QUICK REFERENCE
FOR HEALTHCARE PROVIDERS

Management of Haemophilia

Ministry of Health Malaysia

Malaysian Society of Haematology

Malaysian Society of Paediatric Haematology and Oncology

Academy of Medicine Malaysia

KEY MESSAGES

1. Haemophilia is a group of inherited blood disorders in which there is life-long defect in the clotting mechanism. The most common types are haemophilia A (factor VIII deficiency) & haemophilia B (factor IX deficiency). They are inherited as X-linked recessive traits; therefore, males are affected & females are carriers.
2. A positive family history of haemophilia is present in two-third of patients while another one-third may have spontaneous mutation. Cascade screening for haemophilia should be offered to at least first- & second-degree female relatives if the mother of persons with haemophilia (PWH) is a confirmed carrier.
3. Factor replacement therapy, non-pharmacological & adjunctive treatments are essential in preventing joint damage & other potential serious & life-threatening events in haemophilia.
4. The optimal approach to haemophilia treatment is using prophylactic therapy to prevent bleeds & chronic joint damage, hence reducing short- & long-term complications. Prophylaxis should be given to all persons with severe haemophilia even at a low dosage.
5. Acute bleed in haemophilia should be treated with factor replacement therapy as soon as possible, preferably within 2 hours.
6. Radiosynovectomy should be considered in haemophilic synovitis with recurrent bleeding in the target joint that is refractory to intensive treatment with clotting factor concentrates.
7. Screening for inhibitor should be done in all PWH exposed to factor replacement therapy.
8. Immune tolerance induction should be considered in all PWH with inhibitor.
9. Home therapy should be advocated to all PWH. Haemophilia Medication Therapy Adherence Clinic should be made available in all haemophilia treatment centres.
10. Routine dental examination with preventative care should be conducted regularly in PWH. It should be initiated at the time the baby teeth start to erupt.

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Haemophilia.

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
Ministry of Health Malaysia: www.moh.gov.my
Academy of Medicine Malaysia: www.acadmed.org.my
Malaysian Society of Paediatric Haematology and Oncology: www.maspho.org
Malaysian Society of Haematology: www.haematology.org.my

CLINICAL PRACTICE GUIDELINES SECRETARIAT
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CLINICAL PRESENTATION

PWH can present with the following symptoms:

- easy bruising in early childhood
- 'spontaneous' bleeding particularly into the soft tissues, muscles & joints
- excessive bleeding following trauma or surgery

Newborn with haemophilia can present with spontaneous intracranial bleed.

Table 1. Relationship of bleeding severity to clotting factor level in haemophilia

Severity	Clotting factor level	Bleeding manifestations
Severe	<1 IU/dL (<0.01 IU/ml) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge
Moderate	1 - 5 IU/dL (0.01 - 0.05 IU/ml) or 1 - 5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5 - 40 IU/dL (0.05 - 0.40 IU/ml) or 5% to <40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding is rare

DIAGNOSIS

Screening tests for suspected hereditary bleeding disorders include:

• Prothrombin Time (PT) • Activated Partial Thromboplastin Time (APTT) • Platelet count

The interpretation of the screening tests is illustrated in Table 2.

Table 2. Interpretation of screening tests

PT	APTT	Platelet count	Possible diagnosis
Normal	Prolonged	Normal	Haemophilia A or B
Normal	Normal or prolonged	Normal or reduced	Von Willebrand Disease (VWD)
Normal	Normal	Normal or reduced	Platelet defects

If APTT is prolonged & there is positive family history of haemophilia, proceed to perform FVIII or FIX factor assay. Otherwise, mixing study should be done first. Refer to **Table 3**.

Table 3. Interpretation of mixing test

Mixing study results		Interpretation
Immediate	2-hour incubation	
Corrected	Corrected	Factor deficiency
Corrected	Not corrected	Time dependent inhibitor e.g. FVIII inhibitor
Not corrected	Not corrected	Immediately acting inhibitor e.g. Lupus anticoagulant antibody

PROPHYLAXIS

Primary prophylaxis is preferred in PWH & should commence after first large joint bleed, intracranial bleed, severe intramuscular bleed or before age 3 years old, whichever comes first.

Table 4. Prophylactic therapy regimens in haemophilia

Protocol	Dosage
High dose prophylaxis; Malmo protocol	25 - 40 IU/kg 3 times/week for haemophilia A 30 - 50 IU/kg 2 times/week for haemophilia B
Intermediate dose prophylaxis; Utrecht protocol	15 - 25 IU/kg 2 to 3 times/week for haemophilia A 30 - 50 IU/kg 1 or 2 times/week for haemophilia B (after first/second joint bleed or two bleeds per month)
Low dose prophylaxis	10 IU/kg 2 times/week for haemophilia A 20 U/kg once a week for haemophilia B (secondary prophylaxis)

TREATMENT OF BLEEDING EPISODES

The desired factor level is dependent on site & severity, usually it is given until bleeding resolves. Factor replacement should precede investigation & aim to achieve desired factor level as shown in the **Table 5** e.g. 100%=IU/dL for life-threatening bleed in head, neck & gastrointestinal tract.

Table 5. Suggested plasma peak levels & duration of treatment for acute bleeding in specific sites & surgeries*

Type of Haemorrhage	Haemophilia A		Haemophilia B	
	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 neurovascular 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 neurovascular injury, or substantial blood loss				
• Initial • maintenance	80 - 100 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy	60 - 80 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy
Central Nervous System/head				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 21	60 - 80 30	1 - 7 8 - 21
Throat and neck				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 14	60 - 80 30	1 - 7 8 - 14
Gastrointestinal				
• Initial • maintenance	80 - 100 50	7 - 14	60 - 80 30	7 - 14
Renal				
	50	3 - 5	40	3 - 5
Deep laceration				
	50	5 - 7	40	5 - 7
Surgery (major)				
• Pre-op • Post-op	80 - 100 60 - 80 40 - 60 30 - 50	 1 - 3 4 - 6 7 - 14	60 - 80 40 - 60 30 - 50 20 - 40	 1 - 3 4 - 6 7 - 14
Surgery (minor)				
• Pre-op • Post-op	50 - 80 30 - 80	 1 - 5, depending on type of procedure	50 - 80 30 - 80	 1 - 5, depending on type of procedure

*Table is based on country with no resource constraint.

**IU/dL=%

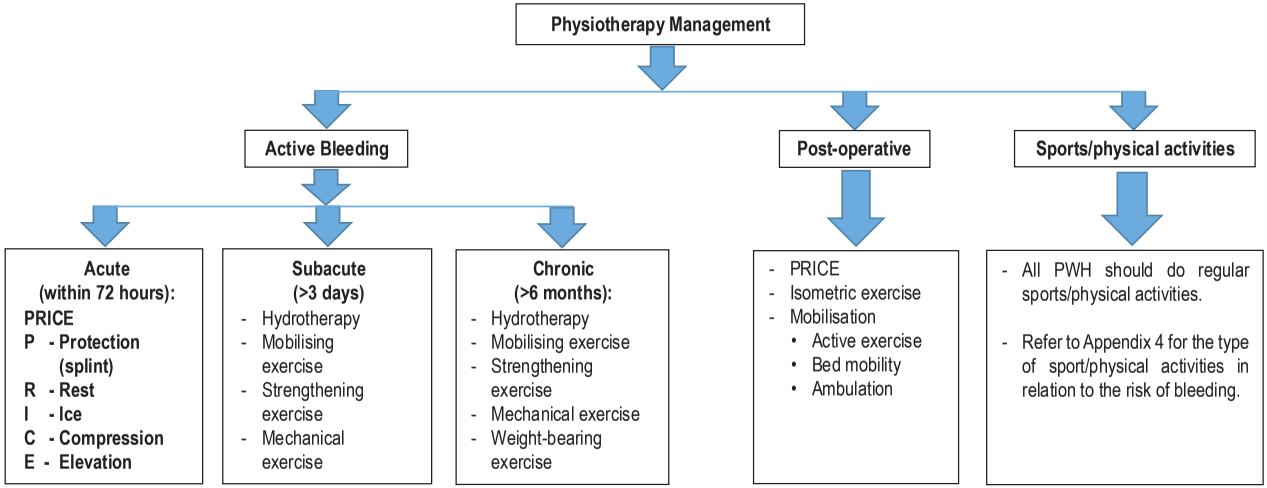
A formula for dose of factor concentrate calculation is as follows:

$$\text{Dose required} = \frac{(\text{desired \% rise - baseline level}) \times (\text{kg body weight})}{K}$$

For severe haemophilia, the baseline level is assumed to be 0%.

K = 2.0 for plasma-derived FVIII (Haemophilia A) or 1.5 for recombinant FVIII
1.0 for plasma-derived FIX (Haemophilia B) or 0.6 for recombinant FIX

PHYSIOTHERAPY MANAGEMENT



- All these activities are preferably carried out within 24-hour of factor infusion.
- Sports & physical fitness are important to maintain good muscle tone to protect the joints from haemophilic-induced injuries, & these activities contribute to improvement in quality of life.
- It is advisable for PWH to use appropriate foot wear which provides good cushioning, arch support & wiggle room for toes to reduce risk of bleeding.
- All haemophilia patients should maintain ideal body weight; overweight is associated with:
  - significant limitation in ROM of the joints
  - increased arthropathic pain & risk of developing target joints
  - increased risk of cardiovascular (CV) diseases which may further damage arthropathic joints

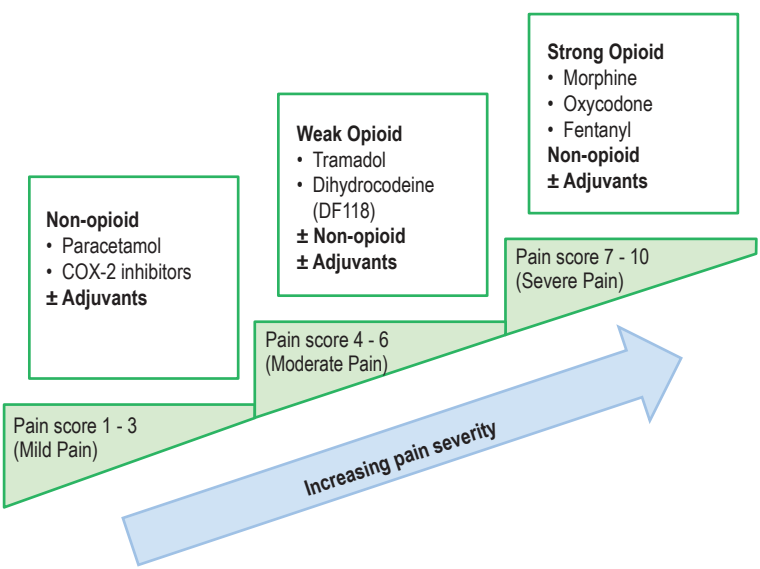
INHIBITORS

The treatment for bleeding in PWH with inhibitor is by using bypassing agents i.e. rFVIIa or aPCC.

- Inhibitors can develop in all patients who have been exposed to factor concentrates
- Presence of inhibitors should be suspected in the following situations:
  - poor response to replacement therapy
  - recovery assays are not as expected
  - increase bleeding episodes despite optimal prophylaxis
- Inhibitor should be screened:
  - at regular interval
    - for children - once every 5 exposure days until 20 exposure days, then every 10 exposure days between 21 & 50 exposure days, then at least twice a year until 150 exposure days
    - for adults with >150 exposure days, every 6 - 12 months
  - after intensive treatment for >5 days, within 4 weeks of the last infusion
  - prior to surgery

ANALGESICS

Pain in PWH may be acute or chronic. Pain assessment can be done using pain scales as recommended by Ministry of Health. Pain management strategies are as follows:



HOME THERAPY

- Requirements for home therapy
  - Initiation of home therapy should only be done after adequate education & training. This is followed by close supervision of its safety & efficacy. Education should include:
    - general knowledge of haemophilia
    - recognition of bleeds & common complications
    - first aid measures
    - dosage calculation, preparation, storage & administration of clotting factor concentrates
    - aseptic techniques & venipuncture techniques (or access of central venous catheter)
    - record keeping
    - proper storage & disposal of needles/sharps, & handling of blood spills

SPECIAL SITUATIONS

- Surgeries for PWH require proper planning & multidisciplinary collaboration.
  - Surgery is scheduled early in the week & early in the day for optimal laboratory & blood bank support.
  - Anaesthesiologist involved has experience in treating patients with bleeding disorders.
  - Pre-operatively, inhibitor screening must be carried out.
  - Adequate monitoring of factor level is required.
  - Adequate quantities of factor concentrates must be available peri-operatively & during the duration of healing &/or rehabilitation.

- For known haemophilia carriers, perinatal care should be undertaken by obstetric unit in close liaison with a haemophilia care centre. A written management plan should include the haemostatic management of the mother & baby.
  - All haemophilia carriers should have FVIII level done during third trimester of pregnancy.
    - If FVIII level is <50 IU/dL, clotting factor replacement is necessary for surgical or invasive procedures during delivery.
  - Gender identification should be determined antenatally in haemophilia carriers.
  - Male newborn is assumed to have haemophilia until proven otherwise.
    - Oral vitamin K should be given instead of IM vitamin K.
    - Hepatitis B & BCG vaccination should be given subcutaneously.
    - Venous sampling for APTT & factor assay should be done as soon as possible to confirm haemophilia.

- All injectable vaccinations for PWH should be given subcutaneously.

- Circumcision in PWH is considered life-threatening & hence it is not obligatory as per Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia Kali Ke-77.

DENTAL CARE

Dental care in PWH:

- comprehensive oral health care should be initiated early within 6 months after the first tooth erupts & no later than 12 months
- routine dental examination & preventive care should be conducted regularly throughout life
- good oral hygiene practice & dietary counselling should be advocated to prevent dental diseases

The type of dental procedures significantly affects the bleeding outcome & can be categorised according to risk of bleeding. The risk of bleeding in dental procedures is shown in **Table 6**.

Table 6. Dental procedures & risk of bleeding

Level of risk	Type of dental procedure
High-risk	• Flap elevation • Teeth extractions • Crown lengthening procedure • Soft tissue biopsy • Scaling &/or root planning • Inferior alveolar nerve block
Low-risk	• Restorative treatment e.g. filling, crown, bridge, etc. • Prosthodontics treatment e.g. denture fabrication, root canal treatment, etc. • Orthodontic treatment

MONITORING

- Monitoring of care in person with haemophilia should include:
  - Annual Bleeding Rate (ABR)
  - inhibitor screening
  - Annual Haemophilia Joint Health Score (HJHS)
  - ultrasound of knee, ankle and elbow when feasible

- ABR is calculated based on the following formula:

$$\text{ABR} = \frac{\text{Number of bleeding events}}{(\text{Number of days receiving treatment}/365.25 \text{ days})}$$

- HJHS is recommended to be done at least once a year.

- Diagnostic imaging provides objective information on the joint status in PWH. In PWH on prophylaxis, imaging of the 6 major joints (knees, ankles & elbows) should be considered at the age of 8 years or before if clinically indicated. When using conventional radiography for assessment, Pettersson Score is recommended.

- Ultrasonography should be part of the assessment when PWH present with musculoskeletal pain as approximately only one-third of the painful musculoskeletal episodes are judged correctly either by the patient or physician.