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# Anaemia and Pallor

## Definition / Supporting Information

Anaemia is a laboratory finding indicating a decrease in red blood cell (RBC) mass below an age-appropriate normative value.

Pallor and anaemia are clinical manifestations of an underlying disease process.

**Keywords / also known as:** pale skin colour, reduced oxyhaemoglobin, vitamin deficiency (B12 / B9 / folate), iron deficiency

## Essential History

**Ask about:**

- Age
  - Nutritional anaemias are common in infants born preterm, toddlers, school-age children, and adolescents.
  - Toddlers (12–24 months) and adolescent girls account for most cases of iron-deficiency anaemia.
  - Coeliac disease typically occurs in early childhood.
  - Inflammatory bowel disease most commonly affects young teenagers.
- Ethnicity
- Consanguinity
- Nutrition
  - Sources of iron, folate, and vitamin $B_{12}$
    - Iron is found in liver, meat, beans, nuts, dried fruit (such as dried apricots), wholegrains (such as brown rice), fortified breakfast cereals, soybean flour and most dark-green leafy vegetables (such as watercress and curly kale).
    - Folate is found in broccoli, Brussels sprouts, liver, spinach, asparagus, peas, chickpeas and fortified breakfast cereals.
    - Vitamin $B_{12}$ is found in meat, salmon, cod, milk, cheese, eggs and some fortified breakfast cereals.
  - A careful history of milk intake should be taken.
    - Was the child weaned on cow's milk?
  - A history of pica suggests iron deficiency and could be associated with lead ingestion

- Medications
  - Medications associated with anaemias include cephalosporins, dapsone, quinolones, levodopa (co-careldopa), methyldopa, nitrofurantoin, NSAIDs, penicillin and derivatives.
    - A detailed medication history should be taken.
- Family history
  - Splenectomy may suggest hereditary spherocytosis.
  - Thalassaemia / sickle cell
  - Glucose-6-phosphate dehydrogenase deficiency (G6PD)
  - Autoimmune disease
    - Pernicious anaemia
- Infections
  - May induce haemolysis or RBC aplasia (eg, parvovirus B19)
- Mouth ulceration / glossitis
  - Inflammatory bowel disease
  - Pernicious anaemia
- Liver disease
- Diarrhoea / melaena
  - The gastrointestinal tract is a common source of blood loss.

## 'Red Flag' Symptoms and Signs

**Ask about:**

- Fatigue / increased sleep in infants
- Irritability
- Poor feeding / weight loss / faltering growth
- Exercise intolerance
- Persistrent or unexplained bone pain
- Fever
- Dizziness
- Headaches
- Shortness of breath (see Dyspnoea)
- Palpitations
- Icterus
- Passing of dark urine (see Haematuria)
- Bruising (bone marrow failure) (see Petechiae and Purpura)
- Melaena

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**Look for:**

- Pallor
  - Nail beds, mucosa, conjunctivae, palmar creases
  - Note that the presence or absence of pallor may not be sufficient to diagnose or exclude anaemia
- Splenomegaly
  - Haemolytic anaemia
- Jaundice
  - Haemolytic anaemia
- Dark urine (see Haematuria)
  - Intravascular haemolysis
- Frontal bossing / maxillary prominence (see Congenital Malformations)
  - Thalassaemia
- Lymphadenopathy and hepatosplenomegaly
  - Leukaemia or lymphoma
- Tachycardia / poor perfusion / flow murmur
  - Decompensation secondary to anaemia
- Loss of consciousness / fainting episodes / blackouts (see Non-Convulsive Paroxysmal Disorders ('Funny Turns'))
- Abdominal pain / chest pain
  - Sickle cell crisis

## Differential Diagnosis / Conditions

- Anaemia in newborns
  - Twin-to-twin transfusions
  - Foeto-maternal bleed
  - Haemorrhagic disease of the newborn
  - Vitamin K deficiency
  - Neonatal infections
  - Thrombi / disseminated intravascular coagulation / Kasabach–Merritt syndrome (multiple cavernous haemangiomas)
  - Diamond–Blackfan anaemia
  - Bone marrow suppression due to infection with parvovirus B19

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Subclassification of anaemias as microcytic, normocytic, and macrocytic greatly reduces the differential diagnoses and limits the number of laboratory tests needed for diagnosis:

- Microcytic anaemia (mean corpuscular volume (MCV) less than appropriate for age)
  - Iron-deficiency anaemia
    - Poor iron intake or absorption
    - Blood loss – consider upper or lower gastrointestinal bleeding (cow's milk protein allergy / coeliac disease / gastric and duodenal ulcers / Meckel's diverticulum / polyps / haemorrhoids / gastritis / inflammatory bowel disease), menorrhagia
  - Lead poisoning
  - Copper deficiency
  - Malnutrition
  - Chronic disease
  - Thalassaemia
    - More common in patients of African or Asian descent (thalassaemia syndromes are more common in patients of Mediterranean descent)
  - Haemoglobin E trait
  - Sideroblastic anaemia
  - Atransferrinemia
  - Inborn errors of metabolism
    - Glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency are X-linked disorders
    - Hereditary pyropoikilocytosis
- Normocytic anaemia (MCV within normal range for age)
  - Infection
  - Acute blood loss
  - Chronic kidney disease
  - Connective tissue disorder
  - Hepatic disease
  - Haemolysis
    - Hereditary spherocytosis
    - Microangiopathic haemolysis (eg, congenital thrombotic thrombocytopenia purpura)
  - Hypersplenism
  - Malignancy
  - Aplastic anaemia
  - Dyserythropoietic anaemia
  - Drugs

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- Macrocytic anaemia (MCV greater than appropriate for age)
  - Megaloblastic anaemias from vitamin $B_{12}$ or folate deficiency
  - Reticulocytosis
  - Postsplenectomy
  - Myelodysplastic syndrome
  - Aplastic anaemia
  - Fanconi's anaemia
  - Diamond–Blackfan anaemia
  - Pearson's syndrome
  - Dyskeratosis congenita
  - Paroxysmal nocturnal haemoglobinuria
  - Down's syndrome
  - Hypothyroidism
  - Hepatic disease
    - Hepatitis may induce aplastic anaemia
  - Drugs (eg, phenytoin, methotrexate)

## Investigations

To be undertaken by non-specialist practitioners (eg, General Practitioner (GP) Team) or by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Haemotology Team(s)):

- Laboratory tests
  - Haemoglobin level and haematocrit and full blood count with differentials to exclude leukopenia and thrombocytopenia
    - Within 48 hours if 'red flag' symptoms or signs
      - See Suspected cancer: recognition and referral [NICE clinical guideline NG12, section 1.10.3]
  - RBC morphology / blood film
  - MCV
  - Reticulocyte count
    - Elevated count implies bone marrow compensation for chronic blood loss or haemolysis
    - Low count (< 1%) may suggest impaired RBC production or acute blood loss
  - Stool tests for occult blood should be performed at several different times to identify intermittent bleeding, unless there is a clear alternative explanation for the anaemia.
  - Offer serological testing for coeliac disease to children with unexplained iron-deficiency anaemia, or other unspecified anaemia
    - Use IgA tissue transglutaminase (tTGA) as the first choice test

    - Use IgA endomysial antibodies (EMA) testing if the result of the tTGA test is equivocal
        - See Coeliac disease: recognition, assessment and management [NICE clinical guideline NG20, section 1.2.3]

To be undertaken by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Haemotology Team(s)):

- Iron studies
    - Measure C-reactive protein (CRP) when measuring ferritin (as may be raised in acute infection / inflammation)
- Liver and renal function tests
- Serum lactate dehydrogenase
- $B_{12}$, folate, intrinsic factor antibodies (pernicious anaemia)
- Haemoglobin electrophoresis
    - Sickle cell disease
    - Thalassaemia
- Red cell membrane studies
    - Hereditary spherocytosis
- Direct antiglobulin test
- Blood group (mother and neonate)
- Kleihauer–Betke test
    - Foeto-maternal haemorrhage
- Fanconi's anaemia screen
- Adenosine deaminase
    - Raised in Diamond–Blackfan anaemia
- Infection screen
    - Toxoplasma gondii, other viruses (HIV, measles etc), rubella, cytomegalovirus and herpes simplex (TORCH) screen
    - Parvovirus PCR
    - Epstein–Barr virus PCR
- Urate
- Thyroid function
- Toxin screens (eg, chronic lead exposure or acute lead intoxication) (see Toxbase [National Poisons Information Service])
- Stool elastase
    - Pearson's syndrome (pancreatic insufficiency)
- Chest radiograph may be required if pulmonary haemosiderosis needs to be ruled out.

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- Bone marrow aspiration and biopsy may be required in patients with anaemia suspected of having bone marrow involvement or abnormalities.
  - Iron stain on bone marrow aspirate (to identify ring sideroblasts in sideroblastic anaemia)

## Treatment Approach

To be undertaken by non-specialist practitioners (eg, GP Team):

- For a child with hypochromic, microcytic anaemia with history of poor iron intake or excessive milk intake:
  - Give a trial of supplemental iron (3–6 mg/kg of elemental iron per day, divided into ≥ 2 doses)
    - Reticulocyte count should increase within 5–7 days
    - Haemoglobin should increase by 20 g/L over 3-4 weeks
    - When the target haemoglobin is reached, a further a three month course of iron is needed to replenish iron stores
    - The most common reason for lack of response is poor compliance.
- Consider referral to a dietician if nutritional anaemia due to inadequate intake or eating disorders

To be undertaken by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Haemotology Team(s)) if not already done:

- Patients with uncompensated anaemia should be admitted to the hospital for observation and possible transfusion.
- Specific treatment depends on the underlying haematological disorder.

## When to Refer

Refer urgently to specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Haemotology Team(s)) if:

- Any ‘red flag’ symptoms or signs
- Haemoglobin level < 80 g/L or haematocrit < 25%
- Anaemia of unknown origin
- Anaemia is associated with disorder in white blood cells or platelets
- Haemoglobinopathy or congenital / acquired haemolytic anaemia is confirmed

Refer to Paediatric Haemotology Team for management of most macrocytic anaemias, as even vitamin $B_{12}$ deficiency in children is rare and requires investigation for possible inborn error of metabolism.

### When to Admit

- Profound anaemia (haemoglobin level < 50 g/L)
- Uncompensated anaemia or anaemia with a rapidly decreasing haemoglobin level

- Anaemia in an ill child

## ‘Safety Netting’ Advice

- Patients treated with supplemental iron should be followed up at 1 week for repeated measurement of reticulocyte count or at 1 month for haemoglobin measurement.
  - If there is no change in reticulocyte count or haemoglobin level, consider non-compliance with therapy, a problem with iron assimilation, or another diagnosis for microcytic anaemia.

## Patient / Carer Information

***Please note: whilst these resources have been developed to a high standard they may not be specific to children.***

- Iron deficiency anaemia (Web page), the NHS website
- Sickle cell anaemia (Web page), the NHS website
- Vitamin B12 or folate deficiency anaemia (Web page), the NHS website
- Thalassaemia (Web page), the NHS website
- Blood transfusion (Web page), the NHS website
- Vitamins and minerals - B vitamins and folic acid (Web page), the NHS website
- Vitamins and minerals - iron (Web page), the NHS website

## Resources

### National Clinical Guidance

Suspected cancer: recognition and referral (Web page), NICE clinical guideline NG12, National Institute for Health and Care Excellence.

Chronic kidney disease: managing anaemia (Web page), NICE clinical guideline NG8, National Institute for Health and Care Excellence.

Coeliac disease: recognition, assessment and management (Web page) NICE clinical guideline NG20, National Institute for Health and Care Excellence.

Faltering growth: recognition and management of faltering growth in children (Web page), NICE guideline NG75, National Institute for Health and Care Excellence.

### Suggested Resources

**Please note: these resources include links to external websites. These resources may not have national accreditation and therefore PCO UK cannot guarantee the accuracy of the content.*

Folic acid for megaloblastic anaemia caused by folate deficiency and haemolytic anaemia (Web page), Medicines for Children

Methotrexate for skin conditions (Web page), Medicines for Children

Multivitamin preparations for vitamin deficiency (Web page), Medicines for Children

Nitrofurantoin for urinary tract infections (Web page), Medicines for Children

Devalia V, Hamilton MS, Molloy AM, British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496-513. [PubMed]

Iron and iron deficiency (PDF), Coeliac UK.

Thomas W, Hinchliffe R, Briggs C, Macdougall I C, Littlewood T, Cavill I, British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013;161(5):639-648. [PubMed]

Anaemia - iron deficiency (Web page), NICE clinical knowledge summary, National Institute for Health and Care Excellence.

Anaemia (Web page), Great Ormond Street Hospital.

Iron deficiency anaemia (Web page), Great Ormond Street Hospital.

## Acknowledgements

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