*ABC of clinical haematology***Haematological disorders at the extremes of life**

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Infants**Anaemia in neonates**

The haemoglobin concentration at birth is 159-191 g/l. It rises transiently in the first 24 hours but then slowly falls to as low as 95 g/l by 9 weeks. By 6 months, the concentration stabilises at around 125 g/l, the lower end of the adult range, increasing towards adolescence. The normal fall in haemoglobin concentration seen in full term infants is accentuated in prematurity and may fall to less than 90 g/l by 4 weeks. Preterm infants are particularly prone to multiple nutritional deficiencies because of rapid growth. Pronounced anaemia may be assumed if the infant gains insufficient weight or is fatigued while feeding.

Common causes of anaemia in newborn infants

- Blood loss—Occult bleeding (fetomaternal, fetoplacental, twin to twin); obstetric accidents; internal bleeding; iatrogenic
- Increased destruction—Immune haemolytic anaemia; infection; haemoglobinopathies; enzymopathies
- Decreased production—infection; nutritional deficiencies

Normal haematology values in newborn infants

	Haemoglobin (g/l)	Red blood cells ($\times 10^{12}/l$)	Mean cell volume (fl)	Nucleated red blood cells (per ml)
Day 1	168-212	4.44-5.84	109.6-128.4	500
Week 1	150-196	4.0-5.6	93.0-131.0	0
Week 4	111-143	3.2-4.0	92.9-109.1	0
Week 8	98-116	2.9-3.9	105.0-81.0	0
Week 12	104-122	3.4-4.0	80.1-95.9	0

Haemolytic disease in newborn infants

Haemolytic disease in newborn infants is due to destruction of fetal red cells by antibodies from the mother that cross the placenta. The most important are antibodies to the RhD antigen. Maternal immunisation is preventable by the prophylactic use of anti-D immunoglobulin, and since its introduction in the 1960s the number of affected babies has fallen dramatically. Anti-D immunoglobulin is administered to non-sensitised RhD negative women, but prophylaxis may fail.

In severely affected fetuses, mortality used to be as high as 40%, with only exchange transfusion available after delivery to correct anaemia and prevent kernicterus. Intrauterine transfusion, initially via the intraperitoneal route, was introduced to prevent problems in the fetus. However, it was the development in the early 1980s of intravascular blood transfusion using fetoscopy into the umbilical artery that dramatically improved survival. Hydrops can be readily reversed in utero, and even in the most severe group the survival rate has been 85%.

Anaemia associated with infection

Cytomegalovirus, rubella, toxoplasmosis, and more rarely congenital syphilis may be associated with anaemia due either to haemolysis or to bone marrow suppression. More recently human parvovirus B19 has been identified as a cause of anaemia and fetal damage. In early pregnancy maternal infection may lead to spontaneous abortion, but in later pregnancy it may lead to selective depression of erythropoiesis with profound anaemia and the development of hydrops. It may also induce an aplastic crisis or chronic haemolysis in

Haemolytic disease in newborn infants

Recommendations for prophylactic anti-D immunoglobulin in RhD negative women

- After delivery if the infant is Rh positive
- After abortion (therapeutic or spontaneous)
- To cover antenatal procedures (amniocentesis, chorionic villus sampling)
- After threatened abortion or miscarriage
- Antenatally at 28 and 34 weeks (not yet universal)

Reasons for failure of prophylaxis

- Failure of administration (commonest cause)
- Inadequate dosage (routine Kleihauer tests should be performed)
- Earlier sensitisation that may not be detectable at birth
- Poor injection technique (should be deep intramuscular)

HIV infection

- HIV may produce a chronic multisystem disease in children
- Perinatal transmission of the virus from an infected woman is the primary route of exposure to the fetus (20-40% of pregnancies)
- Thrombocytopenia occurs in up to 15% of children with HIV infection
- Anaemia is also common, occurring early, usually with the normocytic, normochromic features of chronic disease
- Leucopenia and lymphopenia are also seen, in which the bone marrow shows non-specific features of chronic infection

normal children but is a major problem in those with an underlying haemoglobinopathy.

Malaria is a major health hazard worldwide, and easier travel to endemic areas has increased the problem. Inadequate or non-existent prophylaxis has led to an increase in cases over the past few years; unsuspected infection in neonates, usually caught from the mother, may be associated with a high mortality.

The haemoglobinopathies

β Thalassaemia major is an inherited haemoglobin disorder caused by reduction in β globin chain synthesis. It affects primarily people from the Indian subcontinent and of Mediterranean origin. It presents during the first year of life after the switch from fetal to adult haemoglobin. If production of the latter is reduced, anaemia occurs. The infant presents with failure to thrive, poor weight gain, feeding problems, and irritability. The blood appearances are typical, with severe anaemia associated with microcytosis and hypochromia with pronounced morphological change in the red cells. The infant will be dependent on transfusions unless bone marrow transplantation is feasible. The carrier state (thalassaemia minor or thalassaemia trait) mimics iron deficiency, from which it must be differentiated.

α Thalassaemia presents a similar picture and is a common cause of stillbirth in South East Asia.

Sickle cell disease

Sickle cell disease is caused by a structural abnormality of the β chain and is associated with a steady state haemoglobin of 50-110 g/l. In homozygous sickle cell disease the haemoglobin forms crystals, distorting the red blood cells into a rigid sickle cell shape. It is these sickle cells that block the microvasculature causing sickle cell crises. Mortality and morbidity are increased at all ages, with the peak incidence of death at age 1-3 years. Sickle cell crises are precipitated by infection, hypoxia, dehydration, cold, and exhaustion and are particularly common in adverse environmental or poor socioeconomic conditions. In infants, crises present with the clinical problems of infection, splenic sequestration, and dactylitis. Towards the end of the first year, painful vaso-occlusive crises are more common, and pneumococcal septicaemia related to splenic dysfunction is particularly apparent.

Genetic counselling and prenatal diagnosis have made an important contribution to reducing the number of affected children in countries with a comprehensive screening programme.

Disorders of haemostasis

Deficiencies of clotting factor VIII (haemophilia A) or factor IX (haemophilia B or Christmas disease) may present symptomatically in the first days of life with spontaneous bleeding. Bleeding from the cord or intracranial haemorrhage, however, are fortunately rare. Severe bleeding usually occurs at, for example, circumcision or when mobility increases. Both disorders of coagulation affect 1 in 10 000 of the population. They are X linked and clinically indistinguishable. The diagnosis may be suspected from the family history and can be confirmed antenatally.

Thrombocytopenia

Healthy infants have a platelet count in the adult range ($150-400 \times 10^9/l$). Thrombocytopenia is the most common haemostatic abnormality in newborn infants, occurring in up to a quarter of babies admitted to neonatal intensive treatment units. Asphyxia at birth, infection, and disseminated

Peripheral blood of patient with Hb H disease showing pale red cells (hypochromia) with variation in size and shape (anisopoikilocytosis).

Features of α thalassaemia

Syndrome	Haematological abnormalities	Diagnosis
Silent carrier (- α/α α)*	No anaemia or microcytosis	1-2% Hb Bart's†
Thalassaemia trait (- $\alpha/-$ α)	Mild anaemia and microcytosis	3-10% Hb Bart's
Hb H disease (- $-/-$ α)	Moderate microcytic, hypochromic haemolytic anaemia	20-40% Hb Bart's
Hb Bart's; hydrops syndrome (- $-/-$ -)	Severe microcytic hypochromic anaemia (lethal)	80% Hb Bart's, 20% Hb H‡

*Where α/α α is normal (that is, 4 α genes) and - α represents deletion of one α gene on a chromosome

†Bart's γ_4 tetramers

‡Hb H β_4 tetramers

Antenatal screening for carrier detection of sickle cell disease (with subsequent study of the partners of positive women) should be carried out so that prenatal diagnosis can be offered

In up to 30% of all new cases patients will have no family history of coagulation disorders, and such cases are therefore new mutations

intravascular coagulation are the most common causes of thrombocytopenia. It may also occur after exchange transfusion. Platelet transfusions should be given to any infant whose count is $<20 \times 10^9/l$.

Maternal autoimmune thrombocytopenia may be associated with neonatal thrombocytopenia because of placental transfer of antiplatelet antibodies. Fetal platelet counts rarely drop below $50 \times 10^9/l$, and intracranial haemorrhage is rare either prenatally or at birth. However, the count may fall in the first few days of life, and treatment may be needed at this stage.

There are no reliable predictors of severe thrombocytopenia. Treatment includes platelet transfusions and corticosteroids, but intravenous immunoglobulin is safe and effective in over 80% of infants.

Response of neonate to intravenous immunoglobulin with thrombocytopenia secondary to maternal immune thrombocytopenia purpura.

Neonatal alloimmune thrombocytopenia is associated with severe thrombocytopenia, and intracranial haemorrhage is seen in up to 15% of infants. Maternal platelet counts are normal, and maternal alloantibodies are directed against paternally derived antigens on the infant's platelets (usually HPA-1). In at risk pregnancies fetal blood sampling by cordocentesis should be used to confirm the HPA-1 status. Treatment relies on platelet transfusions in utero, but high dose intravenous immunoglobulin may be of some benefit.

Vitamin K deficiency

Haemorrhagic disease in newborn infants may be associated with vitamin K deficiency. It may be seen in otherwise healthy term infants especially if they are being breast fed. The deficiency may be precipitated if the mother is taking anticonvulsant drugs or warfarin. It may present soon after birth with generalised bruising and internal bleeding or as late as age 1 month.

Treatment is now aimed at prevention by administering vitamin K prophylaxis, although some controversy remains about whether this should be given orally or parenterally.

Elderly people

Haemoglobin concentration gradually declines from age 60 years, with a more rapid fall over the age of 70. The fall is accompanied, however, by a widening of the reference range, such that age dependent ranges are of little value in individuals.

Concentration should be considered in association with the clinical history. In older patients the lower end of the normal range should be reduced to 110 g/l.

Iron deficiency anaemias

Between 10% and 20% of old people will be anaemic, usually with iron deficiency. In many this will be nutritional, owing to difficulties in obtaining and eating food, for both medical and

Common causes of thrombocytopenia

- Immune mediated
 - Neonatal alloimmune thrombocytopenia
 - Maternal immune thrombocytopenia purpura
 - Drug induced
- Infection
 - Viral—for example, cytomegalovirus, HIV, rubella
 - Toxoplasmosis
- Post exchange transfusion
- Disorders of haemostasis
 - Disseminated intravascular coagulation
 - Maternal pre-eclampsia
 - Rhesus isoimmunisation
 - Hypothermia, hypoxia
 - Type IIB von Willebrand's disease
- Liver disease
- Giant haemangioma
- Hereditary thrombocytopenia
- Marrow infiltration

Haemorrhagic disease of newborn infants

Type	Clinical signs	Causes
Early (within 24 hours)	Severe bleeding, often internal	Mother receiving drugs affecting vitamin K—eg, anticonvulsant (phenytoin), warfarin, antituberculosis drugs (rifampicin, isoniazid)
Classic (2-5 days)	Bruising or bleeding from gastrointestinal tract or after circumcision	Breast feeding, full term
Delayed (up to 1 month)	Intracranial haemorrhage, common	Prolonged breast feeding without prophylaxis; chronic diarrhoea, malabsorption, or oral antibiotics

The possibility of an occult gastrointestinal malignancy (for example, caecal carcinoma) leading to iron deficiency anaemia should be considered

social reasons. Aspirin or non-steroidal anti-inflammatory drugs leading to occult gastrointestinal blood loss may also contribute. The problem may also be exacerbated in elderly people as gastric atrophy may occur, leading to poor absorption of iron supplements.

Oral supplements are usually well tolerated and should be continued for three months after the haemoglobin concentration has returned to normal, to replenish the iron stores.

Megaloblastic anaemia

Folic acid deficiency also occurs readily in those who eat poorly and can be easily corrected by supplements. Pernicious anaemia due to vitamin B₁₂ deficiency also occurs in middle and later life and may be associated with weakness and loss of sensation. Vitamin B₁₂ stores normally fall in older people, and deficiency should always be considered with those developing dementia.

Care must be taken to differentiate megaloblastic anaemia from myelodysplastic syndrome, which may be associated with a refractory macrocytic anaemia. Serum concentrations of vitamin B₁₂, folate, and red cell folate should be measured, and occasionally a bone marrow examination may be indicated.

The importance of identifying any deficiency anaemia is that, although the effects may be relatively mild initially, they can progress and severely incapacitate a previously active pensioner. The deficiencies can be easily reversed, and supplements should be continued for as long as the underlying problem remains.

Anaemia of chronic disease

Any prolonged illness such as infection, malignant disease, renal disease, or connective tissue disorder may be accompanied by a moderate fall in the haemoglobin concentration. This seldom drops below 90-100 g/l and is typically normocytic and normochromic. Haematinics will not increase the haemoglobin concentration, which may improve only after treatment of the underlying condition. This condition may not always be apparent, and a general screen may be needed for underlying malignancy or systemic disease.

Findings in anaemia of chronic disease

- Mild normocytic or microcytic anaemia
- Low serum iron concentration and iron binding capacity
- Reduced transferrin saturation
- Normal or raised serum ferritin concentration
- Increased iron in reticuloendothelial stores—for example, bone marrow
- Defective iron transfer to red cell precursors
- Iron reduced in red cell precursors
- Increased red cell protoporphyrin

Malignancies

Most forms of malignancy are more common in elderly people than in the rest of the population. The myelodysplastic syndromes and chronic lymphocytic leukaemia are frequently found incidentally, and their diagnosis does not necessarily indicate the need for treatment. Each patient must be considered individually so that the possible benefits of treatment can be balanced against side effects and considered in the light of any improvement in the quality of life.

The graph is adapted with permission from Newland *et al* (*N Engl J Med* 1984;310:261-2).

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Clinical associations in iron deficiency

Symptoms—Lethargy, lassitude, reduced activity; shortness of breath; angina on effort; intermittent claudication

Signs—Pallor, peripheral oedema; brittle nails, koilonychia; glossitis; stomatitis

Other gastrointestinal findings—Oesophageal web; atrophic gastritis; subtotal villous atrophy with malabsorption

Megaloblastic anaemia: peripheral blood (top) showing macrocytes, tear drops, and multisegmented neutrophils; megaloblastic bone marrow (bottom) showing megaloblasts, giant metamyelocytes, and hypersegmented neutrophil.

Screening tests in anaemia of chronic disease*

- Review of peripheral blood film
- Erythrocyte sedimentation rate
- Liver and renal screen
- Chest radiograph
- Autoantibody screen
- Urine analysis
- Thyroid function studies
- Tumour markers
 - Immunoglobulins (myeloma)
 - Prostate specific antigen
 - α Fetoprotein (liver)
 - Carcinoembryonic antigen (gastrointestinal)

*After history and clinical examination

Further reading

- Hann IM, Gibson BES, Letsky EA, eds. *Fetal and neonatal haematology*. London: Baillière Tindall, 1991.
- Lilleyman JS, Hann IM, eds. *Pediatric hematology*. New York: Churchill Livingstone, 1992.

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