MANAGEMENT OF ANAEMIA IN CHRONIC KIDNEY DISEASE

Prof. Dr. Sk. Abdul Fattah

Professor and Head

Department of Medicine

Shaheed Tajuddin Ahmad Medical College, Gazipur.

Anaemia of chronic Kidney Disease

- anaemia resulting directly from failure of the endocrine and filtering functions of the kidney.
- Normocytic, normochromic anaemia
- Severity of the anaemia is roughly proportional to the degree of impaired renal function.
- Exception :

>Diabetic nephropathy- anaemia is more severe and developes earlier

>Polycystic Kidney Disease- anaemia is less severe, sometimes Polycythaemia.

Table 3.6 Prevalence of anaemia from NHANES III (📖 p. 228)

CKD stage	Median Hb in men (g/dL)	Median Hb in women (g/dL)	Prevalence of anaemia[a]
2	14.9	13.5	1%
3	13.8	12.2	9%
4	12.0	10.3	33%

[a] Hb <12g/dL in ♂; <11g/dL in ♀.

Reprinted from *American Journal of Kidney Diseases*, 41, Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey, 1–12, Copyright (2003), with permission from Elsevier.

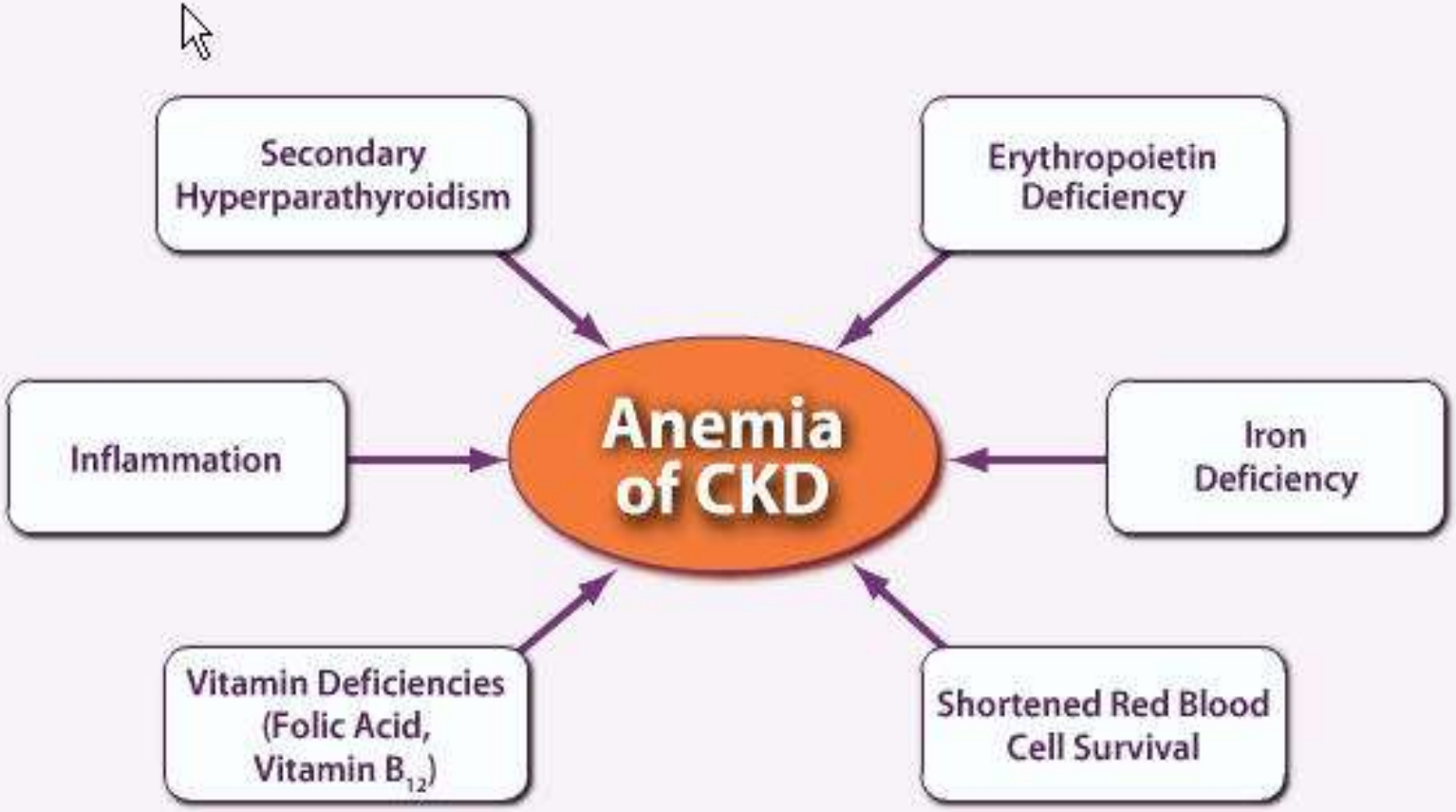
Pathogenesis

• Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia.

• Both red cell life span and the rate of red cell production are reduced, but the latter is more important.

• Erythropoietin (EPO)–induced compensatory increase in erythrocyte production is impaired in CKD.

Factors that may lead to Anaemia



Box 3.2 Differential diagnosis of anaemia in CKD patients

▶ EPO deficiency is not the only cause of ↓ Hb in CKD.

Think of the following before commencing ESA therapy and particularly if disproportionate anaemia or ESA resistance (📖 p. 223):

- Blood loss:
  - Peptic ulcer disease, GI vascular ectasia.
- ↓ red cell survival:
  - Inflammation + oxidative stress + uraemic toxins → RBC membrane and cytoskeletal damage.
  - Haemolysis
- Related to dialysis:
  - Blood loss during treatment ('lost lines').
  - Haemolysis: contaminated dialysate, hypo-osmolar or overheated dialysate, residual sterilizing agents, trauma in blood pump, high flow through narrow gauge needles.
- Haematinic deficiency:
  - Iron deficiency.
  - B12 or folate deficiency.

- Impaired bone marrow response:
  - Chronic infection or inflammation.
  - Uraemic toxins (? underdialysis).
  - Hyperparathyroidism (→ marrow fibrosis).
  - Carnitine deficiency.
  - Aluminium overload; now rare (📖 p. 247).
- Malnutrition.
- Relating to underlying or unrelated disease:
  - Myeloma.
  - Myelodysplasia.
  - Sickle cell disease or other haemoglobinopathy.
  - SLE.
  - Autoimmune haemolysis.
  - Coeliac disease.
  - Occult malignancy.
  - Hypothyroidism.
  - Relating to treatment:
    - — Poor compliance with ESA therapy or incorrect dosing.
    - — Immune suppression.
    - — ACE-I (several mechanisms, including: ↓ endogenous EPO production and ↓ angiotensin II stimulation of erythroid precursors). Rarely mandates cessation of treatment.
    - — Pure red cell aplasia (PRCA) (📖 p. 225).

Why are CKD patients prone to develop iron deficiency?

REDUCED INTAKE

- Poor appetite
- Poor G-I absorption
- Concurrent medication

  e.g. omeprazole
- Food interactions
- ↑ Demand EPO therapy

INCREASED LOSSES

- Occult G-I losses
- Peptic ulceration
- Blood sampling
- Surgical or access Interrventions
- Dialyser losses
- Concurrent meds. – e.g. aspirin
- Heparin on dialysis

Markers of iron status

Several markers of iron status are available. Unfortunately, they lack sensitivity and specificity to predict the response to iron therapy in the context of CKD. It is generally recommended that ferritin and at least one additional test are used.

- **Ferritin**:

  Cellular storage protein and marker of storage iron.

  An acute phase protein, raised in inflammation and liver disease

- **TSAT (Transferrin Saturation):**

  Transferrin is a serum protein involved in iron delivery.

  TSAT = (serum iron / TIBC) x 100.

  A measure of available iron.

- **Percentage hypochromic red blood cells (% HRBC**):

  Measure of the iron incorporated into RBCs.

- **Reticulocyte Hb count (CHr):**

  Measure of the iron incorporated into immature RBCs.

- **Others**: serum transferrin receptor and erythrocyte zinc protoporphyrin levels are mainly research tools at present.

Markers of Iron Status in CKD Patients

Test	Recommended Range
Serum ferritin	100–500 µg/L (CKD) 200–500 µg/L (HD)
Transferrin saturation	20%–40%
Hypochromic red cells	<10%
Reticulocyte hemoglobin content (CHr)	>29 pg/cell
Serum transferrin receptor	Not established
Erythrocyte zinc protoporphyrin	Not established

Figure 79.8 Markers of iron status and the recommended target ranges in chronic kidney disease (CKD).

Approach to Find out Causes of Anaemia in CKD

- Anaemia in CKD is not always anaemia of CKD.
- Suspicion of cause of anaemia from history, physical examination and peripheral blood film should be confirmed by necessary investigations and be followed up after treatment.
- Diagnostic evaluation is considered if :

> Hemoglobin level falls to 11 g/dl or less

> eGFR is less than 60 ml/min/1.73 m^2 ·eGFR greater than this indicates the anaemia more likely to be related to other causes.

➢Presence of symptoms attributable to anaemia.

- Examination of the bone marrow seldom reveals any abnormalities

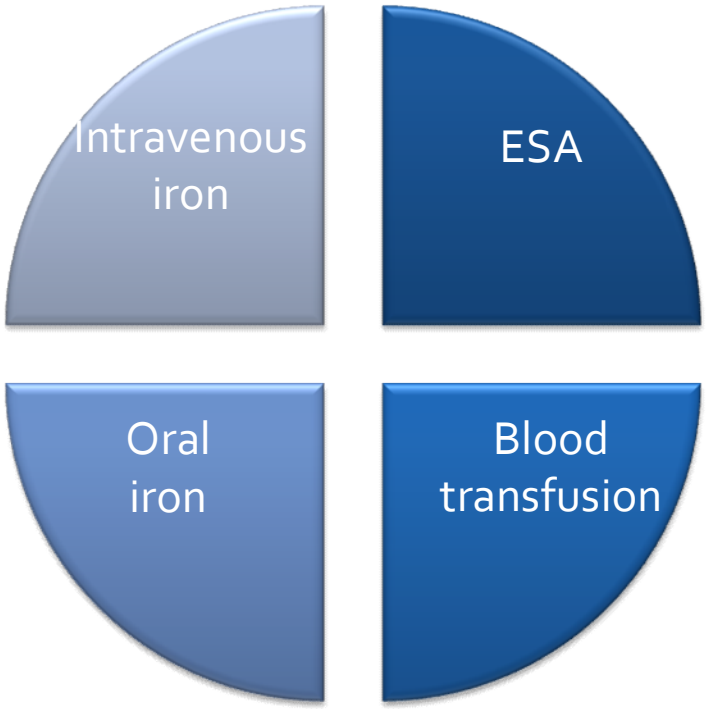
Target Hb for CKD patients

- Complete normalization of the haemoglobin concentration has not been demonstrated to be of incremental benefit to CKD patients.
- There is no particular haemoglobin concentration at which symptoms become manifest in all patients, hence the decision to start treatment in a particular patient is always a matter of judgement.
- As a rule of thumb, if a patient with CKD has Hb below 11 g/dL and symptoms that is attributable to anaemia, then treatment to restore haemoglobin to the range 11 to 12 g/dL is warranted if available
- Current practice is to target a haemoglobin concentration of

  10–11 g/dL.

Overview of Treatment Options Available for the Management of Anaemia in CKD

- Various therapeutic options are available for the management of anaemia in patients with CKD ranging from oral iron therapy to blood transfusions[1,2]



1. Macdougall IC. *Curr Med Res Opin* 2010;26:473–82; 2. Del Vecchio L, Locatelli F. *Expert Rev Hematol* 2014 Aug;7(4):495–506.

Correction of Anaemia in CKD

- Iron therapy- Oral or Intravenous
- ESA-Erythropoiesis Stimulating Agent (Erythropoietin)
- Blood transfusion

- Renal Replacement Therapy (RRT)
  - Renal transplantation
  - Dialysis

Iron Therapy :

- Before starting treatment with ESAs it is important to exclude other causes of anaemia, especially Iron deficiency.
- Trial of oral iron is considered in CKD patients

  > who are not on ESA therapy or Hemodialysis

  > where IV iron therapy is contraindicated

  > patients choice.
- Intravenous Iron therapy is given in patients

  > intolerant to oral iron

  > target Hb level is not reached within 3 months of oral iron

  > on ESA therapy or Hemodialysis

Targets of Iron and ESA therapy

To achieve :

> Hypochromic red blood cells < 6%

> Reticulocyte Hb count > 29 pg

> Transferrin saturation level > 20%

> Serum ferritin level >100 microgram/litre

Erythopoietin therapy

- Treatment is offered to people who are likely to benefit in terms of quality of life and physical function.
- The pros and cons of ESA therapy should be discussed with the patients, their families and carers .
- In terms of efficacy, there is little difference between ESAs.
- It is important to recognize that optimal response to ESAs requires plentiful iron, not simply a level that is not deficient
- Ensure that blood pressure is reasonably controlled before ESAs are given (there were records of hypertensive encephalopathy)
- Should not be started (or doses omitted) if blood pressure is above 160/100 mmHg.

ESAs : the dose and frequency

- Determined by the duration of action and route of administration of ESA.
- adjusted to keep the rate of Hb rise between 10-20 g/litre/month

Hb level below target range may be accepted if

- High dose is required
- target range is not achieved despite escalating ESA doses.

Monitoring HB level :

- Every 2-4 weeks initially
- every 1-3 months in maintenance phase
- More frequently after an ESA dose adjustment.

ESA resistance is considered:

After exclusion of other causes of anaemia when

- Target Hb range is not achieved despite treatment with

> 300 IU/kg/week of SC epoetin or

>450 IU/kg/week of IV epoetin or

> 1.5 microgram/kg/week of Darbepoetin or

- Continued need for high doses ESA to maintain target Hb

ESA-induced Pure Red Cell Aplasia (PRCA)

Indicated by :

- > Anaemia
- > Low reticulocyte count
- > Neutralizing antibodies

Confirmed by :

- > anti-erythropoietin antibodies
- > lack of pro-erythroid progenitor cells in the bone marrow.

Management :

- Stopping ESA
- Red cell transfusion
- Needs specialist referral.

Renal Replacement Therapy

Renal Transplantation

- Prompt and dramatic correction of the anaemia follows successful renal transplantation. Occasionally, polycythaemia may be encountered
- Anaemia is usually corrected over an 8- to 10-week period
- Failure to respond usually can be explained on the basis of hemorrhage, vigorous immunosuppression, or graft rejection

Renal Replacement Therapy

Dialysis

- Red cell production increases slightly in patients on hemodialysis
- As a general rule, anemia is less severe in patients receiving peritoneal dialysis, with consequently lower rhEpo and transfusion requirements.

Blood Transfusion

- Blood transfusion support may be required for patients who fail to respond to rhEpo products
- Iron overload and other complications must be kept in mind.
- To be avoided where possible in people in whom kidney transplant is a treatment option.

- Uraemic bleeding may respond to desmopressin or estrogens, but may require dialysis for treatment in the case of severe uremia

Investigational agents

- More recent work suggests that there may be a defect of the oxygen-sensing system, rendering functioning cells less sensitive to hypoxia and production capacity for erythropoietin may be preserved in chronic renal disease
- Oral Hypoxia Inducible Factor-stabilising compounds are Prolyl hydroxylase inhibitors. Several molecules, e.g., roxadustat, vadadustat, daprodustat and molidustat are in development.
- Stability of HIF-2α in the kidney is increased, which positively affects production of Epo
- Could be an attractive alternative if found to be safe and effective.

- EPO fusion proteins
- Synthetic Erythropoiesis Protein (SEP)
- Peptide-based ESAs
- Non-Peptide-based ESAs
- GATA inhibition
- Haemopoietic cell phosphatase (HCP) inhibitors
- Gene therapy

Concluding Remarks

- Erythropoietin remains the mainstay of treatment of anaemia in CKD patients.
- Overzealous Epo treatment must be avoided.
- Iron loading before Epo treatment is very important.
- Causes of anaemia other than relative lack of erythropoietin must be elucidated.
- Blood transfusion should be the last choice to correct anaemia in CKD.

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