NATIONAL GUIDELINE FOR MANAGEMENT OF ANEMIA IN CHILDREN

Ministry of Health

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1. INTRODUCTION

Anemia is a global health issue. One-fourth of the global population is estimated to be anemic, with cases increasing rapidly for women, expectant mothers, young girls, and children younger than age 5. In 2021, 1.92 billion people globally had anemia. This is an increase of 420 million cases over three decades. In 2021, sub-Saharan Africa and South Asia had the most cases.

The objective of this guideline is to provide healthcare professionals with clear and simple recommendations for the diagnosis, treatment and prevention of Anemia in children. Neonatal anemia is not included in this guideline.

Anemia is defined as a reduction of the hemoglobin concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons. “Normal” hemoglobin and hematocrit (packed red cell volume) vary substantially with age and sex (Table: 1 and 2)

Table :1 Variation of Red Blood Cell indices with ages

Variation of Red Blood Cell indices with Age			
AGE	Hb(gm/dl)	RBC (X 100/L	MCV (fl)
Birth	14.9 – 23.7	3.7-6.5	10 0-135
2 months	9.4-13.0	3.1-4.3	84-105
12 months	11.3-14.1	4.1-5.3	71-85
2-6 year	11.5-13.5	3.9-5.3	75-87
6-12 year	11.5-15.5	4.0-5.2	77-95
12-18 yr. girls	12.0-16.0	4.1-5.1	78-95
12-18 yr. boys	13.0-16.0	4.5-5.3	78-95

Table :2 World Health Organization definition of anemia according to age

The World Health Organization (WHO) definition of anemia				
Age	6 months to 5 years	5 to 11 years	12 to 14 years	15 to 19 years
Hemoglobin(g/dl)	<11	11.5	12	Girls :<12, Boys: <13

The threshold for defining anemia is HB or HCT at or below the 2.5th percentile for age and sex based upon reference data from healthy individuals.

2. ETIOLOGY OF ANEMIA

Causes of anemia in children vary based upon age at presentation, sex, and ethnicity.

2.1. Age of the patient

Birth to three months:

- Physiologic anemia of infancy also called the "Physiologic Nadir" is most common.
- Pathologic anemia includes blood loss, immune hemolytic disease (i.e., Rh or ABO incompatibility), congenital infection, twin-twin transfusion, and congenital hemolytic anemia (e.g., hereditary spherocytosis, glucose-6-phosphate dehydrogenase [G6PD] deficiency)
- Anemia of prematurity.

Three to six months:

Anemia detected at three to six months of age suggests a hemoglobinopathy e.g. Thalassemia and sickle cell anemia. Nutritional iron deficiency is an unlikely cause of anemia before the age of six months in term infants.

2.1.1 Toddlers, children, and adolescents

- Acquired causes of anemia are more likely, particularly iron deficiency anemia.
- Screening for iron deficiency anemia is recommended in all children at 9 to 12 months of age. At that age, children who are exclusively breastfed or breastfed without sufficient iron supplementation are at highest risk for iron deficiency.
- In contrast, infants who primarily receive iron-fortified formula during the first year of life are at risk for iron deficiency after transition to cow milk. Therefore, additional laboratory screening should be considered in children with additional risk factors (e.g., excessive cow milk intake in toddlers 12 to 36 months of age, onset of menarche in adolescent females).

2.1.2 Sex of the patient

Some inherited causes of anemia are X-linked (e.g., G6PD deficiency and X-linked sideroblastic anemia) and occur most commonly in males. In post menarchal girls, excessive menstrual bleeding is an important cause of anemia.

2.1.3. Ethnicity

Ethnic background can be helpful in guiding the work-up for hemoglobinopathies and enzymopathies. Thalassemia syndromes are more common in individuals of Mediterranean and Southeast Asian descent. HGB S and C are most commonly seen in individuals of African or Hispanic descent, and Middle Eastern populations.

G6PD deficiency is more common among Sephardic Jewish individuals; Black individuals from sub-Saharan Africa or Brazil; African Americans; and people from Thailand, Sardinia, Greece, South China, and India.

3. ASSESSMENT

3.1. History

Symptoms attributable to anemia –lethargy, tachycardia, and pallor, irritability and poor oral intake. However, because of the body's compensatory abilities, patients with chronic anemia may have few or no symptoms compared with those with acute anemia at comparable hemoglobin (Hb) levels.

Symptoms of hemolysis – Changes in urine color, scleral icterus, or jaundice may indicate the presence of a hemolytic disorder.

Bleeding symptoms –Bleeding from the gastrointestinal tract, including changes in stool color, identification of blood in stools, and history of bowel symptoms. History of severe or recurrent epistaxis. In adolescent girls, menstrual history should be obtained, including duration and amount of bleeding. Severe epistaxis and/or heavy menstrual bleeding should raise suspicion for an underlying bleeding disorder.

Pica - The intense craving for nonfood items, should be assessed given its strong association with iron deficiency. In young children, pica may manifest as craving dirt, rocks, and paper. In adolescents, craving for ice, or pagophagia, may be more common.

Medication history : Past and current particularly those that may cause haemolysis in children with G6PD deficiency e.g. drugs such as fluoroquinolones, dapsone, nitrofurantoin, and sulfonylureas.

Dietary history: Iron intake -with particular attention to iron-rich foods, breast feeding and cow milk intake, vitamin B12 intake, recent fava/broad bean ingestion (may precipitate haemolysis in children with G6PD deficiency)

Family history: Anaemia, jaundice, gallstones or splenomegaly, family history of inflammatory bowel disease, celiac disease, intestinal polyps, colorectal cancer, consanguineous marriage

Medical history: Any history of underlying disease or chronic illness

Developmental history: Developmental delay can be associated with iron deficiency, lead toxicity, vitamin B12/folic acid deficiency, and Fanconi anemia.

3.1.2. Examination

- Poor growth
- Listlessness or fatigue
- Pallor, Pale conjunctivae
- Tachycardia
- Cardiac murmur, Signs of cardiac failure
- Shortness of breath
- Signs of haemolysis (jaundice, scleral icterus, splenomegaly and dark urine.)
- Hepatosplenomegaly (suggestive of malignancy)
- Sign of other nutritional/ multivitamin deficiency

4. INVESTIGATIONS

- Complete Blood Count (CBC) and RBC indices (MCV, MCH, MCHC)
- Blood film/smear
- Reticulocyte count
- Iron profile*
- Hemoglobin electrophoresis*
- Bone marrow examination *
- DNA test *

The CBC, RBC indices, blood smear, and reticulocyte count are used to focus the diagnostic considerations and guide further testing to confirm the etiology of anemia

*If history, physical examination, and other lab investigation suggest, prompt further investigation is required.

5. CLASSIFICATION OF ANAEMIA ACCORDING TO RED BLOOD CELL SIZE (MEAN CELL VOLUME) AND RETICULOCYTE COUNT

Normal MCV: 87 ± 7 Fl

Reference reticulocyte count:

Child/adult: 0.5 to 2%

Infant: 0.5 to 3.1%

Newborn: 2.5 –6.5%

A normal range for red cell distribution width (RDW) is 12.2 to 16.1 percent in females and 11.8 to 14.5 percent in males.

Microcytic anemia — Microcytic anemia is defined as anemia with a **low MCV** (i.e., ≤2.5th percentile for age and sex) (refer to Table 3). The most common causes of microcytic anemia in children are iron deficiency and thalassemia. The red cell distribution width (RDW) can be helpful in differentiating iron deficiency from thalassemia. Anisocytosis (high RDW) is typical of iron deficiency, whereas the RDW is usually within reference range in patients with thalassemia though elevated RDW can occur.

Table:3 Anemia classification; Microcytic Anemia

MICROCYTIC	
Reticulocytes counts*	
Low / inadequate	**High**
Iron deficiency, Thalassemia trait, lead poisoning, Cupper deficiency, sideroblastic anemia, chronic disease	Hemoglobin C and E disorder

Normocytic anemia — Normocytic anemia is defined as anemia with an MCV within reference range (i.e., between the 2.5th and 97.5th percentile for age and sex). Common causes of normocytic anemia include hemolytic anemias, blood loss, infection,

medication, and anemia of chronic disease. Other causes of normocytic anemia include hypothyroidism and chronic kidney disease. Transient erythroblastopenia of childhood is an acquired red cell aplasia that typically presents with a progressive normocytic anemia in otherwise healthy children and is a diagnosis of exclusion. See table 4.

Table: 4 Anemia classification; Normocytic anemia

Normocytic	
Reticulocytes counts	
Low /inadequate	**High**
Chronic disease/ inflammation aplasia, (TEC, Infection, Drugs), Malignancy, Endocrinopathies, Renal failure, Acute bleeding, Hypersplenism, Dyserythropoietic, Anemia II, Hemophagocytic syndrome	Microangiopathy (HUS, DIC, TTP), Membranopathy (Hereditary spherocytosis), Enzymopathy (G6PD deficiencies, PK deficiency), Hemoglobinopathies (HBSS, SC)

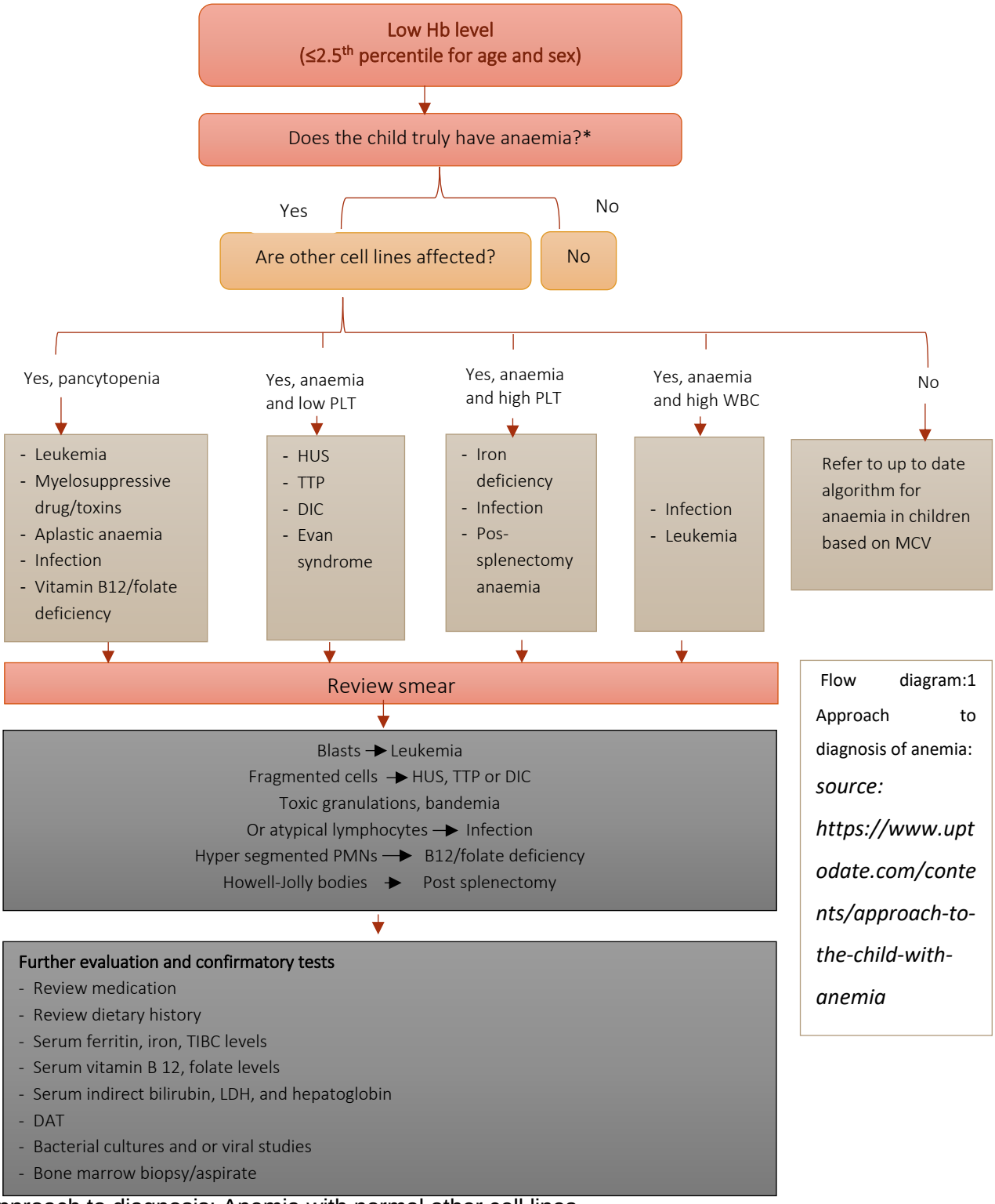
Macrocytic anemia — Macrocytic anemia is defined as anemia with a high MCV (i.e., ≥97.5th percentile for age and sex. Most common causes are folate and vitamin B12 deficiency. See table 5.

Table: 5 Anemia classification; Macrocytic Anemia

Macrocytic Anemia	
Reticulocyte Count	
Low /inadequate	**High**
Folate deficiency, Vitamin B12 deficiency, acquired aplastic anemia, congenital aplastic anemia, drug induced, trisomy 21, Hypothyroidism, Liver disease, Thiamine responsive anemia	Active hemolysis with very elevated reticulocyte count

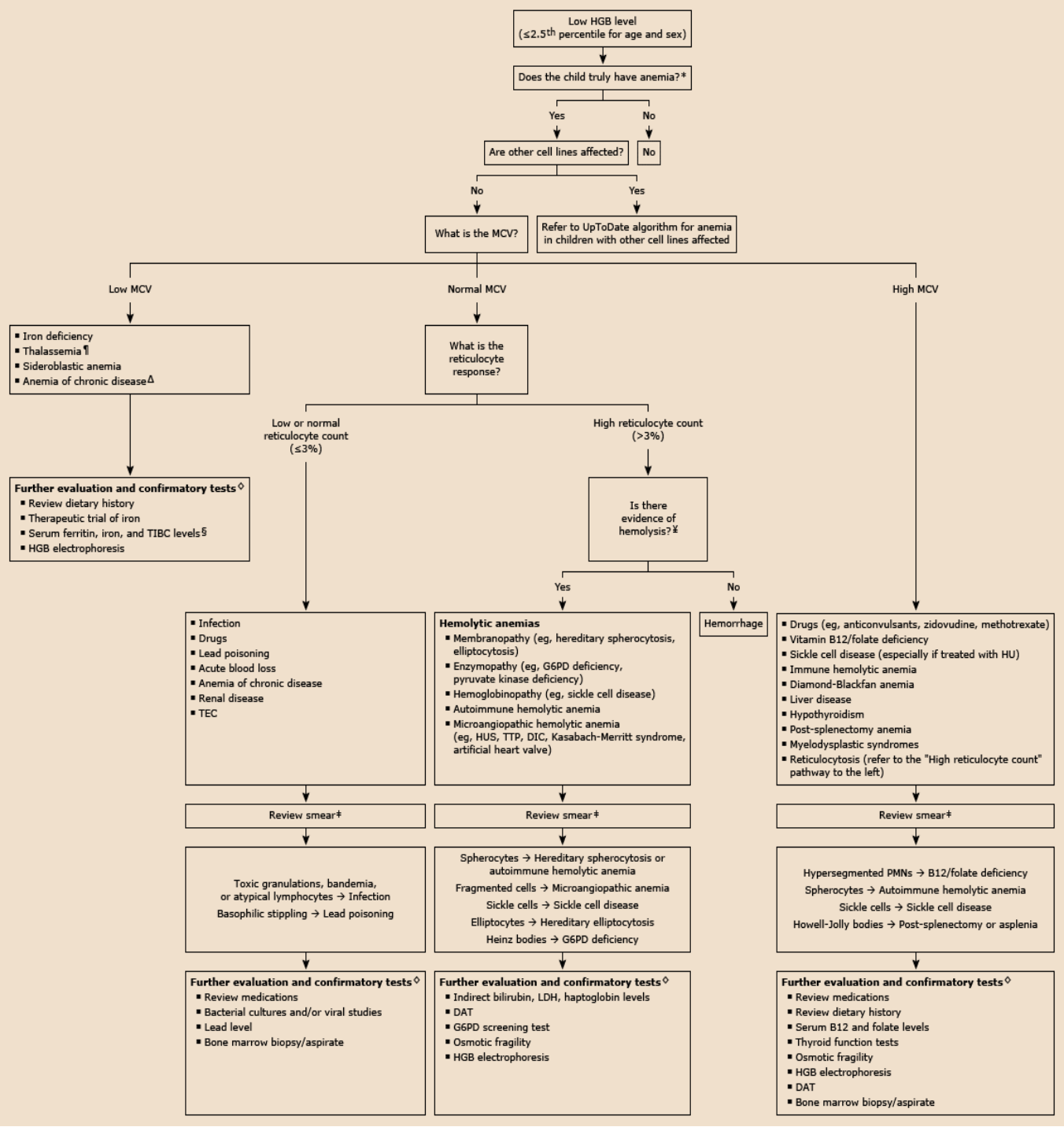
Confirmatory testing — Once the diagnostic possibilities have been narrowed based upon the MCV and reticulocyte count, confirmatory testing is performed. (see below flow diagram 1 and 2)

Approach to diagnosis: Anemia with abnormal other cell lines



Flow diagram:1 Approach to diagnosis of anemia: *source: https://www.uptodate.com/contents/approach-to-the-child-with-anemia*

Approach to diagnosis: Anemia with normal other cell lines



Flow chart: Flow chart: Approach to diagnosis of Anemia: source:

https://www.uptodate.com/contents/approach-to-the-child-with-anemia

6. IRON DEFICIENCY ANEMIA

Iron deficiency is the most common cause of nutritional deficiency in children. Iron deficiency, the most common cause, is responsible for 50% of all anemias. The rate of iron deficiency is higher in developing countries. Iron deficiency anemia develops when body stores of iron drop too low to support normal red blood cells production.

6.1. Causes of Iron Deficiency Anaemia

- **Nutritional**

  It is estimated that only <10% of dietary iron is usually absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the 1 mg/L of iron in cow's and breast milk makes it difficult to maintain body iron. Breastfed infants have an advantage, because they absorb iron 2-3 times more efficiently than infants fed cow's milk; nonetheless, breastfed infants are at risk of developing iron deficiency without regular intake of iron-fortified foods by 6 months of age.

  In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 mo of age and is relatively uncommon thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow's milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight or bottle feeding beyond 12 months of age. Worldwide, **undernutrition** is usually responsible for iron deficiency.

- **Blood loss**

Sources of blood loss, particularly in older children and adolescents, include menstrual losses, recurrent nosebleeds, or intravascular hemolysis with hemoglobinuria. Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to whole cow's milk protein.

- Increase iron demand – Prematurity and growth
- Malabsorption

  Since iron is absorbed in the proximal duodenum with the assistance of gastric acid, gastric bypass procedures or *Helicobacter pylori* infection may interfere with iron absorption. Similarly, inflammation of the bowel from celiac disease and giardiasis may also interfere with iron absorption.

- Worm infestation

  In developing countries, infections with hookworm, *Trichuris trichiura,* and *Plasmodium* often contribute to iron deficiency.

6.2. Clinical and sub-clinical manifestation of Iron deficiency Anemia

Most children with iron-deficiency anemia are asymptomatic and are identified by routine laboratory screening at 9-12 months of age. Normal hemoglobin values vary according to age, gender, race, and method of testing, such as capillary vs venous blood. Pallor is the most recognized clinical sign of iron-deficiency anemia but is not usually visible until the hemoglobin falls to 7-8 g/dL. It is most readily noted as pallor of the palms, palmar creases, nail beds, or conjunctivae. Parents often fail to note the pallor because of the typical slow decline of hemoglobin over time.

Often a visiting friend or relative is the first to notice. Older individuals may report cold intolerance, fatigue, exercise-induced dyspnea, or decreased mental acuity. In mild to moderate iron- deficiency anemia (i.e., hemoglobin levels of 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate and a shift of the

oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted. When the hemoglobin level falls to <5 g/dL, irritability, anorexia, and lethargy develop, and systolic flow murmurs are often heard. If the hemoglobin continues to fall, tachycardia and high output cardiac failure can occur.

Other clinical manifestations include:

- Adverse effects on neurodevelopment, growth, and immunity,
- Reduced exercise capacity and irritability,
- Pica
- Breath-holding spells
- Febrile seizures
- Defects in leukocyte function
- Cerebral vein thrombosis (stroke) is rare presentation

6.3. Laboratory findings

- Complete blood count and Red Cell Indices: low Hb, reduced RBC counts, Low MCV, Low MCH values,
- Blood smear: Microcytic Hypochromic
- Iron study: Low serum Iron, High TIBC, Low serum ferritin

White blood cell (WBC) count is normal, but *thrombocytosis* is often present. Thrombocytopenia is occasionally seen with iron deficiency, potentially confusing the diagnosis with bone marrow failure disorders. Stool for occult blood should be checked to exclude blood loss as the cause of iron deficiency.

A presumptive diagnosis of iron-deficiency anemia is most often made by a complete blood count (CBC) demonstrating a microcytic anemia with a high **RDW****, reduced RBC count, normal WBC count, and normal or elevated platelet count. Other laboratory studies, such as reduced serum ferritin, reduced serum iron, and increased total iron-binding capacity, are not usually necessary unless severe anemia requires a more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy. An increase in

hemoglobin ≥1 g/dL after 1 months of iron therapy is usually the most practical means to establish the diagnosis.

Calculation of **Mentzer Index (MI)** ***(Mean corpuscular volume per red blood cell count) is helpful to differentiate between Iron deficiency anemia and Thalassemia. The Mentzer index of less than 13 suggests Thalassemia and more than 13 suggests Iron deficiency anemia.

***RDW= standard deviation of RBC volume* X100/ *Mean MCV*

****Mentzer Index (MI)=MCV/RBC count*

6.4 Prevention of iron deficiency anaemia

Iron deficiency is best prevented to avoid both its systemic manifestations and the anemia. Nutritional counselling is important for pregnant mother, infant, children, and adolescent girl.

Anemia in pregnancy is associated with increased rates of maternal and perinatal mortality, premature delivery, IUGR, low birth weight, and other adverse outcomes. Pregnant women should receive supplemental iron and folic acid and encourage to take iron containing food.

Delayed (1-3 min) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 sec) puts the infant at risk for iron deficiency.

Breastfeeding should be encouraged, with the addition of supplemental iron at 4 months of age. Infants who are not breastfed should only receive iron-fortified formula (12 mg iron/L) for the 1st yr., and thereafter cow's milk should be limited to <20-24 oz daily. This approach encourages the ingestion of foods richer in iron and prevents blood loss as a result of cow's milk–induced enteropathy.

Routine screening for all children using hemoglobin or hematocrit should be done at age 9-12 month or earlier.

Encourage variety in children's diets to prevent iron deficiency anemia, as sticking to one type of food may limit their iron intake. Food with high iron content are E.g. meat product especially red meat and liver, fish, legumes, dark green leafy vegetables like spinach and broccoli, beets, tofu, dark chocolates, whole grains like oats, dried food like raisins.

6.5. Treatment

Oral Iron medication:

The therapeutic dose should be calculated in terms of elemental iron.

A daily total dose of **3-6 mg/kg of elemental iron** in 1 or 2 doses is adequate, with the higher dose used in more severe cases. The maximum dose is 150-200 mg of elemental iron daily. Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with vitamin C–containing juice, although this timing is usually not critical with a therapeutic dose. Milk or dairy products should be avoided for~1 hour before and 2 hours after each dose to avoid limiting iron absorption. The iron syrup is best given at the back of the mouth with dropper or syringe to avoid discoloration of teeth and gums, followed by rinsing the mouth with water.

Calcium and fiber may decrease the absorption of iron, but this can be overcome with co-administration of vitamin C. Tea is a significant inhibitor of iron absorption. Aside from the unpleasant taste of iron, intolerance to oral iron is uncommon in young children. In contrast, older children and adolescents sometimes have GI complaints that may improve with lower doses of iron. Ferrous sulfate is the gold standard and the preparation of choice. **As there are numerous iron preparations on the market, the pediatrician should check the product label for elemental iron content to avoid under or overdosing**.

In preterm Iron supplement should start at 2 weeks of age. Dose: Elemental iron: 2–4 mg/kg/day (maximum 15 mg).

Iron deficiency is common in exclusive breast feed baby so iron supplement should start from 4 to 6 month of age.

Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron and menstrual control with hormone therapy

6.6 Follow up

If the anemia is mild (Hb ≥ 9 g/dL) the only additional study is to repeat the blood count approximately 1 month after initiating therapy. At this point, the hemoglobin has usually risen by at least 1-2 g/dL and has often normalized.

If the anemia is more severe (Hb < 9 g/dL), earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis, usually within 48-96 hour of instituting treatment. Initial response to therapy is demonstrated by improvement in well-being, reticulocytosis and increase in Hb. The hemoglobin will then begin to increase 0.1-0.4 g/dL/day depending on the severity of the anemia.

Total minimum duration of iron therapy should be of 3 months.

Iron medication should be continued for 2-3 months after blood values normalize to reestablish iron stores. Good follow-up is essential to ensure a response to therapy.

Consider the following if failure to response to oral iron*:*

- Non-compliance
- Inadequate iron dosage

- Unrecognized blood loss
- Impaired GI absorption
- Incorrect diagnosis

Rare conditions e.g. IRIDA (Iron Resistant Iron Deficiency Anaemia- these patients are resistant to oral/ IM iron, may partially respond to parenteral iron.

6.7 Blood transfusion

Generally, NOT required in chronic Iron Deficiency Anaemia unless patient is in overt cardiac decompensation, severely symptomatic (e.g. FTT, poor weight gain).

In patients with chronic anaemia, it is usually safe to plan the transfusion the next morning (during working hours) and take necessary blood investigations prior to transfusion (e.g. FBP, Hb analysis, HIV etc.)

In severe anaemia (Hb < 4 g/dL) low volume RBC cells (< 5mls/kg) is preferred. It is necessary to transfuse slowly over 4-6 hours with IV Frusemide (1mg/kg) midway.

7. THALASSEMIA

Thalassemia refers to a group of genetic disorders of globin-chain production in which there is an imbalance between the α-globin and β-globin chain production. 3% of the world's population carries alleles for β-thalassemia, and in Southeast Asia 5–10% of the population carry alleles for α-thalassemia. 18% of Maldivian population are carrier for beta thalassemia.

β^0-thalassemia refers to the absence of production of the β-globin. When patients are homozygous for the β^0-thalassemia gene, they cannot make any normal β-globin chains (HbA). Also known as β-thalassemia major, or transfusion-dependent thalassemia.

β^+-thalassemia indicates a mutation that makes decreased amounts of normal β-globin (HbA). It is less severe than β^0-thalassemia syndromes.

β-thalassemia intermedia (or non–transfusion dependent) is a clinical diagnosis of a patient with a less severe clinical phenotype that usually does not require regular transfusion therapy in childhood.

In **α-thalassemia**, there is an absence or reduction in α-globin production usually due to deletions of α-globin genes. Normal individuals have 4 α-globin genes; the more genes affected, the more severe the disease. The deletion of 2 α-globin genes results in **α-thalassemia trait**. The deletion of 3 α-globin genes leads to the diagnosis of **HbH disease**. The deletion of all 4 α-globin gene alleles causes profound anemia during fetal life, resulting in **hydrops fetalis.** In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form **Bart hemoglobin (γ4)** in fetal life and **HbH** (β4) after birth. Infants are identified in the newborn period by the increased production of Bart hemoglobin (γ4) during fetal life and its presence at birth.

7.1 β-Thalassaemia major (homozygous β-Thalassaemia)

Two related features contribute to the sequelae of **β-thalassemia syndromes**: inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production leading to ineffective erythropoiesis.

β-Thalassaemia major is an inherited blood disorder presenting with anaemia classically at 4 - 6 months of age.

7.1.1. Symptoms

Common presenting symptoms are pallor, lethargy, failure to thrive and hepatosplenomegaly. The **classic presentation** of children with severe disease includes thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic

bone fractures, marked hepatosplenomegaly, and cachexia and is primarily seen in countries without access to chronic transfusion therapy. In non-transfused patients with severe ineffective erythropoiesis, marked splenomegaly can develop with hypersplenism and abdominal symptoms.

7.1.2. Investigations:

To be done for all new patients.

- Full blood count: (In typical cases, the Hb is usually below 7g/dl)
- Peripheral blood film: Microcytic hypochromic, target cell
- Haemoglobin analysis by electrophoresis or HPLC (High-performance liquid chromatography) (*Mandatory)* HbA decreased or absent, HbF increased, HbA2 variable
- Red cell phenotyping: **(required)** before first transfusion. This test is not useful if the patient has been transfused in the last 3 months
- DNA analysis: Mandatory in prenatal diagnosis, β gene analysis, α gene analysis.
- Infection screen: HIV, Hepatitis B & C, VDRL screen (before first transfusion).

All nuclear family members must be investigated by Hb Analysis for genetic counselling.

1st degree and 2nd degree relatives are encouraged to be screened and counselled.

Antenatal diagnosis - Can be done by chorionic villous sampling at 9-11 weeks period of gestation.

7.1.3 Management

Regular blood transfusion and iron chelation therapy is main stay of treatment. For detail refer to *National thalassemia guidelines*.

7.2 Beta Thalassaemia minor/trait

Carrier of beta thalassaemia, frequently seen in South East Asian, Mediterranean, Arabic families, usually asymptomatic. Microcytic hypochromic red cells with normal or borderline low Hb. Diagnosed on high-performance liquid chromatography (HPLC) or Hb electrophoresis (HbA2 >3.5%, often elevated Hb F). HbA2 may not be elevated in the presence of concomitant iron deficiency, therefore give iron treatment (if ferritin low) before ordering test.
Pre-pregnancy carrier testing of partner is important, ensure parents have been tested if likely to have more children

Thalassemia trait is often misdiagnosed as iron deficiency in children, because the two diagnoses produce similar hematologic abnormalities on CBC. However, *iron deficiency is much more prevalent.* A short course of iron and reevaluation is all that is required to identify children who will need further evaluation. Children who have β-thalassemia trait have a persistently normal red cell distribution width and low mean corpuscular volume (MCV), whereas patients with iron deficiency develop an elevated red cell distribution width (RDW) with treatment. On Hb analysis, patients with β-thalassemia trait have elevated levels of HbA2 and variably increased Hb F. There are “silent” forms of β-thalassemia trait, and if the family history is suggestive, further studies may be indicated.

7.3. Thalassaemia intermedia

A clinical diagnosis where patients present with less severe anaemia at > 2 years of age. Severity varies from being symptomatic at presentation to being asymptomatic until later adult life. Assessment and decision to start regular transfusion is best left to the specialist. All the mandatory bloods pre transfusion investigation is required as per transfusion dependent thalassaemia.

7.4. Alpha Thalassemia: (HB H disease)

Treatment of HbH disease requires ongoing monitoring of growth and organ dysfunction. Dietary supplement with folate and multivitamins without iron is indicated. Older patients may develop decreased bone density with calcium and vitamin D deficiency. Vitamin D supplementation is indicated if the level is low, and adequate dietary calcium intake should be encouraged to promote bone health. Transfuse only if Hb persistently < 7g/dl /or symptomatic of chronic anaemia.

7.5. Alpha Thalassaemia minor/trait

Carrier of alpha thalassaemia, commonly seen in South East Asian, African, Mediterranean, Arabic families. Microcytic hypochromic red cells with normal or borderline low Hb. Cannot be diagnosed on HPLC or Hb electrophoresis. DNA testing required for formal diagnosis (not a first-line investigation, exclude other causes first). Pre-pregnancy carrier testing of partner is important.

8.HAEMOLYTIC ANAEMIA

Acute haemolysis in childhood can be a life-threatening illness and all cases should be discussed with a haematologist. Admit children with haemolytic anaemia for observation. Frequent heart rate monitoring is required to identify tachycardia which may indicate a further drop in Hb.

Repeat FBC within 6-12 hours to detect ongoing haemolysis.

Monitor reticulocyte count and bilirubin. Additional investigations will be guided by blood film findings, Coombs test (direct antiglobulin test), blood group and antibody screening (BGAB), G6PD assay and Eosin-5 maleimide red cell staining (diagnosis of hereditary spherocytosis).

8.1. G6PD deficiency:

Glucose-6-phosphate dehydrogenase (**G6PD**) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, the most common manifestations are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections, certain drugs, and rarely, fava beans. This X-linked deficiency affects >400 million people worldwide, representing an overall 4.9% global prevalence.

Typically, hemolysis ensues in about 24-48 hour after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the Hb concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include aspirin, sulfonamides, rasburicase, and antimalarials, such as primaquine. The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency. In some individuals, ingestion of fava beans also produces an acute, severe hemolytic syndrome, known as **favism**. See appendix 1

8.1.2. Laboratory Findings

The onset of acute hemolysis usually results in a **precipitous fall in hemoglobin and hematocrit**. If the episode is severe, the Hb-binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine.

Unstained or supravital preparations of RBCs reveal precipitated hemoglobin, or **Heinz bodies.** Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood. Also, the blood film may contain red cells with what appears to be a bite taken from their periphery **(“bite cells”)** and **polychromasia** (evidence of bluish, larger RBCs), representing reticulocytosis.

8.1.3. Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal.

Metabolic screening done in Indira Gandhi Memorial Hospital (IGMH) Maldives shows **13% incidence** of G6PD deficiency. G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and it is recommended to screen all newborn for G6PD enzyme activity.

8.1.4. Prevention and Treatment

Prevention of hemolysis constitutes the most important therapeutic measure. When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency should be tested for the defect before known oxidant drugs.

To avoid certain drugs (Refer to Appendix Table 6) and fava beans.

If severe hemolysis has occurred, supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.

9. HEREDITARY SPHEROCYTOSIS

- Due to the inheritance of a defective structural protein (spectrin) in the RBC membrane producing spheroidal and osmotically fragile RBCs
- These RBCs are trapped and destroyed in the spleen due to shortened RBC life span
- Degree of clinical severity is proportional to the severity of RBC membrane defect
- Inheritance: AD in 2/3; AR or *de novo* in 1/3

9.1 Clinical features

- Features of anemia which can be mild, moderate, and severe.
- Intermittent jaundice
- Splenomegaly
- Haemolytic crises
- Pigment gallstones in adolescents and young adults
- Aplastic crises with Parvovirus B19 infections
- Megaloblastic crises

9.2. Laboratory finding:

Common laboratory finding includes:

- Reticulocytosis
- Micro spherocytes in peripheral blood film
- Osmotic fragility is increased
- Elevated MCHC
- Normal direct antiglobulin test
- Autohaemolysis is increased and corrected by glucose

9.3. Treatment

- Folic acid supplements
- Splenectomy (To be delayed as long as possible.)
- In mild cases, avoid splenectomy unless gallstones developed • Splenectomy is avoided for patients < 5 years age because of the

10.HYPOPLASTIC/APLASTIC ANAEMIA

Causes:

- Acute leukemia, aplastic anaemia, infiltrative disorders.
- Drugs (e.g. cytotoxics, chloramphenicol, sulfonamides)
- Viral infection
- Severe nutritional deficiencies (vitamin B12 or folate deficiency) however usually children present with macrocytic red cells. Reticulocyte count is usually low.
- Differential diagnosis based on FBC results: Consider bone marrow infiltration if neutrophils and/or platelets also decreased.
- If isolated anaemia with low reticulocyte count with normal platelet and neutrophil counts, consider transient erythroblastopenia of childhood (TEC) or congenital forms (e.g. Diamond-Blackfan anaemia).
- Bone marrow aspirate is usually required for diagnosis

- Always consult with hematologist or haemato-oncologist for diagnosis and management.

11.VITAMIN B12 AND FOLATE DEFICIENCY

Vitamin B12 and folate deficiency is also known as megaloblastic anemia. It may be seen in exclusively breast-fed infants of mothers with vitamin B12 deficiency, children with a vegan or vegetarian diet, pernicious anaemia, and metabolic disorders. Vitamin B12 and folate deficiency can be associated with failure to thrive or neurodevelopmental problems (regression, seizures, irritability, poor feeding, vomiting). Characteristic blood film findings include macrocytic red cell, teardrop red cells and hyper segmented neutrophils and often neutropenia or thrombocytopenia.

Requires urgent investigation with red cell folate and active vitamin B12. If low active vitamin B12 suggest serum homocysteine and urine methylmalonic acid.

Treatment:

Treatment should be commenced urgently, particularly if neurological symptoms or regression.

Folic acid:

When the diagnosis of folate deficiency is established, folic acid should be administered orally or parenterally at **0.5-1.0 mg/day.**

In infant the dose folic acid is 15 mcg/kg/day OR 50 mcg/day for folic acid deficiency and 0.5 to 1 mg per day for megaloblastic anemia. In pregnancy and lactation, the usual dose of folic acid is 600 mcg /day.

If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 week as a diagnostic test, because a hematologic response can be expected within 72 hr. Doses of folate >0.1 mg can correct the anemia of vitamin B_{12} deficiency but might aggravate any associated neurologic abnormalities. Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 week until a definite hematologic response has occurred. Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate. Transfusions are indicated only when the anemia is severe or the child is very ill.

Prophylactic folic acid is indicated in hemolytic anemia with high reticulocyte count because active hemolysis can consume folate and cause megaloblastic anemia.

Vitamin B12:

Cyanocobalamin is available as a nasal spray as an alternative to parenteral injection. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B_{12} is about **1-3 µg/day**. Hematologic responses have been observed with small doses, indicating that a mini dose may be administered as a therapeutic test when the diagnosis of vitamin B_{12} deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

Red flags in anaemia (consider admission)

- Hb < 7g/dl (including iron deficiency anaemia)
- Lethargy
- Tachycardia, cardiac murmur or signs of cardiac failure
- Features of haemolysis e.g: dark urine, jaundice, scleral icterus

Consider for consultation with local paediatric team: when children have red flag feature

Consider for transfer: After discussing with pediatric consultant/if

12. REFERENCES

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Appendix 1

Agents precipitating hemolysis in G6PD deficiency

Antibacterial medication	Antimalarial medication	Anthelminthics	Others	Chemicals	Illness
Sulfonamides Ciprofloxacin Moxifloxacin Norfloxacin Ofloxacin Dapsone Trimethoprim-sulfamethoxazole Nalidixic acid Chloramphenicol Nitrofurantoin	Primaquine Pamaquine Chloroquine Quinacrine	β-Naphthol Stibophen Niridazole	Acetanilide Vitamin K analogs Methylene blue Toluidine blue Probenecid Dimercaprol Acetylsalicylic acid Phenazopyridine Rasburicase	Phenyl hydrazine Benzene Naphthalene (mothballs) 2,4,6-Trinitrotoluene	Diabetic acidosis Hepatitis Sepsis

Indicator for Iron deficiency Anemia

INDICATOR	SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY	COMMENTS
Hemoglobin (g/dL)	<11.0 for non-Hispanic whites age 0.5-4 yr.	When used alone, has low specificity and sensitivity
Mean corpuscular volume (MCV) (μm^3)	<70 for age 6-24 mo	A reliable, but late indicator of iron deficiency (ID) Low values can also be a result of thalassemia and other causes of microcytosis. False-negative results can be seen in liver disease
Serum ferritin (SF) (µg/L)	Age ≤5 yr.: <12 Children >5 yr.: <15 All age-groups in presence of infection: <30-100	Probably the most useful laboratory measure of iron stores, and helps identify ID; low SF value is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia. SF is an acute-phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) may help to identify these false- negative SF results.
Transferrin saturation	<16%	Inexpensive, but use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations, including inflammatory

		conditions, aging, and nutrition.
Reticulocyte hemoglobin content (CHr) (pg)	Infants and young children: <27.5 Adults: ≤28.0	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False-normal values can occur when MCV is increased and in thalassemia. Not yet widely available on hematology analyzers.
Serum transferrin receptor (sTfR)	Cutoff varies with assay and with patient's age and ethnic origin.	This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response. Levels can be increased in hemolytic anemia or other conditions that increase red cell mass.