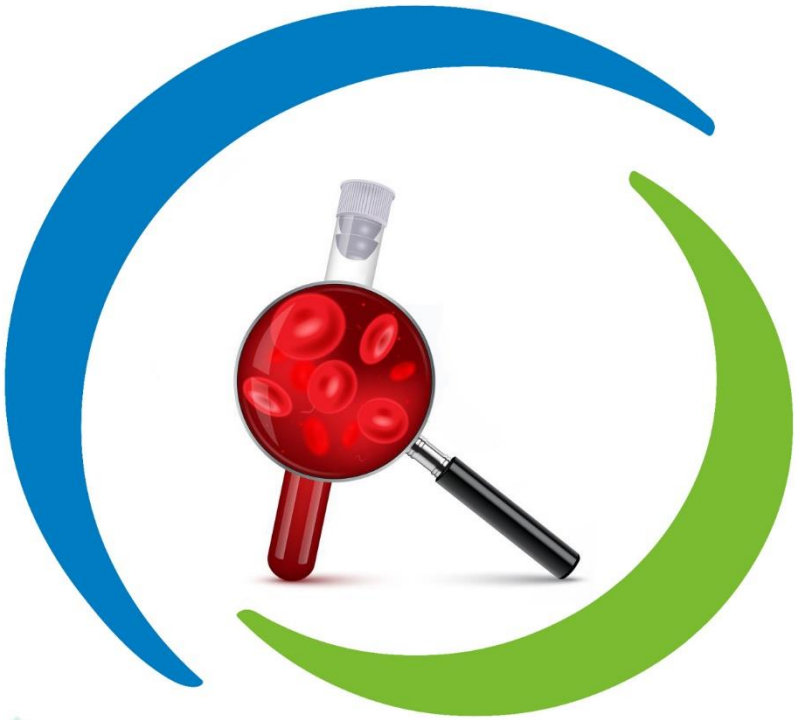
Pediatric Hematology Protocol of EHA



First Edition 2024

Egyptian Clinical Practice Protocols

in

Pediatric Hematology

for

Egypt Healthcare Authority

First Edition

2024

Prepared by

Working Group for Development

of

Egyptian Clinical Practice Protocols

in

Pediatric Hematology

for

Egypt Healthcare Authority

Executive Committee

This protocol was written, reviewed and approved by the Pediatric Hematology Committee of Egyptian Universities (in the order of Alphabets).

1. ***Prof. Ahmed Mansour***, *Professor of Pediatrics, Hematology, Pediatric Oncology and Bone Marrow Transplant, Mansoura University*
2. ***Prof. Alaa Al-Haddad*** *Professor of Pediatric Oncology, Hematology and Pediatric Bone Marrow Transplantation National Cancer Institute*
3. ***Prof. Amal El-Bashlawy*** *Professor of Pediatrics and Pediatric Hematology, Cairo University*
4. ***Prof. Amira Abdel Moneim*** *Professor of Pediatrics, Hematology and Pediatric Oncology, Ain Shams University*
5. ***Prof. Azza Abdel-Gawad Tantawy*** *Professor of Pediatrics, Hematology and Pediatric Oncology, Ain Shams University* ***(Head of the Committee)***
6. ***Prof. Emad Obeid***, *Professor of Pediatric Oncology, Hematology and Pediatric Bone Marrow Transplantation, National Cancer Institute*
7. ***Prof. Huda Hassab***, *Professor of Pediatrics, Hematology, Pediatric Oncology and Bone Marrow Transplantation, Alexandria University*
8. ***Prof. Naglaa Shaheen***, *Consultant of Hematology at Children's Hospital of Egypt and Health Insurance*
9. ***Prof. Nayera Hazaa***, *Professor of Pediatrics, Hematology, Pediatric Oncology and Bone Marrow Transplantation, Ain Shams University*
10. ***Prof. Tamer Hassan*** *Professor of Pediatrics, Hematology, Pediatric Oncology and Bone Marrow Transplant, Zagazig University*
11. ***Dr. Marian Abd El -Messiah,*** *Pediatric Specialist, Coordinator of Hematology Committee*

Disclaimer

Protocols and guidelines outline the recommended or suggested clinical practice; however, they cannot replace sound clinical judgment by appropriately trained and licensed physicians.

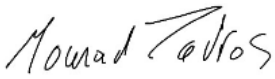
The physician is ultimately responsible for management of individual patients under their care.

Intellectual Property Rights

Supervised & Revised By

➢ ***General Doctor/ Mourad Alfy Ramzy Tadros***

- MD, FRCPCH(UK), MRCPI(Dublin)
- Consultant Paediatrician of Egyptian Military Medical Services.
- Professors of Paediatrics Military Medical Academy
- Head of Training Committee of Paediatrics of Egyptian Military Medical Board
- Consultant Paediatrician of the Medical Advisory Council of Egypt Healthcare Authority (EHA).



➢ ***Prof. Azza Abdel-Gawad Tantawy:*** Professor of Pediatrics, Hematology and Pediatric Oncology, Ain Shams University (Head of the Committee)

Reviewed By

1. ***Dr. Hala Adel:*** Pediatric Consultant, Moderator & coordinator of Medical Advisory Council of Egypt Healthcare Authority (EHA)
2. ***Dr. Huda Karam:*** Pediatric Specialist, Moderator & coordinator of Medical Advisory Council of Egypt Healthcare Authority (EHA)

Cover Designed & Edited By

➢ ***Mr. Bassam Sayed:*** Technical Officer at Medical Advisory Council of Egypt Healthcare Authority (EHA)

PREFACE

Recently, there is an increasing need to provide programs with accurate competency-based assessments to ensure the delivery of high-quality healthcare. The aim of developing these Egyptian Clinical Practice Protocols in Pediatric Hematology is to unify and standardize the delivery of healthcare to any child at all health facilities.

Pediatric Hematology service is usually offered to children below 16 years of age in Egypt.

The current status of healthcare in which avoidable failures are abound. “We train longer, specialize more, use ever-advancing technologies, and still we fail.” Part of the problem, is that the ever-increasing complexity of medicine makes uniform care delivery impractical or impossible. That is, unless there are protocols, checklists, or care paths that are readily available to providers.

Regarding Pediatric Hematology, busy clinicians have all felt the need for a concise, easy-to-use resource at the bedside for evidence-based protocols, or consensus-driven care paths.

In this protocol, we offer comprehensive reviews of selected topics and comprehensive advice about management approaches based on the highest level of evidence available in each case. Our goal is to provide an authoritative practical medical resource for pediatricians.

We hope that such an approach will encourage clinicians to apply available evidence to their practice and also track compliance with desired practices. We hope that practicing pediatricians, fellows and practitioners will find this protocol useful in delivering high-quality clinical care to their patients. We remain open to feedback and suggestions about how to improve this resource and how to make it maximally useful to those delivering care at the bedside in for patients in Pediatric Hematology.

Members of the Working Group

For Development of the Egyptian Clinical Practice Guideline

In Pediatric Hematology

Table of Contents

List of Figures

APPROACH TO ANEMIC INFANT AND CHILD

Is The Patient Anemic?

How Severe Is the Anemia?

- **Ask For Complete Blood Picture**

Anemia is defined as ⇨ Hemoglobin level below the cut off values of hemoglobin for age and sex.

The severity of anemia ⇨ Is determined by hemoglobin level **(table 1)**.

Pallor ⇨ Is suggestive of anemia but is nonspecific.

Table 1 : Hemoglobin levels to diagnose anemia at sea level (g/l)

Population	Non-anemia*	Anemia*		
		Mild	Moderate	Severe
Children 6–59 months of age	110 or higher	100–109	70–99	Lower than 70
Children 5–11 years of age	115 or higher	110–114	80–109	Lower than 80
Children 12–14 years of age	120 or higher	110–119	80–109	Lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110–119	80–109	lower than 80
Men (15 years of age and above)	130 or higher	110–129	80–109	Lower than 80

- **a "Mild" is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency even when no anemia is clinically apparent**

Reference:

- **WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1) (http://www.who.int/vmnis/indicators/haemoglobin, pdf, accessed 6/2/2022**

Assessment of anemic infant and child

History

- Age and sex , history of previous transfusion , history of bleeding , other system disease like renal or inflammatory disease.
- Medication history: past and current, particularly those that may cause hemolysis in the instance of G6PD deficiency.
- Dietary history: iron intake (with particular attention to iron-rich foods, breast feeding and cow's milk intake), vitamin B12 intake, recent fava/broad bean ingestion (may precipitate haemolysis in the case of G6PD deficiency).
- Family history: anemia, jaundice, gallstones or splenomegaly.

Examination

Clinical features suggestive of anemia:

- ✓ **Pallor**
- ✓ **Pale conjunctivae**
- ✓ **Tachycardia**
- ✓ **Cardiac murmur**
- ✓ **Lethargy**
- ✓ **Listlessness**
- ✓ **Poor growth**
- ✓ **Poor concentration**
- ✓ **Weakness**
- ✓ **Shortness of breath**
- ✓ **Signs of cardiac failure**
- ✓ **Signs of haemolysis include jaundice, scleral icterus, splenomegaly and dark urine**

Management

Emergency management of severe anemia with pending heart failure

- It is important to quickly assess the patient's clinical condition in patient with severe anemia
- If the patient is severely pale and sick looking, breathless, has tachycardia, raised jugular venous pressure (JVP) and tender hepatomegaly, it is suggestive of congestive cardiac failure (CCF). Such a patient needs immediate attention and prompt treatment including diuretics, restricted fluids, oxygen support and packed cell transfusion
- Do not waste time in lengthy diagnostic tests and do as minimum tests as require.
- Immediately arrange for packed cell transfusion and remove blood for various tests just before starting transfusion.
- If transfusion is not available in your facility immediately refer the patient under oxygen support to nearest facility with available transfusion therapy

Investigations of anemia in infancy and childhood

- If anemia is suspected begin with a full blood examination including blood film (FBC), and blood indices
- The initial management is based on the complete blood picture / blood film and the Mean Corpuscular Volume (MCV)

Table 2 :Age-Specific Normative Red Blood Cell Values

Age	Mean corpuscular volume (fL)	
	Mean	2 SDs below mean
Full term (cord sample)	108	98
1 month	101	91
2 months	95	84
6 months	76	68
6 months to 2 years	78	70
2 to 6 years	81	75
6 to 12 years	86	77
12 to 18 years (male)	88	78
12 to 18 years (female)	90	78

Reference:

- **Robertson J, Shilkofski N, eds. The Harriet Lane Handbook. 17th ed. Philadelphia, Pa.: Mosby; 2005:337**

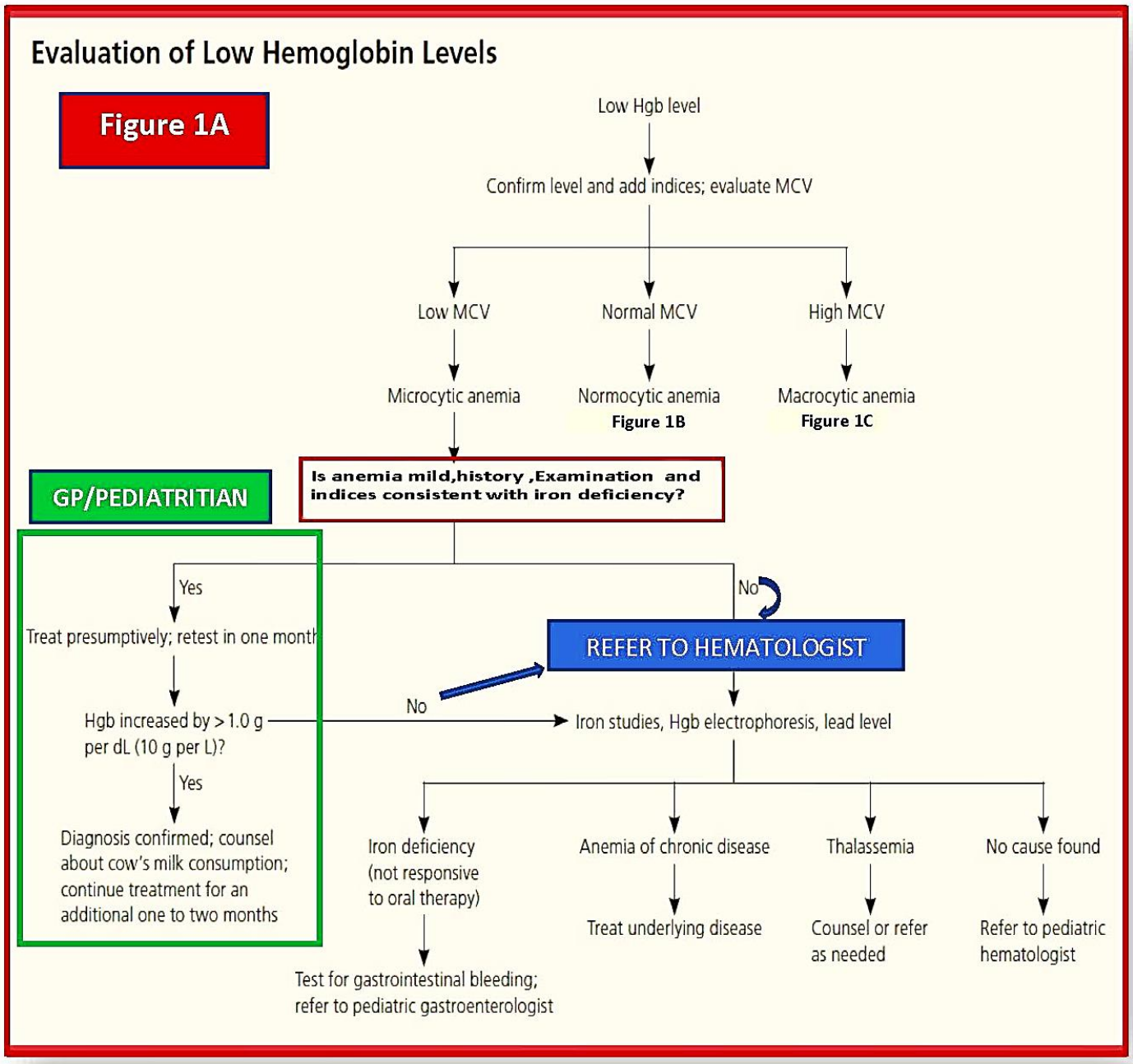


Figure (1A) : Algorithm for management of child with low hemoglobin, low MCV With normal leucocytes and platelets

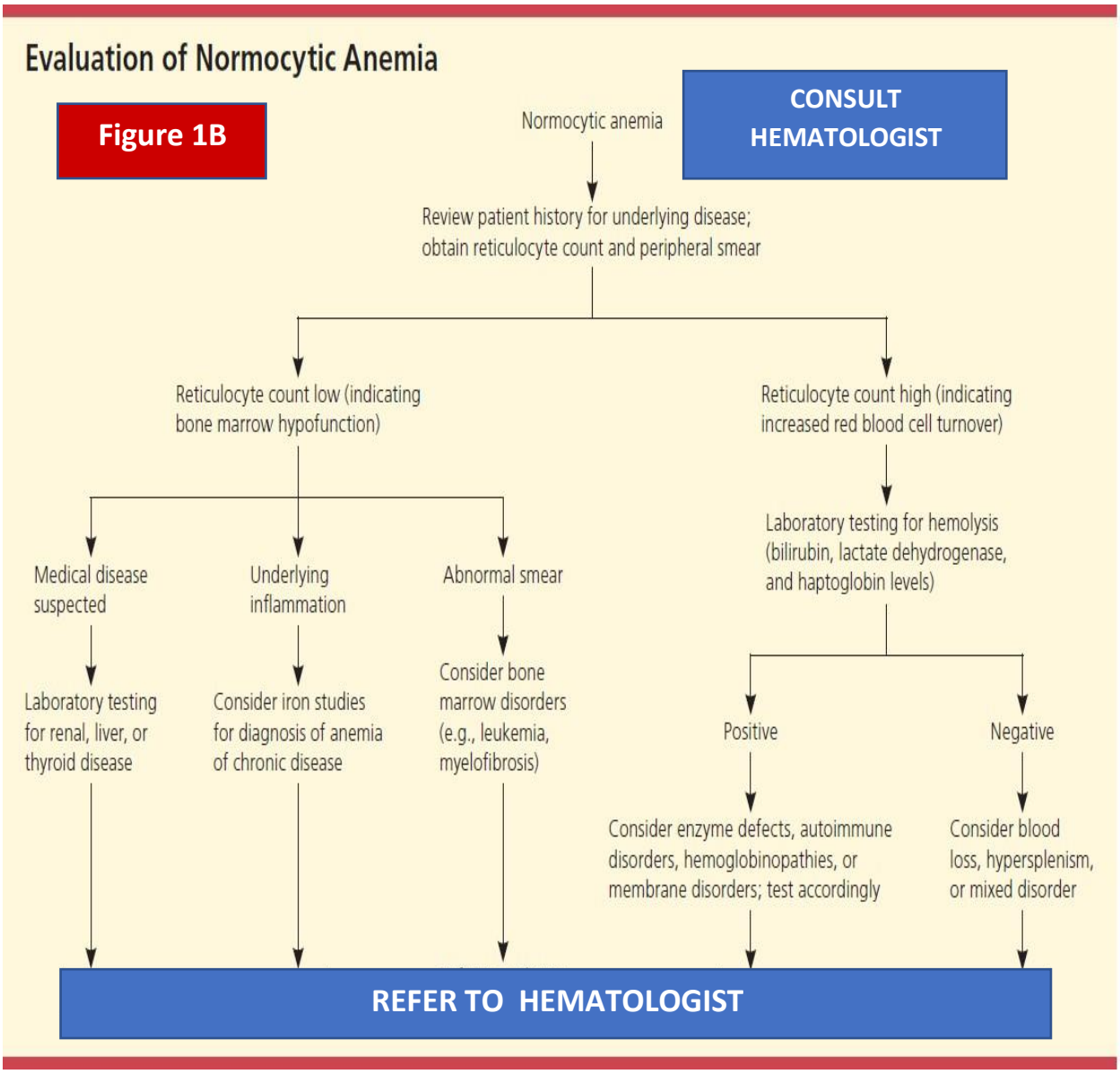


Figure (1B) : Algorithm for management of child with low hemoglobin ,normal MCV With normal leucocytes and platelets

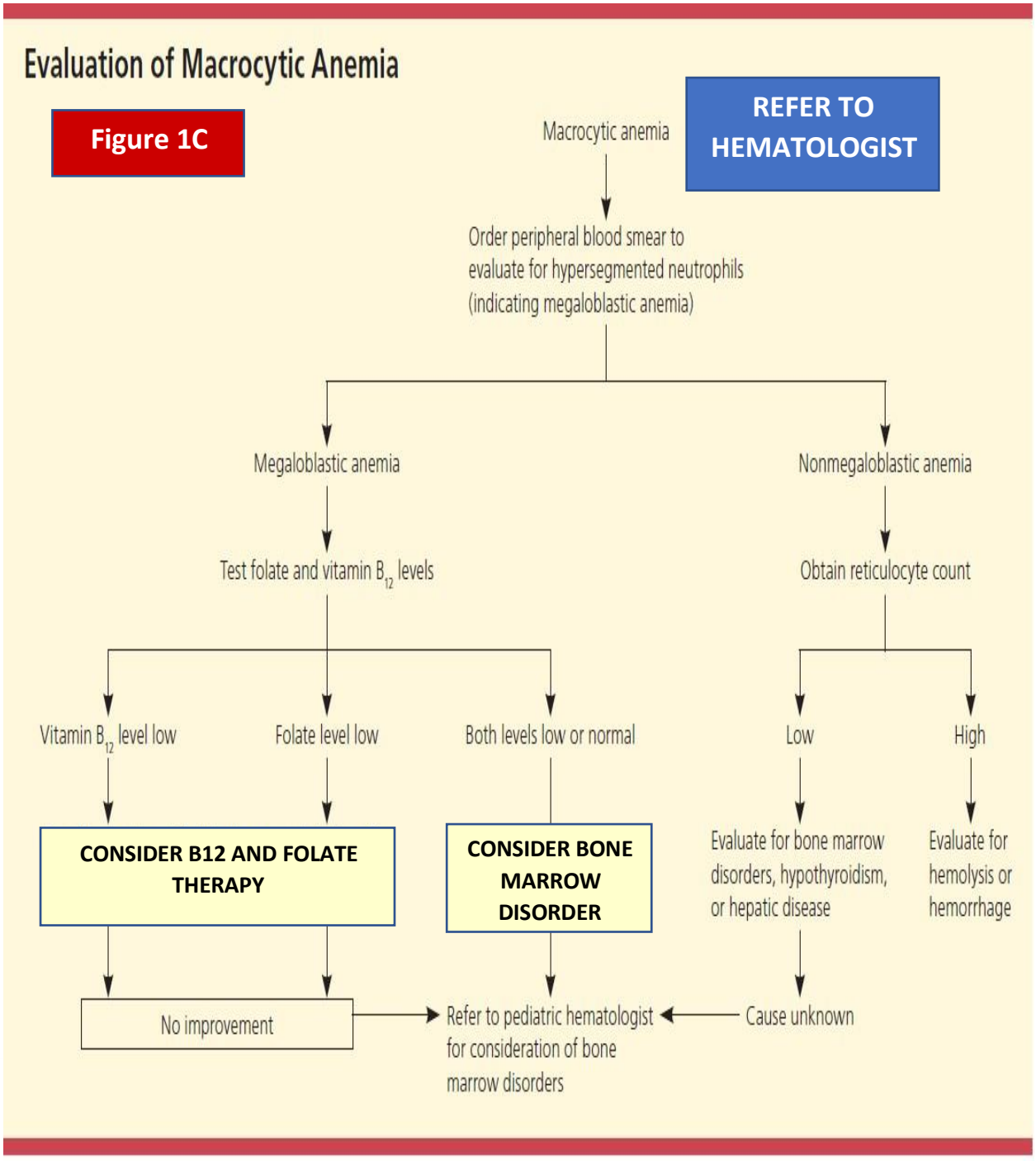


Figure (1C) : Algorithm for management of child with low hemoglobin and increased MCV With normal leucocytes and platelets

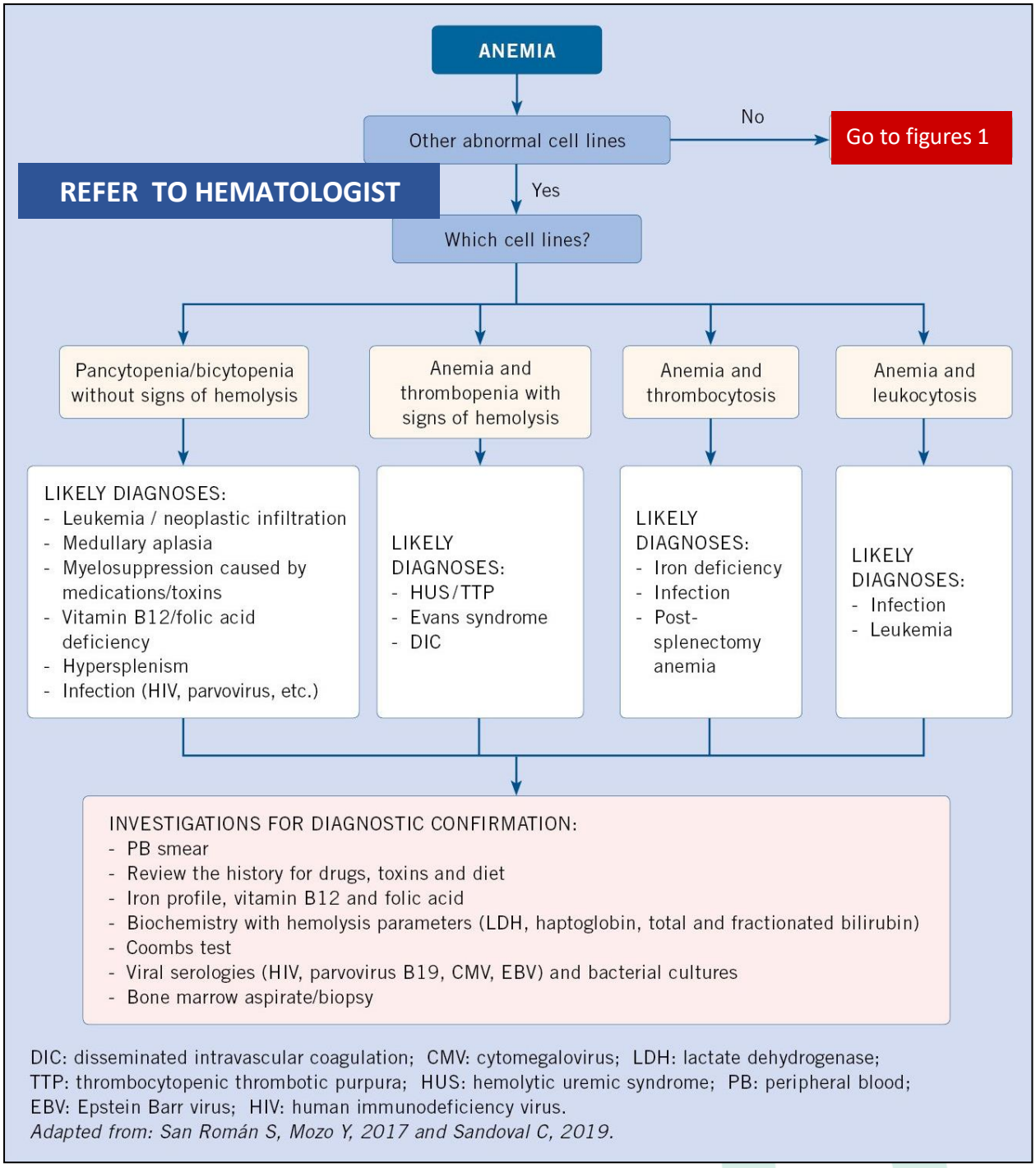


Figure (2): Algorithm for management of child with low hemoglobin with abnormal leucocytes and platelets

Red Flags

(Consider Admission)

- **Hb <60 g/L (including iron deficiency)**
- **Tachycardia, cardiac murmur or signs of cardiac failure.**
- **Features of hemolysis (dark urine, jaundice, scleral icterus).**
- **Associated reticulocytopenia.**
- **Presence of nucleated red blood cells on blood film.**
- **Associated thrombocytopenia or neutropenia may indicate malignancy or an infiltrative disorder.**
- **Severe vitamin B12 or folate deficiency.**
- **Need for red cell transfusion: If the patient is compensated and stable defer transfusion until a definitive diagnosis is made.**

References:

1. Approach to the anemic child .Hastings C A , Torkildson J C , Agrawal A K ; in handbook of pediatric hematology and oncology children's hospital and research center Oakland ; Hastings C A , Torkildson J C, Agrawal A K (editors); Wiley Blackwell publications , 3rd edition . chapter 1 , pages 1-14 , 2021.
2. B. Rosich del Cacho, Y. Mozo del Castillo . Anemia. Classification and diagnosis Pediatr Integral 2021; XXV (5): 214 – 221.
3. Janus J, Moerschel SK. Evaluation of anemia in children. Am Fam Physician. 2010;81(12):1468.
4. Mary Wang Iron Deficiency and Other Types of Anemia in Infants and Children; Am Fam physician. 2016 Feb 15;93(4):270-278.

APPROACH TO THE CHILD WITH HEMOLYTIC ANEMIA

- Hemolytic anemia is defined as the destruction of red blood cells (RBCs) before their normal 120-day life span.
- It includes many separate and diverse entities whose common clinical features can aid in the identification of hemolysis.
- Hemolytic anemia exists on a spectrum from chronic to life-threatening, and warrants consideration in all patients with unexplained normocytic or macrocytic anemia.
- Premature destruction of RBCs can occur intravascularly or extra vascularly in the reticuloendothelial system, although the latter is more common.
- The primary extravascular mechanism is sequestration and phagocytosis due to poor RBC deformability (i.e., the inability to change shape enough to pass through the spleen).
- Antibody-mediated hemolysis results in phagocytosis or complement-mediated destruction, and can occur intravascularly or extra vascularly.
- The intravascular mechanisms include direct cellular destruction, fragmentation, and oxidation.
- Direct cellular destruction is caused by toxins, trauma, or lysis. Fragmentation hemolysis occurs when extrinsic factors produce shearing and rupture of RBCs. Oxidative hemolysis occurs when the protective mechanisms of the cells are overwhelmed.
- The etiologies of hemolysis are numerous as demonstrated in **table (1).**

Table 1: Differential Diagnosis of Hemolytic Anemia in Children

HEREDITARY HEMOLYTIC ANEMIAS

Enzymopathies

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Pyruvate kinase (PKLR) deficiency

Hemoglobin Disorders

- Thalassemias
- Sickle cell disease
- Unstable hemoglobin
- Congenital dyserythropoietic anemias

Membrane Defects

- Hereditary spherocytosis
- Hereditary elliptocytosis and pyro-poikilocytosis

ACQUIRED HEMOLYTIC ANEMIAS

Autoimmune Hemolytic Anemia (AIHA)

- Warm-reactive AIHA
- Cold agglutinin syndrome
- Paroxysmal cold hemoglobinuria (PCH)
- Drug-induced (very rare in children)

Alloimmune Hemolytic Anemia

- Neonatal alloimmune hemolysis
- Post-transfusion hemolysis
  - Acute hemolytic reactions
  - Delayed hemolytic reactions

Traumatic Hemolytic Anemia

- Macrovascular defects-prostheses (dysfunctional mechanical heart valve)
- Microvascular
  - Typical and Atypical Hemolytic uremic syndrome
  - Thrombotic thrombocytopenic purpura
  - Disseminated intravascular coagulation

Hypersplenism

Hemolytic anemia due to toxic effects on the membrane

- Spur cell anemia in severe liver disease
- External toxins
- Animal or spider bites
- Metals
- Organic compounds
- Infection

Paroxysmal Nocturnal Hemoglobinuria

Clinical Presentation

- Hemolysis should be considered when a patient experiences acute jaundice or hemoglobinuria in the presence of anemia. Symptoms of chronic hemolysis include lymphadenopathy, hepatosplenomegaly, cholestasis, and choledocholithiasis. Other nonspecific symptoms include fatigue, dyspnea, hypotension, and tachycardia.

Evaluation

- When hemolysis is suspected, the history should include known medical diagnoses, medications, personal or family history of hemolytic anemia, and a complete review of systems. Physical examination should focus on identifying associated conditions, such as infections or malignancies **(Table 2 and 3)**.

Table 2: Work Up of The Child with Hemolytic Anemia

History assessment for evidence of chronic hemolytic anemia and possible precipitants of an acute event

- Family history
- History of newborn jaundice
- Gallstones
- Splenomegaly or splenectomy
- Episodes of dark urine and/or yellow skin/sclerae
- Anemia unresponsive to iron supplementation
- Medications
- Environmental exposures
- Ethnicity
- Dietary history

The physical exam should be complete, but focused on:

- Skin color (pallor, jaundice, and icteric sclerae)
- Facial bone changes (extramedullary hematopoiesis)
- Abdominal fullness and splenomegaly

The laboratory evaluation includes:

- Complete blood count, RBC indices, and reticulocyte count
- Peripheral blood smear (assess for fragmented forms or evidence of inherited anemia with specific morphological abnormalities)
- Bilirubin, AST, lactate dehydrogenase (LDH)
- Coomb's test, direct and indirect (to exclude antibody-mediated red cell destruction)
- Urinalysis (for heme, bilirubin)
- Plasma haptoglobin
- Parvovirus PCR (if history is suspicious)
- Renal functions

Specific tests for diagnosis may include:

- Osmotic fragility
- Red cell enzyme defects mainly G6PD
- CD 55/59 if suspect PNH
- ADAMTS13 if suspected microangiopathic hemolytic anemia

Table 3: Initial Laboratory Tests for Hemolysis

Initial Laboratory Tests for Hemolysis

Test	Finding in hemolysis	Cause
Haptoglobin	Decreased	Binds free hemoglobin
Lactate dehydrogenase	Elevated	Released from lysis of red blood cells
Peripheral blood smear	Abnormal red blood cells	Based on cause of anemia
Reticulocyte count	Increased	Marrow response to anemia
Unconjugated bilirubin	Increased	Increased hemoglobin breakdown
Urinalysis	Urobilinogen, positive for blood	Free hemoglobin and its metabolites

Table 4: Diagnostic Clues for Hemolytic Anemia

Diagnostic Clues for Hemolytic Anemia

History and physical examination findings	Suggested diagnosis
Diarrhea	Hemolytic uremic syndrome
Family history of hemolytic anemia	Sickle cell disease, hereditary spherocytosis, thalassemias, G6PD deficiency
Fever	Autoimmune hemolytic anemia, disseminated intravascular coagulation, hemolytic uremic syndrome, infection
Hematuria	Paroxysmal nocturnal hemoglobinuria, intravascular hemolysis
Medications	Drug-induced thrombotic microangiopathic anemia, drug-induced immune hemolytic anemia, G6PD deficiency
New-onset jaundice	Any hemolytic anemia
Personal history of cancer	Warm autoimmune hemolytic anemia
Personal history of mononucleosis or *Mycoplasma pneumoniae* infection	Cold autoimmune hemolytic anemia
Recent transfusion history	Hemolytic transfusion reaction

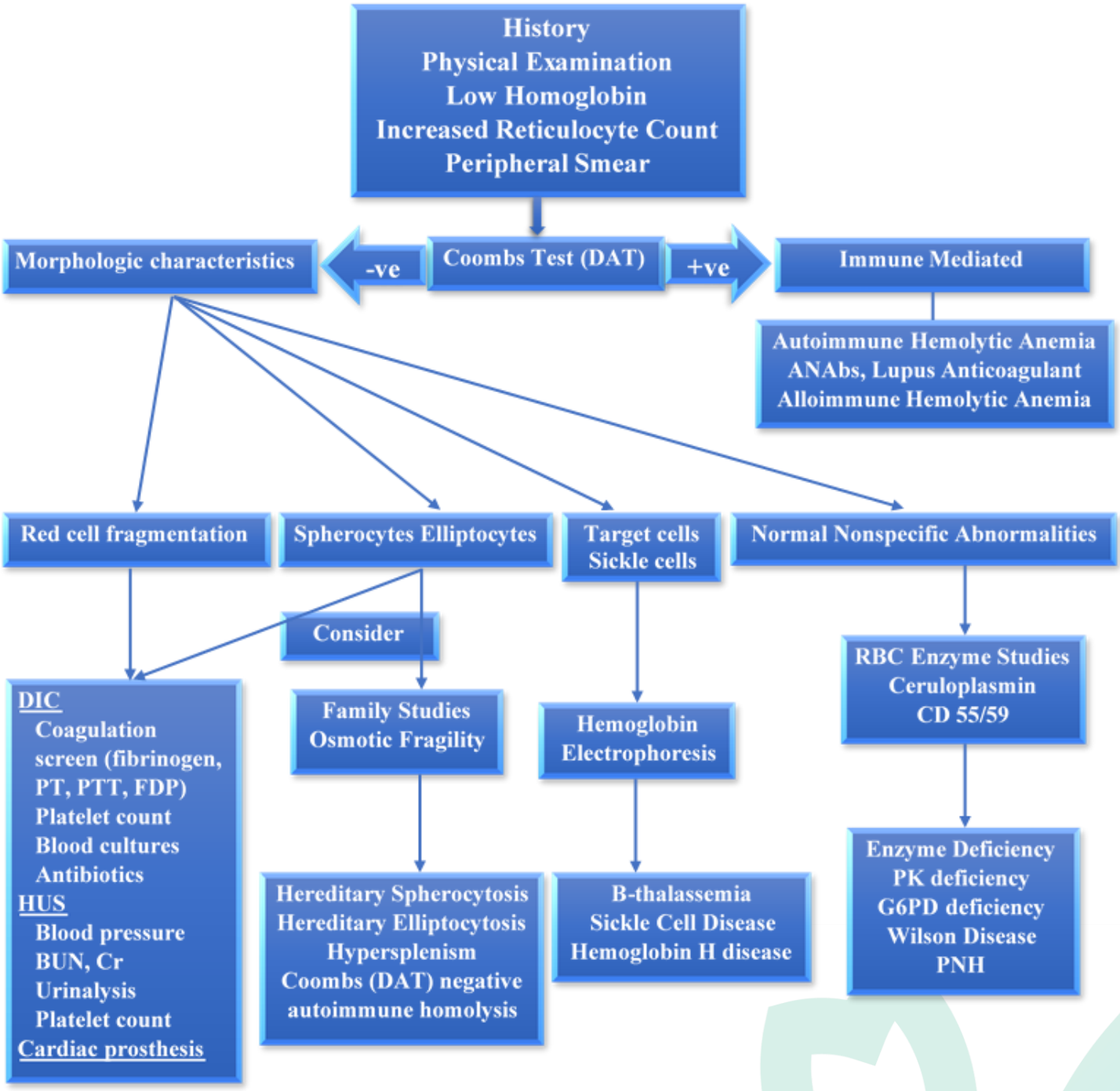


Figure 1: Diagnostic Algorithm to Child with Hemolytic Anemia

References:

1. Phillips J, Henderson AC. Hemolytic Anemia: Evaluation and Differential Diagnosis. Am Fam Physician. 2018 Sep 15;98(6):354-361.

2. Voulgaridou A, Kalfa TA. Autoimmune Hemolytic Anemia in the Pediatric Setting. J Clin Med. 2021 Jan 9;10(2):216.

3. Noronha SA. Acquired and Congenital Hemolytic Anemia. Pediatr Rev. 2016 Jun;37(6):235-46.

IMMUNE HEMOLYTIC ANEMIA

Autoimmune Hemolytic Anemia

- AIHA is caused by autoantibody-mediated destruction. The hallmark of AIHA is a positive DAT result *(direct combs test)*
- AIHA is organized into two primary subgroups based on binding temperatures, referred to as cold and warm agglutinins.
- Many causes of AIHA are idiopathic; however, viral and bacterial infections, autoimmune conditions, connective tissue disorder, lymphoproliferative malignancies, blood transfusions, and transplantations have been associated with AIHA.

Warm AIHA

- Warm AIHA is more common than cold AIHA and involves immunoglobulin G (IgG) antibodies, usually to the Rh complex, that react with the RBC membrane at normal body temperatures. The IgG-coated RBCs are then removed by reticuloendothelial macrophages and sequestered in the spleen, sometimes leading to splenomegaly. Treatment of warm AIHA typically includes the use of glucocorticoids, management of the underlying condition, blood transfusion (if necessary), and supportive care.

Cold AIHA

- Cold AIHA involves IgM antibodies (cold agglutinin titers) that react with polysaccharide antigens on the RBC surface at low temperatures and then cause lysis on rewarming by complement fixation and intravascular hemolysis. Development of these antibodies is associated with infectious or malignant processes. Mycoplasmal pneumonia and mononucleosis are the two most common processes. Treatment of patients who have cold AIHA typically involves supportive measures, avoidance of triggers, and underlying disease management.

References:

1. Phillips J, Henderson AC. Hemolytic Anemia: Evaluation and Differential Diagnosis. Am Fam Physician. 2018 Sep 15;98(6):354-361.

2. Voulgaridou A, Kalfa TA. Autoimmune Hemolytic Anemia in the Pediatric Setting. J Clin Med. 2021 Jan 9;10(2):216.

3. Noronha SA. Acquired and Congenital Hemolytic Anemia. Pediatr Rev. 2016 Jun;37(6):235-46.

DIAGNOSIS AND MANAGEMENT OF G6PD DEFICIENCY

- Glucose-6-phosphate dehydrogenase deficiency, the most common enzyme deficiency worldwide, causes a spectrum of disease including neonatal hyperbilirubinemia, acute hemolysis, and rarely chronic hemolysis. Persons with this condition also may be asymptomatic. This is X-linked inherited disorder . Males are more commonly affected although carrier females can occasionally be symptomatic.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency increases the vulnerability of erythrocytes to oxidative stress in the form of an infection, oxidative drug, or fava beans
- Different gene mutations cause different levels of enzyme deficiency, with classes assigned to various degrees of deficiency and disease manifestation. Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion. Neonatal hyperbilirubinemia may require treatment with phototherapy or exchange transfusion to prevent kernicterus. The variant that causes chronic hemolysis is rare .

There is no cure for G6PD deficiency, and it is a lifelong condition. However, most people with G6PD deficiency have a completely normal life as long as they avoid the triggers.

G6PD Deficiency is rarely fatal as acute hemolysis can lead to anemic heart failure and renal tubular injury and renal impairment related to severe hemolysis.

Three Clinical Phenotypes

1) Neonatal Hyperbilirubinemia
2) Acute Hemolysis
3) Rarely chronic non spherocytic hemolytic anemia

Acute Hemolysis in G6PD-Deficient Patients

- Acute hemolysis is caused by infection, ingestion of fava beans, or exposure to an oxidative drug.
- Hemolysis occurs after exposure to the stressor but does not continue despite continued infection or ingestion. This is thought to be a result of older erythrocytes having the greatest enzyme deficiency and undergoing hemolysis first. Once the population of deficient erythrocytes has been hemolyzed, younger erythrocytes and reticulocytes that typically have higher levels of enzyme activity are able to sustain the oxidative damage without hemolysis. Clinically, acute hemolysis can cause back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin **(*Table 1*).**
- Jaundice, in the setting of normal liver function, typically does not occur until greater than 50 percent of the erythrocytes have been hemolyzed.
- Medications that should be avoided in patients with G6PD deficiency are listed in **Table 2,** and drugs that can be used safely in these patients are listed in **table 3.**
- Hemolysis typically occurs 24 to 72 hours after exposure to oxidant stressor, with resolution within four to seven days. Infection is the most common cause of acute hemolysis in G6PD- deficient persons.
- Oxidative drugs ingested by a woman who is breast-feeding may be transmitted in breast milk and can cause acute hemolysis in a G6PD-deficient child

Table 1: Symptoms and laboratory Evaluation in Patients with G6PD

Symptoms and Laboratory Evaluation in Patients with G6PD and Acute Hemolysis

SIGNS /SYMPTOMS	*Laboratory evaluation*	*Findings in patients with G6PD deficiency and associated acute hemolysis*
Back pain	Complete blood count	Mild to severe anemia
Abdominal pain	Reticulocyte count	Increases four to seven days after hemolysis
Jaundice	Peripheral blood smear	Heinz bodies
Transient splenomegaly	Haptoglobin	Decreased
Hemoglobinuria	Liver function tests	Elevated indirect bilirubin
Scleral icterus	Coombs' test	Negative

Tests for G6PD deficiency include the following:

1) Semi-quantitative tests -The fluorescent spot test (not reliable in females)
2) Quantitative tests (spectrophotometric) - the criterion standard.

Table 2: Drugs to Be Avoided by G6PD - Deficient Patients

• Diaminodiphenyl sulfone (Dapsone) • Flutamide (Eulexin) • Furazolidone (Furoxone) • Isobutyl nitrite • Methylene blue • Niridazole (Ambilhar)	• Nitrofurantoin (Furadantin) • Phenazopyridine (Pyridium) • Primaquine • Rasburicase (Elitek) • Sulfacetamide • Sulfanilamide • Sulfapyridine

Table 3: Drugs to Be Used With Caution in Therapeutic Doses for Patients With G6PD Deficiency (Without Nonspherocytic Hemolytic Anemia)

• Acetaminophen (Tylenol) • Acetylsalicylic acid (aspirin) • Antazoline (Antistine) • Antipyrine • Ascorbic acid (vitamin C): intravenous doses only reported • Benzhexol (Artane) • Chloramphenicol • Chlorguanidine (Proguanil, Paludrine)	• Chloroquine • Colchicine • Diphenyldramine (Benadryl) • Glyburide (glibenclamide, Diabeta, Glynase) • Isoniazid • L-Dopa • Quinine • Streptomycin	• Sulfacytine • Sulfadiazine • Sulfaguanidine • Sulfamethoxazole (Gantanol) • Sulfisoxazole (Gantrisin) • Trimethoprim • Tripelennamine (Pyribenzamine) • Vitamin K

Treatment of Acute Hemolysis in G6PD-Deficient Patients

- The usual treatment for hemolytic anemia in G6PD-deficient patients is supportive care plus removal and avoidance of further triggers
- In severe hemolysis, blood transfusions may be required; hemodialysis may be needed if acute kidney injury occurs.
- Acute hemolytic anemia will prompt testing for G6PD deficiency, which should be done by a quantitative test. A result below 80% of the lower limit of normal must be regarded as G6PD deficient
- **Sometimes, during or immediately after a hemolytic attack, G6PD activity from a G6PD-deficient patient may be within the "normal range" (as a result of both destruction of the oldest cells and reticulocytosis). In such cases, the test must be repeated after 6-8 weeks**

Neonatal Hyperbilirubinemia in G6PD deficiency

- The prevalence of neonatal hyperbilirubinemia is twice that of the general population in males who carry the defective gene and in homozygous females. It rarely occurs in heterozygous females.
- The mechanism by which G6PD deficiency causes neonatal hyperbilirubinemia is not completely understood. Although hemolysis may be observed in neonates who have G6PD deficiency and are jaundiced, other mechanisms play a more important role in the development of hyperbilirubinemia. Hyperbilirubinemia is likely secondary to impairment of bilirubin conjugation and clearance by the liver leading to indirect hyperbilirubinemia.

G6PD deficiency should be considered in neonates who develop hyperbilirubinemia within 1-3 days after birth, a history of jaundice in a sibling, bilirubin levels greater than the 95th percentile

Management

G6PD deficiency can lead to an increased risk and earlier onset of indirect hyperbilirubinemia, which may require phototherapy or exchange transfusion, and can be complicated by kernicterus if not properly managed

References:

1. Frank JE. Diagnosis and management of G6PD deficiency. Am Fam Physician. 2005 Oct 1;72(7):1277-82.

2. Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Blood. 2020 Sep 10;136(11):1225-1240.

3. Bubp J, Jen M, Matuszewski K. Caring for Glucose-6-Phosphate Dehydrogenase (G6PD)-Deficient Patients: Implications for Pharmacy. P T. 2015 Sep;40(9):572-4.

4. Christensen RD, Yaish HM, Wiedmeier SE, Reading NS, Pysher TJ, Palmer CA, Prchal JT. Neonatal death suspected to be from sepsis was found to be kernicterus with G6PD deficiency. Pediatrics. 2013 Dec;132(6):e1694-8.

Guidelines for Management of Thalassemia

The term 'thalassemia' refers to a group of blood diseases characterized by decreased or absent synthesis of one or more of the normal globin chains. According to the chain whose synthesis is impaired, the thalassaemias are called α, β.

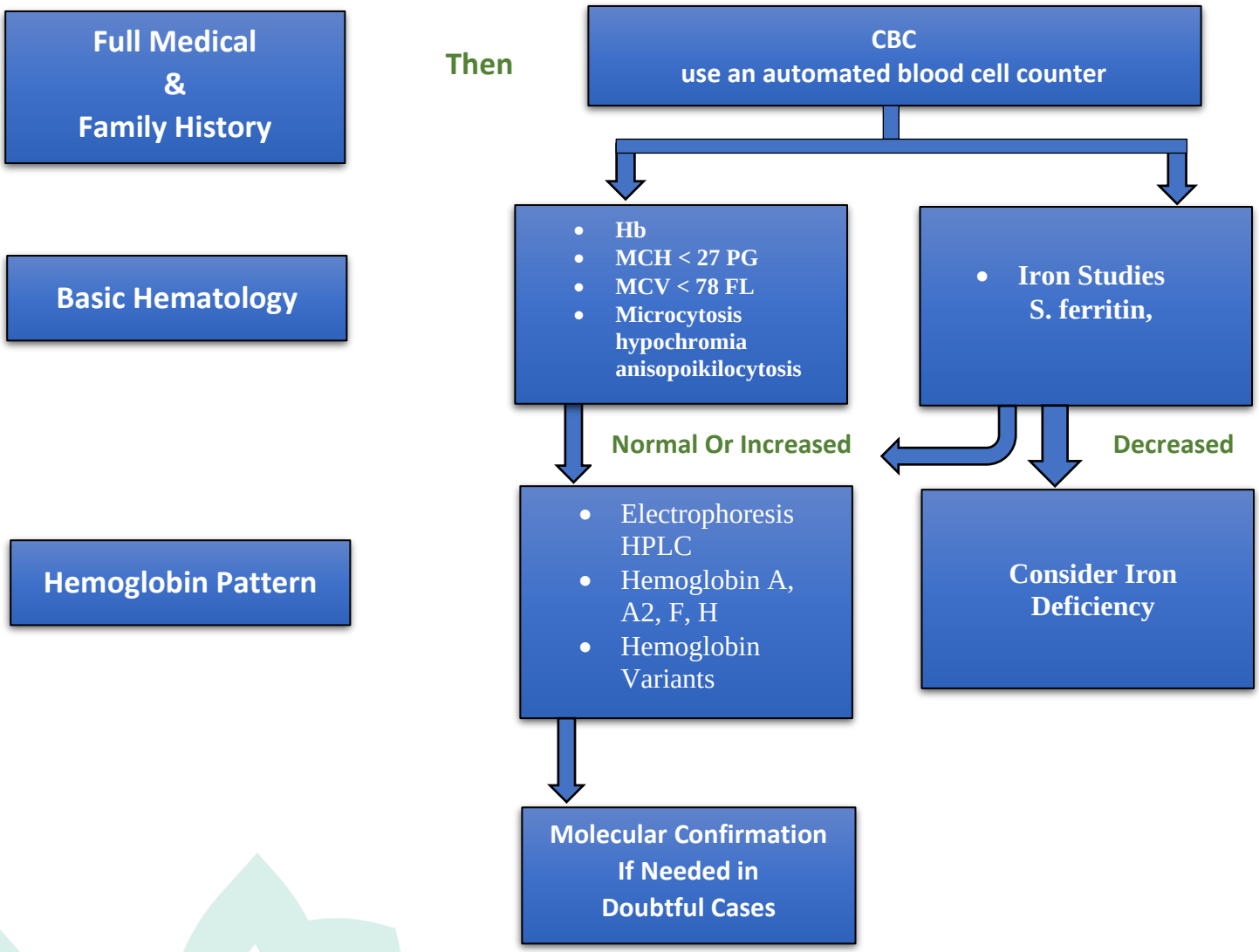


Figure (1): Flow chart for the diagnosis of hemoglobin disorders; steps in carriers screening and disease diagnosis MCH: Mean corpuscular Hb, F: Fetal hemoglobin, MCV: mean cell volume.

Patient presents with pallor, jaundice, anorexia ± poor weight gain

- **Physical examination (pale conjunctiva, ± yellow sclera, ± splenomegaly ± Mongoloid face)**
- **Consanguinity**
- **Family history of similar condition**
- **Family History of splenectomy**
- **Complete blood count and examination of peripheral blood smear**
- **Iron profile**
- **Hemoglobin Electrophoresis**

Differential diagnosis:

- **Iron deficiency anemia**
- **Anemia of chronic disease**
- **Thalassemia minor**
- **Beta-thalassemia major**
- **Thalassemia Intermedia**
- **Other rare chronic anemias**

Figure (2): Work Up for the diagnosis and differential diagnosis of hemoglobin disorders

Table 1: Clinical phenotypes of thalassemia.

Clinical Severity	Phenotype
Silent carrier	• Asymptomatic • No hematological abnormalities
Trait/minor	• Borderline asymptomatic anemia • Microcytosis and hypochromia
Intermedia	• Late presentation > 2 years • Mild-moderate anemia • Mostly **Transfusion-independent** • Clinical severity is variable and ranges between minor to major
Major	• Early presentation < 2 years • Severe anemia • **Transfusion-dependent**

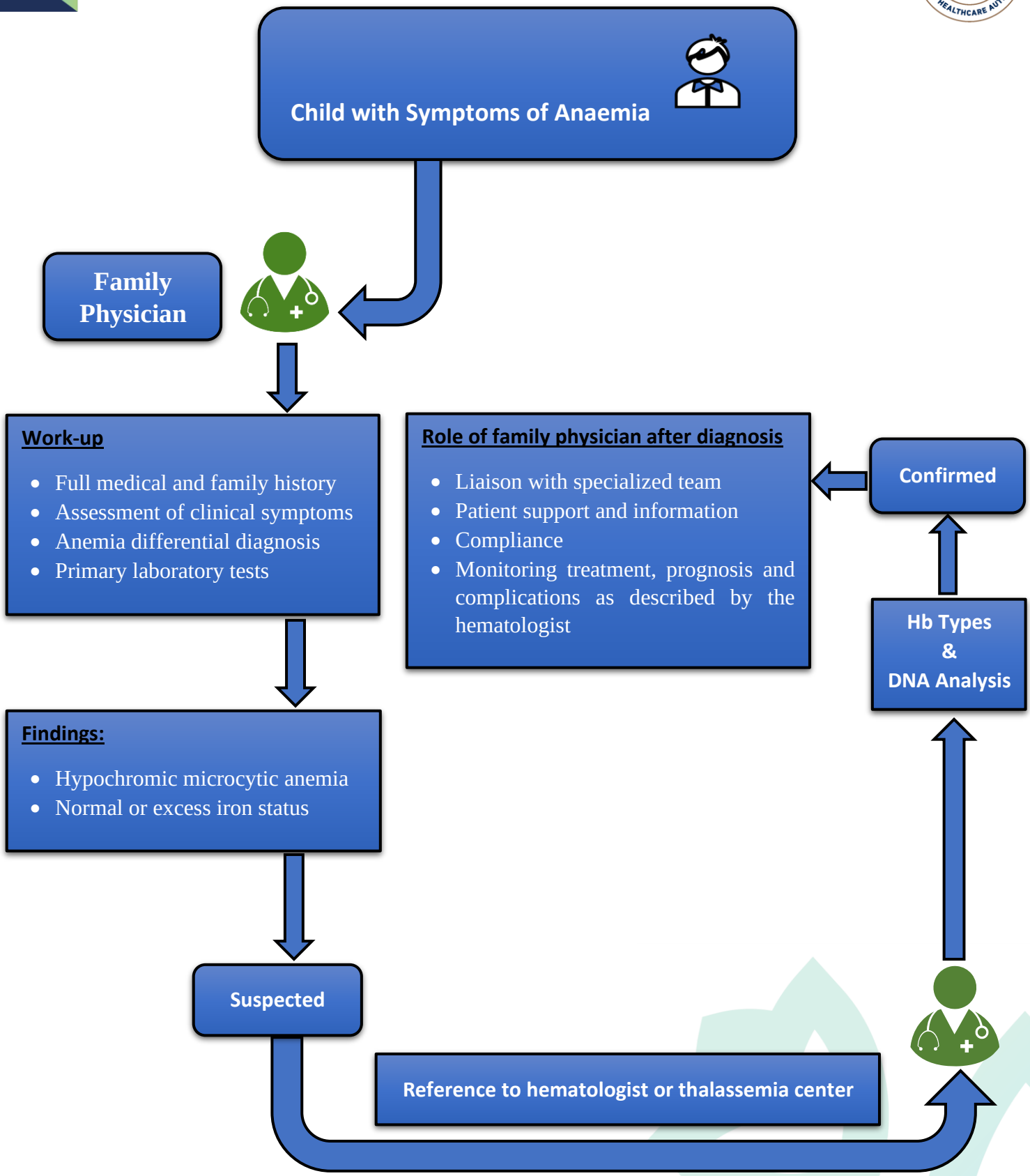


Figure 3 :Clinical suspicion of Thalassemia at primary care

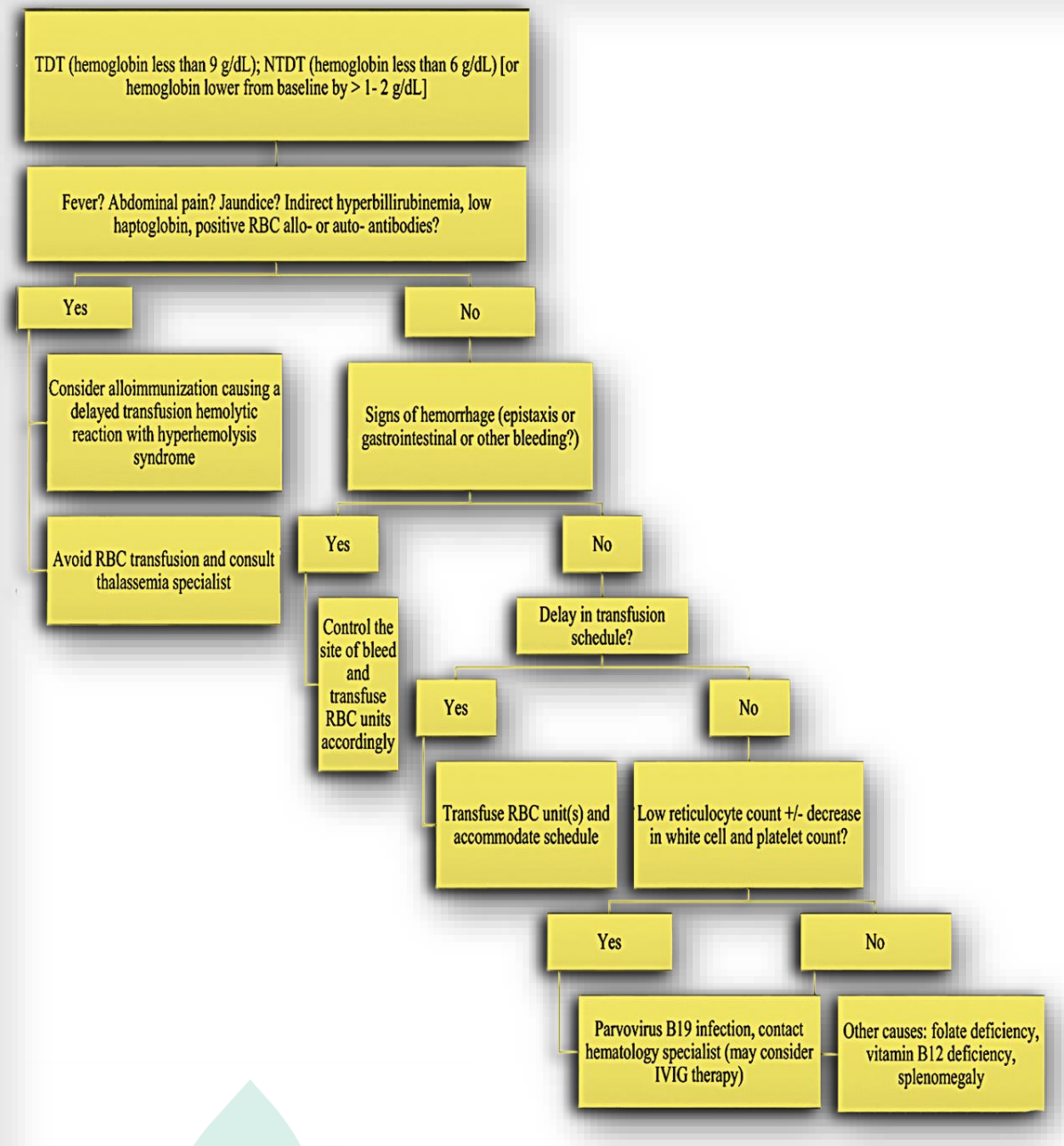


Figure 4 : Thalassemia in the emergency department: special considerations: With Consultation of Hematologist

Reference:

- **Saliba, A.N., Atoui, A., Labban, M. et al. Thalassemia in the emergency department: special considerations for a rare disease. Ann Hematol 99, 1967–1977 (2020). https://doi.org/10.1007/s00277-020-04164-6**

Criteria for initiating transfusion therapy (Decision by the Hematologist)

- **For deciding whom to transfuse, the following should be included in the investigations:**

  ✓ Confirmed diagnosis of thalassemia by clinical and laboratory criteria:
  - Hemoglobin level (Hb) <7 g/dI on 2 occasions, > 2 weeks apart(excluding all other contributory causes such as infections)

AND/OR

- **Clinical criteria irrespective of hemoglobin level:**

  - Significant symptoms of anemia
  - Poor growth / failure to thrive
  - Complications from excessive intramedullary hematopoiesis such as pathological fractures and facial changes
  - Clinically significant extra medullary hematopoiesis

Transfusion thresholds and frequency decided by hematologist

- The recommended treatment for transfusion dependent thalassemia is lifelong regular blood transfusions, usually administered every two or five weeks to maintain the pre transfusion Hb level 9 g/dL.
- This transfusion regimen promotes normal growth, allows normal physical activities, adequately suppresses bone marrow activity in most patients, and minimizes transfusional iron accumulation .
- A higher target pre-transfusion hemoglobin level may be appropriate for patients with heart disease, clinically significant extramedullary hematopoiesis or other medical conditions according to pediatric hematology consultant decision.

Important considerations in Transfusion therapy

- Observation for adverse events, management & reporting are key to the safety of blood transfusion.
- Before first transfusion perform extended red cell antigen typing of patients at least for d,c,e,E.e, and kell red cell phenotype.
- At each transfusion give ABO, Rh(D) compatible blood. Choosing units, compatible units for ABO, Cc, Ee, kell antigen is highly recommended.
- Use leucodepleted packed red cells. Blood bank pre-transfusion filtration is acceptable & Bedside filtration.
- Use washed red cells for patients who have severe allergic reactions.
- Keep a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient.

Treatment of Iron Overload

➢ **Goals of iron chelation therapy:**

- The primary goal of chelation therapy is to maintain safe levels of body iron at all times.
- Once a patient is overloaded, it may take months or years to reduce body storage of iron to safe levels, even with the most intensive treatment.
- Chelation must therefore begin in ß thalassemia major soon after 10 transfusions or when serum ferritin equals or more than 1000 microgm/L
- Chelation must begin in ß intermedia even if non transfused when serum ferritin equals or more than 800 microgm/L
- 24 hours chelation coverage is the ideal, especially in heavily iron loaded patients, to minimize the toxic (labile) iron pools responsible for causing tissue damage.
- **Compliance with chelation therapy determines prognosis**
- **Drugs used for iron chelation include desferasirox , deferiprone and desferoxamine**

Desferasirox (JADENU)
90, 180, 360 mg tablets

Table 2 :The desferasirox dose is based on serum ferritin level

	S. ferritin level (microgram/L)	Dose (mg/kg/day)	Monitoring Tests
NTDT	> 800	**7-14 mg/kg/day**	**CBC/month** S. creatinine/month Urine for proteinuria/month Liver transaminases/ month S. bilirubin (when needed) **S. ferritin / 3 months** Echocardiography / year Ophthalmologic / audiological testing / year (when required)
TDT	1000 – 1500	**21 mg/kg/day**	
	1500 -2500	**24.5 mg/kg/day**	
	> 2500	**28 mg/kg/day**	
	< 500	**7-10 mg/kg/day**	

- Dose: Once daily on empty stomach or with light meal or apple juice in a fixed time.
- Dose adjustment: Every 3-6 months based on S. ferritin in step of 7 mg/kg.

Table 3 :Desferasirox (Jadenu) Adverse events and management

Adverse Event	Management Strategy
Gastrointestinal disturbance (mild-mod diarrhea, abdominal pain, nausea, vomiting).	• Take tab in evening rather than morning. • Avoid solid food for the first few hours. • Avoid Non steroidal Anti-inflammatory drugs and aspirin • If necessary → reduce dose to → 7 mg/kg/day → Titrate in weekly 7 mg/kg/day increments after resolution to return to previous dose.
Rash: (mild-moderate).	• Resolve spontaneously without discontinuation or adjustment.
Rash: (severe)	• Interruption. • Reintroduce after rash resolve at lower dose. • Titrate gradually to previous dose.
Increase in serum liver transaminases (> 4 normal range): (Search for cause hepatitis/cirrhosis). • Transient and non-progressive • Persistent and progressive	• Reintroduce at a lower dose with gradual titration until previous dose • Interruption
Increase in serum creatinine: • Non progressive rise (> 33% above baseline at 2 consecutive measurements) • Progressive rise (S. creatinine > 2 times the age-appropriate upper limit of normal)	• Consider reducing dose by 7 mg/kg/day. • Interrupt.
Cytopenia (unexplained)	• Interruption

Deferiprone
Kelfer: (Cap. 500 mg)
Ferriprox: (Syrup 1 ml = 100 mg)
(Tablets: 500 mg)

Table 4 : Dose of deferiprone based on serum ferritin level in TDT

S. ferritin level (microgram/L)	Dose (mg/kg/day)	Monitoring Tests
TDT > 1000 ug/L	**75 mg/kg/day (in 3 divided doses) after meals**	**CBC / week (1st month)** **CBC/month** S. creatinine/month Urine for proteinuria/month Liver transaminases/ month S. bilirubin / month (when needed) **S. ferritin / 3 months** Echocardiography / year Ophthalmological / audiological testing / year (when needed)

Table 5 : Deferiprone adverse events and management

Adverse Event	Management Strategy
Liver transaminase (> 4 times upper normal level) • **Transient and non-progressive** • **Persistent and progressive**	• Continue by same dose • Stop the drug.
Severe neutropenia, agranulocytosis ANC < 0.5 x 109/L	• CBC / week • Stop drug and not reintroduced
Arthropathy	• Stop drug (if joint symptoms continue despite a reduction in deferiprone dose and are not controlled by NSAI

Desferrioxamine
Desferal

Standard dose

- 20-40 mg/kg for children.
- 50-60 mg/kg for adult.
- Slow S.C. infusion over-8-12 hours/ at least 5-6 times a week using an infusion pump.
- Should started after the first 10-20 transfusion or when serum ferritin level rises above 800 (NTDT) -1000 (TDT) ug/l.
- Recommended to stop administration of desferal in any one with an unexplained fever, until the cause has been identified and effective antibiotic treatment begun.
- **Monitoring schedule:**
  - ✓ **CBC/month**
  - ✓ **S. creatinine/month**
  - ✓ **Urine for proteinuria/month**
  - ✓ **Liver transaminases/ month**
  - ✓ **S. bilirubin (when needed)**
  - ✓ **S. ferritin / 3 months**
  - ✓ **Echocardiography / year**
  - ✓ **Ophthalmologic / audiological testing / year**
- If chelation therapy begins before 3 years of age, careful monitoring of growth and bone development is advised.

Intensive therapy of desferal (50-60 mg/kg / 24 hour / day) 6-7 day/week

➢ INDICATIONS (Decided by consultant hematologist)

- Severe iron overload with persistently very high ferritin values.
- Significant cardiac disease (dysrhythmias / falling of left ventricular function).
- Evidence of very severe heart iron loading (MRI T2*<6 ms).
- Prior to bone marrow transplantation.

Combined Therapy
Desferrioxamine and Deferiprone

Indications

➢ Decided by consultant hematologist

1. When monotherapy with desferrioxamine or deferiprone has failed to control iron overload.
2. Combination can control iron overload in the liver and heart.

Desferrioxamine 40-50 mg/kg/day [5 day/week]
+
Deferiprone 75 mg/kg/day [7 day/week]

If Iron load too high or increasing – rescue therapy to achieve negative iron balance

➢ Decided by consultant hematologist

1. Increasing the daily dose of chelation (within recommended dose)
2. Increasing the frequency of the chelator (within recommended protocol)
3. Switching chelator regimen
4. Rotating or combining chelators
5. DFO (desferoxamine) monotherapy is effective at producing negative iron balance if it is given in sufficient doses and sufficient frequency, but adherence is often a problem.
6. Dose escalation of deferasirox (DFX) is effective in producing negative iron balance .Doses up to 28 mg/kg are effective in patients with high liver iron content or serum ferritin
7. DFP (deferiprone) monotherapy is likely to achieve iron balance at 75 mg/kg in only about one third of patients, with average transfusion rates. It may be increased up to 100 mg/kg with close monitoring. DFO is often added.
8. Rotation of individual monotherapies (sequential chelation) can be helpful in managing individual patients, often for reasons of adherence as much as for specific complications.
9. True ‘combination therapy’ (where two chelators are combined with some degree of overlap pharmacologically) can be useful when monotherapy is inadequate, either to control iron balance or to control iron distribution, particularly in the heart.

Other important medical therapy in thalassemia

a) Vitamin supplementations

1. **Folic a 1-5 mg/day**
2. **Vitamin D:**
   - ✓ For < 4 years old children: 1400 IU vit D daily
   - ✓ For > 4 years old children: 2800 IU vit D daily

   With such doses no need to assess vit D level except if there is clinical evidence of vit D deficiency.
3. **Vit B complex**
4. **Calcium**
5. **Zinc 10-15 mg/day: Starting from age 2 years.**
6. **L-Carnitine: 30-50 mg/kg/day 5 days a week**

b) Hydroxyurea: (Should be prescribed by Hematology Consultant)

- **Not indicated in transfusion dependent thalassemia**
- **Indications of use in non-transfusion dependent thalassemia intermedia**
  - ✓ Patients for which a transfusion course is required but are alloimmunized
  - ✓ Pulmonary hypertension
  - ✓ Extramedullary hematopoietic pseudotumor
  - ✓ Leg ulcers

Dose:

Starting dose of 10 mg/kg/day with dose escalation by 3-5 mg/kg/day every 8 weeks to the maximal tolerated dose, but not exceeding 20 mg/kg/day.

Response:

- Should be evaluated after 3 and 6 months of therapy
- Response defined as a total hemoglobin level increase of >1 g/dl at 6 months
- The drug should be discontinued in patients not showing response.
- Patients showing response should be re-evaluated every 6 months.

Other response parameters: that could be evaluated as indicated:

- ✓ Improvement in growth measures
- ✓ Improvement in functional status and exercise tolerance
- ✓ Improvement in quality of life
- ✓ Improvement in clinical morbidities (pulmonary hypertension, extramedullary hematopoietic pseudotumor, leg ulcers)

Monitoring:

- ✓ Complete blood counts, every two weeks for the first three months then monthly
- ✓ Hepatic and renal function studies, every two weeks for the first three months then monthly
- ✓ History and physical examination evaluating for gastrointestinal, neurologic, or dermatologic side-effects, monthly

Contraindications:

not used in pregnant women and in hepatic or renal dysfunction

c) Allogeneic Stem Cell Transplantation

Indication:

- Transfusion Dependent Thalassemia with HLA matched sibling donor and the patient should be in good performance status

d) Luspatercept

ONLY PRESCRIBED AND FOLLOWED AND MONITORED BY CONSULTANT HEMATOLOGIST IN SPECIALIZED HEMATOLOGY CENTERS

- Luspatercept (Reblozyl) is the most recently approved agent (in the United States and Europe) and by the Egyptian Ministry of Health for the treatment of adults (aged 18 years or more) with transfusion-dependent β-thalassemia given subcutaneous every 3 weeks at a dose of 1mg/kg/dose, It increases hemoglobin and reduces transfusion requirements in TDT by reducing ineffective erythropoiesis

e) Splenectomy

Indications:

- Huge spleen causing dragging pain
- Hypersplenism

Precautions:

- **Preoperative Vaccination**

  - Whenever splenectomy is indicated, patients should receive the following vaccines 2 weeks prior to splenectomy
    - ✓ **Pneumococcal 23-valent polysaccharide vaccine and repeated three to five years later**
    - ✓ **Hemophilus influenzae vaccine**
    - ✓ **Meningococcal polysaccharide vaccine**
  - Patients who underwent splenectomy without being given the vaccines may still benefit from vaccination post splenectomy
  - Influenza vaccine, annually is recommended

➢ **Post operative**

- Long-acting Penicillin for 5 years post-operative in children or till patient is 16 yrs. old.

- Monitor for risk of thrombosis including post operative platelet count and start Aspirin 3-5 mg/kg daily if thrombocytosis.

- Post-splenectomy sepsis remains a risk in all splenectomized thalassemia patients. Therefore, febrile splenectomized patients should undergo rapid evaluation and treatment.

References:

1. Thalassemia International Federation, 2021 Guidelines for the management of transfusion dependent thalassemia , 4th edition version 2.

2. Thalassemia International Federation, Guidelines for the management of non transfusion dependent thalassemia , 2018.

3. Saliba, A.N., Atoui, A., Labban, M. et al. Thalassemia in the emergency department: special considerations for a rare disease. Ann Hematol 99, 1967–1977 (2020).

4. Amal EL Beshlawy, Azza Tantawy and Naglaa Shaheen. Guidelines of Clinical Management of Iron Overload in Thalassemia. 2013.

SEVERE ACQUIRED APLASTIC ANEMIA

Definition

Acquired Aplastic anemia (AA) is a Bone Marrow Failure Disorder characterized by Pancytopenia and Hypocellular bone marrow (a very limited number of hematopoietic stem cells) due to an immune-mediated attack on the bone marrow.

Associated with high mortality rates if left untreated and no single test provides a diagnosis of AA; diagnosis is a process of excluding other bone marrow failure conditions.

Classification

Classification	Criteria
Non-Severe (Moderate)	Hypocellular bone marrow with peripheral blood values not meeting the criteria for severe or very severe aplastic anemia.
Severe	Bone marrow cellularity equal to 25% of the normal control, or 25-50% of the normal control with <30% residual hematopoietic stem cells (HSCs). AND Two of the following peripheral blood criteria: • Neutrophil count: $<0.5\times10^9$/L. • Platelet count: $<20\times10^9$/L. • Reticulocyte count: $<20\times10^9$ /L.
Very Severe	Severe aplastic anemia with neutrophil count $<0.2x10^9$/L.

Diagnostic evaluation of a patient with suspected acquired aplastic anemia

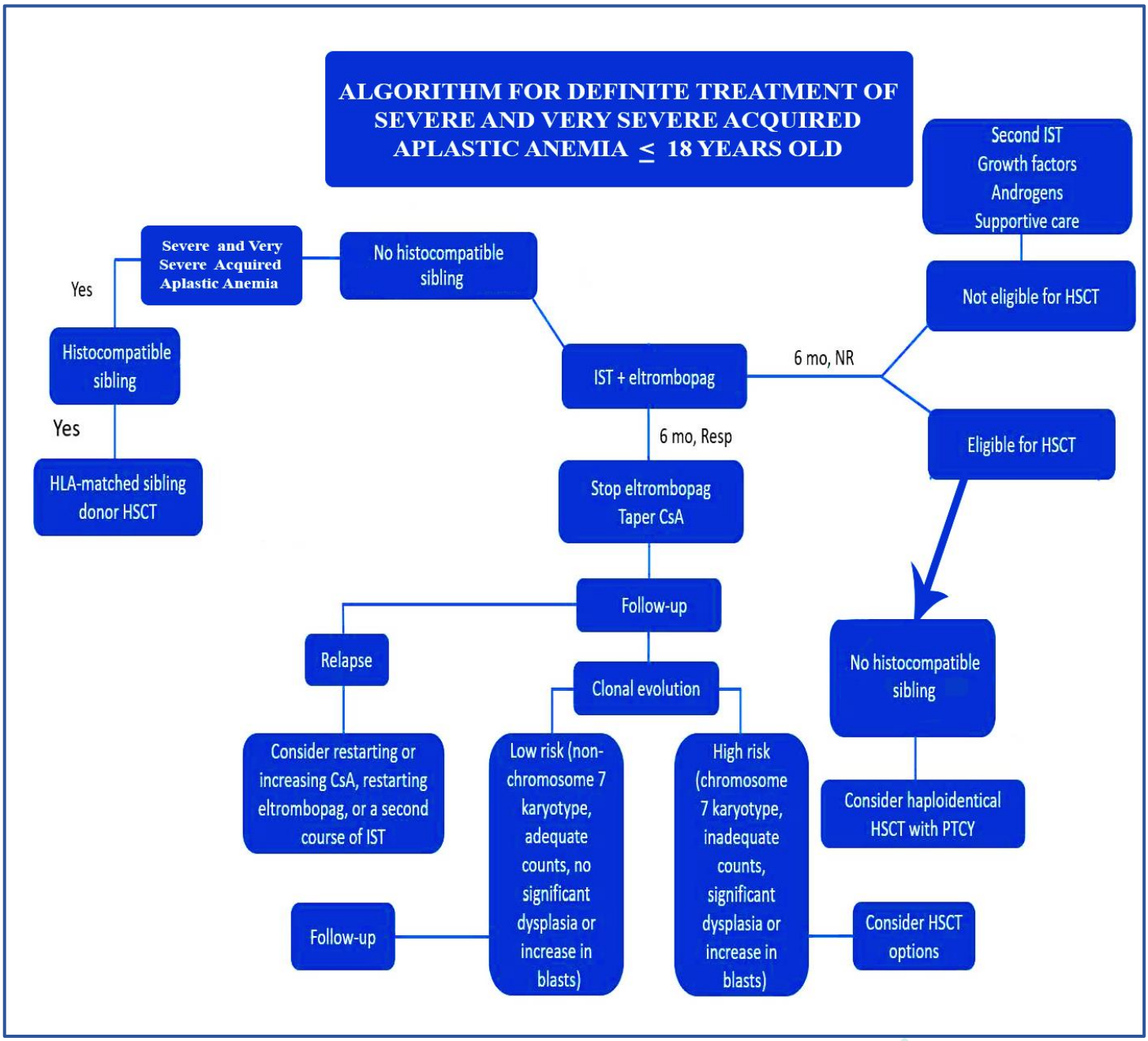
A variety of testing modalities and detailed personal/family history and exposure history are required both in initial screening evaluation and for exclusion of alternative diagnoses.

Initial screening evaluation	
Peripheral blood	CBC with differential, peripheral blood smear, reticulocyte count Complete metabolic panel, LDH, haptoglobin, coagulation parameters
Bone marrow aspirate and biopsy with ancillary studies	Bone marrow aspirate and biopsy Metaphase cytogenetics and FISH panel for MDS-associated chromosomal abnormalities of chromosomes 5, 7, 8, 20 ± Molecular studies
Exclusion of alternative diagnoses	
Infectious	HIV, Hepatitis B/C, parvovirus B19 PCR, EBV, CMV, bacterial, fungal (± mycobacterial testing)
Inherited bone marrow failure	Detailed family history focusing on cytopenias, congenital abnormalities, cancers and lung and liver pathology Chromosomal breakage testing for Fanconi anemia Lymphocyte telomere length for Dyskeratosis congenita Additional syndrome-specific testing if personal or family history are suggestive of specific disorders (IBMF, HLH)
Lymphoproliferative	Flow cytometry and T-cell receptor rearrangement testing for clonal LGL expansion
Medication or toxin-related	Detailed drug and occupational exposure history, with attention to excessive alcohol intake, antibiotics, prior cytotoxic chemotherapeutic agents, and immune-activating agents (e.g. interferon and checkpoint blockade inhibitors)
Nutritional	Vitamin B12, folate, copper, iron studies, ferritin
Rheumatologic	Antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, C- reactive protein
Others (rare)	Exclude other rare etiologies of pancytopenia with a hypocellular marrow: e.g. graft-versus-host disease, HLH

Reference:

- **Peslak SA, et al . Diagnosis and Treatment of Aplastic Anemia. Curr Treat Options Oncol. 2017 Nov 16;18(12):70.**

- Once the diagnostic evaluation is complete, treatment is guided by the AA severity
- For pediatric patients with severe aplastic anemia (SAA) or very severe aplastic anemia (VSAA), a transplant evaluation should be rapidly initiated
- A referral to a tertiary center that specializes in the care of AA patients should be strongly considered.
- Supportive care is mandatory
- Oral cyclosporine with or without elthrombopag has to be started in severe and very severe AA till the workup and evaluation for donors is completed.



Algorithm For Definite Treatment Of Severe And Very Severe Acquried Aplastic Anemia ≤ 18 Years Old

Reference:

- **Modified from Scheinberg P. Acquired severe aplastic anaemia: how medical therapy evolved in the 20th and 21st centuries. Br J Haematol. 2021 Sep;194(6):954-969**

Non-Transplant Therapy in Severe and Very Severe Aplastic Anemia

Immunosuppressive Therapy

- For young patients without matched sibling donor (MSD), immunosuppression with anti-thymocyte globulin (ATG) and cyclosporine A (CsA) combined with eltrombopag is the recommended frontline therapy, offering outcomes comparable to allogeneic BMT
- Horse ATG is the recommended ATG source, based on a randomized-controlled trial of 120 patients showing a superior overall response (68% compared to 37%) and OS (96% compared to 76%) for horse ATG-based IST compared to rabbit ATG-based IST

Cyclosporine

- CSA dose is 5mg/kg/day from d1 to day 365, adjusted to maintain the trough level at 150-250 ng/ml (watching for toxicities mainly renal insufficiency and hypertension) .
- Then tailoring the dose by 5-10%/month up to +24 months(watch for dropping blood counts while reducing CSA).Maintain for longer if no CR has been achieved.

Eltrombopag In Severe and Very Severe Acquired Aplastic Anemia

Revolade (Eltrombopag)

Indication:

- For the first-line, treatment of acquired severe aplastic anemia (SAA) in combination with standard immunosuppressive therapy in adult and Pediatric patients aged 2 years and over who are unsuitable for hematopoietic stem cell transplantation at the time of diagnosis.
- For the treatment of Cytopenias in adult patients with acquired severe aplastic anemia (SAA) who are either treatment-refractory or who have undergone considerable prior therapy and who are not eligible for a hematopoietic stem cell transplant at the time of indication.

Eltrombopag(Revolade) In Frontline Therapy

Starting Dose:

- Recommended Initial Revolade Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia:

Age	Dose Regimen
Patients 12 Years and Older	**150 mg once daily for 6 months**
Pediatric Patients 6 to 11 Years	**75 mg once daily for 6 months**
Pediatric Patients 2 to 5 Years	**2.5 mg/kg once daily for 6 month**

- If baseline ALT or AST levels are > 6x ULN, do not initiate Revolade until transaminase levels are <5xULN.
- Dose Adjustments of Revolade for Elevated Platelet Counts in the First-line Treatment of Severe Aplastic Anemia:

Platelet Count Results	Dose Adjustment or Response
>200 x 10^9/L to ≤400 x 10^9/L	- Decrease the daily dose by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥ 50 x 10^9/L. -In pediatric patients under 12 years of age, decrease the dose by 12.5 mg,
>400 x 10^9/L	Discontinue Revolade for one week. Once the platelet count is<200 x 10^9/L, reinitiate Revolade at a daily dose reduced by 25 mg (or 12.5 mg in pediatric patients under 12 years of age).

Eltrombopag(Revolade) In Refractory Severe And Very Severe Aplastic Anemia

- Use the lowest dose of Revolade to achieve and maintain a hematologic response.
- Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg (Maximum Dose), and may take up to 16 weeks after starting Revolade
- **Initial Dose Regimen:**

  ✓ Initiate Revolade at a dose of 50 mg once daily.

- **Monitoring and Dose Adjustment:**

  ✓ Dose Adjustments of Revolade in Patients with Refractory Severe Aplastic Anemia:

Platelet Count	Dose Adjustment
<50,000/µl following at least 2 weeks of treatment	Increase daily dose by 25 mg to a maximum dose of 150 mg/day
≥100,000/µl to ≤200,000/µl at any point during treatment	Reduce the daily dose by 50 mg. Wait two weeks to assess the effects of this and any subsequent dose adjustments.
>200,000/ µl	Stop Revolade for at least one week. At a platelet count of <150,000/µl reinitiate therapy at a dose reduced by 50 mg.
>200,000/µl after 2 weeks of treatment at the lowest dosage of Revolade	Discontinue Revolade. Reinitiate therapy with 25 mg or the next lower dose once the platelet count is <50,000/µl.

Discontinuation of Revolade is indicated if:

- No hematological response after 16 weeks of therapy of full dose eltrombopag
- New cytogenetic abnormalities are detected
- Excessive platelet count responses
- Important liver test abnormalities developed

Supportive Care

- Throughout the diagnostic and treatment process, patients must be provided aggressive supportive care
- Generally, restrictive transfusion targets (hemoglobin > 7 g/dL, platelets > 10,000 cells/µL) are preferred, especially in potential transplant candidates, given the risk of alloimmunization and transfusional iron overload
- Prophylactic platelet transfusions should be given when the platelet count is <10 · 10^9/l (or <20 X10^9/l in the presence of fever).
- Irradiated blood products should be used to prevent transfusion-associated graft-versus-host disease (GVHD) and specially in candidates of BMT.
- Antifungal prophylaxis with voriconazole or posaconazole should be used in patients with severe neutropenia (absolute neutrophil count < 500 cells/µL) . Intravenous amphotericin should be introduced into the febrile neutropenia regimen early if fevers persist despite broad spectrum antibiotics.
- Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be used during the period of lymphopenia following immunosuppressive therapy, ideally selecting an alternative to trimethoprim-sulfamethoxazole because of its myelosuppressive effects.
- Routine G-CSF use outside of episodes of febrile neutropenia remains controversial
- Iron chelation therapy should be considered when the serum ferritin is >1000 ng/ml.
- The benefits and risks of vaccines in AA also remain controversial due to the risk of immune activation, with some AA guidelines recommending against vaccinations outside of the post-transplant setting

References:

1. Marsh JC, Ball SE, Cavenagh J, et al; British Committee for Standards in Haematology. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol. 2009 Oct;147(1):43-70.

2. Peslak SA, Olson T, Babushok DV. Diagnosis and Treatment of Aplastic Anemia. Curr Treat Options Oncol. 2017 Nov 16;18(12):70.

3. Scheinberg P. Acquired severe aplastic anaemia: how medical therapy evolved in the 20th and 21st centuries. Br J Haematol. 2021 Sep;194(6):954-969

EVALUATION AND EMERGENCY ROOM MANAGEMENT OF THE BLEEDING CHILD

Bleeding in a child can be a diagnostic challenge because of the wide range of possible causes, but making a specific diagnosis is clinically important in order to provide appropriate therapy.

Emergency Initial Critical Points to assess when faced with a child who is actively bleeding or by history has experienced a major hemorrhage

1) **Is the patient continuing to bleed?**
2) **Is the patient hemodynamically stable?**

Patients who are actively bleeding or have occult bleeding and are hemodynamically unstable require rapid initiation of vascular re- expansion and efforts directed at controlling the bleeding.

3) The third critical question is whether the child presenting with bleeding having a bleeding disorder

a. History

- Age , gender ,family history , previous bleeding, previous surgery , drug intake , the nature of the bleeding should be explored with particular attention to location, duration, frequency, and the measures necessary to stop it.

b. Examination

- In addition to the routine examination, the skin should be scrutinized carefully for petechiae, purpura, and venous telangiectasias. The joints should be examined for swelling or chronic changes such as contractures or distorted appearance with asymmetry related to repeated bleeding episodes. Mucosal surfaces, such as the gingiva and nares, should be examined for bleeding.

c. Assess Severity of bleeding by scoring system

d. Initial Laboratory Evaluation

- The purpose is to screen for the presence of a bleeding disorder, categorize the disorder as primary or secondary, and direct further evaluation. Appropriate screening tests include a CBC, peripheral blood smear (PBS), prothrombin time (PT), and activated partial thromboplastin time (APTT, hereafter PTT) and fibrinogen/D-dimers if DIC is suspected Interpretation of lab results refer to algorithm in figure (1).

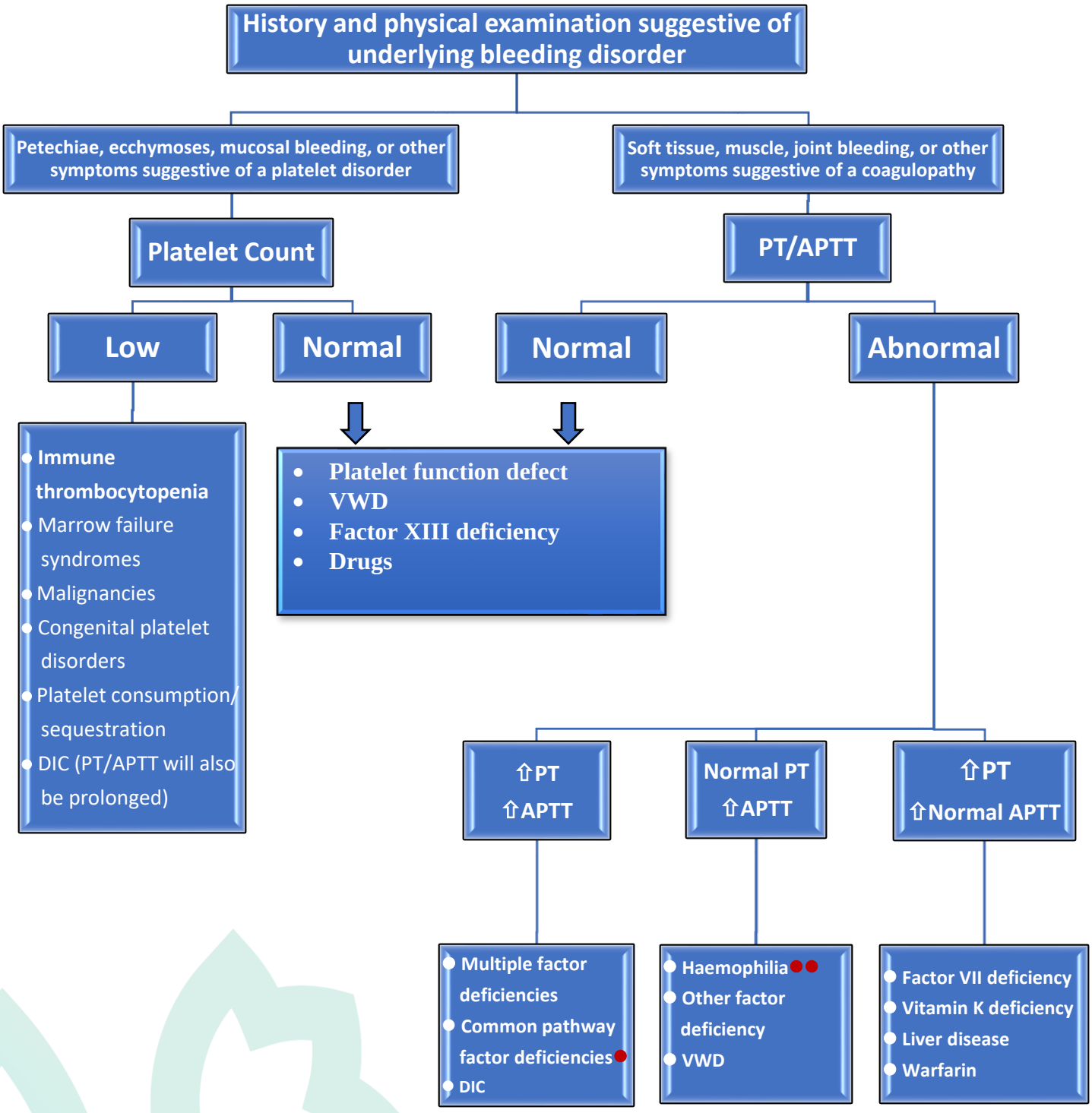


Figure (1): Algorithm for first-line screening in children with suspected bleeding disorder

●**Factor I,II,V,X deficiency**
●●**Factor VIII,IX,XI deficiency**

e. Management

Indications of Therapeutic Platelet Transfusions

- **ITP with major and/or dangerous bleeding (e.g., severe intestinal, intracranial or intraocular haemorrhage)**
- **Acute disseminated intravascular coagulation with major bleeding and platelet count <50×10^6/µL**
- **Platelet function defects (congenital or acquired) with active bleeding**
- **Surgical patient with active bleeding and platelet count <50-100×10^6/µL**

Initial emergency management

"Managed by GP/Pediatritian/hematologist"

- Initial Stabilization
- Vitals should be recorded in a bleeding child as the bleeds may be substantial and life threatening.
- Stabilization of airway, breathing and circulation is the priority in any child in a decompensated state.
- The severity of bleeds governs the speed/extent of investigations versus administration of treatment. e.g., a coagulation disorder with intracranial bleed will require urgent action vs. a patient with hemarthrosis.

Specific management

- This is directed towards the underlying etiology -Please revise specific protocols

Severe undiagnosed coagulation disorder

"Managed by GP/Pediaritian/Hematologist"

- In the setting of severe hemorrhage occurring in an undiagnosed coagulation disorder, fresh frozen plasma (FFP) should be administered, as it contains all the clotting factors.
- The average concentration of factor in FFP is 1 unit/ml; the typical dose is 15 ml/kg

➢ *Bleeding in platelet disorders [managed by hematologist]*

- Platelets are transfused to control bleeding in quantitative or qualitative platelet disorders. Platelets are available as random donor platelets (RDP) or as single donor apheresis platelets (SDAP). Both are effective. SDP has particular indications mainly alloimmunized patients and potential polytransfused patients or preparing for BMT. Transfusion trigger in a thrombocytopenic patient depends not only on the platelet count, but also on its etiology and the clinical condition of the patient. Platelet transfusion is futile and not indicated in majority of patients with immune thrombocytopenia (ITP) as the transfused platelets are quickly destroyed due to circulating antibodies.

➢ *Vitamin k deficiency [managed by GP/Pediaritian/Hematologist]*

- Bleeding Infants with vitamin K deficiency should receive 250–300 µg/kg (maximum 10 mg) of i.v vitamin K without any delay. FFP (10– 15 ml/kg) is indicated if urgent control of bleeding is desired in case of life threatening hemorrhage

➢ *Antifibrinolytic therapy*

"Managed by GP/Pediatritian/Hematologist"

- Given as adjuvant for control of bleeding from mucosal surfaces, particularly epistaxis, gum bleeding and menorrhagia in platelet or coagulation disorders.
- Tranexamic acid dose of 10-20 mg/kg q 6–8h oral or 10mg/kg q 6–8h intravenous (maximum dose of 1 gm/dose)
- Antifibrinolytic therapy is contraindicated in hematuria.

➢ *Recombinant factor VIIa*

"Managed by GP/ Pediatritian /Hematologist"

- The EMA approved indications recombinant factor 7 include treatment of bleeding in children with hemophilia with inhibitors and congenital factor VII deficiency and in bleeding in platelet function defects (e.g., Glanzmann's thrombasthenia), which is not responsive to platelet concentrates.
- Standard dose is 90 µg/kg 2–3 h, till the cessation of bleeding.

"If the patient is known to have a specific coagulation or bleeding disorder Contact the Haematologist" to follow specific disease protocol"

References:

1. Blanchette VS, Breakey VR, Revel-Vilk S (eds): SickKids Handbook of Pediatric Thrombosis and Hemostasis.Basel, Karger, 2013, pp 14–22 (DOI: 10.1159/000346914).

2. Bansal D, Oberoi S, Marwaha RK, Singhi SC. Approach to a child with bleeding in the emergency room. Indian J Pediatr. 2013 May;80(5):411-20.

3. Shin T. S. and Mei J. Haemophilia and Other Bleeding Disorders in Children.Mims Pharmacy2018.

Hemophilia A and B

Background

- Hemophilia is an X-linked bleeding disorder affecting 1 in 6,000–10,000 males and less than 1 in 300,000 females
- Hemophilia A is clotting Factor VIII (8) deficiency
- Hemophilia B is clotting Factor IX (9) deficiency
- Approximately 80% of hemophilia patients have hemophilia A and 20% have hemophilia B.

Management of acute bleeding in hemophilia patient

Assessment

➢ *History*

- Elicit a detailed description of site and mechanism of injury. Internal and joint injuries are often missed
- Determine the type of hemophilia (Factor VIII or IX); the child's clotting factor treatment plan and if there are Factor VIII/IX inhibitors
- Check if the child is on a prophylaxis program and when the most recent dose of factor(s) or non factor therapy was administered

➢ *Examination*

- Assess the site and extent of bleeding
- Assess the impact on function
- Major or suspected bleeding in the head, neck, chest, gastrointestinal tract and abdomen and/or pelvis should be treated with clotting factor immediately, before a full assessment is complete

Table 1: Assessment of severity of hemophilia		
Severity	**Concentration of Clotting Factor (%)**	**Typical Bleeding Picture**
Severe	**<1**	**Frequent bleed episodes are common; predominantly into joints & muscles. Bleeding can occur spontaneously or after a minor injury**
Moderate	**1–5**	**Can bleed after a minor injury. May have bleeding into joints. Severe bleeds occur with moderate trauma, surgery & invasive procedures**
Mild	**>5–40**	**Bleeding occurs with major traumas such as surgery & invasive procedures**

Management

❖ Key Points in Management

1. **Assessment and investigation should not delay factor replacement.**
2. **If there is ongoing bleeding after adequate factor replacement, consider that the patient has developed a factor inhibitor and treat accordingly.**
3. **All children with hemophilia and bleeding should be discussed with a hemophilia treatment center.**
4. **A hemophilia treatment plan should be made, in consultation with a Hematologist, before performing any procedure (eg lumbar puncture).**

➢ *Investigations*

- Clotting factor replacement should not be delayed by investigation
- Imaging of the site of suspected bleeding is dependent on the site and mechanism of injury (trauma)
- Routine coagulation studies are not required if known hemophilia diagnosis
- If surgery is planned or inadequate response to CFC (by observation or history) the assessment of inhibitors is required

➢ *Treatment*

- Most bleeds will require factor replacement with the exception of minor soft tissue injuries and bruising that does not impact on function or mobility
- Prompt clotting factor replacement reduces the pain and long-term consequences of bleeding
- Invasive procedures such as arterial puncture and lumbar puncture must only be performed after clotting factor replacement
- Do not give IM injections

I. Clotting factor replacement

- **Do not delay clotting factor replacement when indicated especially in severe or life-threatening bleeding.**
- **Recombinant clotting factor concentrates or plasma derived clotting factor concentrates are recommended; whatever product is available in emergency situation as long as the patient is known inhibitor negative patient**
- **The dose and protocol of CFR depend on the site of bleeding (tables 2,3)**
  - ✓ **Doses should be rounded up to use whole vials**
  - ✓ The presence of a new inhibitor should be suspected in any child who fails to respond clinically to adequate factor replacement, particularly if the child has been previously responsive
  - ✓ If the child has factor inhibitors (proven or suspected), a special product is required to 'bypass' the inhibitor to initiate clotting ie a bypassing agent
  - ✓ As clotting factor concentrates are not routinely available in all hospitals, children in regional or rural areas should have advanced care plans and ready access to blood products
  - ✓ Whilst it is recommended that children maintain treatment with their established brand of FVIII product, in an emergency situation administration of any brand of FVIII is acceptable.

II. General measures: joint and muscle bleeds

- **For muscle and joint bleeds P.R.I.C.E will limit bleeding and reduce pain. Initiate on arrival**

  - ✓ **P =** Protection (immobilise the affected area in a position of comfort eg splint/slings/crutches)
  - ✓ **R =** Rest
  - ✓ **I =** Ice (apply a cold pack to reduce bleeding and pain)
  - ✓ **C =** Compression bandage (gentle)
  - ✓ **E =** Elevation

III. Venous Access

- **Children with haemophilia are at risk of venepuncture related bleeding. Treat veins with care, apply pressure for at least 3 minutes post venepuncture**
- **In general, IV cannulas are not left in situ on discharge unless discussed with specialist**

IV. Analgesia

- **Do not use products containing aspirin or NSAIDS (eg ibuprofen, diclofenac) as they may worsen bleeding**
- **Paracetamol may be sufficient.**
- **Splinting and immobilization is an effective adjunct for reducing pain**

"Consider consultation with local paediatric team and haemophilia treatment centre when assessing any child with haemophilia with bleeding episodes"

Monitoring of response

- **Clinical assessment of bleeding**
- **Factor 8/9 assay recovery or by PTT follow up**
- **If inadequate response inspite of adequate F8/9 therapy, test for inhibitors is mandatory**

Consider transfer when

- **Child requiring care beyond the level of comfort of the local hospital or treating medical team**
- **Assessing any child with any of:**

  - ✓ Suspected intracranial haemorrhage
  - ✓ Bleeding into neck/throat
  - ✓ Forearm/calf bleed at risk of compartment syndrome
  - ✓ Bleeding into hip or inguinal area (due to risk of iliopsoas haemorrhage)
  - ✓ Undiagnosed abdominal pain
  - ✓ Persistent hematuria
  - ✓ Bleeding causing severe pain

Consider discharge when

- **No active bleeding**
- **Appropriate follow-up is arranged**
- **Patients are provided with a Hemophilia Centre Treatment Card (for their management plan)**

Table 2 Dose and duration of CFC in bleeding in hemophilia A

Hemophilia A			
Type of Hemorrhage	Desired level (IU dL^{-1})	Dose of Factor 8 In severe/moderate HA	Duration (days)
Joint			
	40-60	20-30 units/kg/12 hrs	1-2, May be longer if response is inadequate
Superficial muscle/no N-V compromise (except iliopsoas)			
	40-60	20-30 units/kg/12 hrs	2-3, Sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss			
Initial	80-100	40-50 U/kg every 8-12 hours	1-2
Maintenance	30-60	15-30 units/kg/8-12 hrs	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/Head			
Initial	80-100	40-50 U/kg every 8-12 hours	1-7
Maintenance	50	25 units/kg/8-12 hrs	8-21
Throat and Neck			
Initial	80-100	40-50 U/kg every 8-12 hours	1-7
Maintenance	50	25 units/kg/8-12 hrs	8-14
Gastrointestinal Hemorrhage			
Initial	80-100	40-50 U/kg every 8-12 hours	7-14
Maintenance	50	25 units/kg/8-12 hrs	
Renal			
	50	25 units/kg/8-12 hrs	3-5
Deep laceration			
	50	25 units/kg/8-12 hrs	5-7
Surgery (Major)			
Pre-op	80-100	40-50 U/kg	1-3
	60-80	30-40 U/kg/8-12 hrs	
Post-op	40-60	20-30 U/kg/8-12 hrs	4-6
	30-50	15-25 U/kg/12 hrs	7-14
Surgery (Minor)			
Pre-op	50-80	25-40 U/kg	1-5, depending on type of procedure
Post-op	30-80	15-40 U/kg/8-12 hrs	

Reference:

- Srivastava A, et al; Haemophilia. 2013 Jan;19(1):e1-47

Table 3 Dose and duration of CFC in bleeding in hemophilia B

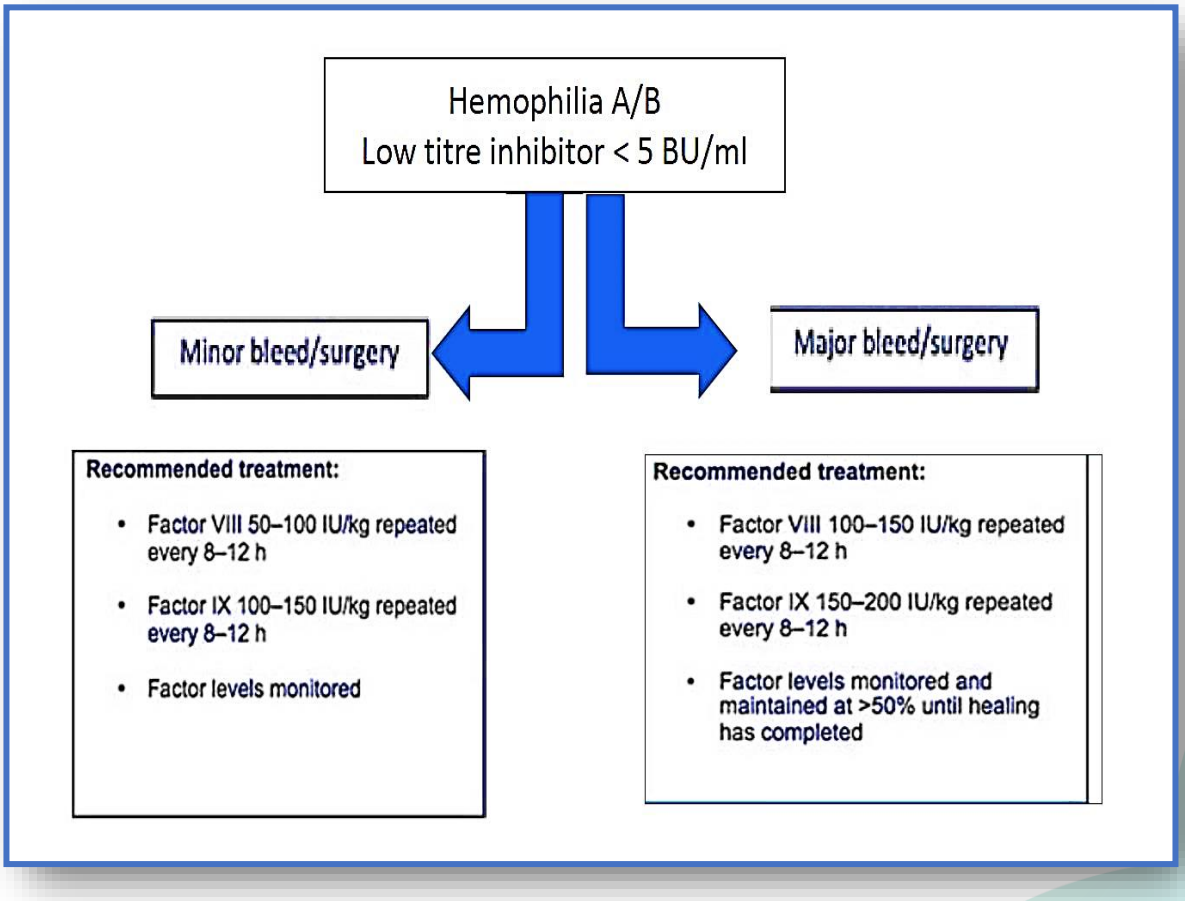
Hemophilia B			
Type of Hemorrhage	Desired level (IU dL^{-1})	Dose of Factor 9 In severe/moderate HB	Duration (days)
Joint			
	40-60	40-60 units/kg/24 hrs	1-2, May be longer if response is inadequate
Superficial muscle/no N-V compromise (except iliopsoas)			
	40-60	40-60 units/kg/24 hrs	2-3, Sometimes longer if response is inadequate
Iliopsoas and deep muscle with NV injury, or substantial blood loss			
Initial	60-80	60-80 U/kg every 8-24 hours	1-2
Maintenance	30-60	30-60 units/kg/12-24 hrs	3-5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/Head			
Initial	60-80	60-80 U/kg every 8-24 hours	1-7
Maintenance	30	30 units/kg/12-24 hrs	8-21
Throat and Neck			
Initial	60-80	60-80 U/kg every 8-24 hours	1-7
Maintenance	30	30 units/kg/12-24 hrs	8-14
Gastrointestinal Hemorrhage			
Initial	60-80	60-80 U/kg every 8-24 hours	7-14
Maintenance	30	30 units/kg/12-24 hrs	
Renal			
	40	40 units/kg/12-24 hrs	3-5
Deep laceration			
	40	40 units/kg/12-24 hrs	5-7
Surgery (Major)			
Pre-op	60-80	60-80 U/kg	1-3
	40-60	40-60 U/kg/12-24 hrs	
Post-op	30-50	30-50 U/kg/12-24 hrs	4-6
	30-50	20-40 U/kg/12-24 hrs	7-14
Surgery (Minor)			
Pre-op	50-80	50-80 U/kg	1-5, depending on type of procedure
Post-op	30-80	30-80 U/kg/12-24 hrs	

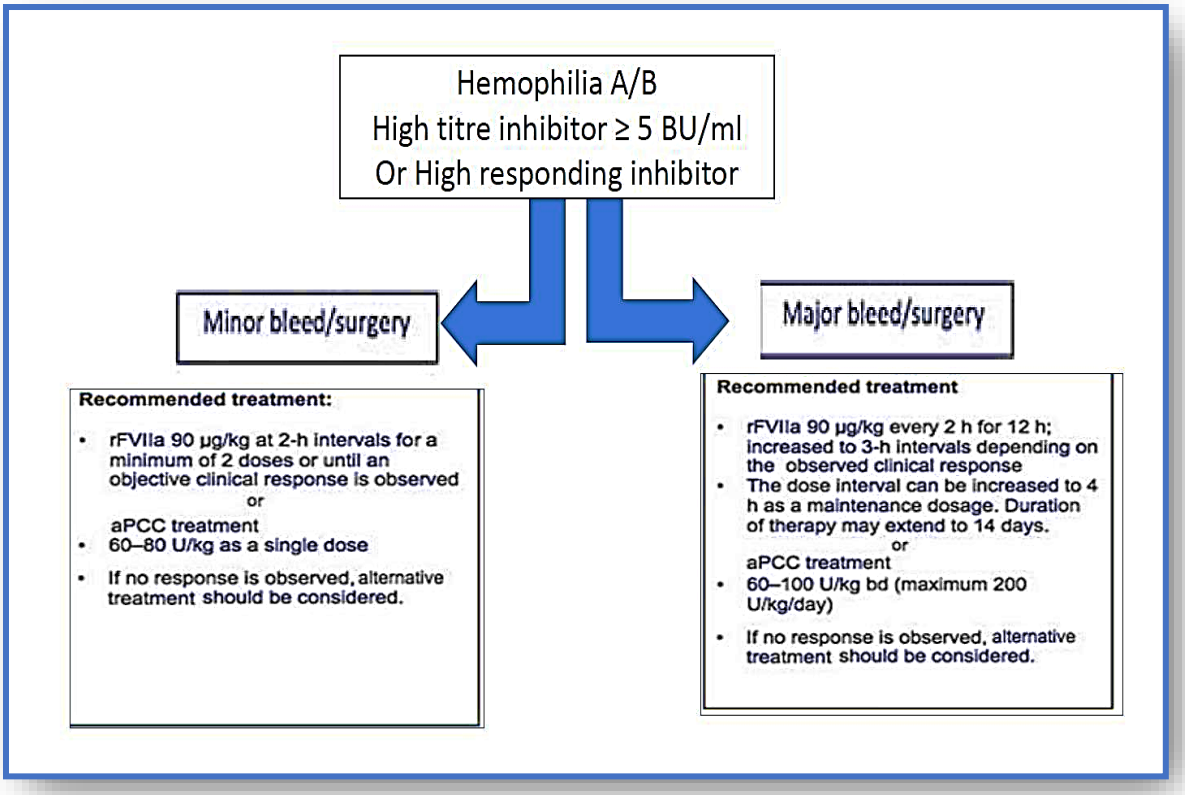
Reference:

- Srivastava A, et al; Haemophilia. 2013 Jan;19(1):e1-47

Management of Acute Bleeding in Hemophilia Patient with Inhibitors

- The development of an inhibitor, an antibody that inactivates the coagulant function of replacement factor, is one of the most serious complications of hemophilia treatment. FVIII inhibitors develop in 20–30% of boys with severe hemophilia A, whereas FIX inhibitors develop in 3–5% with severe hemophilia B. These usually develop within the first 50 exposures to factor replacement.
- Acute bleeding in patients with low-titer inhibitors (<5 BU) can be managed by using larger doses of factor replacement
- Acute bleeding in patients with high titer inhibitors (≥5 BU) require the use of alternative hemostatic agents (Bypassing agents) which include recombinant factor VIIa (rFVIIa; NovoSeven) and activated prothrombin complex concentrates (pd-aPCC; FEIBA)





A high-responding inhibitor is applied if the inhibitor titre is greater than 5 BU at any time

Treatment of Breakthrough Bleedings If Patient on Emicizumab

1) In inhibitor positive patients
2) In inhibitor negative patient

In Hemophilia A With Inhibitors Receiving Emicizumab (WFH 2020 Guidelines)

❖ **The WFH recommends:**

- **Low-responding inhibitors :** clotting factor replacement therapy including FVIII
- **High-responding FVIII inhibitors:** rFVIIa preferred over aPCC due to the risk of thrombotic microangiopathy

- Bleeding episodes should not be treated with aPCC unless no other option is available
- The cumulative dose of aPCC should not exceed 100 U/kg/day
- The use of aPCC at dose higher than 100 U/kg/day for more than 24 hours was associated with thrombotic microangiopathy and thrombotic events

"Thrombotic risks may last for up to 6 months after stoppage of emicizumab during which plasma levels of emicizumab may persist"

Remark:

❖ **Caution is urged when rFVIIa** is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STE myocardial infarction and pulmonary embolism.

In Hemophilia A With Inhibitors Receiving Emicizumab (UKHCDO 2020 Guidelines)

❖ **UKHCDO : UK Hemophilia Center Doctor Organization**

1) ***First-line treatment of bleeds should be with rFVIIa***

- The initial dose of rFVIIa should not exceed 90 µg/kg
- Doses of 45 µg/kg every 4 h may be efficacious for some bleeds
- If lower doses or frequencies of rFVIIa do not result in adequate haemostasis, rFVIIa should be increased to 90 µg/kg every 2 h before it is assumed to have failed

2) ***Human FVIII may be a treatment option if the bleed does not resolve with rFVIIa and inhibitor titres are low***

3) ***If a severe bleed does not respond to rFVIIa and other treatment options are not available:***

- aPCC may be administered at an initial dose of ≤50 U/kg (25 U/kg may be efficacious for some bleeds)
- If a second dose of aPCC is required, the patient should be admitted to hospital for TMA surveillance
- A second dose of 25-50 U/kg may be considered on Day 1 if necessary
- The cumulative dose of aPCC should not exceed 100 U/kg/day

In Hemophilia A Without Inhibitors Receiving Emicizumab (UKHCDO 2020 Guidelines)

❖ **UKHCDO : UK Hemophilia Center Doctor Organization**

1) ***Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve haemostasis; this may be lower than the patients' prior FVIII dose.***

2) ***Co-exposure to emicizumab and FVIII was not reported with any unexpected safety events, serious adverse events, thrombotic events, or thrombotic microangiopathy (TMA).***

Prophylaxis for children with Haemophilia A and B

➢ What is the aim of prophylaxis in the management of a person with haemophilia (PWH)?

➲ ***The primary goal of haemophilia care*** is to prevent bleeding and preserve musculoskeletal function : this is usually achieved by prophylaxis, because outcome measures will clearly differ depending on the joint health status at onset of prophylaxis , prophylaxis protocols are classified as primary, secondary and tertiary.

❖ Primary prophylaxis

- Commences in early childhood at the latest before the second joint bleed or the age of 3 years, in the absence of documented joint disease, with the aim that the child reaches maturity with normal joints .

❖ Secondary prophylaxis

- Commences after two or more joint bleeds, but before the onset of proven joint disease. It is likely that these bleeds have caused subclinical but established, irreversible joint disease.
- Prophylaxis aims to limit the consequence of this damage by preventing further bleeding, maximizing function long-term.

❖ Tertiary prophylaxis

- Commences after the onset of clinically/radiologically apparent joint disease and aims to slow down progression of joint disease, reducing pain and maintaining quality of life. It cannot, however, reverse established joint disease.

➢ Who should receive primary prophylaxis? When to start?

- All patients with severe hemophilia A and B disease (factor 8 or 9 level <1 IU/dl) and all moderate hemophilia A or B with severe phenotype.
- Given after the first joint bleed in children aged two or more years.

➢ Who should receive secondary prophylaxis?

- All patients with severe hemophilia A and B disease (factor 8 or 9 level <1 IU/dl) and all moderate hemophilia A or B with severe phenotype, if not on primary prophylaxis.
- Given after the second or more joint bleeds in children aged two or more years in the absence of osteochondral joint disease.

➢ Who should receive tertiary prophylaxis?

- All patients with severe hemophilia A and B disease (factor 8 or 9 level <1 IU/dl) and all moderate hemophilia A or B with severe phenotype, if not on 1ry/2ry prophylaxis.
- Given in the presence of one or more osteochondral joint disease who is experiencing ongoing bleeding.

❖ Important Note:

"Prophylaxis should be started regardless of age and continued for life following completion of treatment for a spontaneous intracranial bleed or other life threatening hemorrhage, if not already established"

Choice of Product for Hemophilia Prophylaxis

1) Factor replacement or non-factor replacement

- All severe hemophilia A patients and phenotypically severe moderate hemophilia A with factor 8 inhibitors should receive non-factor replacement therapy prophylaxis (Emicizumab, HemLibra).
- All severe hemophilia A patients and phenotypically severe moderate hemophilia A without factor 8 inhibitors should receive factor 8 prophylaxis therapy with exceptions as below.
- Non-factor replacement therapy prophylaxis (Emicizumab, HemLibra) is indicated in severe hemophilia A patients and phenotypically severe moderate hemophilia A without factor 8 inhibitors in the following conditions
    a. After life threatening hemorrhage
    b. After major surgery
    c. In the presence of documented difficult venous access
    d. As primary prophylaxis and early secondary prophylaxis in children more than one year old and no target joint
- All severe hemophilia B patients and phenotypically severe moderate hemophilia B without factor 9 inhibitors should receive factor 9 prophylaxis therapy.

2) Plasma Derived or recombinant Factor 8 or Factor 9

- The European Hematology Agency [EMA] concluded that there was no clear evidence of a difference in the incidence of inhibitor development between Plasma Derived and Recombinant FVIII products.
- The risk of transfusion-transmitted infection with Plasma Derived products is low, but cannot be excluded, and should be taken into consideration when selecting a product.

3) Switch of Factor Replacement Products

- It is preferrable to be maintained on prophylaxis with the same factor replacement product especially in newly diagnosed hemophilia in the first 150 exposure days who are inhibitor negative.
- Switching between factor replacement products for prophylaxis may be performed in patients with more than 150 exposure days and no prior inhibitor. In this group of patients switching is not associated with increased risk of development of inhibitors.

"Whilst it is recommended that children maintain treatment with their established brand of FVIII product, in an emergency situation administration of any brand of Factor 8 or 9 is acceptable"

4) Standard Half Life or Extended Half Life Factor 8 or 9 Products

- At present time the MOH supports Standard half-life factor 8 or 9 products for prophylaxis in hemophilia A/B patients without inhibitors
- Extended half-life products have the potential of decreasing frequency of administration and hence possibly increase patient compliance however not available at present time

How to start factor 8 or 9 prophylaxis in children?

- Factor 8 prophylaxis is given at dose of 25–40 u/kg twice per week, while Factor 9 prophylaxis is given at dose of 40-50 u/kg once per week with follow up of breakthrough bleeds with dose and frequency adjustment and individualization to control the bleeding pattern.

How to start Emicizumab prophylaxis in hemophilia A children when indicated?

- Emicizumab is started at loading dose of weekly 3 mg/kg subcutaneous for 4 doses then the patient is maintained on either protocol of 1.5 mg/kg weekly or protocol of 3 mg/kg every 2 weeks depending on treating physician decision

How long should prophylactic therapy continue?

- Prophylaxis throughout childhood should result in the individual having normal musculoskeletal function and the goal of haemophilia care in adults should be to maintain that function by preventing bleeding. The standard of care should be to continue life-long.

Monitoring for Adverse events

1) Screening and Monitoring for Inhibitors

- Inhibitors are IgG alloantibodies to exogenous clotting factor VIII (FVIII) or factor IX (FIX) that neutralize the function of infused CFCs.
- Inhibitors are detected and measured by the Bethesda assay or Nijmegen-modified Bethesda assay. Inhibitors are positive when Bethesda titer >0.6 BU for FVIII and ≥0.3 BU for FIX. Testing is critical to detect inhibitors early to ensure appropriate treatment.

There are 2 levels of inhibitors, based on the titers observed:	
Low-responding inhibitor <5.0 BU, typically transient	**High-responding inhibitor ≥5.0 BU, typically persistent**
Screening and Monitoring for Inhibitors	
✓ *After initial factor exposure, every 6-12 months and then annually*	
✓ *Failure to respond to adequate CFC replacement therapy*	
✓ *After intensive CFC exposure, e.g., daily exposure for more than 5 days and within 4 weeks of the last infusion*	
✓ *Before major surgery and if suboptimal post operative response to CFC therapy*	
✓ *Poor clinical response to CFC replacement therapy*	

2) Adverse Effects Associated with Emicizumab

- Thrombotic events have been reported with emicizumab use including thrombotic microangiopathy and venous thrombosis, when activated prothrombin complex concentrate is co-administered at a dose >100 u/kg for >24 hours with emicizumab.
- No thrombotic events have been reported in association of emicizumab with FVIII replacement in inhibitor negative patients.

Assessment of clinical efficacy of a prophylaxis regimen

1. **Bleeding rates**

- Bleeding episodes should be reported and reviewed promptly by treating physician in order to review the prophylactic regimen [drug,dose and frequency] and address musculoskeletal factors ,adherence and psycho-social factors.

Recommendation:

❖ The nature and frequency of breakthrough bleeding should be carefully documented and monitored. Any suspected bleeds on a prophylactic regimen should prompt a clinical review.

❖ Adherence to prescribed prophylaxis should be recorded contemporaneously, with systems in place for the clinical team to be alerted to changes in bleeding frequency.

2. **Impact of haemophilia and treatment on daily life**

- The impact of haemophilia and prophylaxis on daily life can be assessed by direct questioning.

Recommendation:

❖ The acceptability of a prophylactic regimen should be discussed with the individual, considering the impact of both haemophilia and prophylaxis on their quality of life, performance of daily activities and physical activity levels.

3. **Musculoskeletal health**

- The role of the specialist haemophilia physiotherapist is to minimise the likelihood of bleeds by maximising strength and biomechanics through exercise, advice and prehabilitation.
- However, as children can develop arthropathy with no history of clinically overt joint bleeding, regular assessment of joint function is essential and can be done using targeted questioning (see above), physical examination and imaging.

3).a Physical Examination and Joint Scoring

- Systematic musculoskeletal examination can reveal changes in gait, joints and muscles/ligaments/tendons due to arthropathy or maladaptive changes due to previous bleeds. This can inform rehabilitative regimens to improve joint function, reducing the likelihood of further bleeds and may also signal the need for an alteration in prophylaxis. This examination should be carried out by a physiotherapist skilled in musculoskeletal examination and with a good understanding of developmental norms.
- Scoring using the Hemophilia Joint Health Score [HJHS] . A deterioration in an individual's joint score should prompt a review of bleeding and the prophylaxis regimen.

Recommendation:

❖ Patients with hemophilia receiving prophylaxis should undergo annual, detailed musculoskeletal assessment by an appropriately trained physiotherapist using a validated objective scoring system.

3).b Joint Imaging

- Plain radiography, while cheap and relatively quick, is insensitive to early arthropathy and current interest is focussed on MRI and ultrasonography (USS).
- MRI scoring is more sensitive to early arthropathic lesions than clinical or X-ray scores, but is time-consuming and expensive.
- There are no longitudinal data showing the predictive value of early MRI changes or how MRI might aid the clinician in monitoring prophylaxis. In addition, young children may require general anaesthesia in order to acquire the imaging.
- Ultrasonography helps to establish the diagnosis of acute haemarthrosis, ultrasonography can detect joint effusions, synovial hypertrophy and osteochondral changes of developing arthropathy. It can be delivered cheaply and simply in the clinic using a limited scanning protocol and has good inter-user consistency, but at present the clinical relevance of early ultrasound changes has not been established.

Recommendation:

❖ Radiological imaging should not be used to assess efficacy of prophylaxis: plain radiographs are insufficiently sensitive and neither MRI nor ultrasonography changes have yet been shown to be predictive of long-term joint function.

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

NE = Non-Evaluable

Sum of Joint Totals + ☐

Global Gait Score ☐

(☐ NE included in Gait items)

HJHS Total Score = ☐

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = > 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Extension loss
(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-Evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-Evaluable

Fish Score

Functional Independence Score for patients with Hemophilia

- This score was developed to measure the functional independence of people with hemophilia.
- FISH is based on observing the performance of daily life activities i8 tasks in n 3 categories
- The activities are graded from 1 to 4, according to the assistance required to perform the tasks.
- The scores achieved in each task are summed giving a total from 8 to 32 points with 32 indicating the highest level of functional independence.

Levels Of Function and Their Scores

1. The subject is unable to perform the activity, or needs complete assistance to perform the activity.

2. The subject needs partial assistance/ aids/ modified instruments/ modified environment to perform the activity.

3. The subject is able to perform the activity without aids or assistance, but with slight discomfort. He is unable to perform the activity like his healthy peers.

4. The subject is able to perform the activity without any difficulty like other healthy peers.

FUNCTIONAL INDEPENDENCE SCORE IN HEMOPHILIA (FISH)

Performance based instrument

Patient Name:	Patient Code:
	Today (dd/mm/yyyy):___/___/___.
A.Self Care	
1. Eating and grooming	○ 1 ○ 2 ○ 3 ○ 4
2. Bathing	○ 1 ○ 2 ○ 3 ○ 4
3. Dressing	○ 1 ○ 2 ○ 3 ○ 4
B. Transfers	
4. Chair	○ 1 ○ 2 ○ 3 ○ 4
5. Squatting	○ 1 ○ 2 ○ 3 ○ 4
C. Locomotion	
6. Walking	○ 1 ○ 2 ○ 3 ○ 4
7. Stairs (12 - 14 steps)	○ 1 ○ 2 ○ 3 ○ 4
8. Running	○ 1 ○ 2 ○ 3 ○ 4
Total Score	

Scores range from 1 - 4 depending on the degree of independence (see scoring key)

Synovectomy

Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding and cannot be controlled by other means.

The decision of synovectomy is the hematology consultant decision and done in hemophilia expert center.

Recommendations:

- Non-surgical synovectomy, guided by ultrasound, is the procedure of choice.
- Chemical synovectomy should be used when appropriate and available. Rifampicin is highly effective and has few side effects; it can be used in an outpatient setting when preceded and followed by factor infusion, analgesics and bed rest.

Immune Tolerance Induction

In hemophilia A and hemophilia B patients with inhibitors , Immune tolerance induction (ITI) involves administration of factor VIII or factor IX in increased doses so that the individual's immune system learns to tolerate the factor VIII/factor IX and ceases to produce inhibitors.

The cost of a full course of treatment is considerable because the amounts of factor VIII or IX used in ITI are relatively large. If successful, however, ITI reduces the risk of bleeds, joint damage and other complications.

The decision of immune tolerance induction and the protocol used is the hemophilia consultant decision and done in hemophilia expert center

Dental Care in Hemophilia

General Measures

- Good oral hygiene for people with hemoplilia should be encouraged to prevent the need for dental work and oral diseases such as gingivitis, dental caries and periodontal disease, which may cause serious gum bleeding. Teeth should be brushed at least twice daily for plaque control, using a soft or medium textured toothbrush and fluoridated toothpaste.

Dental Surgery and Invasive Procedures

- Before any dental surgery or other invasive procedure within the oral cavity, hemostasis management should be individually planned with advice from a hematologist.
- Systemic and/or topical antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid) are effective as adjuvant treatment in the management of dental interventions pre- and postoperatively to reduce the need for factor replacement therapy. Antibiotics should be prescribed only if clinically indicated for management of infection. Antibiotic prophylaxis should be administered to patients with prosthetic joint replacement.
- Any swelling, difficulty swallowing (dysphagia), hoarseness or prolonged bleeding after dental surgery must be reported to the dentist/hematologist immediately.
- For many dental procedures, adequate local anesthesia is necessary, and most dental injections can be delivered safely. High-risk intramuscular oral injections may require systemic hemostatic measures. These measures should be established preoperatively with the advice of a hematologist. Low-risk routes of delivery such as intraligamentary single tooth anesthesia or buccal infiltration injections are effective alternatives to inferior alveolar nerve block.

Guidelines for people with moderate-to-severe hemophilia requiring outpatient/inpatient surgical dental treatment

Procedure	Factor VIII/XI levels required	Pre-, peri- and postoperative schedule
Restorative procedures	Can generally be performed without raising factor levels If nerve blocks are needed, first raise factor level to ≥50% Factor VIII: 25–30 IU/kg/dose Factor IX: 50 IU/kg/dose	Tranexamic acid PO 25 mg/kg every 6 h for 24 h before surgery (adult 500–1000 mg) Continue for 3–7 days (postoperative) Avoid acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory drugs Local measures to control/prevent bleeding should be used
Dental extraction Dento-alveolar or periodontal surgery	Raise factor level to 50–60% Continue factor coverage for 1–2 days (postoperative) if needed Factor VIII: 25–30 IU/kg/dose Factor IX: 50 IU/kg/dose Non-absorbable sutures preferred	Extensive procedures may require hospitalization Tranexamic acid IV 10 mg/kg 1 h before surgery or PO 25 mg/kg/6 h and continue for 7–10 days after procedure Soft diet for 7 days Local measures (tranexamic acid mouth rinse) to control/prevent bleeding should be used Careful brushing around wound site for minimum of 3–5 days postoperatively to avoid disturbing clot and wound healing Antibiotic prophylaxis (in case of bacteremia and possible pre-surgical infection); oral course for 7 days Smoking should be avoided
Major surgery Maxillofacial surgery	*Preoperative* Raise factor level 100% Factor VIII: 50 IU/kg/dose Factor IX: 100 IU/kg/dose *Postoperative* Factor level 50% for 7 days Factor VIII: 25 IU/kg/dose Factor IX: 50 IU/kg/dose	As above Inpatient for 7–10 days
Endodontic treatment	None in moderate hemophilia Raise factor level to 50–60% in severe hemophilia Factor VIII: 25-30 IU/kg/dose Factor IX: 50 IU/kg/dose	As above

Recommendations:

- **Good oral hygiene should be encouraged in people with hemophilia.**
- **Hemostasis management (including systemic and/or topical antifibrinolytics) should be individually planned with advice from a hematologist before any dental work is undertaken.**
- **Patients with prosthetic joint replacement need antibiotic prophylaxis.**
- **Any problems after dental surgery (swelling, difficulty swallowing, hoarseness, prolonged bleeding) must be reported immediately.**
- **Most dental injections can be delivered safely in people with hemophilia.**

References:

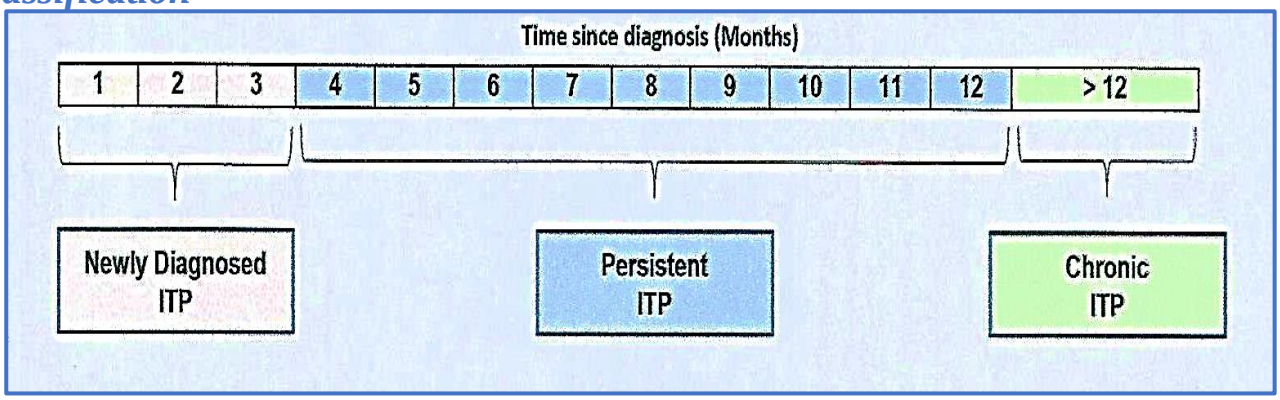
1. Collins, PW, et al. Haemophilia. 2018; 24: 344– 347.
2. Escuriola-Ettingshausen, C, et al. Haemophilia. 2020; 00: 000– 000.
3. Hoffmann-La Roche Ltd. HAVEN 3 protocol v3.
4. Mokhtar, G et al . The Journal of Haemophilia Practice, vol.5, no.1, 2018, pp.83-92
5. Mahlangu J, et al. NEJM 2018;379:811–822.
6. Srivastava A, et al. Haemophilia. 2020 Aug;26 Suppl 6:1-158.
7. Tarawah AM, et al. J Appl Hematol 2011;2:171-8.

IMMUNE THROMBOCYTOPENIA (ITP)

Definition

Immune-mediated disorder characterized by isolated thrombocytopenia (PLT <100 x 10^9 /L) with absence of any obvious underlying cause of the thrombocytopenia.

Classification



Newly Diagnosed ITP

Clinical Workup:

- ✓ **Complete Patient History.**
- ✓ **Physical Examination (Including Bleeding Score).**

"Exclude other thrombocytopenia associated disease and assess bleeding score"

Lab Workup:

- ✓ **Complete Blood Count (CBC).**
- ✓ **Blood Film.**
- ✓ **Reticulocyte Count.**
- ✓ **±Coomb's Test.**
- ✓ **Age ≥ 10 years do ANAbs and anti DNA Abs**
- ✓ **Bone marrow examination is necessary if atypical features like organomegaly , bicytopenia or pancytopenia, abnormal blood film , bone aches …**

Table 1 : Bleeding Score

The Buchannan Score

Severity of Bleeding Symptoms		
Grade I	Minor/ Minimal	Few petechiae (≤100 total) and/or ≤5 small bruises (≤3 cm in diameter)
Grade II	Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm in diameter)
Grade III	Moderate	Mucosal bleeding that does not require immediate medical attention (eg, brief epistaxis, intermittent gum bleeding, menorrhagia)
Grade IV	Severe	Mucosal bleeding or suspected internal hemorrhage that requires immediate medical attention but that is not life-threatening (eg, GI bleeding, severe prolonged epistaxis, muscle or joint hemorrhage)
Grade V	Life-threatening	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage in any site

Table 2: Management of Acute ITP

Clinical Situation	Therapy Options
- Platelets Count < 30 x 10 ⁹ /L **- Bleeding Manifestation Score: 3,4**	➢ **Oral Corticosteroids:** - Prednisolone: 2-4 mg/kg for 5-7 days (Maximum dose of 80mg/day). OR -Dexamethasone: 0.6 mg/kg for 4 days (Maximum dose of 40mg/day). ➢ **± IVIG**
- Life Threatening Bleeding **Bleeding score 5**	➢ **IVIG:** 1 gm/kg/day for 2 days (Maximum Dose of 2gm/kg). + ➢ **Methyl Prednisolone** 20 mg/kg/day for 3-4 days (Maximum Dose of 1gm/day). ± ➢ **With or without Platelets Transfusion according to bleeding severity**

- Follow up: CBC Twice/Week.

Assess the severity of patient's bleeding symptoms
(Refer to Table 1)

Severe bleeding symptoms
Grade IV/V

Is bleeding potentially life-threatening?

Yes

Treatment includes ALL of the following:

- PLT transfusions
- IV methylprednisolone for 3 to 4 days
- IVIG

No

Treatment includes either or both of the following:

- IVIG or IV anti-D
- IV methylprednisolone

Non severe bleeding symptoms
(Grade I to III)

Is the patient at moderate to high risk of severe bleeding complications based on one or more of the following?

- Head trauma without ICH
- Severe unexplained headache
- Planned surgery or procedure that is likely to induce blood loss
- Grade III bleeding symptoms
- PLT <30,000/microL PLUS any of the following risk factors:

-Use of antiplatelet or anticoagulant medications (eg, NSAIDs, heparin)
-Concomitant bleeding disorder (eg, van Willebrand disease)
-Very active lifestyle subjecting the patient to frequent trauma (that cannot be controlled with activity restriction)
-Close follow up and/or other required parental supervision cannot be assured and/or access to medical care is limited

Yes

Is a rapid increase in platelet count desired? (eg, urgent surgery, head trauma)

Yes

Treat with IVIG ± oral steroid

No

Treat with oral glucocorticoids

No

Pharmacologic therapy is generally not indicated
Most patients are managed with watchful waiting

Algorithm for Management of Acute ITP

Pediatric Persistent and Chronic ITP

Criteria

- **Age less than 18 years**
- **Platelet count less than 100,000/cmm**
- **Persistent: ITP for 3 Months or More**
- **Chronic: ITP For 12 Months or More**

Lab Workup

- ✓ **ANA/C3/Anti DNA (Especially for females 10 years of age or older to revise diagnosis if needed)**
- ✓ **±Bone Marrow Aspiration (BMA).**
- ✓ **±Immunoglobulin Profile (If any abnormalities, please consult Immunologist).**
- ✓ **Hepatitis Markers for patients with HCV. If suspected**

THE GOALS IN THE MANAGEMENT OF PERSISTENT AND CHRONIC ITP

1. **The goal of treatment in children with chronic/persistent ITP is to achieve a hemostatic platelet count: minimize risk of bleeding regardless of the platelet count**
2. **Treatment should be always tailored to the individual patient**
3. **Avoid splenectomy and drug toxicity**

Second Line (2nd line) option:
Thrombopoeitin Receptor Agonist (TPO-RA)

➲ **Goal of treatment: Safe hemostatic platelet count.**

Response Measures	Failure Measures
Clinical: No Bleeding,	No hemostatic achievement for > 2 months on maximum dose according to age
Lab: Hemostatic or doubling initial platelet count	

Two thrombopoietin receptor agonists are approved for pediatric use

1. **Eltrombopag (revolade)**
2. **Romiplostim (N-Plate)**

Eltrombopag (revolade)

Indication

- For the treatment of Pediatric patients (aged 1 year and older) with immune (idiopathic) thrombocytopenia (ITP) lasting at least 3 months from diagnosis and a significant tendency to bleed who have not responded to an established treatment (e.g. IVIG, corticosteroids) or become a Steroid dependent.

Starting Dose

- **Pediatric patients aged 1 to 5 years:**
  - ✓ Start with 25mg/day.
  - ✓ Assess the response after 2 weeks.
  - ✓ No data are available on patients in this age group with hepatic impairment.
- **Pediatric patients aged 6 to 17 years:**
  - ✓ Start with 50mg/day.
  - ✓ Assess the response after 2 weeks
  - ✓ For patients with hepatic impairment the starting dose should be reduced to 25 mg.

Dose Adjustment of Revolade

Platelet Count	Dose Adjustment
<50,000/µl after a minimum of 2 weeks' treatment	– Aged 1-5 years: Increase daily dose by 30%. – Aged 6 to 17 years: Increase daily dose by 25 mg, up to a maximum dose of 75mg/day.
≥50,000/µL to <200,000/µl	Maintain the dose
≥200,000/µL to <400,000/µl	– Aged 1-5 years: Reduce daily dose by 30%. – Aged 6 to 17 years: Reduce the daily dose by 25 mg.
>400,000/ µl	– Aged 1-5 years: Stop Revolade (Until the patients reach a platelet count of <150,000/µl, reinitiate therapy at a reduced daily dose). – Aged 6 to 17 years: Stop Revolade (Until the patients reach a platelet count of <150,000/pl, reinitiate therapy at a reduced daily dose).

Revolade follow Up

- The standard dose adjustment, either decrease or increase, would be 25 mg once daily.
- After any Revolade dose adjustment, platelet counts should be monitored at least weekly for 2 to3 weeks.
- To see the effect of any dose adjustment on the patient's platelet response prior to considering another dose increase one should wait for at least 2 weeks.

Discontinuation

- Treatment with Revolade should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Revolade therapy at 75 mg once daily as a maximum dose.

Special Populations

- Renal impairment: Caution and close monitoring are required for the use of Revolade in patients with renal impairment due to the absence of clinical experience.
- Hepatic Impairment: Caution, close monitoring, starting dose 25 mg once daily (For patients with a Child Pugh score ≥5 the starting dose should be reduced to 25 mg Revolade daily).
- Hepatotoxicity: Discontinuation if ALT is >3 x ULN in patients with normal liver function, or ≥3 x baseline whichever is the lower.
- Thrombotic/thromboembolic complications: Cautious use in patients with risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
- Grade 4 neutropenia (<500/µl) and blood count monitoring for Pediatric ITP patients must be performed (as well as additional blood counts in the event of fever).

Method of Administration

- Revolade should be taken at least two hours before or at least four hours after products such as antacids, dairy products or mineral supplements containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc).
- Revolade may be taken with food that does not contain calcium or that only contains a small amount of calcium (<50 mg).

Romiplostim (N-Plate)

Therapeutic indications inPediatrics

- Treatment of chronic primary immune thrombocytopenia (ITP) in paediatric patients one year of age and older who have significant bleed and are refractory to other treatments (e.g. corticosteroids, immunoglobulins) or are steroid dependent
- Chronic ITP not responsive to eltrombobag
- Chronic ITP developed serious adverse event to eltrombobag
- Chronic ITP who cannot tolerate oral therapy
- Comatosed chronic ITP patient

Method of administration

- Treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.
- N-plate should be administered once weekly as a subcutaneous injection.
- Self-administration of N-plate is not allowed for paediatric patients.

Initial dose

- The initial dose of romiplostim is 1 mcg/kg based on actual body weight.
  - **Starting Dose:**
    - ✓ **2-3 mcg/kg/week.**
    - ✓ **Subcutaneous injection, lyophilized powder for reconstitution.**
  - **Dose Adjustment of Nplate:**
    - ✓ **To increase dose by 1-2 mcg/kg/week every 2 weeks until reaching maximum dose.**
    - ✓ **Maximum dose: 10 mcg/kg/week.**

Dose Adjustment

- The patient actual body weight at initiation of therapy should be used to calculate dose. In paediatric patients, future dose adjustments are based on changes in platelet counts and changes in body weight. Reassessment of body weight is recommended every 12 weeks.
- The once weekly dose of romiplostim should be increased by increments of 1-2 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9$/L. Platelet counts should be assessed weekly until a stable platelet count ($\geq 50 \times 10^9$/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed monthly thereafter and appropriate dose adjustments made as per the dose adjustment table below in order to maintain platelet counts within the recommended range. A maximum once weekly dose of 10 mcg/kg should not be exceeded.

➢ **Adjust the dose as follows:**

Platelet count (x 10^9/1)	Action
<50	Increase once weekly dose by 1 µg/kg
> 150 for two consecutive weeks	Decrease once weekly dose by 1 µg/kg
> 250	Do not administer, continue to assess the platelet count weekly After the platelet count has fallen to < 150 x 10^9/1, resume dosing with once weekly dose reduced by 1 µg/kg

Treatment discontinuation

➢ Treatment with romiplostim should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of romiplostim therapy at the highest weekly dose of 10 mcg/kg.

Use in Special population

➢ Patients with hepatic impairment : not be used in moderate to severe hepatic impairment
➢ Patients with renal impairment : Nplate should be used with caution

Adverse events reported include

➢ Reoccurrence of thrombocytopenia and bleeding after cessation of treatment
➢ Increased bone marrow reticulin so follow CBC and film
➢ Thrombotic/thromboembolic complications so not used in patient at TED risk like APLS or SLE
➢ Progression of existing Myelodysplastic Syndromes (MDS)

Third Line (3rd line) option:
Mycophenolate Mofetil (MMF)

- Use:
  - To use Mycophenolate alone or with small dose of steroids.

- Dose:
  - Dose of mycophenolate moftil (Cellcept) Orally 600MG/M2/12 hours

Fourth Line (4th line) option:
Rituximab

- Use:
  - After failure of: 1st, 2nd and 3rd line options
  - Pre-medications: Antihistaminic & Steroids should be used.
  - Immunoglobulin Assay should be done before treatment initiation. **Exclude immune deficiency**

- Dose:
  - 375 mg/m²/week for 4 weeks. **+/- Pulse Steroid**

Fifth Line (5th line) option:
Splenectomy

"RARELY INDICATED IN CHILDREN

1st exclude 1ry immune deficiency and 2ry ITP"

- Use:
  - Failure of other treatment option after > 12 months.
  - Chronic resistant ITP with life threatening bleeding.
  - Age of >5 years.

References:

1. **https://www.ema.europa.eu/en**

2. **https://www.hematology.org/**

3. **https://www.uptodate.com/contents/image?imageKey=PEDS/115184**

4. **Bradbury CA, Pell J, Hill Q, et al. Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia. N Engl J Med. 2021 Sep 2;385(10):885-895.**

Pediatric Hematology

"We offer comprehensive reviews of selected topics and comprehensive advice about management approaches based on the highest level of evidence available in each case. Our goal is to provide an authoritative practical medical resource for pediatricians.
We hope that such an approach will encourage clinicians to apply available evidence to their practice and also track compliance with desired practices."

El Forsan Towers 1, El-Nasr Rd,
Masaken Al Mohandesin, Nasr City, Cairo Governorate

15344

www.gah.gov.eg