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Saudi Commission for Health Specialties

Anemia Clinical Pathway

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SSBD
Saudi Society For Blood Disorders
الجمعية السعودية لأمراض واعتلالات الدم

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ABBREVIATIONS

Sl. No.		
01	ACD	Anemia of chronic disease
02	Anti-IFAB	Anti-intrinsic factor antibodies
03	CBC	Complete blood count
04	CBCD	Complete blood count and differentials
05	eGFR	Estimated glomerular filtration rate
06	ESA	Erythropoietin-stimulating agents
07	dL	Deciliter
08	GI	Gastro-intestinal
09	Hb	Hemoglobin
10	IDA	Iron deficiency anemia
11	IRIDA	Iron refractory iron deficiency anemia
12	LFT	Liver function test
13	MCH	Mean corpuscular hemoglobin
14	MCV	Mean corpuscular volume
15	pmol/L	Picomole per Litre
16	RBC	Red blood cell
17	TIBC	Total iron-binding capacity
18	TSAT	Transferrin saturation
19	tTG	Tissue transglutaminase
20	WBC	White blood cell

INTRODUCTION AND DEFINITIONS

Anemia is strictly defined as a decrease in red blood cell (RBC) mass to a level below normal values for the tested population, age, gender, and sea level (altitude). In anemia, a decrease in the number of RBCs that transport oxygen and carbon dioxide impairs the body's ability for gas exchange. The decrease may result from blood loss, increased destruction of RBCs (hemolysis), or decreased production of RBCs.

Similar to fever, anemia is a sign that requires investigation to determine its underlying cause. However, physicians often overlook mild anemia and its etiology.

There are different classification systems for anemia, but the most popular one is based on mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), as follows:

Microcytic	**MCV <80 fL**
Normocytic	**MCV = 81–99 fL**
Macrocytic	**MCV >100 fL**

Some important definitions

Anemia:
Reduction in one or more RBC parameters (including hemoglobin (Hb), hematocrit concentration, or RBC count) below normal range for gender, age, ethnicity, and sea level

Iron deficiency:
Insufficient total body iron stores caused by increased requirements, decreased intake, increased loss, and/or reduced absorption, with normal Hb level

Iron deficiency anemia (IDA):
Anemia due to insufficient body iron stores
The following laboratory findings are typical for IDA:

- Microcytic anemia
- Hypochromia
- Decreased ferritin

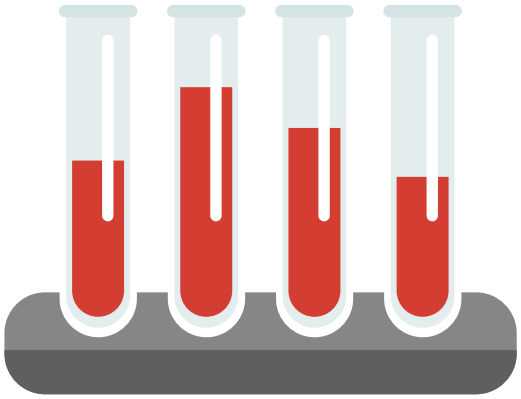
SOME IMPORTANT DEFINITIONS

Normal Hb values for adults

- >130 g/L in men
- >120 g/L in women

For pregnant women:

- >110 g/L in the first or third trimester
- >105 g/L in the second trimester



Classification of anemia severity

- Mild: Hb >100 g/L
- Moderate: Hb 70–100 g/L
- Severe: Hb <70 g/L

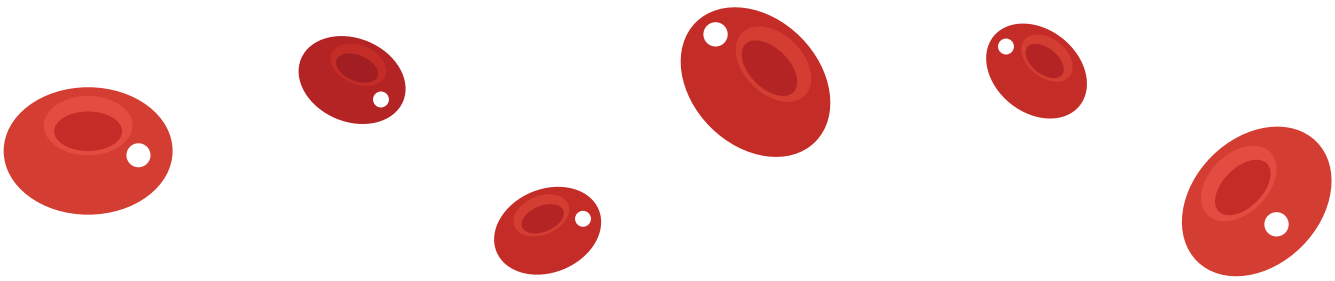
Clinical presentation of anemia

It varies, depending on

- Acuteness of anemia (duration)
- Degree of anemia (severity)
- Oxygen demand

Primary symptoms of anemia

- Easy fatigability and muscle cramps
- Exertional dyspnea
- Dyspnea at rest
- Signs and symptoms of hyperdynamic state, such as bounding pulses and palpitations
- More severe anemia may lead to confusion
- Life-threatening complications, such as congestive heart failure, angina, arrhythmia, and/or myocardial infarction



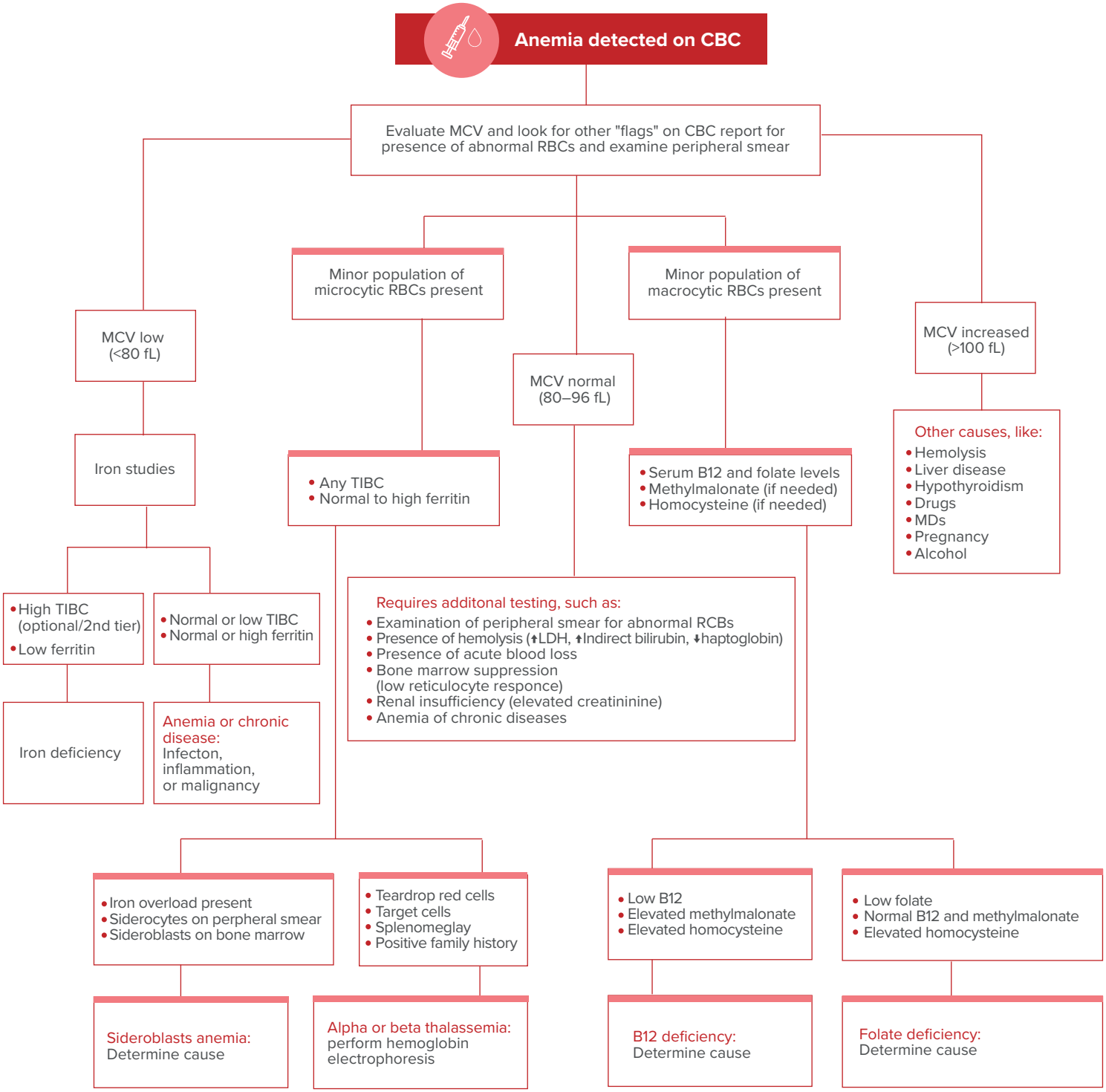
IMPORTANT POINTS IN THE HISTORY FOR ANEMIA

Table 1: Important points in the history for anemia

Microcytic anemia	Macrocytic anemia	Normocytic anemia	Hemolytic anemia	Anemia of chronic diseases
• Family history of hemoglobinopathies • Gastro-intestinal diseases • Blood loss from any site (epistaxis, menorrhagia, melena, hematuria, hematemesis, blood donation) • Bleeding disorder and anticoagulant therapy • Dietary history • Pregnancy, menstruation, and abortions • Gastric surgery Intestinal surgery Intestinal parasites • Sprue • Pica or pagophagia (i.e., compulsive consumption of ice)	• Dietary history • Gastro-intestinal disorders • Drug history • Jaundice • Neurologic manifestations • Medication history (cytotoxics) • Gastric surgery • Intestinal surgery • Older age • Pancreatic insufficiency • Malabsorption	• Blood loss • Gastro-intestinal disorders • Chronic illnesses • Medication history • Dietary history • Malabsorption	• Jaundice, cholelithiasis, dark urine, and splenectomy • Family history of hemoglobinopathies or other anemias • Medication history • Dietary history • Splenomegaly • Neurological manifestations • Renal insufficiency • Lymphoid malignancy • Connective tissue diseases • Transfusion • Recent travel	• Weight loss and recurrent fever • Symptoms suggesting an underlying disease, such as cardiac disease, renal disease, or malignancy • Chronic infections • Inflammatory states • Chronic conditions

DIAGNOSTIC ALGORITHM FOR ANEMIA

Figure 1: Algorithm for diagnosing anemia



MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; CBC, complete blood count; RBC, red blood cell; LDH, lactate dehydrogenase; TIBC, total iron-binding capacity; MDS, myelodysplasia

Figure 2: Algorithm for the management of microcytic anemia

STEP 01

- Complete blood count (CBC)

STEP 02

- Iron studies, including serum ferritin and transferrin saturation (TSAT)
- C-reactive protein (CRP)

STEP 03

- Correct anemia
- Investigate cause if unknown (unless further investigation is not in the patient's best interest)

STEP 04

- Monitor response to replacement therapy
- Treat disease causing the anemia

MCV <80 fL or MCH <27 pg microcytic anemia

- Serum ferritin <30 µg/L with CRP <30 mg/L
- Serum ferritin 30–99 µg/L with CRP >30 mg/L or TSAT <20%

- **Manage as iron deficiency anemia**
- Discuss management with an obstetrician

- Ferritin 30–99 µg/L, CRP low, and TSAT >20
- Ferritin ≥100 µg/L, CRP normal or increased, and TSAT >20%

Iron deficiency anemia

a) Start oral iron therapy.

b) Start with parenteral iron therapy if there is
- History of oral iron intolerance or poor compliance
- Impaired gastro-intestinal absorption
- Hemodialysis
- Major surgery that must take place in <3 weeks
- Symptomatic anemia with hemoglobin <70 g/L

c) Review history and examination for source of chronic bleeding.
- Refer to gastroenterologist if:
  - Adult male
  - Postmenopausal female
  - Premenopausal female with gastro-intestinal
  - symptoms or bleeding
- Refer to gynecologist if there is
  - Post-menopausal bleeding
  - Menorrhagia

Non-iron deficiency microcytic anemia

Assess for
- Acute or chronic inflammatory disease
- Chronic infection
- Malignancy
- Liver disease
- Copper deficiency
- Zinc poisoning
- Thalassemia
- Lead poisoning

Check CBCD and LFTs. **Refer to a hematologist if**
- Thalassemia or sideroblastic anemia is suspected
- Cause of anemia is unknown

Iron deficiency anemia

Check CBC after 4–8 weeks of iron therapy.
If Hb has improved (1–2 g/dL increase):
- Check whether Hb has normalized after 2–4 months of iron therapy.
- Continue iron therapy for another 3 months to replenish iron stores. If no improvement, consider
- Switch to intravenous iron therapy

Anemia of chronic disease

A diagnosis of exclusion; unresponsive to parenteral iron unless iron deficiency is also present

Treat and monitor the underlying cause.

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; CBCD, complete blood count and differentials; LFT, liver function test

DIAGNOSIS AND TREATMENT OF IDA

Introduction

Iron deficiency is the most common nutritional disorder in Saudi Arabia and worldwide. The diagnosis is confirmed in most cases only by full blood examination and serum ferritin level *(for management summary, see algorithm 2)*.

Table 2: Common causes and risk factors for iron deficiency and IDA in adults

Increased requirements ↑	Decreased intake ↓
• Pregnancy (2nd/3rd trimester) • Lactation • Rapid growth spurts (infants, children, adolescents) increased Loss	• Low socioeconomic status • Lack of balanced diet or poor intake • Eating disorder • Age >65 years • Poor access to iron-rich foods, higher rates of infectious diseases, and higher rates of multiparity
Increased loss ↑	**Decreased absorption ↓**

• Menstruating females (at least 10% are estimated to have iron deficiency)
• GI bleeding and other chronic bleeding
• Colon cancer
• Gastric/small bowel cancer
• Hemorrhoids
• Peptic ulcer disease
• Inflammatory bowel disease
• Angiodysplasia
• Esophagitis
• Regular blood donation
• Post-operative patients with significant blood loss
• Hematuria (gross or microscopic)
• Intravascular hemolysis
• Endurance athletics
	• Upper GI pathology
	  ◦ Chronic gastritis (including Helicobacter pylori gastritis, atrophic gastritis)
	  ◦ Celiac disease
	  ◦ Crohn's disease
	  ◦ Gastric lymphoma
	• Medications that decrease gastric acidity or bind iron, e.g. antacids/proton pump inhibitors
	• Gastrectomy or duodenal bypass
	• Bariatric surgery
	• Chronic renal failure

CLINICAL EVALUATION OF IRON DEFICIENCY

Patients with IDA are often asymptomatic, and thorough history and physical examination are important for identifying the cause of iron deficiency *(see Table 1)*. Further evaluation should be based on risk factors.

Evaluation of menorrhagia

There is marked variation in menstrual blood loss among women (10–250 mL/menstrual period), which may result in the overlooking of excessive menstrual losses. Typically, women do not seek medical attention for menorrhagia unless menstrual flow changes. Patients generally report that their menses are normal when asked by clinicians.

For better evaluation, ask about the following:

1. Frequency of period
2. Duration of blood loss
3. How many times she changes pads per day
4. Whether the pads get soaked with blood
5. Presence of clots and their sizes

Consider referring to a gynecologist for management of heavy menstruation or bleeding disorders, for instance, von Willebrand disease.

Diagnosis

Diagnosis of IDA requires laboratory tests to confirm anemia as well as low iron stores.

1. CBC:
   a. Low Hb
   b. Low MCV and MCH (may be normal in early iron deficiency, or with coexisting vitamin B12 or folate deficiency)
   c. High or normal platelet count

2. Serum iron and total iron-binding capacity (TIBC)
   a. Low serum iron and ferritin levels with elevated TIBC levels are typically diagnostic of iron deficiency.
   b. These tests are useful for distinguishing IDA from other microcytic anemias.

3. Serum ferritin level
    a. ≤30 g/L: IDA
    b. 30–99 µg/L: does not exclude iron deficiency (because serum ferritin will be increased by inflammation, and chronic disease)
        i. Increased TIBC, low serum iron, low transferrin saturation, CRP >30 mg/L: IDA
        ii. Decreased TIBC, high serum iron, high transferrin saturation, CRP <30 mg/L: not IDA. Other tests have excluded IDA. (See table 3)
    c. ≥100 µg/L: Not IDA (Identify alternative cause(s). Anemia of chronic disease (ACD) may still be a possibility if transferrin saturation is <20%. Diagnosis of ACD may be important for directing therapy with intravenous (IV) iron and erythropoietin-stimulating agents (ESA).

4. To correctly diagnose iron deficiency in the context of multiple comorbidities, such as inflammation, ferritin threshold of 100 mg/L or even higher values are suggested in combination with low transferrin saturation (≤20%).

Table 3: Tests to differentiate causes of microcytosis

Tests to differentiate causes of microcytosis				
Test	Causes of Microcytosis			
	IDA	Thalassemia	ACD	Lead poisoning/ Sideroblastic anemia
Serum ferritin	Decreased	Increased	Normal to increased	Normal to increased
Serum iron	Decreased	Normal to increased	Normal to decreased	Normal to increased
TIBC	Increased	Normal	Decreased	Normal
Transferrin saturation	Decreased	Normal to increased	Normal to slightly decreased	Normal to increased

TIBC, total iron-binding capacity; IDA, iron deficiency anemia; ACD, anemia of chronic disease

- Review clinical findings for a possible underlying pathology and sources of overt or occult blood loss (e.g., GI, genitourinary tract, nose, or mouth). Clinical evaluation of the cause of iron deficiency is essential.
- Unexplained iron deficiency/IDA

  Adult males, post-menopausal females, and pre-menopausal females with unexplained iron deficiency/IDA should have

  a. referral for GI investigations (upper/lower endoscopy)
  b. screening with urinalysis for genitourinary bleeding
  c. screening for celiac disease

Treatment of IDA

Oral iron replacement is preferred over IV therapy; however, intolerance to oral iron is prevalent as it may cause nausea, vomiting, dyspepsia, constipation, diarrhea, or dark stools.

The choice of an iron compound and route of administration are mainly dependent on

- Presence and degree of anemia
- Reversibility of underlying cause
- Clinical status (age, sex, longstanding vs. recent-onset anemia)

Dosing and considerations

- The usual adult dose for treating IDA is approximately 100 mg elemental Iron daily or every other day.
- Ideally, give 1 hour before or 2 hours after food.
- Iron absorption can be reduced using different medications and supplements, including multivitamins, calcium, and antacid tablets. Space out administration of these agents by at least 2 hours.
- GI upset may be reduced by taking the tablet with food or at night and gradually increasing the dose.
- Supplement with vitamin C (e.g., from orange juice) to improve absorption.
- Multivitamin-mineral supplements should not be used to treat IDA because their iron content is low and absorption may be reduced.
- Avoid taking iron supplements with tea, coffee, or milk.

MONITORING RESPONSE TO ORAL IRON

- The frequency of subsequent monitoring depends on the severity of anemia, the underlying cause of iron deficiency, and the clinical impact on the patient. Reassess by conducting CBC at 4–6 weeks.
- It is recommended that continuous iron therapy be administered for an additional 4 to 6 months (in adults) after the correction of anemia, to replenish the iron stores.
- Ferritin should be rechecked 3–6 months after normalization of Hb levels.

Major reasons for inadequate response to oral iron therapy

- Inadequate iron intake and poor compliance
- Inadequate iron absorption
- Ongoing iron losses or larger body requirement than the absorbed dose
- Coexisting conditions interfering with bone marrow response
- Incorrect diagnosis or more than one cause of anemia

Dietary sources of iron

- Animal-based foods, especially red meat and offal (such as liver), chicken, duck, turkey, eggs, and fish also contain iron
- Plant-based foods such as green vegetables (e.g., spinach, silver beet, and broccoli), lentils, beans, nuts, seeds, and grains

Indications for intravenous iron therapy

IV iron should be considered in patients with confirmed IDA and one or more of the following:

1. Demonstrated intolerance, noncompliance, or lack of efficacy with oral iron, despite modification of dose, timing, and frequency
2. Pregnancy (beyond the first trimester) and postpartum period, for the above reasons or to avoid imminent decompensation/transfusion (e.g., in women who present late and/or have severe anemia)

3. Intestinal malabsorption (e.g., inflammatory bowel disease)
4. Ongoing iron (i.e., blood) losses that exceed absorptive capacity
5. Clinical need for rapid iron supply (i.e., in patients for whom optimization of erythroid response is essential to prevent physiological decompensation/transfusion)
6. Chronic renal impairment in patients who are receiving concomitant ESA therapy
7. Bariatric surgery

IDA during pregnancy

In the absence of active comorbidity, ferritin values ≥100 µg/L indicate adequate iron stores and low likelihood of IDA. Treatment with oral iron has been recommended when ferritin levels are less than 30 µg/L. If necessary, IV iron is considered safe for the second and third trimesters.

Iron deficiency in older adults

- Serum ferritin:
  - Below 50 µg/L should be investigated for iron deficiency in the elderly.
  - Cut-offs between 30 and 100 µg/L have been proposed.
- Serum ferritin levels may also be increased by comorbidity.
- Replacement options are similar to the options for younger patients.
- If standard dosing is not tolerated, low-dose iron therapy (15 mg elemental iron per day, or 30 mg every other day) is an effective treatment in octogenarians, with significantly reduced adverse effects.
- IV iron may also be considered appropriate in some clinical situations.

Iron refractory iron deficiency anemia (IRIDA)

IRIDA is a hereditary disorder characterized by IDA that is typically unresponsive to oral iron supplementation and may be only partially responsive to parenteral iron therapy. IRIDA is due to the uninhibited production of hepcidin. It is characterized by microcytic, hypochromic anemia, and serum hepcidin levels that are inappropriately high for body iron levels.

It is women who are most affected with IRIDA. Even within families, age at presentation, disease severity, and response to iron supplementation vary considerably, with few patients responding to oral iron. But, most patients still require parenteral iron supplementation. Postmenopausal women show an uncommon form of IRIDA with androgen deficiency that causes primary defective iron re-utilization. This particular condition can only be treated with androgen replacement

RBC transfusion

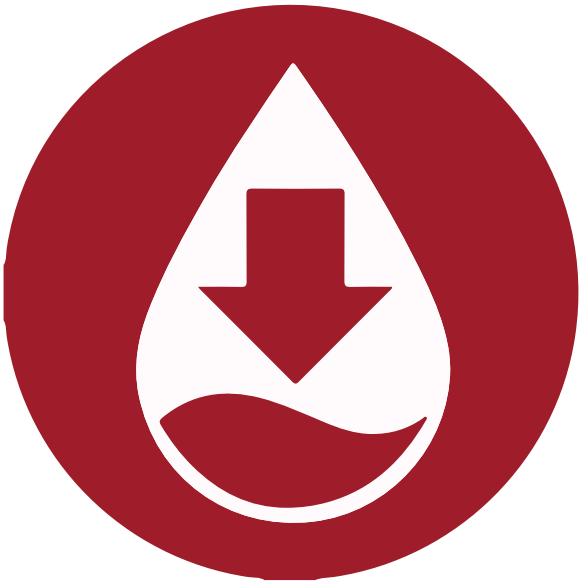
- It should be reserved for immediate management of patients with severe anemia (Hb ≤50 g/L) with evidence of compromised end-organ function (e.g., angina pectoris or cardiac failure), or in whom IDA is complicated by serious acute ongoing bleeding or causing very severe symptomatic anemia.
- Iron therapy should always follow transfusion in order to replenish iron stores.
- When transfusions are necessary, the goal should be to restore Hb to a safe level, but not necessarily to achieve normal Hb levels.

Table 4: Indications for referral

Indications for referral	
Specialty	Indications
Hematologist	• Failure of oral supplementation to achieve normal Hb levels Moderate to severe anemia with unknown cause
Gastroenterologist	• Suspected or overt gastro-intestinal bleeding
Gynecologist	• Menorrhagia • Abnormal vaginal bleeding
Nutritionist	• Poor dietary habits

Table 5: Key recommendations for practice

Key recommendations for practice	
Clinical recommendation	Evidence rating
Measurement of serum ferritin level is the most accurate test for diagnosing IDA.	C
All pregnant women should be screened for IDA.	C
All adult men and postmenopausal women with IDA should be screened for gastro-intestinal malignancy.	C
Screening serology for celiac disease should be considered for all adults, especially men, with IDA.	C



Case 01

A 25-year-old female patient was found to have low Hb on routine testing. She had no symptoms of anemia but had history of poor dietary habits. She had a normal menstrual cycle. Physical examination revealed severe pallor and pulse rate of 90 beats per minute.

Investigations

CBC showed normal WBC and RBC counts, Hb was 75 g/L, MCV and MCH were low, platelet count was 550 × 109/L, and serum ferritin level was 8 µg/L. The patient was diagnosed as a case of IDA and was started on oral iron (Ferose 100 mg twice daily). She was instructed to take iron tablets on an empty stomach for better absorption.

Six weeks later, the patient was re-evaluated. She had tolerated oral iron very well without significant side effects, her Hb had improved to 103 g/L, and her platelet count was 354 × 109/L. She was advised to continue oral iron.

Four months later, her CBC showed Hb of 122 g/L, platelet count of 325 × 109/L, and serum ferritin of 31.5 µg/L. The oral iron dose was decreased to once daily. Six months later, her CBC showed normal.

Hb level and platelet count, serum ferritin was 40.5 µg/L, but MCV and MCH were still low, with mild erythrocytosis. Hb electrophoresis was performed and showed elevated Hb A2 at 4%.

Therefore, the patient was diagnosed with beta-thalassemia minor with IDA, which had been corrected.

She was referred to a clinical dietician for instructions regarding improving dietary habits.

Case 02

A 31-year-old female patient was found to have anemia but was asymptomatic. She had history of poor dietary habits. By direct detailed questioning, it was found that she had menorrhagia (heavy bleeding during the first 3 days of menstruation, with large clots).
Physical examination was unremarkable.

Investigations

The WBC count was normal, Hb was 87 g/L, and platelet count was 430 × 109/L.
Serum ferritin level was 5 µg/L. She was diagnosed as a case IDA and was started on oral iron twice daily. She was instructed to take iron tablets on an empty stomach and abstain from coffee and tea at least 2 hours before and after taking oral iron.

Four weeks later, her CBC showed Hb level of 90 g/L and platelet count was elevated at 450 × 109/L.
The patient stated that she stopped taking oral iron because of constipation.

Because of side effects of oral iron and persisting heavy menstrual flow, she was placed on IV iron and was referred to the gynecology clinic.

Four months later, her CBC showed Hb of 129 g/L and ferritin of 165 µg/L.

One year later, she was found to be anemic with Hb of 95 g/L and ferritin of 15 µg/L.
She admitted to not attending gynecology clinic, and she was still having heavy menstrual flow.
She was restarted on IV iron and was referred again to the gynecology clinic.
Six months later, her CBC showed Hb of 123 g/L, menorrhagia had improved, and she had started to change her dietary habits.

Case 03

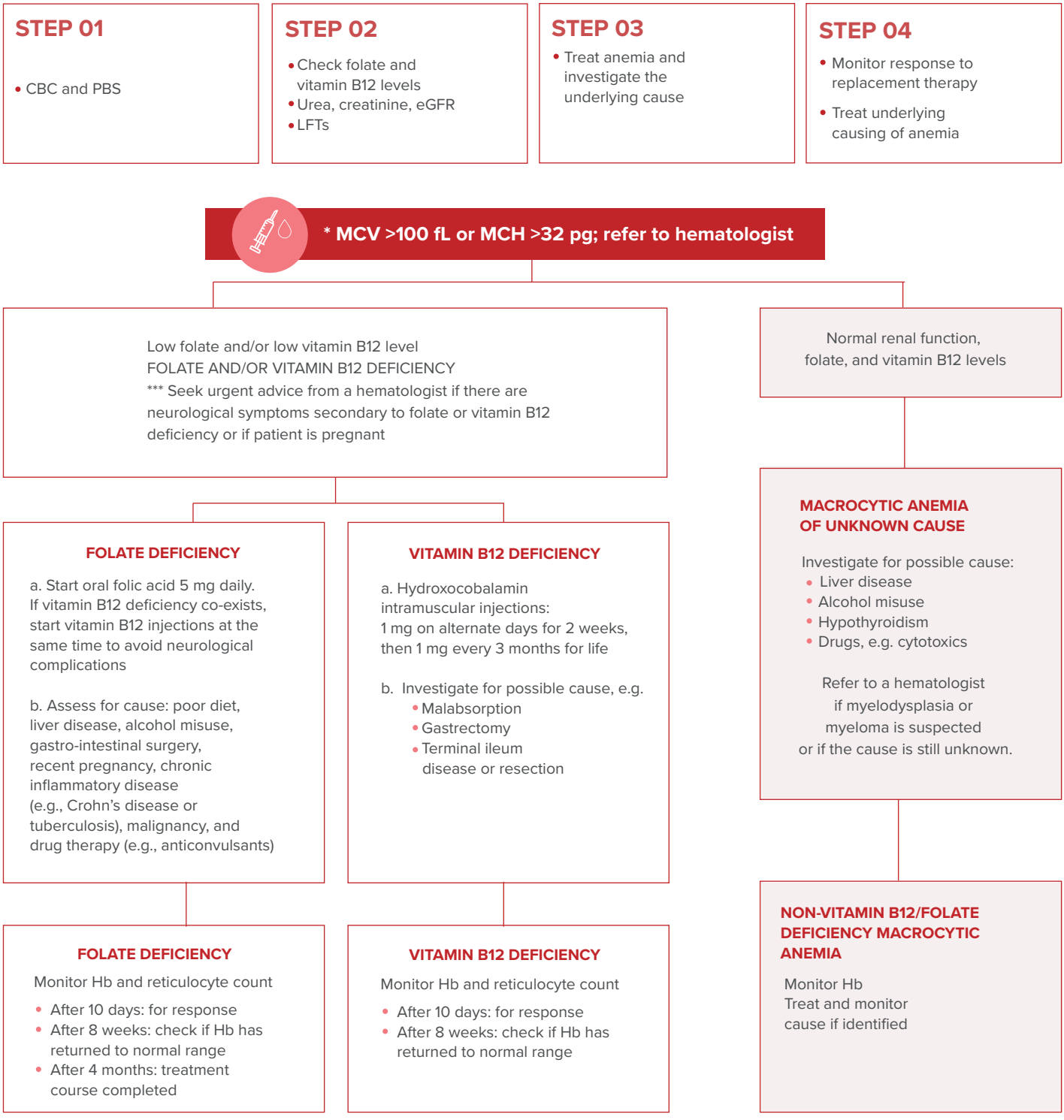
A 60-year-old male patient presented with periodic palpitations and was found to be anemic. He is known to be diabetic and hypertensive on treatment and with good control. He denied any history of blood loss. No history of melena. Physical examination was remarkable for pallor only.

Investigations

His CBC showed normal WBC, Hb was 95 g/L, and platelet count was normal. His serum ferritin level was 56.7 µg/L. ESR and CRP were requested and both were elevated at 70 mm/hour and 65 mg/L respectively. Occult blood test for stool was requested, and he was started on oral iron replacement.

Four weeks later, patient was re-evaluated. He was asymptomatic and tolerating oral iron. His Hb was 115 g/L, and stool was positive for occult blood in 3 samples. He was referred to gastroenterology unit, and colonoscopy was performed, which revealed a colonic mass. Biopsy and histology of the mass proved it to be colon cancer. The patient was referred to general surgery unit for surgical treatment.

Figure 3: Algorithm for the management of macrocytic anemia



MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; CBC, complete blood count; LFT, liver function test; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; PBS, peripheral blood smear.

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF COBALAMIN (VITAMIN B12) AND FOLATE DEFICIENCY

Introduction

- Vitamin B12 and folate levels should always be assessed together due to their close metabolic relationship. Low intake or poor absorption of folate leads to low serum folate level, whereas vitamin B12 deficiency can be due to poor intake of animal products (e.g., vegan diet), low absorption due to various reasons (including low gastric acidity, anti-parietal cell or anti-intrinsic factor antibody (anti-IFAB), pancreatic insufficiency, and diseases of the terminal ilium), and exposure to nitrous oxide *(for management summary, see algorithm 3*).

Folate

- Sources: green vegetables, nuts, and liver
- Can be synthesized by gut bacteria
- Store are depleted after 3 months of restriction
- Absorbed in the duodenum and proximal jejunum

Vitamin B12

- Sources: meat and dairy products, but not plants
- Stores are depleted after 3 years of restriction
- Absorbed in the terminal ilium after binding to intrinsic factor from the stomach to form a complex

Normal Values for Adults

- Serum B12: 180–914 ng/L
- Serum folate: 2–20 µg/L
- RBC folate: 31.7–115.5 nmol/L

Differential Diagnoses of Macrocytosis (MCV >100 fL)

- Alcohol and/or liver disease (especially if macrocytosis is accompanied by thrombocytopenia and anemia is mild or absent)
- Vitamin B12/folate deficiency
- Hypothyroidism
- Hemolytic anemia
- Myelodysplasia

- Drugs, especially anti-metabolites that interfere with DNA synthesis and cell division; for example, hydroxycarbamide, azathioprine, methotrexate, trimethoprim, and zidovudine and other nucleoside reverse transcriptase inhibitor treatments for human immunodeficiency virus infection
- Aplastic anemia or other causes of bone marrow stress

Indications for evaluating vitamin B12 and folate Levels

1. Hematological

- Either isolated macrocytosis or macrocytic anemia
- Megaloblastic anemia
- Pancytopenia (especially if MCV >120 fL)
- Unexplained anemia

2. Neurological or psychiatric

- Peripheral neuropathy
- Cognitive changes, e.g. dementia
- Optic neuritis

3. Gastro-intestinal

- Possible malabsorptive processes
- Angular cheilosis or sore, beefy red tongue
- Post-gastric and bariatric surgery

Diagnostic workup

1. Clinical evaluation for cobalamin and folate deficiency

- Thorough history and physical examination to help identify the cause

2. Full blood picture

- Low Hb
- MCV >100 fL or MCH >32 pg (may be normal initially, or with coexisting iron deficiency)

3. Serum cobalamin assay

- Currently, it is the standard initial routine diagnostic test. It is done with a widely available, low-cost, automated method.
- The World Health Organization (WHO) recommended levels <150 pmol/L (203 pg/mL) for the diagnosis of B12 deficiency.

4. Serum folate

- Serum folate concentration reflects recent folate status and intake.
- Serum folate level <10 nmol/L (4 ng/mL) is indicative of folate deficiency.

5. Red cell folate

- Red cell folate level helps assess the tissue folate status during the lifetime of red cells and is therefore regarded as an indicator of longer-term folate status when compared with serum folate assay.
- The WHO recommended red cell folate <340 nmol/L (151 ng/mL) for the diagnosis of folate deficiency.

Investigation of the cause of cobalamin deficiency

1. Anti-intrinsic factor antibodies (anti-IFABs)

If positive, the test has a high positive predictive value. (95%; i.e., high specificity) for pernicious anemia. Negative IFAB assay does not, however, rule out pernicious anemia (hereafter referred to as Ab-Neg PA).

2. Gastric anti-parietal cell antibodies

This assay has low specificity for pernicious anemia, despite being positive in 80% of cases.

3. Thyroid function tests and anti-thyroid antibodies

4. Test for celiac disease

Tissue transglutaminase-IgA assay (tTG-IgA)

5. Tests for generalized malabsorption (if symptoms are suggestive)

These include serum calcium, vitamin D, folate, and ferritin levels. We recommend that fecal tests, such as fecal fats and elastase, should only be requested by a gastroenterologist.

6. Schilling test

This is designed to provide objective evidence of some form of vitamin B_{12} malabsorption (part 1) and whether the malabsorption can be corrected with additional oral intrinsic factor (part 2) or after a course of antibiotic therapy (part 3). The test is very rarely performed these days because of its high cost and the difficulty in sourcing the radioactively labeled cobalamin used in the test.

Treatment of cobalamin (vitamin B12) deficiency

General rules

- Oral administration of cobalamin is effective only in situations of low dietary intake.
- In most conditions, intramuscular (IM) or deep subcutaneous (SC) administration in patients with bleeding disorders or on anticoagulation is preferred.

Parenteral administration

- Hydroxocobalamin has replaced cyanocobalamin as the therapeutic form as the former is retained in the body for a longer period.
- Several regimens have been recommended.
- We recommend 1 mg hydroxocobalamin IM (or deep SC) injections every other day for 2 weeks, followed by 1 mg q1–3 months.

Oral supplements

- Advantages of oral supplementation include ease of administration and low cost.
- The effectiveness of oral therapy may be compromised if a malabsorptive condition is the cause of the deficiency.
- Dosing is 1 mg/day.

Treatment of folate deficiency

- The cause of the deficiency determines the dose of folic acid necessary for treatment.
- Start by administering B12, 1 mg IM once, and then start folic acid 5 mg per oral (PO) daily (requirement is 0.5–1 mg/day).

- For treatment of folate-deficient megaloblastic anemia (due to dietary insufficiency, pregnancy, or antiepileptics), 5 mg of folic acid is administered daily. In pregnancy, it is continued until term.
- For chronic hemolytic states and renal dialysis, the suggested prophylactic dose is 5 mg daily.

Monitoring of response to therapy

- The duration of therapy for pernicious anemia patients will be lifelong, while for those with food malabsorption, it will be until the underlying condition is corrected.
- Response should be monitored with reticulocyte counts, serum lactate dehydrogenase (LDH), and an appropriate increase in Hb levels.
  - After 10 days, clinical and laboratory responses should be assessed.
  - After 8 weeks, Hb level is expected to return to the normal range
  - After 4 months, the treatment course should be completed.
- Annual monitoring of blood cobalamin levels is recommended in patients with non-nutritional cobalamin deficiency.

Major reasons for inadequate response to therapy

1. Inadequate intake

a .The patient is not taking the supplements.
b. The patient is taking an insufficient dose.

2. Inadequate absorption

a. Coexisting inflammation
b. Intestinal mucosal disorders (e.g., celiac disease and inflammatory bowel disease)
c. Impaired gastric acid secretion (which may be due to use of proton pump inhibitors)
d. *Helicobacter pylori* colonization

3. Coexisting conditions interfering with bone marrow response

a. Superimposed infection, inflammation, malignancy, or renal failure
b. Concomitant iron deficiency
c. Coexisting primary bone marrow disease or suppression

Patient education

- The prognosis, duration of therapy, and significance of monitoring response must be explained clearly to patients, especially those who will need lifelong therapy.
- Vegetarians, particularly strict vegans, should be advised for dietary alterations or oral supplementation.
- Dietary recommendations for foods rich in folate and vitamin B12 should be given.

Case 01 (vitamin B12 deficiency)

A 55-year-old man of African descent presented to our hospital with a history of repeated falls, postural dizziness, progressive fatigue, and generalized weakness over the course of three months. His medical history was unremarkable. He was not taking any medications, and he denied smoking or alcohol consumption. He had no significant family history of any illness.

Examination

He was afebrile, blood pressure was 94/55 mmHg without postural change, and his pulse was 89 beats/min. His neurological examination revealed an unstable, wide-based, ataxic gait. His sensory modalities were grossly preserved. His systemic examination results were unremarkable.

Investigations

CBC revealed Hb of 61 g/L, MCV of 100 fL, thrombocytopenia of 87 × 109/L, and leukopenia of 2.8 × 109/L. Peripheral blood smears demonstrated hypersegmented neutrophils and schistocytes. His serum vitamin B12 level was decreased at 22 ng/L (180–914 ng/L), and his serum LDH level was elevated at 1,135 U/L. The patient's iron studies, folate, thyroid-stimulating hormone, liver enzymes, fibrinogen, serum protein electrophoresis, tTG-IgA, Hb A1c, coagulation panel, electrolytes, and serum creatinine assay results were all within normal limits. Anti-IFABs were detected. His blood type was B+.

Computed tomography of the head showed mild cerebral atrophy. Mild cerebral atrophy along with increased signal intensity throughout the dorsal aspect of the cervical and thoracic spine was established with magnetic resonance imaging. This was consistent with symptoms of vitamin B12 myelopathy.

The diagnosis of severe vitamin B12 deficiency secondary to pernicious anemia was established based on low serum vitamin B12 level and the presence of anti-IFABs.

Treatment course

Daily IM injections of vitamin B12 at 1 mg were initiated for the patient for one week, followed by weekly injections for the next four weeks together with folic acid 5 mg PO daily. He was subsequently prescribed monthly injections of vitamin B12 for continued use until prescribed otherwise.

Case 02 (folate deficiency)

A 60-year-old woman with general pancytopenia was admitted to the hospital for investigation. She gave a history of increasing fatigue and paraesthesia in the hands and feet over the last six months. Her surgical history included a gastric bypass 20 years ago. She does not smoke or drink alcohol.

Examination

The patient appeared pale and obese in the abdominal area, with a body mass index of 31 kg/m^2. Her respiratory rate was rapid at 27 breaths/min. Her blood pressure was 130/78 mmHg and heart rate was 94 beats/min. Blood vessels of the extremities had diminished pulses bilaterally, which may be the cause of her paresthesia. She had hypoactive bowel sounds. Otherwise, her systemic examination was unremarkable.

Investigations

CBC revealed Hb level of 86 g/L with MCV of 130 fL, thrombocytopenia of 125 × 109/L, and leukopenia of 3.2 × 109/L. Peripheral blood smear revealed hypersegmented neutrophils; serum vitamin B12 was 11 ng/dL; folate was 3.2 ng/dL; methyl-malonic acid was 0.75 mmol/L; and anti-parietal cell antibodies and anti-IFABs were negative.

The patient was diagnosed with B12 and folate deficiency with megaloblastic anemia secondary to gastric bypass and malabsorption combined with probable deficient dietary intake.

Treatment course

She was administered daily IM vitamin B12 at 1 mg, together with 5 mg PO folic acid for one week, followed by weekly vitamin B12 injections and PO folic acid for the next four weeks. She was subsequently prescribed monthly injections to be continued with folate supplements of 5 mg weekly, until laboratory values of folate and vitamin B12 were normal.
Nutritional counseling was provided.

Figure 4: Algorithm for the management of normocytic anemia

STEP 01

- Check CBC and other tests for evidence of hemolysis

STEP 02

- Iron studies, including ferritin and TSAT
- Check folate and vitamin B12 levels
- Urea, creatinine, eGFR
- Reticulocyte count, LDH, haptoglobin, and bilirubin

STEP 03

- Treat anemia and investigate the underlying cause

STEP 04

- Monitor response to replacement therapy
- Treat underlying causing of anemia (if appropriate)

MCV 80–100 fL, MCH 27–32 pg normocytic anemia

Low folate and/or low vitamin B12 level
FOLATE AND/OR VITAMIN B12 DEFICIENCY
*** Seek urgent advice from a hematologist if there are neurological symptoms secondary to folate or vitamin B12 deficiency or if patient is pregnant

Folate deficiency

a. Start oral folic acid 5 mg daily. If vitamin B12 deficiency co-exists, start vitamin B12 injections at the same time to avoid neurological complications

b. Assess for cause: poor diet, liver disease, alcohol misuse, gastro-intestinal surgery, recent pregnancy, chronic inflammatory disease (e.g., Crohn's disease or tuberculosis), malignancy, and drug therapy (e.g., anticonvulsants)

Vitamin B12 deficiency

a. Hydroxocobalamin intramuscular injections:
1 mg on alternate days for 2 weeks, then 1 mg every 3 months for life

b. Investigate for possible cause, e.g.
- Malabsorption
- Gastrectomy
- Terminal ileum disease or resection

Folate deficiency

Monitor Hb and reticulocyte count

- After 10 days: for response
- After 8 weeks: check if Hb has returned to normal range
- After 4 months: treatment course completed

Vitamin B12 deficiency

Monitor Hb and reticulocyte count

- After 10 days: for response
- After 8 weeks: check if Hb has returned to normal range

Normal renal function, folate, and vitamin B12 levels

Macrocytic anemia of unknown cause

Investigate for possible cause:
- Liver disease
- Alcohol misuse
- Hypothyroidism
- Drugs, e.g. cytotoxics

Refer to a hematologist if myelodysplasia or myeloma is suspected or if the cause is still unknown

Non-vitamin B12/folate deficiency macrocytic anemia

Monitor Hb.
Treat and monitor cause if identified

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; CBCD, complete blood count and differentials; LFT, liver function test; TSAT, transferrin saturation; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LDH; lactate dehydrogenase; IDA, iron deficiency anemia; ESA, erythropoietin-stimulating agents

Management of normocytic normochromic anemia

The possible etiologies of normocytic normochromic anemia are classified into three:
1. Blood loss
2. Hemolysis
3. Decreased production of RBCs

In most anemias, one of these causes is the dominant factor, although, more than a single cause may play determining roles in certain anemias. For example, pernicious anemia may be attributed to the decreased production of erythrocytes, but hemolysis also contributes significantly to its severity.

Investigations

- Complete blood count and differentials
- Peripheral blood smear
- Renal function test
- Liver function test (LFT)
- LDH
- Reticulocyte count
- Serum ferritin
- Serum vitamin B12 and folate levels
- ESR and CRP

Patients should also have thorough

- Evaluation for blood loss (see microcytic anemia)
- Evaluation for hemolysis
- Evaluation for decreased RBC production

Treatment of normocytic normochromic anemia

- Treatment is individualized and depends on the etiology.
- For combined deficiency (IDA, folate, and/or B12), treat IDA and macrocytic anemia as above.
- For hemolytic anemia, refer to a hematologist.
- For anemia of chronic kidney disease, refer to a nephrologist.
- If decrease production is suspected, refer to a hematologist.

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