 082 882 6420