CHAPTER 3

BLOOD AND BLOOD-FORMING ORGANS

APPROACH TO A CHILD WITH A HAEMATOLOGICAL PROBLEM

Common blood products – dosing, volumes and storage

Red cell products:

Storage: 1–6 °C (refrigerator).

Administration: Use blood administration sets.

- Paediatric red cell concentrate (25–150 mL).
- Paediatric red cell concentrate, leucodepleted (75 mL).
- Packed cells (volume in mL) = 4 x weight x desired increase in haemoglobin.
- Whole blood, leucodepleted (485 mL): used in exchange transfusion; volume to be infused in mL = 6 x weight x deficit.

Platelet products:

Storage: Do not refrigerate, use immediately.

Administration: Use special platelet administration sets.

- Paediatric platelet concentrate, single donor, apheresis, leucodepleted (50–60 mL).
- Platelet concentrate, single donor, apheresis, leucodepleted (100–300 mL).
- Random donor, pooled platelets (200–300 mL).
- Platelet concentrate = 5–10 mL/kg used for ordering but administer the entire volume.

Plasma products:

Storage and administration: Transfuse immediately after reconstitution and issue.

Clotting Factors:

- Fresh frozen plasma (FFP) (75 mL) *(kept in blood bank)*.
  - 15 mL/kg/dose (100 IU/unit).
- Fresh dried plasma (FDP) (260 mL) *(can be kept on the shelf).*
  - 15 mL/kg/dose (100–160 mL).
- Cryoprecipitate – fibrinogen rich (30 mL).
  - 1 unit/10 kg/dose (150–200 IU/unit).
- Factor VIII concentrate.
  - 25–50 IU/kg/dose (100–500 IU/unit).

- Factor IX concentrate.
  - 40–60 IU/kg/dose.

For current prices, see: https://sanbs.org.za/product-price-list/

3.1 ANAEMIA, APLASTIC

D61.0

DESCRIPTION

Pancytopenia caused by bone marrow failure with a hypocellular bone marrow without infiltration or fibrosis. May be acquired or inherited. Inherited bone marrow failure syndromes include Fanconi anaemia, which has specific associated phenotypic features and chromosomal abnormalities.

DIAGNOSTIC CRITERIA

Clinical

» Pallor, petechiae, purpura, bleeding, with frequent and/or severe infections.
» Phenotypic features of Fanconi anaemia include:
  > Café-au-lait spots (skin pigmentary changes),
  > short stature and dysmorphic faces,
  > hypoplasia/absence of the radius, fingerised thumb,
  > microcephaly, small eyes, hyperreflexia,
  > renal tract and cardiac abnormalities,
  > hypogonadism.

Investigations

» Full blood count shows anaemia (may be macrocytic), leucopenia and thrombocytopenia.
» Hypoplastic bone marrow.

GENERAL AND SUPPORTIVE MEASURES

Limit the liberal use of blood products as the patient may become sensitised and jeopardise future bone marrow transplant prospects.
Avoid contact sport.

MEDICINE TREATMENT

For symptomatic anaemia (usually Hb < 7 g/dL):

- Packed red cells, IV, 4 x weight x deficit in haemoglobin.
  - Use leukocyte depleted products.

For active bleeding:

- Platelets, IV, 20 mL/kg, administered immediately and rapidly over 15–30 minutes through a platelet giving set.

- If transplant is a possibility, use single donor, apheresis platelets rather than pooled, random donor platelets; preferably group specific.
- Use the whole unit, unless the volume compromises cardiovascular status, (particularly in neonates). Apheresis platelets are available in paediatric volumes.

For fever (T > 38 ºC), manage as febrile neutropenia in discussion with appropriate specialist/subspecialist with broad-spectrum antibiotics.
Take blood cultures first.

For febrile neutropenia:
Within 48 hours of admission:
- Ceftriaxone, IV, 50 mg/kg twice daily.

PLUS
- Gentamicin, IV, 6 mg/kg daily.

After 48 hours from admission:
Consider local antimicrobial resistance patterns when treating empirically, however, if this is not known then:
- Piperacillin-tazobactam, IV, 100 mg/kg 8 hourly.

Antibiotic adjustment based on microbiology results.

REFERRAL
» All cases of suspected aplastic anaemia.
» Stabilise patient before transport with blood and/or platelet transfusions, if necessary, after consultation with a paediatrician or paediatric haematologist.
» All cases for consideration for bone marrow transplant or immunosuppressive therapy in the case of acquired aplastic anaemia.

3.2 ANAEMIA, HAEMOLYTIC
D55–59

DESCRIPTION
Anaemia caused by excessive destruction of red blood cells.
Destruction may be due to:
» Corpuscular defects:
  > abnormalities of the cell membrane (e.g. hereditary spherocytosis),
  > enzyme abnormalities (e.g. G6PD deficiency), or
  > abnormal haemoglobin (e.g. sickle cell anaemia, thalassaemia).
» Extra-corpuscular defects:
  > Autoimmune or isoimmune:
    idiopathic warm- or cold-antibodies,
    infection-triggered, e.g. Mycoplasma pneumoniae,

medicine-related, e.g. penicillin,
secondary to autoimmune disorders, e.g. SLE, juvenile arthritis,
secondary to tumours, e.g. lymphoma, thymoma.

> Non-immune:
secondary to microangiopathy, e.g. haemolytic uraemic syndrome,
infections causing haemolysis, e.g. malaria,
miscellaneous causes, including hypersplenism.

DIAGNOSTIC CRITERIA

Clinical

» Pallor, jaundice, fatigue.
» Splenomegaly.

Investigations (before transfusion)

» Full blood count.
» Evidence of haemolysis:
> anaemia,
> reticulocytosis,
> decreased haptoglobin,
> unconjugated hyperbilirubinaemia,
> increased lactate dehydrogenase (LDH),
> urobilinogen in the urine.
» Direct Coombs test (direct antiglobulin) is positive with autoimmune haemolysis.
» Haemoglobin electrophoresis.
» Renal function is abnormal in haemolytic uraemic syndrome.
» Exclude other autoimmune disorders.
» Consider underlying neoplasms.
» In patients receiving recurrent transfusions (e.g. thalassaemia), monitor ferritin levels 3 monthly and discuss with referral centre if > 1000 ng/mL.

GENERAL AND SUPPORTIVE MEASURES

» After appropriate investigations, transfuse and then discuss with paediatrician or paediatric haematologist.
» Coombs-positive autoimmune haemolytic anaemia may require transfusion with the least incompatible blood (if cross-matching yields no compatible units).
» In G6PD deficiency, avoid medicines known to cause haemolysis (e.g. aspirin, sulphonamides and primaquine) **and** be sure to give the patient a list of such medicines at discharge.

MEDICINE TREATMENT

Warm-antibody autoimmune haemolytic anaemia

Under specialist supervision:

- Prednisone, oral, 2 mg/kg/day until a satisfactory response is obtained.
  - Continue treatment for a minimum of 4 weeks.
  - Taper dose slowly over several weeks while monitoring for relapse.

Chronic haemolytic anaemia

All patients indefinitely:

- Folic acid, oral, 2.5 mg daily between birth and 6 months and 5 mg daily for > 5 kg and/or 6 months to 5 years.

SURGICAL TREATMENT

Splenectomy for hereditary spherocytosis with Hb < 10 g/dL and transfusion dependent, but **only** after 5 years of age and following consultation with a paediatric haematologist.

Pre-splenectomy immunization

Two weeks prior to surgery:

- Pneumococcus conjugate vaccine (PCV)-13, IM, 0.5 mL followed by pneumococcus polysaccharide (PPV)-23, IM, 0.5 mL 8 weeks later.
- Haemophilus influenzae, type B (Hib) booster, IM, 0.5 mL.
- Meningococcal conjugate vaccine (MCV), IM, 0.5 mL.

Post-splenectomy

- Phenoxymethylpenicillin, oral, 12 hourly.
  - If < 5 years: 125 mg.
  - If > 5 years: 250 mg.
  - Give until at least 18 years of age.
- Annual influenza vaccine, IM, 0.5 mL.
- After splenectomy:
  - Pneumococcus conjugate vaccine (PCV)-13, IM, followed by pneumococcus polysaccharide (PPV)-23, IM (a month later).
  - Haemophilus influenzae, type B (Hib) and meningococcal conjugate vaccine (MCV) booster.

Note: For catch-up of routine conjugate pneumococcal vaccination:

- < 12 months of age: 3-dose series.
- 12 months of age and older: 2 doses, 8 weeks apart. (See Primary Healthcare Standard Treatment Guidelines, Chapter 13: Immunisation).

REFERRAL

» Any child with haemolytic anaemia, e.g. thalassaemia, especially those who are transfusion dependent (more than 10 transfusions) to assess for chelation therapy.

» All cases associated with evidence of haemolysis as above should be managed in consultation with a paediatrician or paediatric haematologist.

3.2.1. THALASSAEMIA

D56

DESCRIPTION

Hereditary single gene defect causing abnormal production or translation of beta-globin mRNA, resulting in foetal haemoglobin (HbF) production. Presents with pallor, jaundice, fever, failure to thrive, abdominal distension hepatosplenomegaly, and skeletal changes.

DIAGNOSTIC CRITERIA

Investigations

» Microcytic, hypochromic anaemia.
» Haemoglobin electrophoresis.
» Genetic studies.
» Family screening.

MEDICINE TREATMENT

β-Thalassaemia major – homozygous:

- Regular blood transfusions to maintain Hb between 9.5 and 14 g/dL.

REFERRAL

» All cases for confirmation of diagnosis and a comprehensive care transfusion program.
» For consideration of chelation therapy once ferritin > 1000 ng/mL (generally after having received 20–25 units of PRCs).

3.2.2 ANAEMIA, SICKLE CELL

D57

DESCRIPTION

Haemolytic anaemia due to homozygous inheritance of sickle cell mutation. Patients may experience complications:

» Painful vaso-occlusive crises.
» Haemolytic crises (usually secondary to infection).
» Aplastic crises.
» Thrombotic crises, e.g. acute chest syndrome, priapism or stroke.
» Splenic sequestration.
» Severe infections.

DIAGNOSTIC CRITERIA

Clinical

» Pallor, jaundice, fatigue all of which may worsen abruptly (sequestration crisis, aplastic crisis).
» Features of complications:
  > painful swelling of the hands and feet (dactylitis),

> bone pain, abdominal pain,
> chest pain, fever, dyspnoea (acute chest syndrome),
> convulsions, hemiparesis,
> priapism.

Investigations

» Laboratory features of haemolytic anaemia. See section 3.2: Anaemia, haemolytic.
» Haemoglobin electrophoresis shows an SS pattern (both parents will be AS).

GENERAL AND SUPPORTIVE MEASURES

» Avoid exposure to cold, dehydration and stress.
» Increase fluid intake during painful crises.
» Heat and/or massage for pain.

MEDICINE TREATMENT

For sequestration crisis or aplastic crisis:

- Packed red cells, IV, 15 mL/kg.
  - Do not transfuse Hb > 13 g/dL as this may increase blood viscosity and consequently raise the risk of vasculopathy.

If hypoxic:

- Oxygen, by face mask.

Exchange transfusions may be used to treat severe complications (see referral criteria).

Prophylaxis against infection

Prophylaxis is given to all children because functional asplenia is present by 1–2 years of age.

- Routine vaccinations during infancy.
- Catch up conjugate pneumococcal vaccine:
  - If < 12 months of age: 3-dose series.
  - If 12 months of age and older: 2 doses, 8 weeks apart.
    - Pneumococcal polysaccharide vaccine at 2 years (at least 8 weeks after conjugate vaccine). Repeat vaccination as a booster 5 years after the initial dose.
- Annual influenza vaccination.
- Haemophilus influenzae, type B (Hib) booster, IM, 0.5 mL.
- Meningococcal conjugate vaccine (MCV), IM, 0.5 mL.
- Phenoxymethylpenicillin, oral, 12 hourly.
  - < 5 years: 125 mg
  - > 5 years: 250 mg
  - Give indefinitely.

Treatment

Analgesia as required:

- Paracetamol, oral, 15 mg/kg 6 hourly.

AND

- Ibuprofen, oral, 10 mg/kg 8 hourly.
- Hydroxyurea, oral, 15 mg/kg.
  - Increase by 5 mg/kg every 12 weeks.
  - Maximum dose: 35 mg/kg daily.

Infections

All children with axillary temperature ≥ 38 °C:

- Ceftriaxone, IV, 50–80 mg/kg/dose once daily.

Acute chest syndrome

Consult a paediatrician.

REFERRAL

» All children with sickle cell anaemia should be managed in consultation with a paediatric haematologist or paediatrician.
» All children with severe complications that may benefit from exchange transfusion or intensive care, e.g. stroke, severe vaso-occlusive disease and acute chest syndrome.
» All cases of stroke should be referred for a regular transfusion program.

3.3 ANAEMIA, MEGALOBLASTIC

D53.1

DESCRIPTION

Anaemia caused by a deficiency of folate and/or vitamin B_{12}.

DIAGNOSTIC CRITERIA

Clinical

» Pallor and fatigue.
» History of chronic diarrhoea.

Investigations

» Megaloblastic anaemia: elevated MCV (mean corpuscular volume) and MCH (mean corpuscular haemoglobin).
» Macro-ovalocytes on blood smear, hypersegmentation of neutrophils.
» Decreased serum vitamin B_{12} or red blood cell folate.
» Investigations to identify the reason for folate or vitamin B_{12} deficiency, e.g. malabsorption.
» Pancytopenia in severe cases.
» Actively exclude leukaemia and aplastic anaemia, which may cause macrocytosis.

GENERAL AND SUPPORTIVE MEASURES

» Dietary modifications to ensure adequate intake of folate and vitamin B_{12}.

» Packed red blood cell transfusion for symptomatic anaemia. Try to avoid blood transfusion until all investigations have been done.

MEDICINE TREATMENT

Folic acid deficiency:

- Folic acid, oral, 5 mg daily until haemoglobin returns to normal value for age. Prolonged treatment may be needed for malabsorption states and congenital deficiencies.

Vitamin B_{12} deficiency:

- Vitamin B_{12}, IM, 100 mcg monthly. Should be given together with folate to prevent developmental of subacute combined degeneration of the spinal cord. Prolonged treatment may be needed.

REFERRAL

» All cases of megaloblastic anaemia, except clear nutritional folate deficiency.

3.4 ANAEMIA, IRON DEFICIENCY

D50.9

DESCRIPTION

Iron deficiency is the most common cause of anaemia. The commonest causes of iron deficiency anaemia are poor nutritional intake, excessive milk ingestion and blood loss due to parasites (whipworm and hookworm).

Lower limits of normal haemoglobin:

Age	Hb (g/dL)
Birth	13.5
6 weeks	9.5
3 months	10.0
6–12 months	10.5
12–18 months	10.5
18 months–4 years	11.0
4–7 years	11.0
7–12 years	11.5
12 years and older	12 (F) : 13 (M)

DIAGNOSTIC CRITERIA

Clinical

Symptoms and signs vary with the severity of the deficiency:

» pallor,
» fatigue,
» irritability,
» behavioural and cognitive effects.
» delayed motor development,
» pica,
» soft ejection systolic murmur,

Investigations

» Haemoglobin below normal for age.
» Hypochromic, microcytic anaemia.
» Low MCV (mean corpuscular volume) and MCH (mean corpuscular haemoglobin), increased red cell distribution width.
» Decreased serum iron, ferritin and transferrin saturation.
» Elevated total iron-binding capacity.
» Stool examination to identify intestinal parasites or to confirm occult blood loss.
» Iron studies are not necessary if nutritional iron deficiency is strongly suspected. Document a response to a trial of iron therapy to confirm the diagnosis.

Note:
Chronic infections may also cause microcytic, hypochromic anaemia.
See section 3.5: Anaemia of chronic disorders (infection or disease).

GENERAL AND SUPPORTIVE MEASURES

» Dietary adjustment.
» Counselling.

MEDICINE TREATMENT

Treatment

In the presence of an acute, severe infection, delay initiating iron supplements until the infection resolves.

- Iron (elemental), oral, 3 mg/kg/dose 12 hourly with meals.
  - Follow up monthly.

Elemental iron per preparation

Ferrous gluconate elixir	350 mg/5 mL	40 mg elemental iron per 5 mL	8 mg elemental iron per mL
Ferrous gluconate syrup	250 mg/5 mL	30 mg elemental iron per 5 mL	6 mg elemental iron per mL
Ferrous lactate drops	25 mg/mL	25 mg elemental iron per mL	1 mg elemental iron per 0.04 mL

Ferrous sulphate compound tablets	170 mg	~65 mg elemental iron per tablet	~65 mg elemental iron per tablet

The expected response is an increase in Hb of ≥ 2 g/dL in 3 weeks.
Continue for 3–4 weeks after Hb is normal to replenish body iron stores.
The reticulocyte count will increase if there is a positive response and may be useful where the diagnosis is in doubt, if done within 1–2 weeks after iron therapy is started.

Treat for intestinal helminths
Children 1–2 years of age:
- Mebendazole, oral, 100 mg 12 hourly for 3 days.

Children > 2 years of age:
- Mebendazole, oral, 500 mg as a single dose immediately.

CAUTION
Iron is extremely toxic in overdose, particularly in children.
All medication should be stored out of reach of children.

Prophylaxis
All preterm babies, day 15 to 1 year:
- Iron (elemental), oral, 2 mg/kg daily.
- Multivitamin, drops, oral, 0.3 mL daily for formula fed babies.
- Multivitamin, drops, oral, 0.6 mL daily for breastfed babies.

REFERRAL
» Patients not responding to adequate therapy.
» Patients in whom easily treatable causes for non-response have been excluded, e.g.:
  > non-adherence to therapy,
  > on-going GIT/other blood loss,
  > on-going infection.

3.5 ANAEMIA OF CHRONIC DISORDERS (INFECTION OR DISEASE)
D63

DESCRIPTION
Anaemia caused by chronic infection or disease. This may be due to interference with nutrient supply or suppression of haemopoiesis. Iron may be trapped in the reticuloendothelial system resulting in relative iron deficiency.

Symptomatic anaemia may manifest with tachypnoea, tachycardia not attributable to other causes and heart failure.

DIAGNOSTIC CRITERIA

Clinical

» Pallor, fatigue.
» Features of malnutrition or chronic infection, e.g. TB, HIV, chronic renal failure.
» Autoimmune disease may be present.

Investigations

» Haemoglobin low with usually normocytic, normochromic red cells (may be microcytic).
» TST, chest X-ray and renal function tests.

GENERAL AND SUPPORTIVE MEASURES

» Emphasise a nutritionally balanced diet that is adequate in protein, vitamins and minerals for nutritional rehabilitation.
» Transfuse for symptomatic anaemia only.

MEDICINE TREATMENT

» Treat the underlying cause, e.g. TB infection.
» Defer iron treatment until acute diseases are controlled, then provide extra iron (see above) and multivitamins.

REFERRAL

» All cases with unresolving anaemia and no cause found.

3.6 HAEMOPHILIA A AND B

D66.7/D66.8

DESCRIPTION

Haemophilia A and B are lifelong chronic bleeding disorders caused by a lack of clotting factor VIII and clotting factor IX, due to mutations in the Factor VIII and Factor IX genes respectively. Acute bleeding presentation depends on the severity of the condition (see classification below). Bleeding can occur into any tissue, but intraarticular bleeds are the clinical hallmark of haemophilia.

Haemophilia complications include haemarthrosis that may lead to chronic arthropathy, intracranial haemorrhage, soft tissue and muscle haematomas. In a known person with haemophilia, pain/tingling in a joint suggests early-onset bleeding.

Early consultation and regular follow-up with a haematologist or clinician with expertise in managing such patients is advisable. All patients diagnosed with haemophilia should attend a designated specialised Haemophilia Treatment Centre with a dedicated multi-disciplinary health care team at least annually for adults or six-monthly for paediatric patients. The details of available Haemophilia Treatment Centres can be accessed at: https://haemophilia.org.za/haemophilia-treatment-centres-htcs/. All patients diagnosed with haemophilia should be enrolled in the South African Bleeding Disorders Registry (access relevant co-ordinators at: https://haemophilia.org.za/haemophilia-nurses-office/).

Those eligible for prophylaxis with factor VIII or IX (see below) may receive factor replacement therapy at a healthcare facility twice a week. Home-based care with self-infusion (parent/care-giver administration) of factor VIII or IX is the goal for all patients, if feasible.

Haemophilia severity classification

Class	Clotting factor	Factor level	Signs
Mild	VIII or IX	> 5 – <40%	Occasional bleeds, usually after trauma or surgery
Moderate	VIII or IX	1–5%	Less frequent bleeds than severe; usually post trauma/surgery/dental extraction. Some patients may, however, display a severe bleeding phenotype.
Severe	VIII or IX	< 1%	Spontaneous bleeds, particularly joint and muscle

(Adapted from White et.al. Journal of Thrombosis *and* Haemostasis*. 2001)*[1]

DIAGNOSTIC CRITERIA

Clinical

» Major bleeds:
  - > central nervous system (CNS) - intracranial
  - > severe injury
  - > muscle compartment (e.g. forearm and calf)
  - > gastrointestinal tract
  - > neck/throat (airway)
  - > advanced joint and soft tissue
  - > hip and iliopsoas muscle

» Minor bleeds:
  - > early joint bleed
  - > soft tissue
  - > mouth and gum
  - > muscle
  - > epistaxis
  - > haematuria

» Pain/tingling in a joint of a patient with haemophilia suggests bleeding.

Investigations

Baseline

» Normal white cell count and platelets; may have anaemia due to blood loss or iron deficiency.
» Normal INR
» Prolonged activated partial thromboplastin time (aPTT)
» APTT correction studies
» Factor VIII or IX plasma level < 50%
» HIV, hepatitis B, and hepatitis C testing if status not known

Non-responders to factor replacement or those previously diagnosed with inhibitors

» Inhibitor screen (Bethesda or Nijmegen assays)

GENERAL AND SUPPORTIVE MEASURES

» Patient, family and community education
» Enrolment in the South African Bleeding Disorders registry *(*access relevant co-ordinators at*:* *https://haemophilia.org.za/haemophilia-nurses-office/)*
» Medic Alert bracelet (or similar)
» Dental care (see below for management of tooth extraction)
» Avoid contact sport

Exercise great caution when taking blood specimens (no arterial samples).
Taking blood from femoral veins is contra-indicated.
Do not insert or use central lines unless done as part of life-saving efforts.
Do not aspirate joints.
Avoid IM injections. Avoid aspirin and other NSAIDs.

TREATMENT GUIDELINES

Treatment approaches are divided into two main categories: prophylaxis and on demand (episodic) treatment following a bleed.

Prophylaxis

Prophylaxis aims to prevent the number of bleeds and prevent or delay the development of joint arthropathy and other sequelae. Primary and secondary prophylaxis should be considered in consultation with a Haemophilia Treatment Centre.

In consultation with a Haemophilia Treatment Centre, prophylaxis is sometimes needed in patients presenting with a target joint.

Treatment On Demand (Episodic treatment)

Episodic treatment for bleeding episodes is referred to as on demand therapy (i.e. the use of factor replacement therapy when bleeding occurs).

Home treatment

Haemophilia Treatment Centres promote home treatment of bleeds. Patients or caregivers must be educated on the storage, reconstitution and administration of clotting factor concentrate and provided with a supply of clotting factor concentrate to be kept at home for use in case of a bleed and/or for prophylaxis. Clotting factor concentrate use and bleeding episodes are monitored through an appropriate chart (or bleeding diary), which can be reviewed at consultations and medication collection.

TREATMENT – ACUTE MANAGEMENT OF BLEEDS

For pain (as required):

Refer to Chapter 20: Pain Control

Do not use NSAIDs, including aspirin.

For bleeding episodes

Emergency treatment while awaiting transfer, if indicated.

If serious bleeding in a known patient with haemophilia, and no factor is available:

- Lyophilised plasma (FDP), IV, 20 mL/kg over 20-30 minutes. Lyophilised plasma contains a minimum of 0.4 units/mL of each coagulation factor.

OR

- Fresh frozen plasma (FFP), IV, 10 - 15 mL/kg over 20-30 minutes.

LoE III[2]

Acute joint bleeds – Infuse CFC, intravenous, first (refer to section 3.6.1 or section 3.6.2 for dosing guidance) with the following adjunctive measures:

» Apply ice packs: 5 minutes on and 10 minutes off.
» Rest the affected joint/limb until pain-free and there is no further swelling.
» Avoid weight-bearing.
» Splint. Do not use circumferential casts.
» Elevate the affected limb.
» **Do not** aspirate affected joints.
» Do not request an X-ray of the affected joint unless there is a strong suspicion of a fracture.

Give clotting factor concentrate until the patient is pain-free and the joint's range of motion is normal. Administration should be 12 hourly (for Haemophilia A) for major bleeds but may be daily for minor bleeds.

For mucous membrane bleeds

- Tranexamic acid, oral, 15 - 25 mg/kg/dose 6-8 hourly.
  - Contraindicated in haematuria.

- Use with caution with factor IX complex or factor VIII inhibitor-bypassing agent (FEIBA), preferably only 12 hours after administration of the factor.

For dental extraction/male circumcision/minor surgical procedures
Check that inhibitors are absent.
Admit for the procedure and post-procedure care and observation in a facility with experience in haemophilia management.

Haemophilia A:

- Factor VIII, intravenous, 50 units/kg, immediately before extraction.

AND

- Tranexamic acid, oral, 25 mg/kg/dose 6–8 hourly, starting 2 hours before the procedure and continued for 5 days post-procedure.

Haemophilia B:

- Factor IX/factor IX complex, intravenous, 40 units/kg, immediately before extraction.

Ideally, elective surgery should be performed at a tertiary/quaternary centre in consultation with a clinical haematologist. In emergencies, treat it as a major bleed and consult the local Haemophilia Treatment Centre as soon as feasible.

3.6.1 HAEMOPHILIA A/FACTOR VIII DEFICIENCY (NO INHIBITORS)

D66

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia A (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis:	Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis:	Prophylaxis initiated after joint damage has occurred

- Factor VIII, intravenous 25 units/kg, twice weekly.

Proposed rounded dosing for paediatric patients
The clotting factor should be rounded to the nearest full vial to avoid wastage.

Age in years	Average weight (kgs)	IU required per dose	Rounded dose (IU)	Available products
0 - 1 years	8	200	300	1 x 300IU
1 - 2 years	11	275	300	1 x 300IU
2 - 3 years	13.5	337.5	500	1 x 500IU
3 - 4 years	15.5	387.5	500	1 x 500IU
4 - 5 years	17.5	437.5	500	1 x 500IU
5 - 6 years	19.5	487.5	500	1 x 500IU
6 - 7 years	22	550	600	2 x 300IU
7 - 8 years	24	600	600	2 x 300IU
8 - 9 years	27	675	800	1 x 300IU plus 1 x 500IU
9 - 10 years	30	750	800	1 x 300IU plus 1 x 500IU
10 - 11 years	34	850	1000	2 x 500IU
11 - 12 years	38	950	1000	2 x 500IU
>12 (adults)	50	1250	1300	2 x 500IU plus 1 x 300IU
>12 (adults)	60	1500	1500	3 x 500IU
>12 (adults)	70	1750	1800	3 x 500IU plus 1 x 300IU

TREATMENT ON DEMAND

Minor bleeds:

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor VIII, intravenous, 20 – 40 units/kg
  - If there is evidence of ongoing bleeding after 12 hours, consult with a local haemophilia treatment centre.

Major bleeds:

Advanced muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

- Factor VIII, intravenous, 40 - 50 units/kg.
  - Use all the contents of the appropriate volume ampoule.
  - All of these patients need hospitalisation.
  - Discuss all patients promptly with the local Haemophilia Treatment Centre.

LoE:III[3]

Intracranial bleeds

- Factor VIII, intravenous, 40 – 50 units/kg 6 hourly.

Decrease frequency of dosing if the trough factor level is > 50%, if possible.

3.6.2 HAEMOPHILIA B/FACTOR IX DEFICIENCY (WITH NO INHIBITORS)

D67

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia B (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis:	Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis:	Prophylaxis initiated after joint damage has occurred

- Factor IX, intravenous 25 units/kg, twice weekly.

TREATMENT ON DEMAND

Minor bleeds

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor IX/factor IX complex, intravenous, 50 units/kg immediately as a single dose.
  - If there is evidence of ongoing bleeding after 12 hours, consult the local Haemophilia Treatment Centre.

Major bleeds

Major muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

- Factor IX/factor IX complex, intravenous, 50-80 units/kg.
  - All these patients need hospitalisation.

Discuss all patients promptly with the local Haemophilia Treatment Centre to plan ongoing treatment and factor replacement.

LoE:III[4]

3.6.3 HAEMOPHILIA WITH INHIBITORS

Refer for assessment and planning with a haematologist.

REFERRAL

» All cases with **suspected** or established haemophilia (prolonged aPTT and normal INR), for assessment, genetic counselling and planning of management, to a Haemophilia Treatment Centre.

3.7 VON WILLEBRAND DISEASE

D68.0

DESCRIPTION

Von Willebrand disease is the most common congenital bleeding disorder and is due to reduced amounts or abnormal forms of von Willebrand factor.

DIAGNOSTIC CRITERIA

Clinical

» Recurrent epistaxis, prolonged bleeding from lacerations, easy bruising or gum bleeds, menorrhagia.

Investigations

» Reduction in one or more of the following:
  > von Willebrand factor antigen,
  > ristocetin co-factor or collagen binding activity,
  > factor VIII activity.

GENERAL AND SUPPORTIVE MEASURES

» Apply pressure to the bleeding site.
» For tooth socket bleeds, bite down on a piece of gauze.
» For epistaxis, see Chapter 17: Ear, nose, throat, section 17.4: Epistaxis (nose bleeds).

Avoid aspirin and other NSAIDs.

MEDICINE TREATMENT

For bleeds:

- Factor VIII, (Factor VIII-containing von Willebrand factor).
  - Initial dose: 50 units/kg.

For mucous membrane bleeds:

- Tranexamic acid, oral, 25 mg/kg/dose 6–8 hourly.

For menorrhagia:

- Combined oral contraceptive, low dose.

Also refer to Adult STGs and EML; Chapter 5 Gynaecology, section 5.2 Uterine Bleeding, Abnormal.

REFERRAL

» All suspected cases of von Willebrand disease to a Haemophilia Treatment Centre for diagnostic assessment and treatment.
» Symptomatic thrombocytopenia.

3.8 HAEMORRHAGIC DISEASE OF THE NEWBORN

P53

See section 19.8.1: Haemorrhagic disease of the newborn.

3.9 IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

D69.3

DESCRIPTION

A common bleeding disorder of childhood due to the immune-mediated destruction of platelets.

It occurs most frequently in children aged 2 to 5 years and often follows infection with viruses (including HIV) and medications. Chronic ITP (more than 6 months duration) occurs in 10 to 20% of children with ITP.

Complications are rare, but include severe haemorrhage and bleeding into vital organs.

DIAGNOSTIC CRITERIA

Clinical

» Sudden onset of bruising and bleeding, either spontaneously or after minor trauma, into the skin and mucous membranes and rarely elsewhere in an otherwise well child.
» The lesions may range from pinpoint petechial bleedings to large ecchymoses, and are often increased on pressure points.
» Epistaxis is common.
» Exclude child abuse.
» The presence of the following makes the diagnosis of ITP unlikely:
  > splenomegaly,
  > hepatomegaly,
  > lymphadenopathy,
  > masses,
  > joint swelling,
  > bone pain,
  > rashes present other than petechiae or ecchymoses.

Investigations

» Thrombocytopenia with normal white cell count and differential, and normal haemoglobin and red cell morphology, other than the effects of blood loss. Mean Platelet Volume (MPV) is often increased.
» Normal INR (PT) and partial thromboplastin time (PTT).

» Abundant megakaryocytes on bone marrow aspiration with normal erythroid and myeloid cellularity.
» A normal LDH and uric acid help to rule out leukaemia.
» Indications for bone marrow biopsy/aspiration: Prior to starting steroids, or any other abnormality on FBC or any atypical cells on differential count.
» Test all newly diagnosed cases for HIV.

Follow up patients with a diagnosis of ITP not confirmed with bone marrow aspiration for development of new clinical signs and abnormalities on laboratory investigations.

GENERAL AND SUPPORTIVE MEASURES

» Avoid:
  > platelet transfusions unless bleeds are life-threatening,
  > contact sport, injury and trauma, and
  > dental procedures in the acute phase.
» Reassure patient and family that resolution usually occurs.

MEDICINE TREATMENT

Avoid medication that affects platelet function, e.g. NSAIDs, and aspirin.

Acute ITP

Most cases are self-limiting and will resolve without treatment. Consider such conservative management for mild cases (in discussion with relevant specialist/subspecialist).

Active bleeding:

- Prednisone, oral, 4 mg/kg/dose as a single daily dose for 4 days.
  - Stop after 4 days without tapering dose.

Chronic ITP

Intermittent treatment if platelets $\leq 10 \times 10^9$/L **and** significant bleeding episodes:

- Prednisone, oral, 4 mg/kg/dose as a single daily dose for 4 days.
  - Stop after 4 days without tapering dose.

Acute life-threatening bleeds (e.g. intracranial bleeding): (acute or chronic ITP)

- Methylprednisolone, IV, 30 mg/kg/dose administered over 30–60 minutes as a single daily dose for 3 days.
  - Maximum dose: 1 g.
  - Beware of arrhythmias, hypertension, etc.
  - Check BP daily.

AND

After administration of methylprednisolone:

- Paediatric platelet concentrate, leucodepleted, 5–10 mL/kg over 20 minutes.

Refer to specialist for advice on further management.

SURGICAL TREATMENT

Consider splenectomy in children 5 years and older with chronic ITP for more than one year plus significant bleeding or substantial limitation in activities as a result of the ITP.

Pre-splenectomy

- 2 weeks prior to surgery:
  - PCV-13, IM, 0.5 mL, followed by PPV-23, IM, 0.5 mL 8 weeks later.
  - Hib booster, IM, 0.5 mL.
  - Meningococcal vaccine, IM, 0.5 mL.

Post-splenectomy

- Phenoxymethylpenicillin, oral, 12 hourly.
  - If < 5 years of age: 125 mg.
  - If > 5 years of age: 250 mg.
  - Give indefinitely until at least until 18 years.
- Pneumococcal polysaccharide vaccine. Repeat vaccination as a booster 5 years after the initial dose.
- Annual influenza vaccine.
- Hib and MCV boosters every 5–10 years.
- Catch up conjugate pneumococcal vaccine:
  - If < 12 months of age: 3-dose series.
  - 12 months of age and older: 2 doses, 8 weeks apart.

REFERRAL

» Suspected ITP with unusual features such as splenomegaly or lymphadenopathy.
» ITP complicated by severe haemorrhage, bleeding into vital organs or an intracranial haemorrhage.
» ITP needing surgery.
» ITP that fails to resolve in 6–12 months on adequate treatment (chronic ITP).
» If there is no local capacity to fully investigate the condition.

3.10 THROMBOTIC THROMBOCYTOPENIC PURPURA/ HAEMOLYTIC URAEMIC SYNDROME

M31.1/D59.3

DESCRIPTION

An acute syndrome that presents with diarrhoea/dysentery (although diarrhoea-negative cases are increasingly recognised) with varying

combinations of the following: Non-immune microangiopathic haemolytic anaemia with fragmentation haemolysis (schistocytes), thrombocytopenia often with purpura, acute kidney injury, fever and neurologic abnormalities.

DIAGNOSTIC CRITERIA

Investigations

» HIV testing.
» INR and PTT are normal as compared to DIC where they are abnormal.
» Stool for Shiga toxin producing *E. coli.*
» Blood cultures.
» FBC and smear.
» Urea and electrolytes.

MEDICINE TREATMENT

Specialist initiated

- Fresh frozen plasma (FFP), IV, 30 mL/kg/day over 20-30 minutes in 3–4 doses.

OR

- Freeze dried plasma (FDP), IV, 30 mL/kg/day over 20-30 minutes in 3–4 doses.

For infections

- Ceftriaxone, IV, 50–80 mg/kg once daily.

Need for platelet transfusion to be discuss with a haematologist.
Early dialysis – discuss with a nephrologist.

REFERRAL

All patients – early consultation and transfer to a regional centre.

3.11. DISSEMINATED INTRAVASCULAR COAGULATION

D65

DESCRIPTION

Complication of an underlying condition, e.g. severe sepsis that is characterized by widespread activation of the clotting cascade leading to consumption of platelets and clotting factors with generalized bleeding.

DIAGNOSTIC CRITERIA

Investigations

» Prolonged INR and PTT.
» Thrombocytopenia
» Decreased fibrinogen.
» Increased D-dimers.
» Repeat test for monitoring.

» Identify the cause.

MEDICINE MANAGEMENT

For low fibrinogen:

- Cryoprecipitate, IV, 1 unit/10 kg.

For an abnormal INR or PTT:

- Fresh frozen plasma (FFP) or Freeze dried plasma (FDP), IV, 15 mL/kg over 20-30 minutes.

Active bleeding with low platelets:

- Apheresis platelet transfusion, IV, 5–10 mL/kg over 20 minutes.

No bleeding with low platelets:

- No platelet transfusion.

REFERRAL

All unresponsive cases to a regional hospital.

3.12 VENOUS THROMBO-EMBOLIC DISEASE

I82

DESCRIPTION

An occlusive or non-occlusive thrombus in the venous circulation, with or without pulmonary embolus. Associated risk factors include central venous catheters, venous stasis, endothelial damage and hypercoaguable states, e.g. nephrotic syndrome. Causes include protein C and S deficiency, factor V Leiden and antithrombin III deficiency.

DIAGNOSTIC CRITERIA

Clinical

Depends on the site of thrombosis, may be silent.

» Deep venous thrombosis of an extremity presents with unilateral limb swelling.
» Upper extremity thrombus may present with associated facial and neck oedema.
» Pulmonary embolus presents with sudden onset of shortness of breath and chest pain.
» Cerebral sinus venous thrombosis presents with seizures or other neurological symptoms and signs.
» Renal vein thrombosis presents with haematuria, thrombocytopenia, oliguria and renal failure if bilateral.

Investigations

» Doppler ultrasonography, CT scan or MRI demonstrate thrombosis or embolus.

» D-dimer, antithrombin III, protein C, protein S, factor V Leiden and antiphospholipid antibody testing may reveal underlying thrombophilia.

GENERAL AND SUPPORTIVE MEASURES

» Appropriate fluid restriction and electrolyte management if in renal failure.

If hypoxic:

- Oxygen by face mask.

For acute thrombotic episode:

- Low molecular weight heparin (LMWH), e.g.
  - Enoxaparin sodium, SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin (UFH), IV, administered over 10 minutes as a bolus followed by an initial maintenance dose as a continuous infusion.

	Bolus	Initial maintenance dose
Preterm neonates	25–50 units/kg	15 units/kg/hour
Term neonates	75–100 units/kg	28 units/kg/hour
Children	75–100 units/kg	20 units/kg/hour

Note: Term neonates need a higher maintenance dose per body weight compared with older children.

Target levels

If available, LMWH dosing can be guided by anti-Xa levels 3–4 hours after dose.

For UFH

PTT: 60–85 seconds or 2–3 times the baseline value (if normal for age).
Monitor PTT 4 hours after bolus injection and adjust the continuous IV dose according to the result (see table below).

Nomogram for adjusting UFH dose*

PTT (seconds)	Bolus (units/kg)	Hold infusion (minutes)	Dose change	Repeat PTT (hours)
< 50	50	0	Increase by 20%	4
50–59	0	0	Increase by 10%	4
60–85	0	0	No change.	24
86–95	0	0	Decrease by 10%	4
96–120	0	30	Decrease by 10%	4
> 120	0	60	Decrease by 15%	4

*The sensitivity of the PTT towards UFH depends on the reagent used.

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Maintain PTT 2.5–3.5 times the control.
Discontinue heparin once a therapeutic INR is achieved with warfarin.

AND

- Warfarin, oral, 0.1 mg/kg daily from day 1.
  - Target INR: 2–3.
  - Continue warfarin therapy for 3–6 months if no underlying severe thrombophilia.
  - Inherited thrombophilic conditions may need lifelong therapy.
  - Beware of drug interactions.

Weight	Starting dose of warfarin
10–20 kg	2.5 mg alternate days
20–35 kg	2.5 mg daily
35–50 kg	2.5 mg alternating with 5 mg daily
> 50 kg	5 mg daily

Adjust schedules using combinations of 2.5 mg and 5 mg **or** 5 mg and 7.5 mg **or** 7.5 mg and 10 mg if a standard daily dose does not provide a therapeutic INR. For example: 2.5 mg Monday, Wednesday, Friday and 5 mg Tuesday, Thursday, Saturday and Sunday.

REFERRAL

» All patients to an appropriate centre for diagnostic imaging.
» Long-term management of thrombophilic states should be in consultation with a paediatric haematologist or paediatrician.

3.13 SPECIAL CONSIDERATIONS IN HIV-INFECTED CHILDREN

In addition to the usual causes of blood disorders in childhood, HIV-infected children are at increased risk of developing anaemia, thrombocytopenia and neutropenia secondary to drugs (especially zidovudine in the case of

anaemia), opportunistic infections or neoplasms. They are also at increased risk of thrombo-embolic disease secondary to vasculopathy or the induction of a thrombophilic state.

3.13.1 THROMBOCYTOPENIA

D69.6

DESCRIPTION

Most cases of thrombocytopenia in children with HIV infection are due to immune thrombocytopenic purpura.
Exclude other causes of thrombocytopenia if the diagnosis is made clinically.

DIAGNOSTIC CRITERIA

Clinical

» Bleeding tendency in a child with HIV infection.
» Asymptomatic finding on full blood count.

Investigations

» Thrombocytopenia with normal white cell count and red cell indices, apart from the effects of blood loss.
» Normal INR and partial thromboplastin time (PTT).
» Abundant megakaryocytes on bone marrow aspiration with normal erythroid and myeloid cellularity.
» Indications for bone marrow investigation: Prior to starting steroids or any other abnormality on FBC or any atypical cells on differential count.

GENERAL AND SUPPORTIVE MEASURES

» As for the HIV-uninfected child.
» Avoid:
  > platelet transfusions, unless life-threatening bleeds,
  > contact sport, injury and trauma,
  > dental procedures in acute phase,
  > medications that affect platelet function, e.g. NSAIDs and aspirin.
» Check for interactions with ARTs.

MEDICINE TREATMENT

As for the HIV-uninfected child.

Initiate ART if not already initiated.

Acute ITP

Active bleeding:

- Prednisone, oral, 4 mg/kg/24 hours as a single daily dose for 4 days.

REFERRAL

» All children with refractory symptomatic thrombocytopenia.

References

[1] G C White 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J0; Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 2001 Mar;85(3):560.

[2] South African National Blood Services. The use of blood and blood products in South Africa. 6th Edition, 2023. https://www.wcbs.org.za/wp-content/uploads/2023/11/SANBS-Clinical-Guidelines-Booklet-2023-FA-v1.pdf

[3] Factor VIII: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor VIII: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723

[4] Factor IX: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor IX: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723