Anaemia of Chronic Disease

The World Health Organization's criterion for anaemia in adult men is haemoglobin (Hb) values less than 130 g/L, non-pregnant women less than 120 g/L and pregnant women less than 110 g/L. Children aged 6 months to 6 years are considered anaemic at Hb levels less than 110 g/L, and children aged 6-11 years are considered anaemic when Hb levels are less than 115 g/L.

**Anaemia of chronic disease** (ACD) may be secondary to:

- Chronic infection.
- Inflammation - including connective tissue disorders.
- Neoplasia.

Anaemia is also commonly associated with chronic kidney disease.

**Pathogenesis**

ACD is still not fully understood. Different causes contribute to anaemia in chronic diseases, including diversion of iron, reduced erythropoiesis and reduced response to erythropoietin.

- Interleukin-6 appears to be the central mediator of ACD in a range of inflammatory diseases, including end-stage kidney disease and rheumatoid arthritis [2].
- ACD is associated with hyposideraemia (low serum iron) and altered iron transport. Cytokines are implicated by reducing erythropoiesis and increasing iron sequestration in the reticuloendothelial system [3].
- Interleukin-6 induces the expression of hepcidin, which suppresses the expression of the iron transporter, ferroportin-1, so inhibiting the absorption of iron from the duodenum and the release of iron from the reticuloendothelial system [2].
- Hepcidin is a peptide hormone produced by the liver and is a key regulator of iron homeostasis [4].
- Hepcidin binds to the iron export protein, ferroportin, causing ferroportin to be phosphorylated and degraded in lysosomes [3].
- Hepcidin inhibits iron release from the reticuloendothelial system. Increased expression of hepcidin also leads to decreased iron absorption and iron-deficient anaemia. The regulation of iron absorption across the epithelium of the proximal small intestine is essential for maintaining body iron concentrations [3].

The anaemia of chronic kidney disease is thought to be slightly different. See also separate Anaemia in Chronic Kidney Disease article.

**Presentation**

The presentation may be quite subtle in a patient who already has chronic disease. The presentation may include the new onset or increased tiredness, pallor, breathlessness and tachycardia.

**Investigations**

ACD typically occurs despite adequate reticuloendothelial iron stores.

- Reduced serum iron, transferrin and total iron-binding capacity.
- Exclusion of a mixed cause for anaemia - B12 and folate levels.
Measuring serum ferritin is essential in investigating unexplained anaemia:
- Serum ferritin concentration is directly related to reticuloendothelial iron stores, and normally 1 μg/L serum ferritin roughly corresponds to about 8 mg of storage iron.
- Normal or raised ferritin is typical in ACD \[5\]. This is because of the increased storage and retention of iron within the reticuloendothelial system. There are also increased ferritin levels due to immune activation accompanying the chronic disease.
- In the presence of inflammation, ferritin concentrations may remain normal even when reticuloendothelial iron stores are absent.
- High erythrocyte sedimentation rate (ESR).
- Red cells are often normochromic, normocytic but may be hypochromic, microcytic (as frequently seen in rheumatoid arthritis and Crohn's disease).
- Bone marrow examination for iron is the definitive test for deficiency - very uncomfortable and expensive.
- Estimation of soluble transferrin receptor (if available):
  - Measurement of soluble transferrin receptor provides a marker of bone marrow iron stores and improves the diagnosis of iron-deficiency anaemia, therefore helping to differentiate between iron-deficiency anaemia and ACD \[6\].
  - The test is much more expensive than ferritin measurement.

Bone marrow examination for the sole purpose of assessing iron stores is rarely justifiable \[7\].

Differential diagnosis
- Other causes of anaemia, particularly iron-deficiency anaemia.
- Any other cause of general deterioration in a patient with chronic disease.

Management
Treatment of the underlying condition should cause the Hb level to rise.

Pharmacological treatment
- The degree of anaemia is often mild and does not require treatment.
- Iron supplements should only be used for patients with established iron deficiency.
- Transfusion of packed red blood cells should be reserved for patients who have severe, symptomatic anaemia. This is a palliative measure only and its use should be weighed against the associated risks with transfusion - eg, volume overload, iron overload and transfusion reaction.
- Novel erythropoiesis-stimulating protein (NESP) - darbepoetin alfa - stimulates erythropoiesis by the same mechanism as recombinant human erythropoietin (rHuEPO) but it is biochemically distinct:
  - It has a threefold greater serum half-life and can maintain Hb levels as effectively as rHuEPO in anaemic patients with chronic kidney disease, with less frequent dosing \[8\].
  - Also, consider erythropoiesis-stimulating agents in rheumatoid arthritis, heart failure and cancer \[9, 10\].

Prognosis
Usually this will depend on the underlying cause of the anaemia. However, the severity of the anaemia and the speed with which it developed can play a significant role. Similarly, the age of the patient and the existence of other comorbid conditions influence outcome.

Further reading & references
1. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity; World Health Organization, 2011
2. Raj DS; Role of Interleukin-6 in the Anemia of Chronic Disease. Semin Arthritis Rheum. 2008 Mar 11;
7. Guideline for the laboratory diagnosis of functional iron deficiency; British Committee for Standards in Haematology (May 2013)

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