# Anaemia of Chronic Disease (ACD)

Anaemia of chronic disease (ACD), also known as anaemia of inflammation (AI), is a common type of anaemia, particularly in hospital populations. It occurs in the setting of chronic infection, chronic inflammation or neoplasia.

## Inflammatory Diseases Associated with the Development of ACD

I. Infections (acute and chronic)
   A. Viral infections including HIV
   B. Bacterial
   C. Parasitic
   D. Fungal
   E. Helminth
II. Malignancies
   A. Haematologic
   B. Solid tumor
III. Autoimmune
   A. Rheumatoid arthritis
   B. Systemic lupus erythematosus and connective tissue diseases
   C. Vasculitis
   D. Inflammatory bowel disease
IV. Chronic kidney disease and inflammation

**Pathophysiology—Cornerstones**

The anaemia is not related to bleeding, haemolysis or marrow infiltration, is mild, with haemoglobin in the range of 85–115 g/L, and is usually associated with a normal MCV (normocytic, normochromic),

**Hepcidin**
***Master Regulator of Iron Homeostasis***

Pathogenesis It has recently become clear that the key regulatory protein that accounts for the findings characteristic of ACD is hepcidin, which is produced by the liver.

Hepcidin production is induced by pro-inflammatory cytokines, especially IL-6. Hepcidin binds to ferroportin on the membrane of iron-exporting cells, such as small intestinal enterocytes and macrophages, internalising the ferroportin and thereby inhibiting the export of iron from these cells into the blood.

The iron remains trapped inside the cells in the form of ferritin, levels of which are therefore normal or high in the face of significant anaemia.

- Iron retention within the reticulo-endothelial system
- Inadequate formation and function of erythropoietin
- Impairment of erythrocyte progenitor formation

**ACD Diagnosis**

| Parameter | ACD | IDA |
|---|---|---|
| Serum iron concentration | **Reduced** to normal | Reduced |
| Transferrin levels | **Reduced** to normal | Increased |
| Transferrin saturation | **Reduced** to normal | Reduced |
| Ferritin | Normal to **increased** | Reduced |
| Serum transferrin receptor | Normal | Increased |
| Percentage hypochromic RBC | Normal | High |
| Cytokines (TNF, IL-1, IL-6) | **Increased** | Normal |

**ACD Best Therapy**

Treatment or Cure of the Underlying Disease!

**Current Therapeutic Options in ACD**

- Blood transfusions
- Recombinant human erythropoietin
- Iron

Therapeutic measures are aimed to increase haemoglobin levels in ACD patients

**ACD Therapy**
***Blood Transfusions***

- Can be readily used for rapid correction of severe anaemia
- Immediate increase of haemoglobin
- 1 unit contains ~200 mg of iron

***Iron***

- **NO,** if infections or cancer underlie ACD; ferritin >100 ng/mL
- May favor proliferation of pathogens
- By countering iron-withholding strategy
- By impairing immune function
- May not reach erythroid cells due to diversion into reticulo-endothelial system

- May cause tissue damage via formation of toxic radicals by the Fenton reaction (triggered by TNF-a)
- However, in autoimmune diseases, iron may inhibit pro-inflammatory immune effector pathways, thus reducing disease activity
- What to do in ACD with true iron deficiency (ACD and bleeding)?
- Iron is needed for basic metabolic functions
- How to substitute iron?
- Iron is very poorly absorbed in ACD (down-regulation of ferroportin in the duodenum by hepcidin)
- IV iron administration is very effective in inflammatory bowel disease and ACD

**Iron Therapy in Dialysis Patients**

Prospective study investigating the incidence of infectious complications in ESRD patients receiving IV iron therapy

- Group 1: ferritin <100 ng/mL and TfS <20%
- Group 2: ferritin >100 ng/mL and TfS >20%
- Observation period: 1 year

Frequency of septicaemia in Group 2 was 2.5-fold higher than in Group 1

Too much iron may be harmful in ACD!

**Why Is the Differential Diagnosis Between ACD and ACD + IDA Important?**

- Because these patients need contrasting therapies!!!
- No iron in ACD
- Iron needed in ACD/IDA

**Therapy—Erythropoietin-Stimulating Agents (ESA)**

- Effective in increasing haemoglobin levels in ACD: patients with cancer, infections, and autoimmune disorders
- Response rate to treatment depends on underlying disease, stage, immune activation, and iron availability
- Increase of haemoglobin with ESA treatment is associated with a decreased need for blood transfusions

**Therapeutic End Points**

- Normalization of haemoglobin levels in end stage renal disease patients was associated with a significant increase of cardiovascular mortality as compared with patients with haemoglobin levels below the normal range
- Dialysis patients: risk of death was highest with haematocrit levels between 33% and 36%
- **Avoid over-correction of anaemia (Hgb >12 g/dL)**
- **Currently recommended therapeutic end point: Hgb 11–12 g/dL**