NATIONAL CLINICAL GUIDELINES

THE DIAGNOSIS & MANAGEMENT OF ANAEMIAS IN CHILDREN

Ministry of Public Health

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المبادئ الإرشادية السريرية لدولة قطر
NATIONAL CLINICAL GUIDELINES FOR QATAR

وزارة الصحـــــة العامـــــة
Ministry of Public Health
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Abbreviations

The abbreviations used in this guideline are as follows:

ACD	Anaemia of Chronic Disease
AIHA	Autoimmune Haemolytic Anaemia
CBC	Complete Blood Count
CRP	C-Reactive Protein
DAT	Direct Antiglobulin Test
ESA	Erythropoiesis-Stimulating Agent
G6PD	Glucose-6-Phosphate Dehydrogenase
GDF15	Growth Differentiation Factor 15
Hb	Haemoglobin
IDA	Iron Deficiency Anaemia
IV	Intravenous
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SCD	Sickle Cell Disease
TIBC	Total Iron-Binding Capacity

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1 Information about this Guideline

1.1 Objective and Purpose of the Guideline

The purpose of this guideline is to define the appropriate diagnosis and management of anaemia in children i.e. <18 years of age. The objective is to guide the appropriate prevention, investigation, treatment, and referral of patients presenting to provider organisations in Qatar. It is intended that the guideline will be used primarily by healthcare professionals in primary and specialist settings.

1.2 Scope of the Guideline

This guideline covers the following aspects of care:

- Definitions and classification of anaemia in children.
- Investigation of anaemia.
- Prevention and treatment of iron deficiency anaemia in infants and children.
- Overview of management of other microcytic, normocytic and macrocytic anaemias.

1.3 Editorial Approach

This guideline document has been developed and issued by the Ministry of Public Health of Qatar (MOPH), through a process which aligns with international best practice in guideline development and localisation. The guideline will be reviewed on a regular basis and updated to incorporate comments and feedback from stakeholders across Qatar.

The editorial methodology, used to develop this guideline, has involved the following critical steps:

- Extensive literature search for well-reputed, published evidence relating to the topic.
- Critical appraisal of the literature.
- Development of a draft summary guideline.
- Review of the summary guideline with a Guideline Development Group, comprised of practising healthcare professionals, subject matter experts and patient representatives, from across Qatar.
- Independent review of the guideline by the National Clinical Guidelines & Pathways Committee, appointed by the MOPH, from amongst stakeholder organisations across Qatar.

Whilst the MOPH has sponsored the development of the guideline, the MOPH has not influenced the specific recommendations made within it.

1.4 Sources of Evidence

The professional literature published in the English language has been systematically queried using specially developed, customised, and tested search strings. Search strategies are developed to allow efficient yet comprehensive analysis of relevant publications for a given topic and to maximise retrieval of articles with certain desired characteristics pertinent to a guideline.

For each guideline, all retrieved publications have been individually reviewed by a clinical editor and assessed in terms of quality, utility, and relevance. Preference is given to publications that:

1. Are designed with rigorous scientific methodology.
2. Are published in higher-quality journals (i.e. journals that are read and cited most often within their field).
3. Address an aspect of specific importance to the guideline in question.

Further information about the literature search and appraisal process is included in Appendix B.

1.5 Evidence Grading and Recommendations

Recommendations made within this guideline are supported by evidence from the medical literature and where possible the most authoritative sources have been used in the development of this guideline. In order to provide insight into the evidence basis for each recommendation, the following evidence hierarchy has been used to grade the level of authoritativeness of the evidence used, where recommendations have been made within this guideline.

Where the recommendations of international guidelines have been adopted, the evidence grading is assigned to the underlying evidence used by the international guideline. Where more than one source has been cited, the evidence grading relates to the highest level of evidence cited:

- **Level 1 (L1):**
  - Meta-analyses.
  - Randomised controlled trials with meta-analysis.
  - Randomised controlled trials.
  - Systematic reviews.

- **Level 2 (L2):**
  - Observational studies, examples include:
    - Cohort studies with statistical adjustment for potential confounders.
    - Cohort studies without adjustment.
    - Case series with historical or literature controls.
    - Uncontrolled case series.
  - Statements in published articles or textbooks.

- **Level 3 (L3):**
  - Expert opinion.
  - Unpublished data, examples include:
    - Large database analyses.
    - Written protocols or outcomes reports from large practices.

In order to give additional insight into the reasoning underlying certain recommendations and the strength of recommendation, the following recommendation grading has been used, where recommendations are made:

- **Recommendation Grade A (RGA):** Evidence demonstrates at least moderate certainty of at least moderate net benefit.
- **Recommendation Grade B (RGB):** Evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended.
- **Recommendation Grade C (RGC):** Evidence demonstrates potential harm that outweighs benefit; additional research is recommended.
- **Recommendation of the GDG (R-GDG):** Recommended best practice based on the clinical experience of the Guideline Development Group members.

1.6 Guideline Development Group Members

The following table lists members of the Guideline Development Group (GDG) nominated by their respective organisations and the Clinical Governance Group. The GDG members have reviewed and provided feedback on the draft guideline relating to the topic. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

Guideline Development Group Members		
Name	**Title**	**Organisation**
Dr Mohammed Abulaban	Senior Consultant, Paediatric Haematologist, Head of Paediatric Haematology	Hamad Medical Corporation
Dr Taiseer Abdel Raouf Ahmed	Consultant Paediatrician	Qatar Petroleum
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Dr Jazaier Waheeb Hussain Alrawi	Consultant Paediatrician	Medical Services Department, Ministry of Interior
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Ms Mariamma Joseph	Nurse	Al Emadi Hospital
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Dr Anwar Hasan	Consultant Paediatrician	Al Ahli Hospital
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Dr Ahmed Adel Ibrahim Khalil	Clinical Pharmacist	Hamad Medical Corporation
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Dr Majda Abdulwadood Mohamad ALGenae	Senior Consultant Paediatrician	Primary Health Care Corporation
Dr Naima Al Mulla	Senior Attending Physician, Paediatrics	Sidra Medicine
Dr Rekha Nirwan	Haematologist	Aster DM Healthcare

1.7 National Clinical Guidelines & Pathways Committee Members

The following table lists members of the National Clinical Guidelines & Pathways Committee (NCGPC), appointed by the MOPH. The NCGPC members have reviewed and provided their feedback and approval of the guideline document. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

National Clinical Guidelines & Pathways Committee (NCGPC) Members		
Name	**Title**	**Organisation**
Ms Huda Amer Al-Katheeri	Chair of the NCGPC, Director of Strategic Planning & Performance Department	Ministry of Public Health
Shk Dr Mohammed Hamad J. Al Thani	Co-Chair of the NCGPC, Director of Public Health	Ministry of Public Health
Dr Hani Ben Hassen Al Kilani	Senior Consultant, Executive Director for Corporate Clinical Policy and Guidelines	Hamad Medical Corporation
Prof Anthony Akobeng	Chair Clinical Practice Guidelines Committee	Sidra Medicine
Dr Alshaymaa Mohammed A. M. Al-Motawa	Consultant Family Medicine	Qatar Petroleum
Dr Basil Bashqawi	Accreditation Coordinator, Dept of Health Professions	Ministry of Public Health
Dr Abi Khalil Charbel	Associate Professor of Medicine Consultant Cardiology	Weill Cornell Medicine-Qatar
Dr Paul Dijkstra	Director of Medical Education	Aspetar
Dr Mohammed Elrishi	Senior Consultant Endocrine, Diabetes, and Internal Medicine	Al Ahli Hospital
Dr Dahlia Mustafa Hassan	Senior Consultant Family Medicine	Primary Health Care Corp
Dr Ghassan Youseph Hommos	Senior Consultant Endocrinology	Al Emadi Hospital
Dr Egon Toft	VP and Dean	College of Medicine, Qatar University

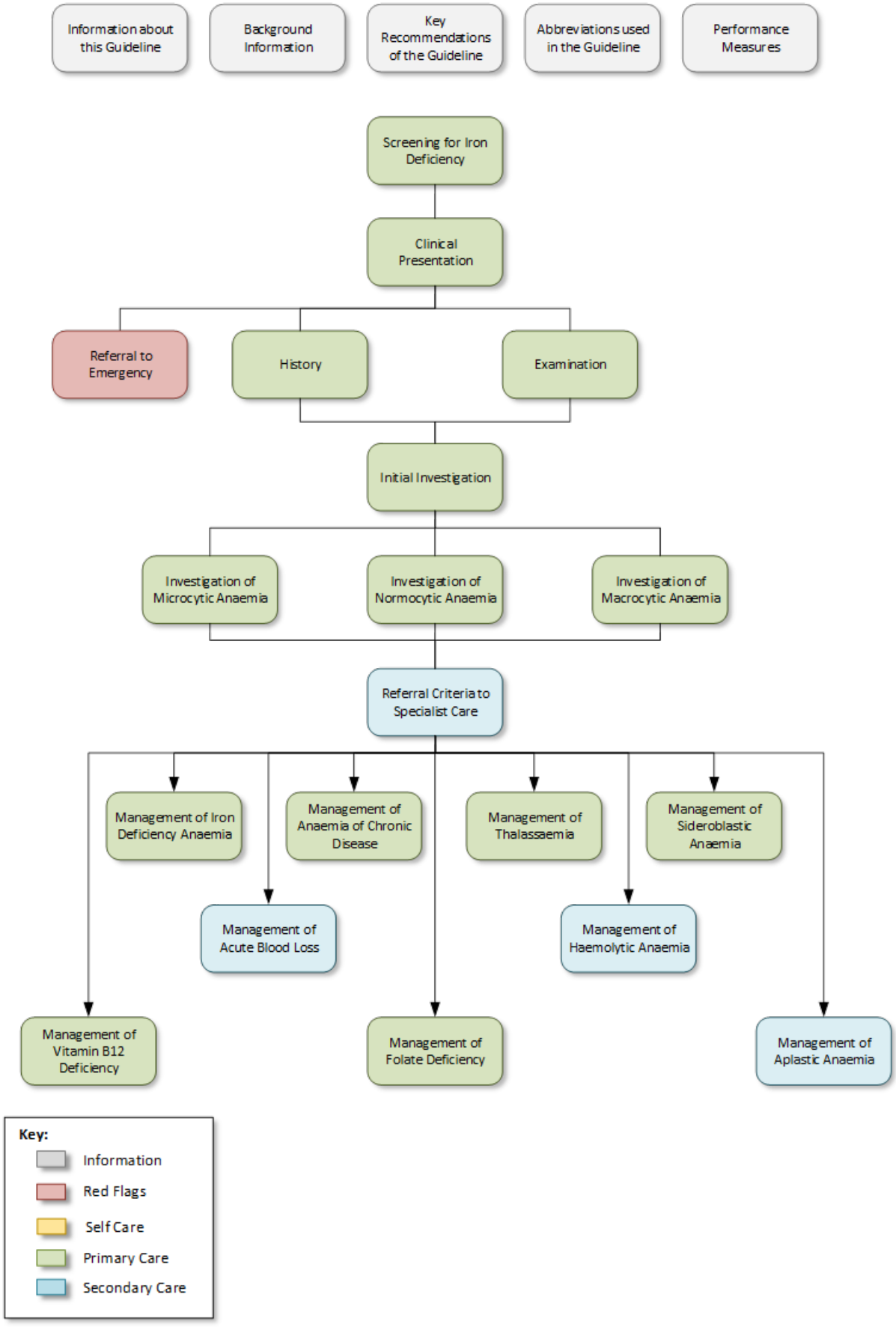
1.8 Responsibilities of Healthcare Professionals

This guideline has been issued by the MOPH to define how care should be provided in Qatar. It is based upon a comprehensive assessment of the evidence as well as its applicability to the national context of Qatar. Healthcare professionals are expected to take this guidance into account when exercising their clinical judgement in the care of patients presenting to them.

The guidance does not override individual professional responsibility to take decisions which are appropriate to the circumstances of the patient concerned. Such decisions should be made in consultation with the patient, their guardians, or carers and should consider the individual risks and benefits of any intervention that is contemplated in the patient's care.

2 Anaemias in Children - Pathway

Click on a box below to see the relevant page of the Pathway.



3 Key Recommendations of the Guideline

The key recommendations of this guideline are as follows:

Definitions (*Section 4.1*):

- Anaemia requires a full diagnostic evaluation aimed at establishing the underlying cause [1–3] [**L2**].
- Anaemia is defined as:
  - Haemoglobin (Hb) concentration ≤2 standard deviations below the mean of healthy population of the same gender and age (see *Table 4.1*) [4,5] [**L1**].

Prevalence (*Section 4.3*):

- The overall prevalence of anaemia in infants in Qatar was 23.5% in 2018[12].
- Iron deficiency anaemia (IDA) is more prevalent among non-Qatari infants (10.9%) compared with Qatari infants (1.7%) and more prevalent among infants born to housewives and to families of low income[12].

Prevention (*Section 5*):

- Microcytic anaemia due to iron deficiency is the most common cause of anaemia in children.
- To prevent iron deficiency anaemia the following preventive measures should be considered [15–18] [**L1, RGA**].
- **Pregnancy & Childbirth (***Section 5.1***):**
  - Counselling on iron nutrition and birth spacing:
  - Delayed umbilical cord clamping:
- **Breast-fed Term Infants (***Section 5.2***):**
  - After weaning from breast an additional source of iron (c. 1 mg/kg/day of elemental iron[16]) is recommended[15,16] [**L1, RGA**].
  - Iron-fortified infant formula[15] and supplementary foods[16] are preferred and should be provided until the age of 12 months [15] [**L1, RGA**].
  - Cow's or goat's milk is not recommended until after the age of 12 months[15] [**L1, RGA**].
- **Formula-Fed Term Infants (***Section 5.3***):**
  - An iron-fortified formula is recommended in formula-fed term infants until the age of 12 months[15–18] [**L1, RGA**].
  - Iron-fortified cereal is however not needed in infants feeding iron-fortified formula[15] [**L1, RGB**].
  - Cow's or goat's milk is not recommended until after the age of 12 months[15] [**L1, RGA**].
- **Pre-Term Infants (***Section 5.4***):**
  - Preterm infants who are exclusively breastfed should receive iron supplementation or iron-fortified formula [15,17] [**L1, RGA**].
  - Supplementation should begin at no later than 1 month of chronological age and continue until 12 month of age [15–17] [**L1, RGA**].
  - The daily requirement is 2–3 mg/kg/day of elemental iron [15–17] [**L1, RGA**].
  - All low birth weight infants (<2500 g) should receive iron supplementation until 6 months of age [17,19] [**L1, RGA**].
  - Preterm infants with weight appropriate for gestational age, fed with iron-fortified formula, do not require additional iron supplementation [15] [**L1, RGB**].
  - As iron supplementation may be inappropriate in some cases (e.g., in premature infants with bone marrow failure), the decision about it should be taken by a neonatologist and not by a primary care physician [**R-GDG**].
- **Children Aged > 6 Months (***Section 5.5***):**
  - From 6 months of age, all children should receive iron-rich solids (e.g. iron-fortified infant cereal or pureed meats) [16,17] [**L1, RGA**].

  - Ascorbic acid-rich foods (see *Table 5.1*) are recommended to improve iron absorption [15,16] [**L1, RGA**].
  - If there is a delay in starting iron-rich solids, oral iron supplementation 1 mg/kg/day is recommended until appropriate dietary sources are introduced[17] [**L1, RGA**].
  - Routine iron supplementation is otherwise generally not required in children >1 year of age[17] [**L1, RGA**] but may be considered during periods of rapid growth.
- **Preschool Age and School Age Children (***Section 5.6***):**
  - Hookworm infestation is a recognised cause of chronic faecal blood loss and iron deficiency in older infants, preschool age children, and school age-children[24].
  - Screening school children with stool analysis should be performed when contamination with parasites is suspected [**R-GDG**].
  - In confirmed cases, parasite control measures including periodic deworming and treatment of children affected should be instituted.

Clinical Assessment (*Section 6*):

- Most infants and children with mild anaemia are asymptomatic[2,5].
- If present, signs and symptoms may vary in severity depending on the degree of anaemia[3].
- The evaluation of a child with anaemia should begin with a thorough history.
- Patient history may be taken from both the child (if able) and parent or caregiver (when required).
- If anaemia is suspected, a thorough physical examination should be performed[4,9] (see *Section 6.3*).

Screening for Iron Deficiency Anaemia (*Section 7.1*):

- Universal screening and assessment of risk factors for IDA should be performed at approximately 1 year of age [18,26] [**L1, RGA**].
- Selective screening (see *Table 7*) can be performed at any age in populations of infants and children who are at high risk for IDA [4,16,18,26] [**L1, RGA**].

Initial Laboratory Assessment (*Section 7.2*):

- The goal of the initial laboratory assessment is to determine whether patient has isolated anaemia or if other cell lines are affected and to guide further testing to confirm the aetiology of anaemia [4,5] [**L1, RGA**].
- Initial laboratory studies should include [3,4,16] [**L1, RGA**]:
  - Complete blood count with differentials.
  - Peripheral blood smear.
  - A reticulocyte count may be obtained.
  - Stool analysis for occult blood and worms.

Further Investigation and Diagnosis (*Section 8*):
Microcytic Anaemia:

- If microcytic anaemia is suspected, further testing to narrow the diagnostic possibilities should include:
  - Serum ferritin:
    - While serum ferritin is a sensitive marker for iron status, it is also an acute phase reactant and is therefore elevated in inflammatory conditions.
    - Therefore, serum ferritin measurement alone may mask the diagnosis of iron deficiency and testing with the full iron profile should always be attempted along with C-reactive protein [**R-GDG**].
  - C-reactive protein.
  - Iron, and total iron-binding capacity.
  - MCV and RDW tests.

Normocytic Anaemia:

- If haemolytic anaemia is suspected, further testing should include [2,4,5,8]:
  - Peripheral smear and reticulocyte count if not initially ordered.
  - Serum indirect bilirubin, lactate dehydrogenase, and haptoglobin levels.
  - Additional testing for specific aetiologies should be guided by blood film picture and may include:
    - Direct antiglobulin test.
    - G6PD deficiency screening test.
    - Osmotic fragility.
    - Haemoglobin electrophoresis.
- If aplastic anaemia or another cause of bone marrow failure is suspected:
  - The patient should be urgently referred to haematologist for bone marrow aspirate and/or biopsy.

Macrocytic Anaemia:

- Use the algorithm in Figure 8.3 to guide further investigation and diagnosis of the macrocytic anaemia.

Other Diagnostic Considerations (*Section 8.4*):

- When diagnosing anaemia in children and adolescents, consider the following:
  - IDA is the most common type of anaemia in children [5].
  - α-thalassaemia minor is frequently seen in South East Asian, Mediterranean, African, and Middle Eastern children[5,9].
  - β-thalassaemia minor is less common in African children.
  - Paroxysmal nocturnal haemoglobinuria is very rare in childhood or adolescence [2].
  - Normochromic normocytic anaemia can occur in patients with chronic inflammation, chronic disease (e.g. renal disease), and acute blood loss [9].
  - Consider other cell lines for evaluation of causes of anaemia [28]:
    - Thrombocytosis with IDA, infection, haemolytic-uremic syndrome, thrombotic thrombocytopenic purpura.
    - Pancytopenia with aplastic anaemia, myelodysplastic syndrome leukaemia.
  - If haemorrhage is suspected in the absence of trauma, review the most common non-traumatic causes of bleeding, which include [3] [**L2**]:
    - Gastrointestinal.
    - Gynaecological.
    - Genitourinary.
  - Bone marrow infiltration, fibrosis, various myeloproliferative diseases, and sideroblastic anaemias must be confirmed by bone marrow biopsy [2] [**L2, RGA**].

Referral to Specialist Care (*Section 9.2*):

- The patient should be referred to a paediatric haematologist if any of the following are suspected or diagnosed [4,5,9] [**L1, RGA**]:
  - Autoimmune haemolytic anaemia.
  - Parenteral therapy is required.
  - Thalassaemia major.
  - A myelodysplastic syndrome [**R-GDG**].
  - Aplastic anaemia [**R-GDG**].
  - Sickle cell disease apart from sickle trait [**R-GDG**].
  - Megaloblastic anaemia.
  - Leukaemia/lymphoma
  - Chronic bleeding of unknown cause.
  - Cause of anaemia is unknown.

  - Anaemia is refractory to treatment (after one month).
  - A second opinion is required [**R-GDG**].
- All patients with IDA should also be referred to a dietician for the dietary measures [4] [**L2, RGA**].

Referral to Paediatric Emergency Centres (*Section 9.3*):

- If any of the following red flags are present, the patient should be referred to a Paediatric Emergency Centre[4,9] [**L1, RGA**]:
  - Severe anaemia whether symptomatic or asymptomatic.
  - Acute haemolytic crisis.
  - Severe vitamin B_{12} or folate deficiency.
  - Tachycardia, cardiac murmur or signs of cardiac failure.
  - Moderate to severe blood loss.
  - Associated thrombocytopenia or neutropenia may indicate malignancy or an infiltrative disorder.
  - Marasmus or kwashiorkor.
  - Need for red cell transfusion.
- All children aged >14 years should be referred to adult emergency services at HMC as the HMC paediatric scope of practice is up to 14 years old [4] [**L1**].

Management of Iron Deficiency Anaemia (IDA) (*Section 10.1*):

- IDA is indicated by [1,8,30] :
  - Low MCV (see *Section 4.2* for details).
  - Low MCH and MCHC.
  - Microcytic hypochromic red cells on peripheral blood film.
  - Low serum iron.
- In patients with early iron deficiency and anaemia of chronic disease (where there may be a functional iron deficiency), MCV and MCH can be normal.
- There may also be an associated iron deficiency with chronic blood loss and haemolysis.
- Ferritin, B_{12} and folate should also be assessed in all cases of anaemia, irrespective of MCV[29,31].
- The underlying cause of the IDA should be investigated and documented appropriately [**R-GDG**].
- The therapeutic management of IDA in children and adolescents includes both [4,17] [**L2, RGA**]:
  - Dietary therapy (see *Section 10.1.1*) which consists of:
    - Dietary counselling [4] [**L2, RGA**]:
    - Education of the patient and their families [4] [**L2, RGA**].
  - Oral iron therapy (see *Section 10.1.2*):
    - The recommended oral therapeutic dose of elemental iron for children is 3-6 mg/kg/day [4,17] [**L1, RGA**].
    - See iron formulations in *Table 10.1* and *Appendix A*.
- Red blood cell (RBC) transfusion should be reserved for patients with haemodynamic compromise and risk of cardiovascular instability [8,17] [**L2, RGA**].
- Compliance and response to iron replacement therapy should be re-evaluated with CBC, reticulocyte count and serum ferritin after 4 weeks [4] [**L2, RGA**]:

Management of Anaemia of Chronic Disease (*Section 10.2*):

- The presence of a chronic inflammatory condition, such as infection, autoimmune disease, kidney disease, or cancer is required for diagnosis to be made (see *Section 10.2.1*).
- It may present as normocytic or microcytic anaemia and low reticulocyte count[2,30]. IDA and ACD frequently co-exist but it is important to differentiate between them [30].
- Other laboratory features of ACD include [1,2,8,30]:
  - Low or normal MCV.

  - Low serum iron.
  - Decreased transferrin saturation.
  - Increased reticuloendothelial iron.
- The mainstay of treatment is to reverse the underlying inflammatory or malignant process if possible to improve the degree of anaemia [30] [**L2, RGA**].
- Iron therapy is not recommended in patients with ACD [30] [**L2, RGB**] unless ACD is accompanied by IDA or there is a true deficiency of iron [25,30].
- Erythropoiesis-stimulating agents (ESAs) may be appropriate in a subset of patients with ACD [8,25] [**L1**].
- The ESA must be prescribed by a renal consultant/ nephrology specialist [33].

Management of Other Microcytic Anaemias:

- Refer to *Section 10.3* for detailed guidance on the management of thalassaemias.
- Refer to *Section 10.4* for detailed guidance on the management of sideroblastic anaemias.

Management of Haemolytic Anaemias (*Section 11.2*):

- Children with haemolytic anaemias should be admitted for observation [9] [**L2, RGA**].
- Treatment varies depending on the type of haemolysis.
- All cases of acute haemolysis in children should be reviewed by a Haematologist.
- Refer to *Section 11.2.1* for detailed guidance on the management of Sickle Cell Haemoglobinopathies and Sickling Crises.
- Refer to *Section 11.2.2* for detailed guidance on the management of G6PD deficiency.
- Refer to *Section 11.2.3* for detailed guidance on Autoimmune Haemolytic Anaemias.

Management of Vitamin B_{12} Deficiency (*Section 12.1*):

- Vitamin B_{12} deficiency is indicated by[1,9,52]:
  - Very high MCV.
  - Low serum vitamin B_{12} level.
  - Teardrop RBCs.
  - Hypersegmented neutrophils.
  - Elevated methylmalonate level.
  - Often neutropenia or thrombocytopenia is present.
  - May be associated with pancytopenia.
  - May be associated with neurodevelopmental problems.
- Non-pharmacological treatment should include dietary counselling and advice on how to improve dietary intake of B_{12}-rich foods [20,53–55] [**L1, RGA**].
- The general strategy of treatment involves repletion with B_{12} with intramuscular injections or oral vitamin therapy [20,53,55] [**L1, RGA**].
- The duration and route of treatment depends on the etiology of the condition [53].
- There are two formulations available [20,54,55]:
  - Hydroxocobalamin [56].
  - Cyanocobalamin [57].
- In infants and children with clinical deficiency and neurological symptoms, the treatment must be started urgently [9,54] [**L2, RGA**]:
- Dietary deficiency:
  - Infants: 250-1000 mcg IM once daily for 1-2 weeks, followed by weekly dosing until patient recovers [58].
  - Patients with neurologic symptoms can be treated with doses of 1000 mcg [59,60].
- Malabsorption:

    - Infants, children, and adolescents: 250-1000 mcg IM daily or every other day for 1 week, then weekly for 4-8 weeks, and then monthly for life; younger children should receive monthly doses of 100 mcg [7,58,61].
- Patients with a deficiency in intrinsic factor (e.g. pernicious anaemia) should continue B_{12} parenterally [53].
- Other children may switch to oral supplements once they feel well, have no diarrhoea, feeding improved, and maternal stores are replaced [53,54] [**L2, RGA**].
- Several regimen may be considered in children without neurological symptoms [53,54] [**L2, RGA**]. The total duration of the treatment usually comprises 3-6 months [54].
    - Older children with mild disease:
        - Oral B_{12} 1000mcg daily.
    - Subclinical, dietary deficiency:
        - Oral B_{12} 50-200 mcg daily.
    - Supplement (not deficient, no dietary intake):
        - Oral B_{12} 50-100mcg daily or alternate daily.

Management of Folate Deficiency (*Section 12.2*):

- Folate deficiency is indicated by [1,52]:
    - Very high MCV.
    - Low folate levels.
    - Normal methylmalonate levels.
    - Increased homocysteine level.
- Non-pharmacological treatment should include dietary counselling and advice on how to improve dietary intake of folate-rich foods [20,21] [**L1, RGA**]. Diets rich in fruits and vegetables are recommended [21] [**L2, RGA**].
- The general strategy of treatment involves repletion of folic acid to restore folate levels. All patients with folate deficiency should be offered supplemental folic acid. Consider the following options [21,52] [**L2, RGA**]:
    - Oral folic acid 1-5mg daily.
    - Intravenous, subcutaneous, or intramuscular formulations in patient who cannot tolerate oral medications.
- The duration of treatment depends on the aetiology of the condition [8,21]:
    - A treatment course for 4 months is usually sufficient.
    - Longer therapy is recommended if the underlying cause of folate deficiency persists (e.g. in patients with malabsorption).

Management of Aplastic Anaemia (*Section 12.3*):

- Aplastic anaemia is a rare disorder in children [63].
- The more frequently found type in children is the inherited aplastic anaemia (e.g. bone marrow failure syndrome) [64,65].
- Aplastic anaemia is defined by [64,65]:
    - Peripheral blood pancytopenia.
    - Hypocellular bone marrow.
    - Absence of infiltration, dysplasia or fibrosis.
- To make the definitive diagnosis of aplastic anaemia, bone marrow biopsy is required [**R-GDG**] and at least two of the following must be present [64,66]:
    - Hb <10 g/dL.
    - Platelet count <50 $x10^9$/L.
    - Neutrophil count <1.5 $x10^9$/L.
- All patients with confirmed diagnosis of aplastic anaemia should be managed in specialist settings by a paediatric haematologist [**R-GDG**].

- The main treatment approaches include [63,65] [**L1, RGA**]:
    - Haematopoietic stem cell transplantation.
    - Immunosuppressive therapy.

4 Background Information

4.1 Definitions

Anaemia requires a full diagnostic evaluation aimed at establishing the underlying cause [1–3] [**L2**].

Anaemia is defined as:

- Haemoglobin (Hb) concentration ≤2 standard deviations below the mean of healthy population of the same gender and age (see *Table 4.1*) [4,5] [**L1**].

Age:	6-59 Months	5-11 Years	12-14 Years	15-18 Years	
Gender:	-	-	-	Girls	Boys
Anaemia Threshold	<11 g/dL	<11.5 g/dL	<12 g/dL	<12 g/dL	<13 g/dL

Table 4.1: Hb levels required to diagnose anaemia at sea level[6].

4.2 Classification

Anaemia can be classified in different categories based on parameters listed below.

Aetiological mechanisms (see details in *Section 4.3*):

- Blood loss anaemia: Overt and occult blood loss.
- Impaired red blood cells (RBC) production (see details in *Section 4.3.2*):
  - Nutritional deficiencies (e.g. Iron, vitamin B_{12}, folate, and protein deficiencies).
  - Chronic disorders (e.g. chronic infections or inflammation, malignancies)
  - Bone marrow failure or infiltration (Aplastic anaemia, leukaemia, lymphoma)
  - Inherited anaemia (e.g. thalassaemia)
- Excessive RBC destruction or haemolytic anaemia due to (see details in *Section 4.3.3*):
  - Intrinsic defects in RBC.
  - Extrinsic defects in RBC.

Severity level (see details in *Table 4.2(1)*):

	Age:	6-59 months	5-11 years	12-14 years	15-18 years	
	Gender:	-	-	-	Girls	Boys
Level	**Mild**	10.0-10.9 g/dL	11.0-11.4 g/dL	11.0-11.9 g/dL	11.0-11.9 g/dL	11.0-12.9 g/dL
	Moderate	7.0-9.9 g/dL	8.0-10.9 g/dL	8.0-10.9 g/dL	8.0-10.9 g/dL	8.0-10.9 g/dL
	Severe	<7.0 g/dL	<8 g/dL	<8.0 g/dL	<8.0 g/dL	<8.0 g/dL

Table 4.2(1): Hb levels to determine severity of anaemia at sea level[6].

Morphological parameters:

- Haemoglobin content, i.e. the mean cell haemoglobin concentration (MCHC) of erythrocytes:
  - Hypochromic: MCHC < 27pg/L
  - Normochromic: MCHC 27-32pg/L
- Size of the erythrocytes, i.e. the mean corpuscular volume (MCV) of erythrocytes (*Table 4.2(2)*):
  - Microcytic: MCV is below the normal range.
  - Normocytic: MCV falls within the normal range.
  - Macrocytic: MCV is above the normal range.

Age:	6-23 Month	2-4 Years	5-7 Years	8-11 Years	12-14 Years		15-17 Years	
Gender:	-	-	-	-	Girls	Boys	Girls	Boys
MCV	77 μM^3	79 μM^3	81 μM^3	83 μM^3	85 μM^3	84 μM^3	87 μM^3	86 μM^3
Lower Limit	70 μM^3	73 μM^3	75 μM^3	76 μM^3	78 μM^3	77 μM^3	79 μM^3	78 μM^3

Table 4.2(2): Normal and minimal values of MCV in infants and children of different age [7].

4.3 Aetiology

4.3.1 Microcytic Anaemia

Main causes of microcytic anaemia include[1,5]:

- Thalassemia syndromes and thalassaemic hemoglobinopathies (e.g., haemoglobin [Hb]E, Hb Lepore).
- Iron deficiency anaemia (IDA,the most common cause), resulting from:
  - Chronic blood loss.
  - Dietary deficiency of iron.
  - Malabsorption of iron, including:
    - Gastric surgery.
    - Coeliac disease.
    - Extensive bowel resection.
  - Increased demand for iron.
- Anaemia of chronic disease (ACD) late phase, resulting from:
    - Chronic infections (e.g. tuberculosis).
    - Chronic inflammatory conditions (e.g. Systemic lupus erythematosus and other connective tissue diseases).
    - Malignancies (e.g. lymphoma)
- Sideroblastic anaemia, resulting from:
  - Inherited disease:
    - X-linked inheritance.
  - Acquired disease:
    - Myelodysplasia.
    - Myeloproliferative disorders.
    - Myeloid leukaemia.
- Lead poisoning.

4.3.2 Normocytic Anaemia

Normocytic anaemia may result from three main processes [2,3]:

- Increased red blood cell destruction.
- Decreased erythropoiesis.
- Loss of blood.

Causes of normocytic anaemia due to **increased red blood cells destruction** include [1,2,5,8,9]:

- Haemolytic disorders due to intrinsic defects in RBC:
  - Haemoglobinopathies such as:
    - Homozygous sickle cell disease (SCD).
    - Heterozygous sickle haemoglobin C disease.
  - Disorders of red cell membranes such as:
    - Hereditary spherocytosis.
    - Hereditary elliptocytosis.
  - Red blood cell enzyme deficiencies such as:
    - Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
    - Pyruvate kinase deficiency.
  - Paroxysmal nocturnal haemoglobinuria.
- Haemolytic disorders due to extrinsic defects in RBC:
  - Immune haemolytic anaemia:
    - Autoimmune haemolytic anaemia (AIHA): e.g. warm and cold reactive anaemias.
    - Haemolytic disease of the newborn (HDN).
    - Drug-induced anaemias.
  - Macroangiopathic haemolytic anaemia seen in children with:
    - Mechanical heart valves.
    - Aortic stenosis
  - Microangiopathic disorders such as:
    - Disseminated intravascular coagulopathy.
    - Haemolytic-uraemic syndrome.
    - Thrombotic thrombocytopenic purpura.
  - Miscellaneous causes such as:
    - Drugs increasing the risk of haemolysis (e.g. penicillin, cephalosporins., erythromycin, procainamide).
    - Infections (including congenital parvovirus B19).
    - Blood transfusion reactions.

Causes of normocytic anaemia due to **decreased erythropoiesis** may include [1,2,5,8,9]:

- Primary causes:
  - Marrow aplasia or hypoplasia.
  - Pure red blood cell aplasia.
  - Myelophthisic anaemia.
  - Myeloproliferative disorders.
- Secondary causes:
  - Anaemia of chronic disease (early phase).
  - Chronic renal failure.
  - Liver disease.
  - Endocrine deficiencies.
  - Inflammatory disorders.
  - Infections.
  - Cancer.
  - HIV and AIDS.
- Drugs:
  - Antiepileptic medications.

  - Azathioprine.
  - Sulphonamides.
  - Isoniazid.
  - Procainamide.
  - Penicillamine.
  - Chloramphenicol.
- Expansion of plasma volume:
  - Pregnancy in adolescents.
  - Over-hydration.

Causes of normocytic anaemia due to **blood loss** may include [1,2,5,8,9]:

- Overt blood loss (e.g. surgery, accidents, epistaxis, menorrhagia).
- Occult blood loss (e.g. gastrointestinal bleeding)

4.3.3 Macrocytic Anaemia

Causes of macrocytic anaemia include [1,3,5,8,9]:

- Megaloblastic anaemia due to:
  - Vitamin B_{12} or folate deficiency.
  - Medications:
    - Azathioprine.
    - Hydroxycarbamide.
    - Methotrexate.
    - Anticonvulsants (e.g. phenytoin, valproic acid).
    - Trimethoprim/sulfamethoxazole.
    - Metformin.
    - Cholestyramine.
    - Antiretroviral agents (e.g. zidovudine, stavudine, lamivudine).
    - Antimetabolites (e.g. hydroxyurea and 6-mercaptopurine).
    - Tetracycline.
    - Erythromycin.
    - Nitrofurantoin.
    - H2 blockers.
    - Proton pump inhibitors.
    - Colchicine.
  - Fanconi anaemia
  - Orotic aciduria.
- Non-megaloblastic anaemia:
  - Hypothyroidism.
  - Hypersplenism.
  - Non-alcoholic liver disease.
  - Congenital aplasia.
  - Haemolysis.
  - Primary bone marrow dysplasia (including myelodysplasia and myeloproliferative disorders).

4.4 Prevalence

The global anaemia prevalence in 2010 was estimated to be 32.9% with the burden highest in children <5 years old[10]. Microcytic anaemia due to iron deficiency remains the most common type of anaemia worldwide[5,11,12], whilst macrocytic anaemia is very rare in children[5].

The WHO reported that the prevalence of anaemia in children <5 years old remained >30% in Qatar in the period from 1994 to 1997[13]. Local reports published in 1995, estimated the prevalence of IDA in Qatar as 28.3% and 23.9% in preschool boys and girls, respectively [14].

Since 1990s, the prevalence rate of anaemia in preschool children (<5 years old) has dropped from 30% [13] to reach a nadir of 25% in 2012 and 2013[13]. By 2016, the prevalence of anaemia had increased slightly to reach 26.3%[13].

A study from 2018[12] reported that iron deficiency anaemia (IDA) is more prevalent among non-Qatari infants (10.9%) compared with Qatari infants (1.7%) and more prevalent among infants born to housewives and to families of low income. The overall prevalence of anaemia in infants in Qatar was 23.5%.

5 Anaemia Prevention

Microcytic anaemia due to iron deficiency is the most common cause of anaemia in children. To prevent iron deficiency anaemia the following preventive measures should be considered [15–18] [**L1, RGA**].

5.1 Pregnancy and Childbirth

Premarital screening in soon-to-be married couples is recommended [**R-GDG**]. Further counselling should be provided to couples with abnormal results [**R-GDG**].

- **Counselling on iron nutrition and birth spacing:**
  - Pregnant women should be advised about adequate iron nutrition and the need to maintain adequate body iron at birth to avoid gestational iron deficiency and other factors that causes low birthweight and premature delivery.
  - Pregnant women should be advised on birth spacing to allow the recovery of iron reserves after a previous pregnancy.

- **Delayed umbilical cord clamping:**
  - For about 120 to 180 seconds after delivery improves iron status (ferritin levels) of the newborn and within the first 2-6 months of age. This is especially beneficial in those vulnerable to iron deficiency including premature or small for gestational age infants.

5.2 Breast-Fed Term Infants

In healthy full-term infants, iron storage from in utero is adequate for the first 4-6 months of life. Additional iron supplementation is not required in exclusively breast fed term infants in the first 6 months of life if their mothers have sufficient dietary intake[11,17] [**L1, RGA**].

After weaning from breast an additional source of iron (c. 1 mg/kg/day of elemental iron[16]) is recommended[15,16] [**L1, RGA**]. Iron-fortified infant formula[15] and supplementary foods[16] are preferred and should be provided until the age of 12 months [15] [**L1, RGA**].

Cow's or goat's milk is not recommended until after the age of 12 months[15] [**L1, RGA**].

5.3 Formula-Fed Term Infants

An iron-fortified formula is recommended in formula-fed term infants until the age of 12 months[15–18] [**L1, RGA**]. Iron-fortified cereal is however not needed in infants feeding iron-fortified formula[15] [**L1, RGB**].

Cow's or goat's milk is not recommended until after the age of 12 months[15] [**L1, RGA**].

5.4 Preterm Infants

Preterm infants who are exclusively breastfed should receive iron supplementation or iron-fortified formula [15,17] [**L1, RGA**]. Supplementation should begin at no later than 1 month of chronological age and

continue until 12 month of age [15–17] [**L1, RGA**]. The daily requirement is 2–3 mg/kg/day of elemental iron [15–17] [**L1, RGA**].

All low birth weight infants (<2500 g) should receive iron supplementation until 6 months of age [17,19] [**L1, RGA**]. Preterm infants with weight appropriate for gestational age, fed with iron-fortified formula, do not require additional iron supplementation [15] [**L1, RGB**].

Note: As iron supplementation may be inappropriate in some cases (e.g., in premature infants with bone marrow failure), the decision about it should be taken by a neonatologist and not by a primary care physician [**R-GDG**].

5.5 Children Aged >6 Months

From 6 months of age, all children should receive iron-rich solids (e.g. iron-fortified infant cereal or pureed meats) [16,17] [**L1, RGA**]. Ascorbic acid-rich foods (see *Table 5.1*) are recommended to improve iron absorption [15,16] [**L1, RGA**].

If there is a delay in starting iron-rich solids, oral iron supplementation 1 mg/kg/day is recommended until appropriate dietary sources are introduced[17] [**L1, RGA**]. Routine iron supplementation is otherwise generally not required in children >1 year of age[17] [**L1, RGA**] but may be considered during periods of rapid growth.

The recommended daily iron requirements for children 1-3 years and 4-8 years of age are about 7mg and 10mg respectively, and these can be achieved through consumption of iron-rich foods (see *Table 5* for details).

Consumption of large quantities (>700ml daily) of non–iron-fortified cow's or goat's milk may increase the risk of iron deficiency in children >1 year old and is, therefore, not advised [16] [**L1, RGC**].

Sources of Heme Iron	
Meat	Lean beef, veal, lamb, poultry, liver
Fish	Canned sardines, canned light tuna
Sea foods	Shellfish (clams, shrimp, oysters, mussels)
Miscellaneous	Egg yolk, nutritional yeast
Sources of Non-Heme Iron	
Vegetables	Spinach, okra, sweet potatoes, winter squash, white potatoes
Grains and legumes	Dried peas, dried bean, legumes, whole grain, bread and fortified cereal, brown rice, enriched pasta, tofu, soybeans
Fruits	Dried fruits (prunes, raisin, figs), tomato juice, prune juice
Miscellaneous	Molasses, egg yolk, nutritional yeast
Enhancers of iron Absorption (Vitamin C-rich foods)	
Vegetables	Brussels sprouts, broccoli, cabbages, tomatoes, asparagus, bell pepper, cauliflower, potatoes, spinach, turnips
Fruits	Citrus (fruits and juices), strawberries, cantaloupe

Miscellaneous	Green chili sauce and salsa
Inhibitors of Iron Absorption	
Polyphenols and tannins	Tea and coffee
Phytates	Bran
Calcium	Dairy products (milk, yogurt, cheese), fish (sardines, canned salmon), tofu, broccoli, almonds, figs, turnip greens and rhubarb
Vitamin B_{12}-rich foods	
Meat	Beef, poultry, lamb or veal liver and kidneys
Fish	Salmon, cod fish, sardines, tuna, trout
Sea foods	Shellfish (clams, shrimp, oysters)
Dairy products	Milk, yogurt, cheese
Miscellaneous	Eggs, fortified cereals
Folate-rich foods	
Meat	Liver
Vegetables	Broccoli, brussels sprouts, asparagus, other green leafy vegetables (cabbage and spinach)
Grains	Peas, chickpeas, brown rice, fortified cereals

Table 5: Dietary prevention of vitamin deficiency and nutritional anaemias in children[4,16,20–22].

5.6 Preschool and School Age Children

A recent study showed that there is a relatively high prevalence of common helminths, especially hookworms (overall prevalence 1.22 %) among immigrant residents in Qatar[23].

Hookworm infestation is a recognised cause of chronic faecal blood loss and iron deficiency in older infants, preschool age children, and school age-children [24]. Screening school children with stool analysis should be performed when contamination with parasites is suspected [**R-GDG**]. In confirmed cases, parasite control measures including periodic deworming and treatment of children affected should be instituted.

6 Clinical Assessment

6.1 Clinical Presentation

Most infants and children with mild anaemia are asymptomatic[2,5]. If present, signs and symptoms may vary in severity depending on the degree of anaemia[3].

Presenting features that are common to most anaemias include [3,4,17,25]:

- Weakness or tiredness.
- Fatigue, lethargy or decreased activity.
- Light-headedness or dizziness.
- Headache.
- Poor concentration.
- Irritability.
- Reduced feeding.
- Worsened school performance.
- Pallor.
- Palpitations.
- Chest pain.
- Shortness of breath.
- Cold distal extremities.
- Claudication.
- Pica (abnormal cravings for non-food items, e.g. ice, sand).

6.2 History

The evaluation of a child with anaemia should begin with a thorough history. Patient history may be taken from both the child (if able) and parent or caregiver (when required).

General points to elicit include [1,4,5,9]:

- Age of the patient.
- Ethnicity.
- Symptoms and degree of anaemia.
- Symptoms of malabsorption including:
    - Indigestion.
    - Diarrhoea.
    - Steatorrhea.
    - Abdominal distention.
- Parasitic infection.
- Past medical history.
- Family history, including:
    - Anaemia.
    - Jaundice.
    - Gallstones.
    - Splenomegaly.
    - Inflammatory bowel disease.
    - Telangiectasia or angiodysplasia.
    - Coagulopathies.
- History of recent travel.
- History of drugs and toxin exposure.

- Special health care needs.

Additional points to elicit about **infants and young children** include [4,5]:

- Antenatal history.
- Birth and neonatal history:
  - Complications of labour.
  - Gestational age at birth.
  - Birth weight.
  - Duration of birth hospitalisation.
  - History of jaundice and or anaemia in the newborn period.
  - Hb level after delivery (for small gestational age).
  - Review of the results of newborn screening.
- Feeding status:
  - Breastfeeding.
  - Mixed (breast milk & formula) feeding.
  - Formula feeding.
- Nutritional history:
  - Timing of solid food Introduction.
  - Supplement intake.
  - Assess oral intake.
  - Any food allergies.
  - Food-medication (drug) interaction.
- Developmental history:
  - Determine if the child has attained age-appropriate developmental milestone.

Additional points to elicit about **adolescents** include [1,4,5,9]:

- GI ulceration/bleeding e.g.:
  - Dyspepsia, gastro-oesophageal reflux disease, history of peptic ulcer.
  - Haemorrhoids.
  - Passing blood per rectum.
  - Passing black motions, confirm they are not taking iron tablets.
- Past medical history.
- Dietary history:
  - Eating habits.
  - Anorexia, bulimia, obesity and eating disorders.
  - Food intolerances.
  - Recent fava/broad bean ingestion.
  - Any restricted diets:
    - Vegetarian.
    - Vegie diet.
    - Macrobiotic diet.
    - Low intake of meat, fish, poultry or iron-fortified foods.
- Menstrual history of female adolescents:
  - Age of menarche.
  - Frequency, duration, interval, estimated blood loss.
  - Obstetric history.
  - Pregnancy during adolescence (recent or current).
- Medication history:
  - Medications increasing the risk of anaemia are listed in *Section 4.2*.
- Growth spurt.
- Frequent blood donations.
- Alcohol intake and substance abuse.
- Recent immigration from a developing country.

6.3 Physical Examination

If anaemia is suspected, a thorough physical examination should be performed including[4,9]:

- General physical examination
  - Vital signs:
    - Heart rate.
    - Blood pressure.
    - Respiratory rate.
  - Anthropometric measurements:
    - Weight and height.
    - Head circumference (for children ≤2 years).
    - Body mass index (BMI, for children ≥3 years).
  - Conjunctiva, palms and nail beds for pallor.
  - Skin and sclera:
    - Hyperpigmentation
    - Petechiae, purpura
    - Jaundice
    - Cavernous hemangioma.
    - Ulcers on lower extremities.
    - Nail changes (flattened and brittle, spoon nail).
  - Presence of facies that may suggest possible aetiology:
    - Frontal bossing.
    - Prominence of the malar and maxillary bones.
    - Thinning of the lateral aspect of eyebrows.
    - Angular stomatitis.
  - lymphadenopathy.
- Neurological examination:
  - Sign of peripheral neuropathy.
  - Developmental delay.
  - Cognitive impairment.
- Cardiovascular examination:
  - Tachycardia.
  - Postural hypotension.
  - Murmur.
- Signs and symptoms of other illnesses:
  - Ulceration.
  - Mucositis.
  - Bilateral oedema (in case of cardiac, renal, or hepatic cause).
  - Hepatosplenomegaly.
  - Dark urine.

7 Initial Investigation

7.1 Screening for Iron Deficiency Anaemia

Universal screening for IDA should be performed at approximately 1 year of age [18,26] [**L1, RGA**]. Selective screening (see *Table 7*) can be performed at any age in populations of infants and children who are at high risk for IDA [4,16,18,26] [**L1, RGA**]:

Age of Screening	Children that Require Screening for IDA

9-12 Months and 15-18 Months	• Preterm infants and low-birthweight infants.
	• Infants fed a diet of non-iron-fortified infant formula for greater than 2 months.
	• Infants introduced to cow's milk before age 12 months.
	• Breast-fed infants who do not consume a diet adequate in iron after age 6 months (i.e. who receive insufficient iron from supplementary foods).
	• Children who consume >700mls of cow's milk daily.
	• Children with special health-care needs:
	  ○ On medications that interfere with iron absorption.
	  ○ May have chronic infection or inflammatory disorders.
	  ○ May follow restricted diets.
	  ○ May experience extensive blood loss from a wound, an accident, or surgery.

Annual Screening at 2-5 Years	• Children following a low-iron diet. • Children with limited access to food because of poverty or neglect. • Children with special health-care needs (see above). • Children from low-income families. • Migrant children. • Recently arrived refugee children.
Annual Screenings in Adolescents	• Underweight, malnourished, or obese adolescents. • Adolescents following alternatives diets with low iron intake. • Females who have heavy menstrual blood loss (>80 ml/month). • Adolescents who are found to have anaemia at earlier screenings. • Patients with history of blood donation. • Athletes participating with endurance training. • Adolescents with periods of rapid growth.

Table 7: Screening schedule for children with increased risk of IDA[4,15,16,27].

In patients with infection and those who had infection within the past 2 weeks, the screening should be postponed [15] [**L1**].

7.2 Initial Laboratory Assessment

The goal of the initial laboratory assessment is to determine whether patient has isolated anaemia or if other cell lines are affected and to guide further testing to confirm the aetiology of anaemia [4,5] [**L1, RGA**]. Initial laboratory studies should include [3,4,16] [**L1, RGA**]:

- Complete blood count with differentials.
- Peripheral blood smear.
- A reticulocyte count may be obtained.
- Stool analysis for occult blood and worms.

8 Further Investigation and Diagnosis

8.1 Investigation of Microcytic Anaemia

If microcytic anaemia is suspected, further testing to narrow the diagnostic possibilities should include:

- Serum ferritin*.
- C-reactive protein.
- Iron, and total iron-binding capacity.
- MCV and RDW tests.

*While serum ferritin is a sensitive marker for iron status, it is also an acute phase reactant and is therefore elevated in inflammatory conditions. Therefore, serum ferritin measurement alone may mask the diagnosis of iron deficiency and testing with the full iron profile should always be attempted along with C-reactive protein [**R-GDG**].

Refer to *Figure 8.1* below. Each of the common diagnoses is discussed in further detail in the subsequent sections.

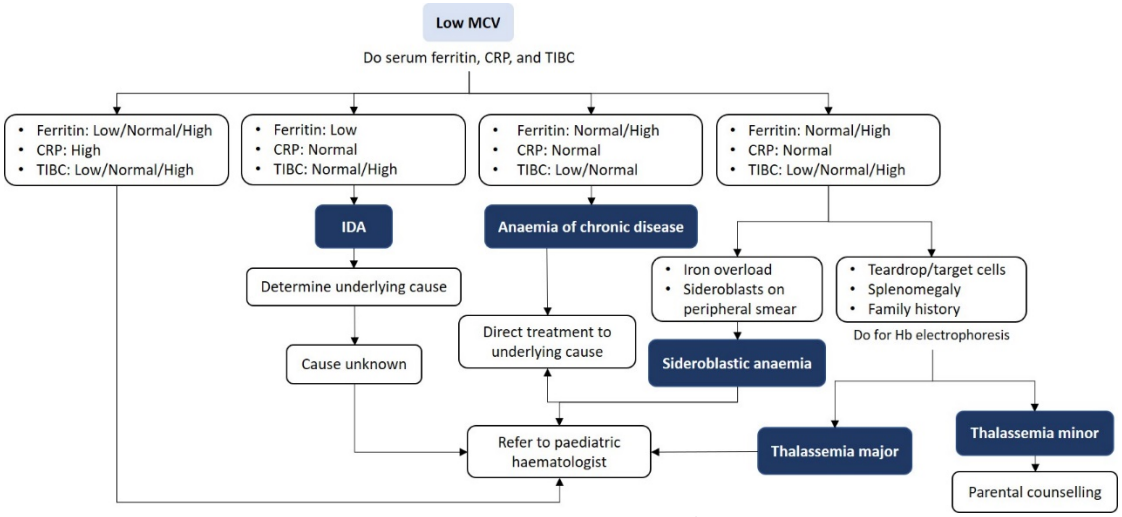


Figure 8.1: Algorithm for the investigation of microcytic anaemia [4,5,8].

8.2 Investigations of Normocytic Anaemia

If haemolytic anaemia is suspected, further testing should include [2,4,5,8]:

- Peripheral smear and reticulocyte count if not initially ordered.
- Serum indirect bilirubin, lactate dehydrogenase, and haptoglobin levels.
- Additional testing for specific aetiologies should be guided by blood film picture and may include
    - Direct antiglobulin test.
    - G6PD deficiency screening test.
    - Osmotic fragility.
    - Haemoglobin electrophoresis.

If aplastic anaemia or another cause of bone marrow failure is suspected:

- The patient should be urgently referred to haematologist for bone marrow aspirate and/or biopsy.

Use the algorithm in *Figure 8.2* to guide further investigation and diagnosis of the normocytic anaemia. Also, see notes below. Each of the common diagnoses is discussed in the subsequent sections.

View Pathway

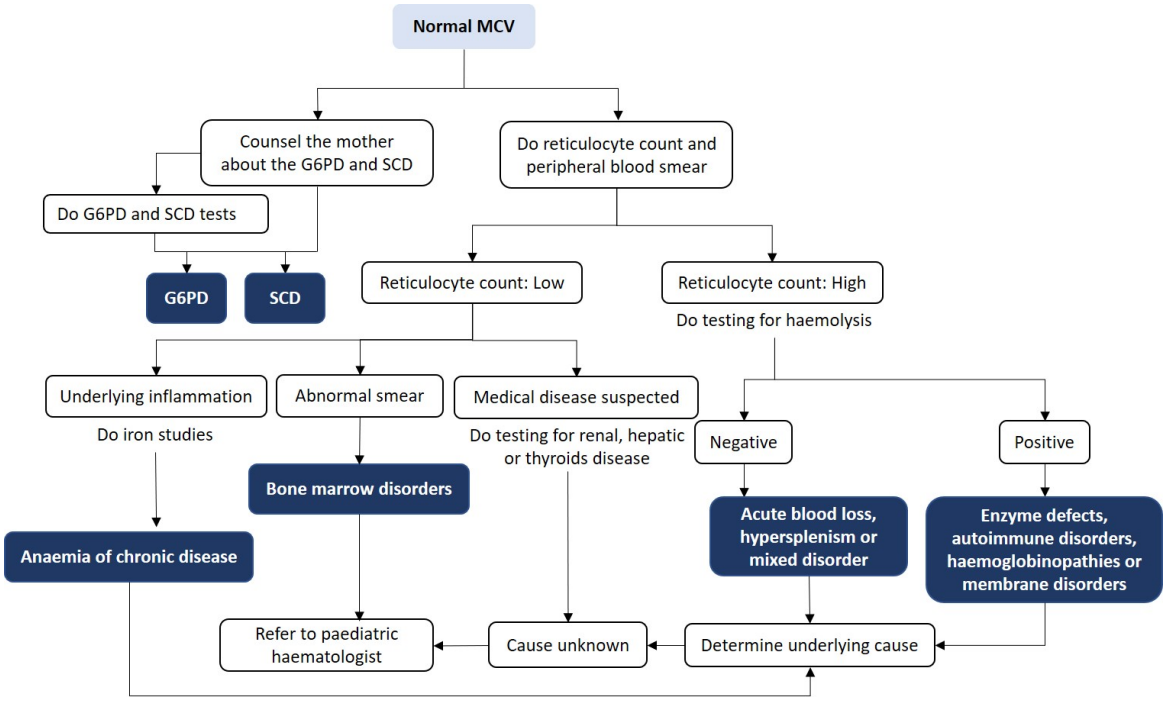


Figure 8.2: Algorithm for the investigation of normocytic anaemia [2,4,5,8].

8.3 Investigations of Macrocytic Anaemia

Use the algorithm in *Figure 8.3* to guide further investigation and diagnosis of the macrocytic anaemia. Also, see notes below. Each of the common diagnoses is discussed in further detail in the subsequent sections.

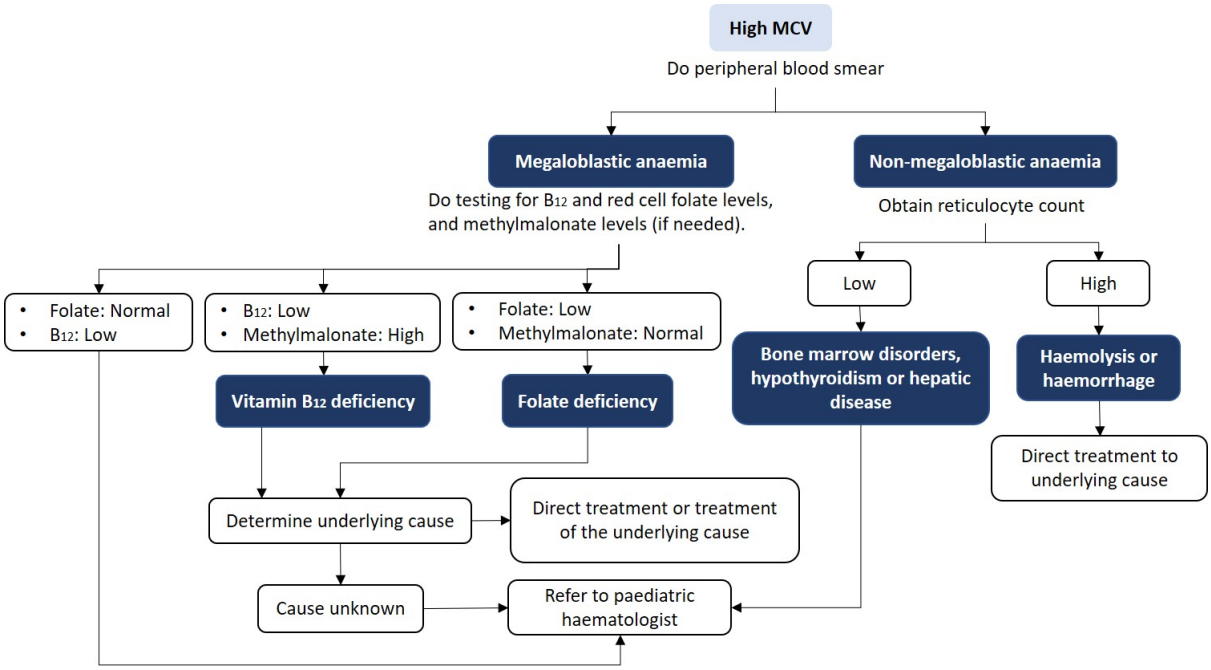


Figure 8.3: Algorithm for the investigation of macrocytic anaemia [4,5,8].

8.4 Other Diagnostic Considerations

When diagnosing anaemia in children and adolescents, consider the following:

- IDA is the most common type of anaemia in children [5].
- α-thalassaemia minor is frequently seen in South East Asian, Mediterranean, African, and Middle Eastern children[5,9].
- β-thalassaemia minor is less common in African children.
- Paroxysmal nocturnal haemoglobinuria is very rare in childhood or adolescence [2].
- Normochromic normocytic anaemia can occur in patients with chronic inflammation, chronic disease (e.g. renal disease), and acute blood loss [9].
- Consider other cell lines for evaluation of causes of anaemia [28]:
    - Thrombocytosis with IDA, infection, haemolytic-uremic syndrome, thrombotic thrombocytopenic purpura.
    - Pancytopenia with aplastic anaemia, myelodysplastic syndrome leukaemia.

If haemorrhage is suspected in the absence of trauma, review the most common non-traumatic causes of bleeding, which include [3] [**L2**]:

- Gastrointestinal.
- Gynaecological.
- Genitourinary.

Bone marrow infiltration, fibrosis, various myeloproliferative diseases, and sideroblastic anaemias must be confirmed by bone marrow biopsy [2] [**L2, RGA**].

9 Initial Management and Referral Criteria

9.1 Primary Care Management

The management of suspected anaemia in primary care should follow the following clinical steps [29]:

- Establish the presence of anaemia (see *Sections 6 and 7.2*).
- Establish the type of anaemia (*see Section 8*).
- Commence appropriate corrective treatment if iron deficiency anaemia is the likely aetiology (see *Sections 10* for details).
- Refer to secondary or specialist care for further appropriate investigation and management (see *Section 9.2 and 9.3* for referral criteria).
- Monitor patient's response to the corrective treatment (see *Section 10.1.4*).
- Follow up of patients that are referred to secondary care.

9.2 Referral to Specialist Care

The patient should be referred to a paediatric haematologist if any of the following are suspected or diagnosed [4,5,9] [**L1, RGA**]:

- Autoimmune haemolytic anaemia.
- Parenteral therapy is required.
- Thalassaemia major.
- A myelodysplastic syndrome [**R-GDG**].
- Aplastic anaemia [**R-GDG**].
- Sickle cell disease apart from sickle trait [**R-GDG**].
- Megaloblastic anaemia.
- Leukaemia/lymphoma
- Chronic bleeding of unknown cause.
- Cause of anaemia is unknown.
- Anaemia is refractory to treatment (after one month).
- A second opinion is required [**R-GDG**].

Consider referral to paediatric haematologist when necessary (see *Sections 8.2* to *Section 8.4*) [2,4,5,8] [**L1, RGA**]. All patients with IDA should also be referred to a dietician for the dietary measures [4] [**L2, RGA**].

9.3 Referral to Paediatric Emergency Centre

If any of the following red flags are present, the patient should be referred to a Paediatric Emergency Centre[4,9] [**L1, RGA**]:

- Severe anaemia whether symptomatic or asymptomatic.
- Acute haemolytic crisis.
- Severe vitamin B_{12} or folate deficiency.
- Tachycardia, cardiac murmur or signs of cardiac failure.
- Moderate to severe blood loss.
- Associated thrombocytopenia or neutropenia may indicate malignancy or an infiltrative disorder.
- Marasmus or kwashiorkor.
- Need for red cell transfusion.

All children aged >14 years should be referred to adult emergency services at HMC as the HMC paediatric scope of practice is up to 14 years old [4] [**L1**].

10 Management of Microcytic Anaemias

Use the table below to differentiate between microcytic anaemias. Additional condition-specific characteristics are also provided in respective sections below.

	IDA	ACD	Thalassemia	Sideroblastic anaemia
MCV/MCH	Low	Normal or low	Low	Low
RDW	High	Normal or slightly high	Normal or low	High
Serum iron	Low	Low	Normal	Normal or high
TIBC	High	Normal or low	Normal	Normal or low
Ferritin	Low	Normal or high	Normal	Normal
Transgelin	Very low <10	Low	-	-
GDF 15	Normal	Low	-	-
Hepcidin	Normal	High	-	-
Pap smear	Target cells	Bone marrow	Teardrops or target cells	Pappenheimer bodies in the red cells and/or sideroblasts

Table 10: Characteristics of different microcytic anaemia types [**R-GDG**].

10.1 Iron Deficiency Anaemia

IDA is indicated by [1,8,30] :

- Low MCV (see *Section 4.2* for details).
- Low MCH and MCHC.
- Microcytic hypochromic red cells on peripheral blood film.
- Low serum iron.

The underlying cause of the IDA should be investigated and documented appropriately [**R-GDG**].

NB:

- In patients with early iron deficiency and anaemia of chronic disease (where there may be a functional iron deficiency), MCV and MCH can be normal.
- There may also be an associated iron deficiency with chronic blood loss and haemolysis.
- **Ferritin, B_{12} and folate should also be assessed in all cases of anaemia, irrespective of MCV[29,31].**

Once a cause has been identified, first-line treatment should be initiated.

The therapeutic management of IDA in children and adolescents includes both [4,17] [**L2, RGA**]:

- Dietary therapy (see *Section 10.1.1*).
- Oral iron therapy (see *Section 10.1.2*).

10.1.1 Dietary Therapy

Dietary treatment should cover the following aspects of therapy:

- Dietary counselling [4] [**L2, RGA**]:
  - Measures to improve dietary intake of iron-rich foods are highly recommended [17] [**L1, RGA**]. (Also see *Table 5.1*)
  - Dietary changes alone are usually insufficient to treat IDA [17,32] [**L1, RGC**].

- Education of the patient and their families [4] [**L2, RGA**]. The following information should be provided:
    - General information regarding an iron rich diet.
    - List of iron-rich food.
    - Food that enhance absorption of iron.
    - Increase the intake of heme-iron sources.
    - Avoidance of iron inhibitors.

10.1.2 Iron Medications

A list of the iron medications presently registered in Qatar is provided in *Appendix A.*

10.1.2.1 Oral Iron Therapy

Oral iron therapy is the first-line therapy in most patients with iron deficiency or IDA [5,17] [**L1, RGA**].
Iron supplementation should be given:

- To correct IDA, until normal Hb level is achieved [4] [**L2, RGA**].
- To replenish the body store, supplementation should be continued for at least 3 months [4,17] [**L2, RGA**].

The recommended oral therapeutic dose of elemental iron for children is 3-6 mg/kg/day [4,17] [**L1, RGA**]. Consider formulations listed in *Table 10.1*. Note that different oral iron preparation contain different elemental iron doses [5,17]. See also *Appendix A*.

- Oral iron is best absorbed 1 hour before or 2 hours after meal [17].
- Consider supplementation with ascorbic acid (e.g. orange juice) to enhance absorption [8,17].
- Don't administer with milk or milk products [**R-GDG**].
- In case of poor compliance and tolerability, consider the following actions [8,17]:
    - Lowering doses or intermittent dosing.
    - Splitting the daily iron into 2-3 doses.
    - Taking iron with food or at night to reduce gastrointestinal adverse effects.
    - Increasing the dose gradually.
    - Prescribing alternative iron compounds.
- Be aware that oral iron may adversely reduce absorption of other medications [1].

Formulation	Notes
Ferrous fumarate	Only tablets are available.
Ferrous sulfate	Different forms are available: • Drops and oral solution. • Elixir and liquid. • Syrup. • Capsules and spansules. • Regular and extended-release tablets.
Polysaccharide-iron complex and ferrous bisglycinate chelate	Capsules and elixir are available.

Table 10.1: Paediatric appropriate oral iron therapy and dose [5,17].

Over-the-counter multivitamin and mineral supplements are not recommended to treat IDA due to the low iron content [17] [**L2, RGB**]. Inform the patient and their family that iron formulations can cause temporary staining of the teeth [17].

10.1.2.2 Intramuscular Iron Therapy

Intramuscular iron is effective but is not recommended due to the following reasons [17] [**L2, RGC**]:

- It is painful.
- It may be associated with permanent skin staining.
- Intramuscular injections are not safer than intravenous infusions.

10.1.2.3 Intravenous Iron Therapy

Consider intravenous (IV) iron if any of the following is present [4,8,17,25] [**L1, RGA**]:

- Contraindications, intolerance or non-compliance with oral preparations.
- Comorbidities affecting absorption (e.g. gastric surgery, short gut syndrome).
- Bone marrow response.
- Target Hb levels are not reached within 3 months.
- Patient is receiving erythropoietic stimulating agents.
- Ongoing blood loss that exceeds iron absorptive capacity.
- Requirement for rapid iron repletion.
- Genetic disorders of iron transport.
- Patient is receiving haemodialysis.
- Major surgery in < 8 weeks.

If IV therapy is required refer the patient to a specialist. The following iron preparations may be required:

- Ferric carboxymaltose [17][**L2, RGB**].
- Iron saccharate [17][**L2, RGA**].

Allergic and anaphylactic reactions to IV iron (especially to iron polymaltose) are possible [17,32] [**L2, RGC**].

- Premedication with steroids and antihistamine may be considered [17] [**L2**]:
    - Cetirizine:
        - Infants 6 months and child <2years: 2.5mg.
        - Children 2-5years: 2.5-5mg.
        - Children >5 years: 5-10mg.
    - Hydrocortisone (2–4 mg/kg IV; maximum 100 mg).
- IV administration at a low dose and high frequency may be more appropriate [25] [**L1, RGB**].

10.1.3 Blood Transfusions

Red blood cell (RBC) transfusion should be reserved for patients with haemodynamic compromise and risk of cardiovascular instability [8,17] [**L2, RGA**].

10.1.4 Follow-up

Compliance and response to iron replacement therapy should be re-evaluated with CBC, reticulocyte count and serum ferritin after 4 weeks [4] [**L2, RGA**]:

- If Hb increases, the treatment should be continued for 3 months and CBC repeated [4] [**L2, RGA**].
    - Iron therapy should continue after anaemia has been corrected for:

        - 3 months in children and adolescents.
    - The total duration of treatment is usually 3-6 months.
- If suspected IDA does not respond to treatment, further investigations may be required (see *Section 8.2*) [5] [**L1, RGA**].
- If the patient is unable to tolerate oral iron supplements or there is no improvement with oral iron, consider intravenous injections (see *Section 11.1.1*) [8,17] [**L1, RGA**].

10.2 Anaemia of Chronic Disease

ACD is a multifactorial anaemia. The presence of a chronic inflammatory condition, such as infection, autoimmune disease, kidney disease, or cancer is required for diagnosis to be made (see *Section 10.2.1*). It may present as normocytic or microcytic anaemia and low reticulocyte count[2,30]. IDA and ACD frequently co-exist but it is important to differentiate between them [30].

Other laboratory features of ACD include [1,2,8,30]:

- Low or normal MCV.
- Low serum iron.
- Decreased transferrin saturation.
- Increased reticuloendothelial iron.

10.2.1 Associated Chronic Diseases

ACD is frequently associated with chronic infection and inflammations, including [1,2,30]:

- Infections:
    - Bacterial (e.g. tuberculosis).
    - Viral.
    - Parasitic.
    - Fungal.
- Malignancies:
    - Haematological.
    - Solid tumours.
- Autoimmune diseases:
    - Juvenile rheumatoid arthritis.
    - Systemic lupus erythematosus and related conditions.
    - Vasculitis (e.g. Henoch-Schönlein purpura and Kawasaki disease).
    - Sarcoidosis.
    - Inflammatory bowel disease (Crohn's disease).
- Organ dysfunction:
    - Chronic kidney disease/failure.
    - Chronic heart disease/failure.

The level of anaemia correlates with the activity of the underlying disease.

10.2.2 Treatment of the Underlying Disorder

The mainstay of treatment is to reverse the underlying inflammatory or malignant process if possible to improve the degree of anaemia [30] [**L2, RGA**].

10.2.3 Iron Therapy

Iron therapy is not recommended in patients with ACD [30] [**L2, RGB**] unless ACD is accompanied by IDA or there is a true deficiency of iron [25,30].

10.2.4 Erythropoiesis-Stimulating Agents

Erythropoiesis-stimulating agents (ESAs) may be appropriate in a subset of patients with ACD [8,25] [**L1**]. In patients with absolute iron deficiency, ESA therapy must be accompanied by the iron deficiency management (see *Sections 10.1* and *10.2.2*) [25,30] [**L1, RGA**].

The ESA must be prescribed by a renal consultant/ nephrology specialist [33]. ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumour progression or recurrence [34].

If ESA therapy is required, consider the following medications:

- Epoetin alfa and its biosimilars (epoetin alfa and zeta): 50 units/kg 3 times per week [35] [**L1, RGA**].
- Epoetin beta [35] [**L1, RGA**]:
    - Correction phase: 40 units/kg IV.
    - Maintenance phase: 20 units/kg IV.
- Darbepoetin alfa [35] [**L1, RGB**]:
    - In epoetin alfa naive patients: 0.45 mcg/kg subcutaneous or IV every week.
    - Patients not receiving dialysis may also be initiated at a dose of 0.75 mcg/kg once every 2 weeks [**R-GDG**].
    - In patients switching from epoetin alfa: the dose is based on the weekly epoetin alfa dose.

The initial ESA dose and ESA dose adjustments should be based on[35]:

- Patient's Hb level.
- Target Hb.
- Observed Hb increasing rate.
- Clinical circumstances.

The effectiveness of ESAs therapy should be assessed after an agreed interval[25] [**L1, RGA**]. Decision on whether or not to continue using ESAs should be made jointly with the patient [25] [**L1**].

10.2.5 Blood Transfusion

RBC transfusion should be reserved for patients who belong to one of the following groups [8,30] [**L2, RGA**]:

- Severe or life-threatening anaemia.
- Where the patient has symptomatic anaemia (symptoms are listed in *Section 6.1*).
- A co-morbid disorder for which a moderately low Hb level imposes additional risk.

10.3 Thalassaemia

Thalassaemia is an inherited hemoglobinopathy disorder that result in ineffective erythropoiesis and may result in haemolysis [1,5].

Thalassaemia is indicated by [1,8] :

- Low MCV (see *Section 4.2* for details).

- Teardrop red cells on peripheral blood film.
- Splenomegaly may be present.
- Positive family history may be present.

The Mentzer index (estimated as MCV/RBC count) may be used to differentiated thalassemia from IDA [5] [**L1**]: A Mentzer index <13 suggests thalassemia, and an index >13 suggests IDA.

10.3.1 Classification and Management

Thalassaemia may be classified according to the affected globin chain [5]:

- α-thalassaemia.
- β-thalassaemia.

Thalassaemia may be classified into the following clinical syndromes [1,5,8,9]:

- **Thalassaemia Minor**:
  - Heterozygous alpha or β-thalassaemia.
  - Patients are symptomless.
  - Anaemia is mild or undetectable with CBC.
  - No treatment is necessary unless the patients have coincidental haematological pathology.
  - If a coexisting IDA is present, the Hb electrophoresis may be normal. Therefore, it is important to treat any suspected IDA, prior to testing for thalassaemia [**R-GDG**].
  - Pre-marital testing and genetic counselling may be indicated [**R-GDG**].

- **Thalassaemia Intermedia**:
  - May be due to a range of causes of impaired globin chain synthesis.
  - Patients may be symptomatic with moderate anaemia.
  - Splenomegaly and bone deformities may be present.
  - Recurrent leg ulcers, gallstones, and infections may also be seen.
  - Refer all patients to a paediatric haematologist for specialist review and management [**R-GDG**].

- **Thalassaemia Major**:
  - Patients are usually identified at neonatal screening or when they present with failure to thrive in their first year of life.
  - Severe anaemia is detected with CBC.
  - Radiographic findings include: 'hair on end' appearance of bone.
  - Refer all suspected cases to a haematologist for specialist review and management [**R-GDG**].

10.4 Sideroblastic Anaemia

Sideroblastic anaemia is a type of anaemia when iron is produced in sufficient amounts and deposited in mitochondria of RBC instead of being used to produce Hb [36,37]. Depending on the type of mutation, sideroblastic anaemia can be diagnosed in patients with microcytic or macrocytic anaemia [37].

Sideroblastic anaemia is indicated by[36,37]:

- Low MCV (see *Section 4.2* for details).
- Low MCH.

- Normal to high iron levels.
- Normal CRP.
- Pappenheimer bodies in the red cells.
- Ring sideroblasts are seen in bone marrow aspirates using Prussian Blue or Perl's stain.

10.4.1 Classification

Sideroblastic anaemia may be classified into the following categories[36,37]:

- Hereditary:
  - Caused by mutations in genes that are involved in heme synthesis, iron-sulfur cluster biogenesis, or mitochondrial metabolism.
  - The X-linked mutation in the aminolevulinate synthase is the most common type.
- Acquired (uncommon in children):
  - Primary causes include clonal hematologic disorders:
    - Myelodysplastic syndrome with ring sideroblast.
    - Refractory anaemia with ring sideroblasts.
  - Secondary causes include:
    - Drugs (antibiotics, hormones, copper-chelating agents and chemotherapy).
    - Toxins (e.g. lead).
    - Alcohol use.
    - Copper deficiency.
    - Chronic neoplastic disease.
    - Tumors.
- Idiopathic (of unknown origin).

10.4.2 Management

In patients with the X-linked sideroblastic anaemia, treatment with vitamin B6 (oral pyridoxine) should be considered [36,37] [**L2**]:

- Children: 5-25mg/day for 3 weeks then 2.5-5mg/day in multivitamin products [**R-GDG**].
- Adolescents: 10-20 mg/day for 3 weeks then 2-5mg/day in multivitamin products [**R-GDG**].

RBC transfusion should be reserved for patients with severe or life-threatening anaemia, who are not responsive to pyridoxine [37]. For patients who require chronic transfusion, iron chelation must be considered to avoid iron overload [37] [**L2, RGA**].

To remove excess iron, consider subcutaneous or intramuscular desferrioxamine [36,37] or oral chelators when serum ferritin is >1000 ng/L [37] [**L2, RGA**].

If sideroblastic anaemia is acquired, the responsible agent must be identified and avoided [36,37] [**L2, RGA**]. Drugs should be replaced or discontinued.

Patients and their parents or caregivers should be advised about the following [37] [**L2, RGA**]:

- Nutritional modifications may be required to replace coper in patients with copper deficiency.
- Iron-rich containing food that could exacerbate more iron overload should be avoided.
- Balanced nutrition is an important preventive measure.
- Tight glycaemic control is required in patients with syndromic congenital sideroblastic anaemia as they are at increased risk of diabetes.
- Alcohol, isoniazid, and lead poison should be avoided.
- Close adherence to treatment is very important.
- Regular follow-up examinations with haematologist are encouraged.

11 Management of Normocytic Anaemias

11.1 Acute Blood Loss Anaemia

Patients that are unstable should be transferred urgently to the Paediatric Emergency Center for resuscitation and stabilization[6].

The general strategy of treatment should be aimed at[3] [**L2, RGA**]:

- Restoring blood volume.
- Treating the cause of the bleeding.

11.1.1 Classification and Management of Blood Loss

Blood loss is classified according to the lost volumes[3,38]:

- Class I:
  - <15% loss of blood volume.
  - No significant change in vital signs.
  - Does not require intervention.
- Class II:
  - 15-30% loss of blood volume.
  - May cause tachycardia, reduced pulse pressure, and peripheral vasoconstriction.
  - Volume repletion with crystalloids is usually required.
  - Blood transfusion is usually not recommended.
- Class III:
  - 30-40% loss of blood volume.
  - Signs and symptoms include hypotension, tachycardia, and shock.
  - Crystalloid resuscitation and blood transfusion are recommended.
- Class IV:
  - >40% loss of blood volume.
  - Lethal unless rapid, aggressive resuscitation is initiated with massive transfusion of blood products, crystalloids, and pressors.

Monitor patients' response to treatment[6,26]:

- Vital signs.
- Pulse oximetry, and cardiac status.
- A repeat haematocrit is mandatory.

11.2 Haemolytic Anaemia

Children with haemolytic anaemias should be admitted for observation [9] [**L2, RGA**]. Treatment varies depending on the type of haemolysis. All cases of acute haemolysis in children should be reviewed by a Haematologist.

The following is recommended [9,39] [**L2, RGA**]:

- Frequent heart rate monitoring for tachycardia which may indicate a further drop in Hb.
- Repeated CBC within 6-12 hours of presentation to detect ongoing haemolysis.
- Monitor the haemoglobin level, reticulocyte count, indirect bilirubin, LDH and haptoglobin in patients with haemolytic anaemia to determine the response to therapy.
- Urine haemoglobin and hemosiderin should be monitored to evaluate recovery in those with severe intravascular haemolysis.

- Patients should receive prophylactic folic acid because active haemolysis can consume folate and cause megaloblastic picture.
- Corticosteroids should be considered in patients with AIHA (See *Section 11.2.3*)
- Transfusions should be avoided unless absolutely indicated. However, transfusions may be necessary for patients with a severely compromised cardiopulmonary status. In this case packed red blood cells should be administered slowly to avoid cardiac stress.
- Penicillin and other medications (see *Section 4.2.2*) that can cause immune haemolysis should be discontinued in children who develop haemolysis.

11.2.1 Sickle Cell Haemoglobinopathies

Sickle cell haemoglobinopathies are caused by structurally abnormal haemoglobin with a genetic defect in the β-globin [5,40]. Sickle cell haemoglobinopathies are indicated by [8,40]:

- Deformation or sickling of red cells under conditions of hypoxia, acidity, and cellular dehydration.
- Microvascular occlusion, sepsis, haemolysis and ischaemia of tissues (sickling crisis).

11.2.1.1 Classification

Sickle cell haemoglobinopathies are classified according to the haemoglobin abnormality [40–42]:

- **Sickle cell anaemia** (HbSS):
  - Homozygous for sickle Hb gene.
  - The most common and the most serious form of the disease.
- **SCD-SC** (HbSC):
  - Heterozygous combination of sickle gene mutation and HbC gene mutation.
- **Sickle β-thalassemia**:
  - Heterozygous combination of sickle gene mutation and thalassemia gene mutation.
  - Subclassified into:
    - Sickle β plus thalassaemia (HbS/β+).
    - Sickle β zero thalassaemia (HbS/β0).
- **Sickle cell trait** (HbAS):
  - Heterozygous combination of the normal haemoglobin gene with the sickle cell gene.
- **Other** (HbSD disease, HbSE disease, HbSO Arab disease).

11.2.1.2 Routine Clinical Laboratory Evaluations

Consider collecting a series of baseline values for each patient [41] [**L1**]. They may be compared with values at times of acute illness. A typical schedule of routine clinical laboratory evaluations includes [41]:

- CBC with WBC differential, reticulocyte count:
  - In children 3-24 months old – once in 3 months.
  - In children >24 months old – once in 6 months.
- Percent HbF:
  - In children 6-24 months old – once in 6 months.
  - In children >24 months old – annually.
- Renal function (creatinine, BUN, urinalysis):
  - Children >12 months old – annually.
- Hepatobiliary function (ALT, fractionated bilirubin):
  - Children >12 months old – annually.
- Pulmonary function (transcutaneous O_2 saturation):
  - Children >12 months old – once in 6 months.

11.2.1.3 Immunisation

In addition to routine immunisations, children with SCD require additional vaccination [41] [**L1, RGA**]:

- Seasonal influenza vaccination is recommended[41] [**L1**].
- Consider pneumococcal polysaccharide vaccine Pneumovax 23 (PPV-23) in addition to Prevnar 13 (PCV13) [**R-GDG**].

11.2.1.4 Antibiotic Prophylaxis

Antibiotic prophylaxis is recommended in children from 2 month to 5 years of age to prevent pneumococcal infections[41] [**L1, RGA**]. Consider the following regimen[41]:

- Children <3 years of age: penicillin VK 125 mg by mouth twice daily.
- Children >3 years of age: penicillin VK 250 mg by mouth twice daily.
- If oral penicillin is contraindicated, consider an injection of 1.2 million units of long-acting benzathine penicillin G every 3 weeks.
- If patient is allergic to penicillin, consider erythromycin ethyl succinate (20 mg/kg) divided into 2 daily doses.

Continuation of antibiotic prophylaxis is possible in children >5 years old[41] [**L1, RGB**]. Discussion with parent is required prior making the decision[41] [**L1**].

11.2.1.5 Sickle Crisis

Patients with the **sickle cell trait** are usually asymptomatic[41]. Patients with the **SCD** and **sickle cell anaemia** may present with the following problems[40]:

- Vaso-occlusive crisis.
- Infection and fever.
- Acute chest syndrome.
- Acute splenic sequestration.
- Aplastic crisis.
- Stroke.
- Priapism.

Acute crises may occur spontaneously, or may be precipitated by stress factors (especially in people with the sickle cell trait)[40]:

- Infection.
- Dehydration.
- Hypoxia.
- Sedatives and local anaesthetics.
- Procedures (e.g. surgery).
- Travel.
- Recent hospital admission.

11.2.1.6 Management of Sickle Crisis

Pain should be treated aggressively with analgesics administered IV or intranasally (see *Section 11.2.1.8*)[40,43] [**L2, RGA**]. Adequate hydration is required [40,43]:

- Oral fluids are recommended [40] [**L2, RGA**].
- IV fluids may be considered [40] [**L2, RGA**].
- Excess fluids after initial resuscitation should be avoided to reduced risks of chest crisis[40] [**L2, RGC**].

- RBC transfusion may be necessary [40] [**L2, RGA**].

Refer all cases to a haematologist for specialist review and management [40] [**L2, RGA**].

11.2.1.7 Management of Fever

All patients are functionally asplenic and are at increased risk for invasive disease and infections particularly by encapsulated organisms (e.g. pneumococcus, meningococcus, haemophilus) [40,41].

In children with SCD, antipyretics are not recommended at first signs of fever [41] [**L1**].

All children with fever (>38.5°) and signs of infection (chills, lethargy, irritability, poor feeding, vomiting) should be evaluated promptly [41] [**L1**]. If a child has no obvious source of infection, a minimum evaluation should include [40,41] [**L1**]:

- Blood and urine culture.
- CBC.
- Reticulocyte count.
- Chest X-rays (for children <3 years of age).

Broad-spectrum antibiotics (e.g. 3rd generation cephalosporin) should be administered immediately after the blood is taken for tests [40,41] [**L1, RGA**]. Also, consider antibiotics covering atypical organisms (e.g. clarithromycin or azithromycin) [40] [**L2, RGA**]. The preferred route of administration is IV [40,41] [**L1, RGA**].

11.2.1.8 Management of Pain

Pain episodes can start suddenly or following illness and stress [40,41].

Typical vaso-occlusive pain may involve limbs, abdominal viscera, ribs, sternum, vertebrae, and sometimes skull bones [41]. If pain occurs in chest and is accompanied by respiratory symptoms, acute chest syndrome should be considered rather than vaso-occlusive episode [40] [**L2**].

Consider the following medications for pain management [40,41,43] [**L2, RGA**]:

- Mild pain:
  - Acetaminophen (paracetamol).
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen).
- Moderate to severe pain:
  - Mild opioids (e.g. codeine) in younger children.
  - Stronger NSAIDs and opioids (e.g. morphine) in older children and adolescents.

Consider hydroxycarbamide (hydroxyurea) for the prevention of recurrent painful crisis in patients with SCD [43,44] [**L1, RGA**].

11.2.1.9 Education

Education of the patient and their families is required and should include the following aspects [41] [**L1, RGA**]:

- Training physical examination skills (e.g. palpation of spleen).
- Localisation, assessment of severity, and treatment of pain.
- Avoidance of vaso-occlusive complications.
- Signs and dangers of infection.
- Proper administration of prophylactic antibiotics.

11.2.2 G6PD Deficiency

G6PD deficiency is the most common enzymopathy worldwide [45]. It is an X-linked genetic disorder that includes more than 300 allelic variants [2,45,46].

G6PD deficiency is indicated by [45]:

- Decreased Hb.
- Low RBC counts.
- Reticulocytosis.
- Increased lactate dehydrogenase.
- Increased unconjugated bilirubin.
- Bite cells and Heinz bodies.

11.2.2.1 Classification

G6PD deficiency may be classified according to the magnitude of the enzyme deficiency and hemolysis severity [46]:

- Class I: severely deficient variants associated with chronic non-spherocytic haemolytic anaemia.
- Class II: severely deficient with <10% residual activity.
- Class III: moderately deficient with 10-60% residual activity.

11.2.2.2 Management

The primary management of G6PD deficiency includes [45] [**L2, RGA**]:

- Supportive care.
- Removal and avoidance of further triggers (see Tables 11.2.1 and 11.2.2).
- Hemodialysis may be considered in patients with acute kidney injury.

RBC transfusions should be reserved for patients with severe or life-threatening anaemia [45] [**L2, RGA**].

11.2.2.3 High Risk Medications

Certain medications that should be avoided or used with caution in G6PD deficient patients due to high risk of haemolysis (see *Table 11.2(1)*)[45–47] [**L2, RGC**].

Medications that should be avoided	Medications that may be used with caution
• Diaminodiphenyl sulfone (Dapsone). • Flutamide (Eulexin). • Furazolidone (Furoxone). • Isobutyl nitrite. • Methylene blue. • Niridazole (Ambilhar). • Nitrofurantoin (Furadantin). • Phenazopyridine (Pyridium). • Primaquine. • Rasburicase (Elitek). • Sulfacetamide. • Sulfanilamide.	• Acetaminophen (Tylenol) • Acetylsalicylic acid (aspirin) • Antazoline (Antistine) • Antipyrine • Ascorbic acid (vitamin C): IV doses • Benzhexol (Artane) • Chloramphenicol • Chlorguanidine (Proguanil, Paludrine) • Chloroquine • Colchicine • Diphenyldramine (Benadryl) • Glyburide (glibenclamide, Diabeta, Glynase)

Medications that should be avoided	Medications that may be used with caution
• Sulfapyridine. • Ciprofloxacin. • Levofloxacin. • Doxorubicin. • Sulfamethoxazole (Gantanol).	• Isoniazid • L-Dopa • Quinine • Streptomycin • Sulfacytine • Sulfadiazine • Sulfaguanidine • Sulfisoxazole (Gantrisin) • Trimethoprim • Tripelennamine (Pyribenzamine) • Vitamin K and analogues

Table 11.2(1): Medications associated with hemolysis in G6PD deficient patients and medications that are reasonably safe[45–47].

11.2.2.4 Foods and Chemicals Triggering Haemolysis

Scant literature describes foods, chemicals, and supplements that can trigger haemolysis in G6PD-deficient individuals [48]. There is insufficient evidence to reach a clear conclusion regarding the risks of various substances.

Substances that should be avoided	Substances that should be used with caution
• Fava beans & food cross-contaminated with fava beans. • Naphthalene dye. • Aniline dye. • Henna.	• Food colouring agent: 1-phenylazo-2-naphthol-6-sulphonic acid. • *Acalypha indica.* • *Coptis chinensis.*

Table 11.2(2): Dietary products and chemicals triggering haemolysis in G6PD-deficient individuals[48,49].

11.2.3 Autoimmune Haemolytic Anaemia

Autoimmune Haemolytic Anaemia (AIHA) is a decompensated acquired hemolysis caused by the host's immune system acting against its own red cell antigens [50].

AIHA are typically indicated by [1,8,50]:

- High MCV (may be normal in the early stages of the disease).
- Reticulocytosis (may be normal in the early stages of the disease).
- Positive Coombs test (direct antiglobulin test (DAT)).
- Splenomegaly may be present.
- RBCs may be abnormal on peripheral smear:
  - Spherocytosis.
  - Polychromasia.
  - Anisopoikilocytosis.
- Lactate dehydrogenase may be raised.
- Indirect bilirubin may be raised, while alanine transaminase remains normal.
- Haptoglobin may be decreased.

11.2.3.1 Classification and Aetiology

Main causes of **cold AIHA** include [1,50]:

- Cold haemagglutinin disease:
  - Idiopathic.
  - Primary.
  - Secondary due to:
    - Malignancy:
      - Chronic lymphocytic leukaemia.
      - Non-Hodgkin lymphoma.
      - Solid organ.
    - Infections:
      - Mycoplasma.
      - Viral infections including infectious mononucleosis.
    - Autoimmune disease.
    - Post-allogeneic haematopoietic stem cell transplantation.
- Paroxysmal cold haemoglobinuria:
  - Idiopathic.
  - Primary.
  - Secondary due to:
    - Infections:
      - Adenovirus.
      - Influenza A.
      - Syphilis.
      - Cytomegalovirus.
      - Infectious mononucleosis.
      - Varicella zoster virus.
      - Measles.
      - Mumps.
      - *Mycoplasma pneumoniae*.
      - *Haemophilus influenzae*.
      - *Escherichia coli.*

Main causes of **warm AIHA** include [1,50]:

- Idiopathic.
- Primary.
- Secondary due to:
  - Neoplasia:
    - Chronic lymphocytic leukaemia.
    - Lymphoma.
    - Solid organ.
  - Infections:
    - Hepatitis C.
    - Human immunodeficiency virus.
    - Cytomegalovirus.
    - Varicella zoster virus.
    - Pneumococcal infection.
    - Leishmaniasis.
    - Tuberculosis.
  - Immune dysregulation:
    - Connective tissue disorders (e.g. systemic lupus erythematosus, Sjögren's syndrome, scleroderma).

- Ulcerative colitis, primary biliary cirrhosis, and sarcoidosis.
- Post transplantation Immune deficiency syndromes (e.g. common variable immunodeficiency).

Main causes of **mixed type AIHA** include [50]:

- Primary.
- Secondary due to:
  - Lymphoma.
  - Infection.
  - Systemic lupus erythematosus.

11.2.3.2 Clinical Presentation

In addition to the symptoms and signs of anaemia described in *Section 5*, patients may also present with[1,50]:

- Splenomegaly.
- Jaundice.
- Haemoglobinuria.
- Acute haemolytic crisis:
  - Fever.
  - Rigors.
  - Back pain.
  - Abdominal pain.
  - Shock.

11.2.3.2 Management

If drug-induced AIHA is suspected, the relevant medication must be stopped and replaced with an alternative [50] [**L1, RGA**].

General strategies of AIHA treatment include:

- Supplementation with folic acid patients with primary AIHA [50] [**L1, RGA**].
- Thromboprophylaxis in patients who are at risk of venous thrombosis [50] [**L1, RGA**].
- Consider corticosteroids (e.g. prednisone) [50,51] [**L1, RGB**]. Risk assessment is required in patients receiving steroids to prevent glucocorticoid-induced osteoporosis and gastrointestinal bleeding [50] [**L1, RGA**].
- Intravenous immunoglobulins may be considered as adjunctive therapy to steroids [51] [**L1, RGB**].

Blood transfusion should be reserved for patients with severe or life-threatening anaemia [50] [**L1, RGA**].

The level of anaemia correlates with the activity of the underlying disease and treatment of the underlying inflammatory or malignant process can improve the degree of anaemia [50] [**L1, RGA**].

12 Management of Macrocytic Anaemias

12.1 Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency is indicated by [1,9,52]:

- Very high MCV.
- Low serum vitamin B_{12} level.
- Teardrop RBCs.
- Hypersegmented neutrophils.
- Elevated methylmalonate level.
- Often neutropenia or thrombocytopenia is present.
- May be associated with pancytopenia.
- May be associated with neurodevelopmental problems.

12.1.1 Aetiology

Vitamin B_{12} deficiency has three primary etiologies [52,53]:

- Autoimmune (i.e. pernicious anaemia).
- Malabsorption.
- Dietary Insufficiency.

Common causes of vitamin B_{12} deficiency include [54]:

- In newborns and infants <6 months of age:
    - Maternal deficiency.
    - Metabolic causes, especially in patient with severe metabolic disturbances (e.g. acidosis or vomiting).
- In children from 6 months to middle childhood:
    - Dietary deficiency.
    - Maternal deficiency.
    - Malabsorption.
- In children from middle childhood to juvenile age:
    - Pernicious anaemia.
    - Gastritis.
    - Malabsorption.
    - Medications.

12.1.2 Screening and Evaluation

Routine screening for vitamin B_{12} deficiency is not recommended [55] [**L1, RGB**]. Screening should only be considered in patients with risk factors [55] [**L1, RGA**].

If a vitamin B_{12} deficiency is suspected, collect a complete patient's history and evaluate physical conditions with an increased emphasis on gastrointestinal and neurologic findings (see also *Section 7*) [53].
Specifically, ask about the following [5,20,52–55]:

- Current and previous dietary intake:
    - Prolonged vegan diet.
    - Consumption of animal products.
    - Maternal dietary history in breast fed infants.
- Symptoms of anaemia or other cytopenias (jaundice, fatigue, and pallor).
- Signs and symptoms of vitamin B_{12} deficiency:
    - Neurological symptoms, e.g.:

        - Numbness.
        - Poor motor coordination.
        - Abnormal gait.
        - Delay or regression of developmental milestones.
        - Memory lapses.
    - Neuropsychiatric signs, e.g.:
        - Irritability.
        - Psychosis.
        - Cognitive impairment.
        - Seizures.
    - Peripheral neuropathy.
    - Subacute combined degeneration of the spinal cord:
        - Weakness and ataxia of lower limbs.
        - Classic triad of signs – extensor plantar reflexes, brisk knee reflexes, absent ankle reflexes.
    - Psychological symptoms, particularly depression and confusion.
    - Glossitis and mouth ulcers.
    - Olfactory impairments.
    - Poor responses to vibration, touch, pain, position.
    - Visual disturbance and optic atrophy.
    - Skin pigmentation changes and oedema in infants.
- Underlying disorders resulting in malabsorption or symptoms of malabsorption (e.g. diarrhoea, failure to thrive).
- Drug history, especially the following:
    - Metformin.
    - Proton pump inhibitors.
    - H2 receptor antagonists.
    - Trimethoprim-sulfamethoxazole.
    - Phenytoin.
    - Neomycin.
    - Colchicine.
    - Combined oral contraceptive pill.
- Alcohol intake in adolescents.

Diagnostic testing (*Sections 7.4 and 8*) should only be considered in patients with suspected clinical manifestations [55] [**L1, RGA**].

12.1.3 Management

Non-pharmacological treatment should include dietary counselling and advice on how to improve dietary intake of B_{12}-rich foods [20,53–55] [**L1, RGA**].

The general strategy of treatment involves repletion with B_{12} with intramuscular injections or oral vitamin therapy [20,53,55] [**L1, RGA**]. The duration and route of treatment depends on the etiology of the condition [53]. There are two formulations available [20,54,55]:

- Hydroxocobalamin [56].
- Cyanocobalamin [57].

In infants and children with clinical deficiency and neurological symptoms, the treatment must be started urgently [9,54] [**L2, RGA**]:

- Dietary deficiency:

    - Infants: 250-1000 mcg IM once daily for 1-2 weeks, followed by weekly dosing until patient recovers [58].
    - Patients with neurologic symptoms can be treated with doses of 1000 mcg [59,60].
- Malabsorption:
    - Infants, children, and adolescents: 250-1000 mcg IM daily or every other day for 1 week, then weekly for 4-8 weeks, and then monthly for life; younger children should receive monthly doses of 100 mcg [7,58,61].
- Patients with a deficiency in intrinsic factor (e.g. pernicious anaemia) should continue B_{12} parenterally [53].
- Other children may switch to oral supplements once they feel well, have no diarrhoea, feeding improved, and maternal stores are replaced [53,54] [**L2, RGA**].

Several regimen may be considered in children without neurological symptoms 53,54 [**L2, RGA**]. The total duration of the treatment usually comprises 3-6 months 54.

- Older children with mild disease:
    - Oral B_{12} 1000mcg daily.
- Subclinical, dietary deficiency:
    - Oral B_{12} 50-200 mcg daily.
- Supplement (not deficient, no dietary intake):
    - Oral B_{12} 50-100mcg daily or alternate daily.

Prophylactic treatment in high risk patients before B_{12} levels fall is not recommended [53] [**L2, RGB**].

If vitamin B_{12} deficiency coexists with folate deficiency, the former should be treated first [8,21,55] [**L1, RGA**].

12.1.5 Follow-up

Rapid clinical improvement is usually seen with replacement. If B_{12} deficiency was prolonged, neurological impairment may persist for longer [54].

In infants and children with severe deficiency, homocysteine and methylmalonate levels should be reevaluated [54] [**L2**]:

- 1-2 weeks after initiation of the treatment.
- 3 months after initiation of the oral therapy.
- Regularly until several months after completing the treatment.

Patients with subclinical deficiency should be evaluated for B_{12} levels at 3 months after initiation of the oral therapy [54] [**L2**].

Patients with deficiency due to metabolic causes and deficiency in intrinsic factors require individual life-long management by a specialist [54] [**L2**].

12.2 Folate Deficiency

There is no standard serum folate level that indicates deficiency [62]. Usually, serum folate <7 nmol/L (3 µg/L) is considered as deficient [52,62] [**L1**]. Folate deficiency is indicated by [1,52]:

- Very high MCV.
- Low folate levels.
- Normal methylmalonate levels.
- Increased homocysteine level.

12.2.1 Aetiology

Folate deficiency has four primary etiologies [21]:

- Congenital deficiencies of enzymes.
- Dietary Insufficiency.
- Malabsorption.
- Occurrence subsequent to vitamin B_{12} deficiency.

12.2.2 Screening and Evaluation

If folate deficiency is suspected, collect a complete patient's history and evaluate physical conditions with an increased emphasis on gastrointestinal findings (see also *Section 7*) [21].
Specifically, ask about the following [20,21]:

- Current and previous dietary intake:
    - Consumption of leafy vegetables, citrus fruits, and animal products.
    - Maternal dietary history in breast fed infants.
- Symptoms of anaemia or other cytopenias (jaundice, fatigue and pallor).
- Signs and symptoms of folate deficiency*:
    - Reduced sense of taste.
    - Diarrhoea.
    - Numbness and tingling in the feet and hands.
    - Muscle weakness.
    - Depression.
- Underlying disorders resulting in malabsorption or symptoms of malabsorption (e.g. celiac disease, achlorhydria).
- Drug history, especially the following:
    - Methotrexate.
    - Phenytoin.
    - Sulfasalazine.
    - Trimethoprim.
- Alcohol intake in adolescents.

*Note: Most symptoms of folate deficiency (except for the neurological features) overlap with symptoms of vitamin B_{12} deficiency [21].

12.2.3 Management

Non-pharmacological treatment should include dietary counselling and advice on how to improve dietary intake of folate-rich foods [20,21] [**L1, RGA**]. Diets rich in fruits and vegetables are recommended [21] [**L2, RGA**].

The general strategy of treatment involves repletion of folic acid to restore folate levels. All patients with folate deficiency should be offered supplemental folic acid. Consider the following options [21,52] [**L2, RGA**]:

- Oral folic acid 1-5mg daily.
- Intravenous, subcutaneous, or intramuscular formulations in patient who cannot tolerate oral medications.

The duration of treatment depends on the aetiology of the condition [8,21]:

- A treatment course for 4 months is usually sufficient.
- Longer therapy is recommended if the underlying cause of folate deficiency persists (e.g. in patients with malabsorption).

If vitamin B_{12} deficiency coexists with folate deficiency, the former should be treated first [8,21,55] [**L1, RGA**].

12.2.4 Follow-Up

Re-evaluation of CBC and reticulocyte count should be carried out according to the following schedule [8,20] [**L1, RGA**] :

- 10 days after initiation of the treatment to determine a response.
- 8 weeks after initiation of the treatment to confirm normalisation of CBC.
- 4 months after initiation of the treatment or when the treatment has finished.

Annual blood tests may be required to monitor the condition [20] [**L1, RGA**].

12.3 Aplastic Anaemia

Aplastic anaemia is a rare disorder in children [63]. The more frequently found type in children is the inherited aplastic anaemia (e.g. bone marrow failure syndrome) [64,65].

Aplastic anaemia is defined by [64,65]:

- Peripheral blood pancytopenia.
- Hypocellular bone marrow.
- Absence of infiltration, dysplasia or fibrosis.

To make the definitive diagnosis of aplastic anaemia, bone marrow biopsy is required [**R-GDG**] and at least two of the following must be present [64,66]:

- Hb <10 g/dL.
- Platelet count <50 $x10^9$/L.
- Neutrophil count <1.5 $x10^9$/L.

12.3.1 Aetiology

Aplastic anaemia can be inherited or acquired but in the majority of cases a definitive cause remains unknown (idiopathic) [64].

12.3.2 Classification

Depending on blood count and findings from bone marrow aspiration, aplastic anaemia can be classified according to Camitta's criteria into the following categories[65] [**L2, RGA**]:

- Non-severe:
  - Decreased bone marrow cellularity and peripheral blood cytopenia are present but their levels are not low enough to fulfil the criteria for severe aplastic anaemia.
- Severe:
  - Bone marrow cellularity <25%; and at least two of the following:
    - Platelet count <20 000*10^6/L; or
    - Reticulocyte count <60 000*10^6/L; or
    - Neutrophil count <500*10^6/L; or
- Very severe:
  - Bone marrow cellularity <25%; and at least two of the following:
    - Platelet count <20 000*10^6/L; or

- Reticulocyte count <60 000*10^6/L; or
- Neutrophil count <200*10^6/L.

12.3.3 Management

All patients with confirmed diagnosis of aplastic anaemia should be managed in specialist settings by a paediatric haematologist [**R-GDG**].

12.3.3.1 Supportive Care

Prevention of infection is very important in patients with aplastic anaemia [64,65]. Antimicrobial prophylaxis may be considered on an individual basis [64] [**L2, RGB**].

Haematopoietic growth factors (e.g. granulocyte colony-stimulating factor) are not recommended as monotherapy [65] but may be considered to rise neutrophil counts and reduce infections [64,65] [**L2, RGB**].

Adolescents should receive an age appropriate consultation about [64] [**L2, RGA**]:

- Menarche and possible severe haemorrhage.
  - Menstrual suppression may be considered [64] [**L2, RGA**].
- Sexual practices as they increase the risk of infectious and haemorrhagic complications.

12.3.3.2 Blood Transfusion

Blood transfusions should be provided as required to ensure safety of the patient [64,65] [**L2, RGA**]:

- In transfusion dependent patients with serum ferritin is >2000-2500 µg/L, iron chelation must be considered to remove excess iron [64,65] [**L2, RGA**]. Review the following medications [65]:
  - Desferrioxamine.
  - Deferasirox.
  - Deferiprone is not recommended [65] [**L2, RGC**] .
- Paediatric multivitamins containing iron are not recommended [64] [**L2, RGC**].

12.3.3.3 Definitive Treatment

The main treatment approaches include [63,65] [**L1, RGA**]:

- Haematopoietic stem cell transplantation.
- Immunosuppressive therapy.

13 Key Considerations for Patient Preferences

Patient preferences refer to patient perspectives, beliefs, expectations, and goals for health and life, and to the steps employed by individuals in assessing the potential benefits, harms, costs, and limitations of the management options in relation to one another. Patients may have preferences when it comes to defining their problems, identifying the range of management options and selecting or ranking the outcomes used to compare these options.

It is important for healthcare professionals to develop an understanding of the patient as an individual and the unique way in which each person experiences a condition and its impact on their life.

The following recommendations are therefore made for physicians and other healthcare professionals regarding general principles of patient care in Qatar:

- **Respect Patients:** Treat patients with respect, kindness, dignity, courtesy and honesty. Ensure that the environment is conducive to discussion and that the patient's privacy is respected, particularly when discussing sensitive, personal issues. Ask the patient how they wish to be addressed and ensure that their choice is respected and used.

- **Maintain Confidentiality:** Respect the patient's/legal authorised representative's right to confidentiality and avoid disclosing or sharing patients'/legal authorised representative's information without their informed consent. In this context, students and anyone not directly involved in the delivery of care should first be introduced to the patient/legal authorized representative before starting consultations or meetings and let the patient/legal authorized representative decide if they want them to stay.

- **Clarify Third-Party Involvement:** Clarify with the patient at the first point of contact whether and how they like their partner, family members or carers to be involved in key decisions about their care or management and review this regularly. If the patient agrees, share information with their partner, family members or carers.

- **Obtain Informed Consent:** Obtain and document informed consent from patients/legal authorised representatives, in accordance with MOPH policy and guidance.

- **Encourage Shared Decision Making:** Ensure that patients are involved in decision making about their own care, or their dependent's care, and that factors that could impact the patient's participation in their own consultation and care including physical or learning disabilities, sight, speech or hearing impairments and problems with understanding, reading or speaking English are addressed.

- **Disclose Medical Errors:** Disclose errors when they occur and show empathy to patients.

- **Ensure Effective Communication:** Explore ways to improve communication including using pictures, symbols or involving an interpreter or family members. Avoid using medical jargon. Use words the patient will understand and confirm understanding by asking questions.

- **Ensure Continuity of Care:** Provide clear and timely sharing of patient information between healthcare professionals especially at the point of any transitions in care.

14 Performance Measures

A list of potential performance measures is given below in *Table 14.1* [67].

Number	Numerator	Denominator
ANC01	The number of infants who were screened for IDA at least once in last 12 months.	The number of infants seen in the last 12 months.
ANC02	The number of patients aged <18 years who repeat CBC after one month of receiving iron therapy.	The number of patients aged <18 years who are diagnosed with IDA and received iron therapy in the last 12 months.
ANC03	The number of patients aged <18 years who were referred to an Emergency Department for treatment of anaemia in the last 12 months.	The number of patients age <18 years who were diagnosed with anaemia in the last 12 months.

Table 14.1: Performance measures.

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Appendix A: Iron Medications Registered in Qatar

Table A.1 below provides a list of the iron medications presently registered in Qatar.

Number	Trade Name	Generic	Dosage form
1	Mild Iron	Vitamin C (ascorbic acid) 60 mg Folic Acid (folate). 400 mcg Vitamin B_{12} (cyanocobalamin)8 mcg Iron (ferrous bisglycinate) 28 mg	Capsules
2	Iron 65mg	Iron (as Ferrous Sulfate 361mg) 65 mg	Tablets
3	SENTINEL IRON	Iron (Ferrous Gluconate 256) 28 mg	Tablets
4	IroVit Oral Drops	Iron 15 mg/ml	Oral Liquid Drops
5	GENTLE IRON capsules	Iron 25 mg (as iron bisglycinate chelate)	Capsules
6	IRON 136 MG	FERROUS SULFATE (Iron 136)	Tablets
7	GNC IRON 18 MG	FERROUS FUMARATE 95.833 MG (Iron 18mg)	Tablets
8	SENTINEL FERROUS SULFATE 325 mg (65 mg IRON)	SENTINEL FERROUS SULFATE 325 mg (65 mg IRON)	Tablets
9	IRON 40 mg.	Iron 40mg	Tablets
10	Iron 14 mg	Iron 14 mg	Tablets
11	GNC IRONCHEL 18	IRON CHELATE 18mg	Capsules
12	NATUREFIT EASY IRON	Vitamin C (as ascorbic acid) 60mg, Folate (as folic acid) 400mcg, Vitamin B-12 (as cyanocobalamin) 8mcg, Iron (as ferrous bis-glycinate) 28mg	Capsules
3	Tardyferon 80	Iron 80 mg (as Ferrous Sulphate)	Film Coated Tablet

Number	Trade Name	Generic	Dosage form
14	Ferinject	Iron (as carboxy maltose)50	Solution for injection
15	Xeratec	Iron (as Sucrose)100mg/5ml (20 mg/ml)	Solution for injection
16	Ferimax Syrup	Iron III Hydroxide Polymaltose complex50 mg/5 ml	Syrup
17	Fefol Spansule	Folic acid 0.5mg Dried Ferrous sulphate 150mg (47 mg iron)	Capsules

Table A.1: Iron Medications Registered in Qatar [**R-GDG**].

Appendix B: Detailed Description of the Literature Search

A systematic search for existing literature on the low back pain was performed in the period July 7th-20th, 2020. Review of additional literature based on GDG request was performed in the period February 14th-18th.

The search for clinical practice guidelines on anaemia diagnosis and/or management was performed in the *PubMed* database and websites of relevant organisations and societies including the *Wold Health Organisation, National Organization for Rare Disorders (NORD), British Society for Haematology, American Cancer Society,* and other. The present guideline is primarily based on practice guidelines by American Academy of Family Physicians and CDC Recommendations and is supplemented with other relevant studies.

Peer-reviewed scientific publications were found in PubMed and via *Google Scholar* Internet search engine. Non-peer reviewed studies were identified in *bioRxiv*. Books were checked on PubMed. Information published on medical websites and drug prescribing information sheets were found via Google search engine.

The included publications were identified using the term “anemia OR anaemia AND children” and specified with the following terms in combinations:

Guideline, paediatric, infant, adolescent, prevalence, Qatar, assessment, screening, investigation, diagnosis, microcytic, normocytic, macrocytic, iron, vitamin, B12, folate, megaloblastic, haemolytic, autoimmune, aplastic, sickle cell, aplastic, thalassemia, deficiency, examination, classification, management, prevention, treatment, cyanocobalamin, hydroxocobalamin, diet, food, rich, transfusion, referral, specialist, follow-up, outcome, performance, quality measures/standards.

Figure B.1 on the next page demonstrates graphically the results of the search and application of exclusion criteria.

View Pathway

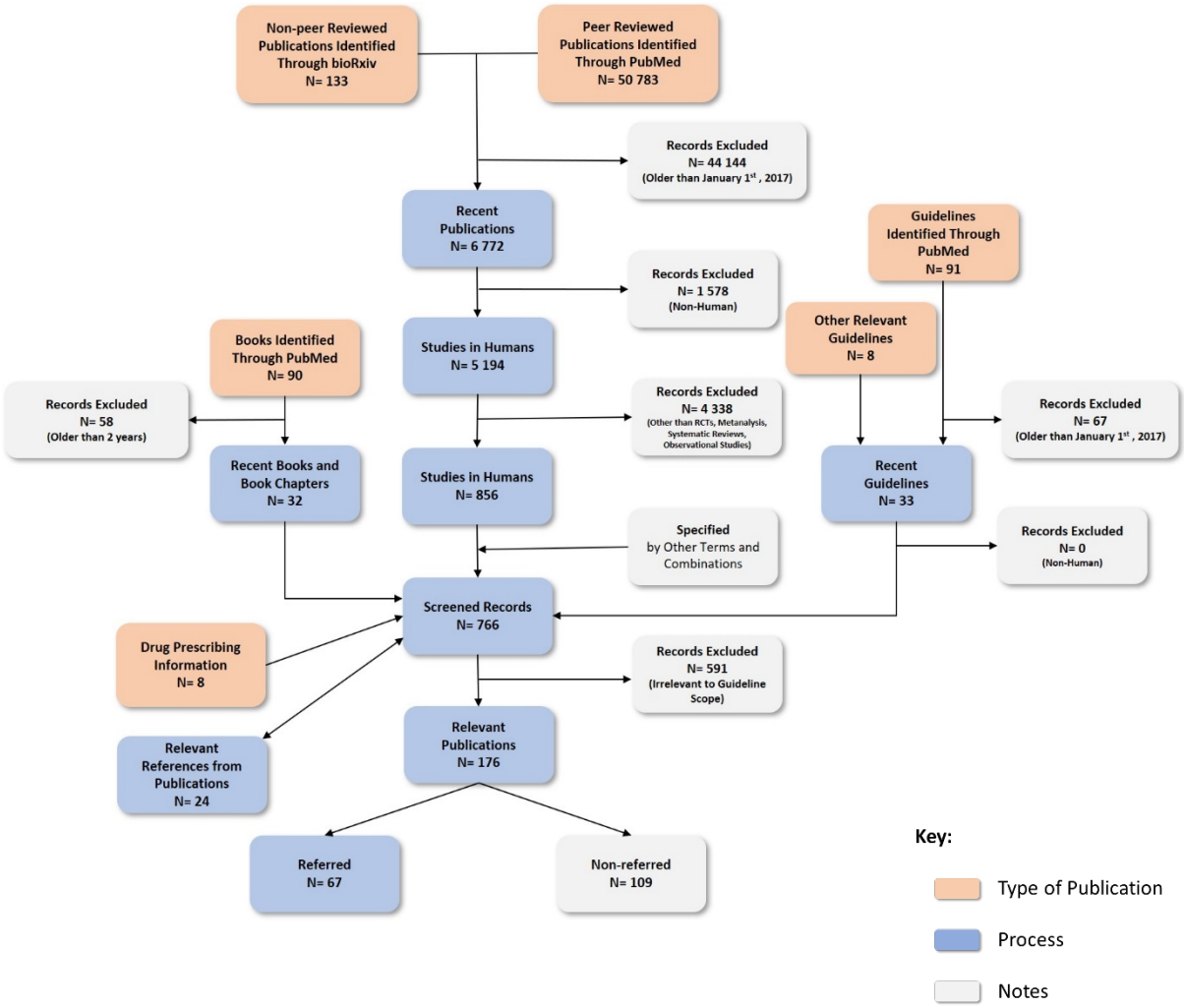

Fig B.1: Literature search results and application of exclusion criteria.

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