ANEMIA in CKD

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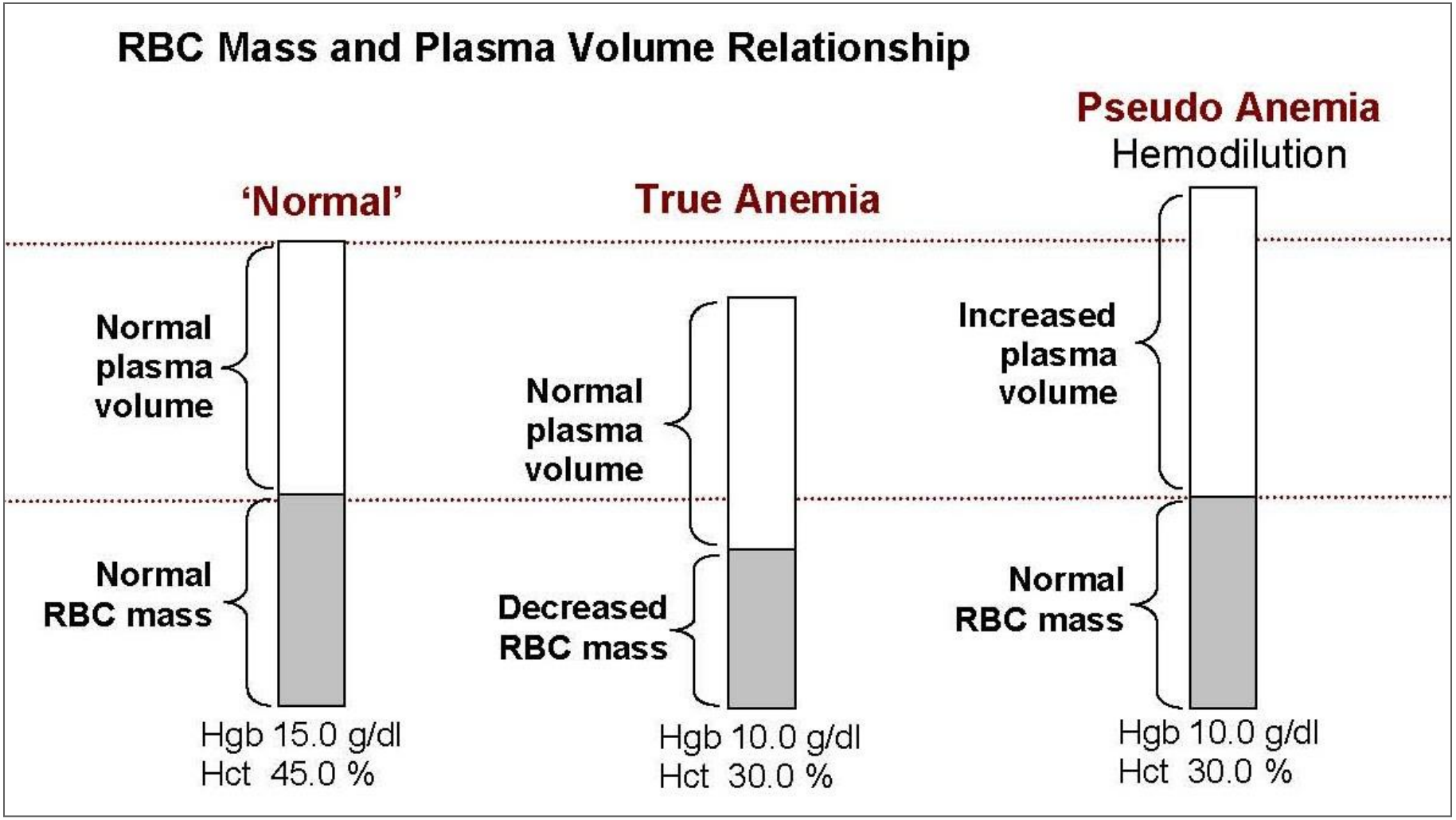
3.1. Introduction

3.1.1. Definition of Anemia

- Anemia is a decrease in the RBC count, Hgb and/or HCT values as compared to normal reference range for age and sex
  - ‘True’ anemia:
    - decreased RBC mass and normal plasma volume
  - Pseudo or dilutional anemia:
    - normal RBC mass and increased plasma volume
      - An increase in plasma volume can occur in Pregnancy, volume overload (IVs) congestive heart failure
    - Low Hgb and HCT values

Definition of Anemia cont'd



3.1.1. Definition of Anemia cont'd…..

- Anemia must also relate to the level of hemoglobin the individual normally possesses.
  - If an adult male usually maintains a hemoglobin level of 16g/dl, and over a period of days is noted to have decreased to 14g/dl, this must be considered significant even though both values are within the normal range for an adult male.

3.1.1. Definition of Anemia cont'd…..

- Various diseases and disorders are associated with decreased hemoglobin levels. These include:
  - Nutritional deficiencies
  - External or internal blood loss
  - Increased destruction of RBCs
  - Ineffective or decreased production of RBCs
  - Abnormal hemoglobin synthesis
  - Bone marrow suppression by toxins, chemicals, or radiation & replacement by malignant cells
  - Infection

3.1.1. Definition of Anemia cont'd…..

- Functionally anemia is defined as tissue hypoxia (inability of the body to supply tissue with adequate oxygen for proper metabolic function)
  - Anemia with normal or raised hemoglobin levels, hematocrit, or RBC count.

- Generally anemia is not a disease, but rather the expression of an underlying disorder or disease.

3.1.1. Definition of Anemia cont'd…..

- Anemia may develop when:
  - RBC loss or
  - Increase destruction
  - Impaired of bone marrow production

3.1.2.Hematologic Response to Anemia

- Tissue hypoxia causes increased renal release of erythropoietin (EPO) to accelerate bone marrow erythropoiesis

- The normal bone marrow can increase its activity 7-8 times normal
  - Marrow becomes hypercellular

3.1.3. Physiologic Response to Anemia

- Ability to adapt to anemia depends on:
  - Age and underlying disease
  - Cardio/pulmonary function
  - Rate at which anemia develops (BM can compensate easier if the onset of anemia is slow),
  - Underlying disease

3.1.4. Clinical features:

- **Symptoms of hypoxia**: decreased oxygen delivery to the tissues/organs causes:
  - fatigue , faintness, weakness, dizziness, headaches, dyspnea, poor exercise tolerance, leg cramps.

3.1.4.Clinical features cont'd….:

Signs of anemia

- general signs include pallor of mucous membrane, which occur if the Hgb concentration is less than 9g/dl,
- specific signs are associated with particular types of anemia, for example, jaundice in hemolytic anemia, leg ulcer in sickle cell anemia

3.1.5. Diagnosis of anemia cont'd……

Patient history cont…….

- Tiredness
- Muscle fatigue and weakness
- Headache and vertigo (dizziness)
- Dyspnea
- Overt signs of blood loss such as hematuria (blood in urine) or black stools

3.1.5. Diagnosis of anemia cont'd……

C. Lab investigations

1. A complete blood count, CBC
   - RBC count
   - Hematocrit (Hct)
   - Hemoglobin
   - RBC indices (MCV, MCH, MCHC)
   - Reticulocyte count
2. Blood smear examination to evaluate:
   - Poikilocytosis
   - Leukocytes or Platelets abnormalities

3.1.5. Diagnosis of anemia cont'd……

-Fe, TIBC, Ferritin

-Folic Acid, Vit B12

-….

3.1.5. Diagnosis of anemia cont'd…..

Lab investigation cont'd……

3. A bone marrow smear and biopsy to observe:
   - Maturation of RBC and WBC series
   - Ratio of myeloid to erythroid series
   - Abundance of iron stores (ringed sideroblasts)
   - Presence or absence of granulomas or tumor cells
   - Presence of megakaryocytes

Methods of Classification cont'd

III. Increased blood loss (Acute, Chronic)

- Retic count is typically high
- Anemia results when red cell loss exceeds the bone marrow's capacity to increase its activity

IV. Increased destruction of RBCs (hemolytic anemias)

- Retic count is typically high
- Anemia results when red cell destruction exceeds the bone marrow's capacity to increase its activity

Methods of Classification cont'd

Morphologic Categories of Anemia

1. **Normocytic Normochromic anemia (normal red cell indices)**
   - Blood loss anemia
   - Hemolytic anemia
   - Aplastic anemia
   - Chronic diseaes
   - Renal insufficciency

Methods of Classification cont'd

Morphologic Categories of Anemia

- **Microcytic hypochromic**
  - Iron deficiency anemia
  - Sideroblastic anemia
  - Lead poisoning
  - Thalassemia
  - Chronic diseases

Methods of Classification cont'd

Morphologic Categories of Anemia

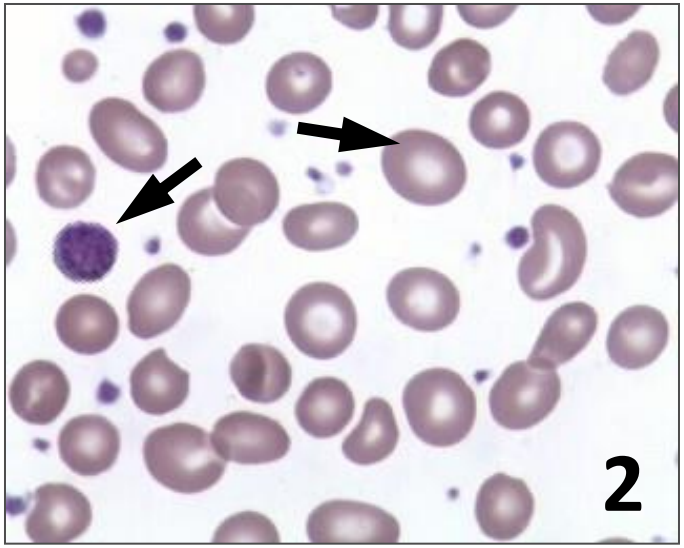
- **Macrocytic Normochromic**

(high MCV and MCH, normal MCHC)

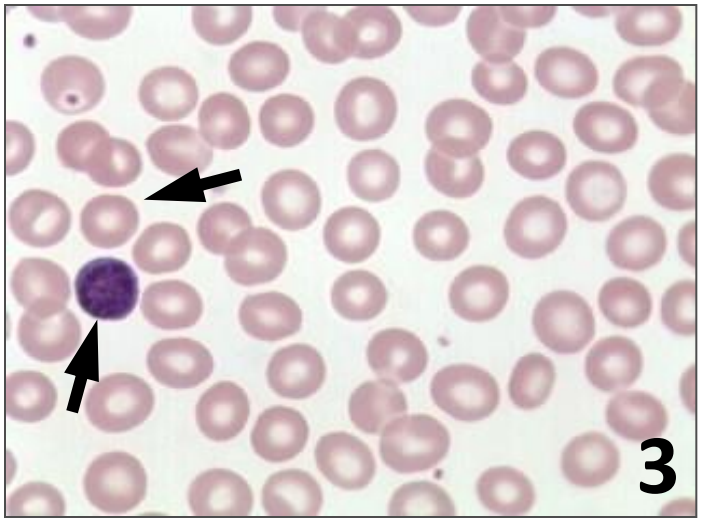
  - Megaloblastic anemia
  - Liver disease
  - Post splenectomy
  - Hypothyroidism
  - Stress erythropoiesis

Morphologic Categories of Anemia

1 Microcytic/hypochromic



2 Macrocytic/Normochromic



3 Normocytic/Normochromic

C. Anemia of chronic disease

- Anemia of chronic disease (ACD) – inability to use **iron** and decreased response to EPO
  - Very common anemia, #2

- Associated with systemic disease, including chronic inflammatory conditions:
  - Rheumatoid arthritis
  - Chronic renal disease
  - Thyroid disease
  - Malignancies
  - Tuberculosis
  - Chronic fungal infections etc

ACD pathogenesis

- **Lactoferrin** is an iron biding protein in the granules of neutrophils
- Its avidity for iron is grater than transferrin
- During infection or Inflammation, neutrophil-lactoferrin released into plasma and Scavenges available iron
- Bind to macrophage and liver cells (because they have receptor for lactoferrin

- **Cytokines:** Produced by macrophages during inflammation and contribute to ACD by inhibiting erythropoiesis

Lab Diagnosis

- Blood findings
  - Early stage: normocytic normochromic
  - Late stage: hypochromic microcytic,
  - Low serum iron, low TIBC, normal or high serum ferritin
- Leukocytosis
- Abundant storage of iron in macrophage (Prusian blue)

Anemia of Chronic Kidney Disease

Etiology. The anemia of chronic kidney disease (CKD) is primarily due to insufficient production of the erythropoietin (EPO).

EPO required for erythropoiesis generally is produced by endothelial cells of renal tubules.

Decreased GFR >>>Decreased EPO

End-stage kidney disease (ESKD) >>>HCT: 18%–24%

Other factors may play important contributory roles. Also, patients with ESKD may develop any of the other causes of anemia common in nonuremic subjects.

manifestations of anemia:

Due to: Decreased oxygen delivery to tissues and to the heart's compensatory changes.

The most prominent symptoms of anemia: fatigue and dyspnea.

Symptoms develop slowly

Diminished sense of well-being, difficulty concentrating, dizziness, sleep disorders,

cold intolerance, and headaches.

Cardiac response: increased cardiac output and left ventricular hypertrophy >>

worsening dyspnea and palpitations Exacerbations of angina.

Other problems: include deranged hemostatic function, impaired immune function, and diminished cognitive and sexual function., claudication, and transient ischemic attacks may also be observed.

Physical examination

- pallor, which may be best detected on the palms of the hands, the nail beds, and the oral mucosa.
- A systolic ejection murmur due to increased cardiac flow may be heard over the precordium.

Treatment

- **Epoetin alfa**
- **Darbepoetin alfa:**synthetic analog of erythropoietin
- **Peginesatide** is a synthetic peptide

Benefits of anemia treatment with ESA

- **Effect on outcomes:** increased mortality, particularly when the hemoglobin concentration is <10 g/dL
- **Reduction in transfusion-related complications**
- **Improved quality of life and overall sense of well-being**

Risks of ESA Therapy:

- Cancer
- Stroke

Indications for ESA therapy and target hemoglobin:

- A reasonable hemoglobin target for patients on dialysis would be 9.5–11.5 g/dL (95–115 g/L).

Effect of volume status on target hemoglobin

- When Hgb is assessed prior to a hemodialysis session, extracellular
- volume tends to be high, and so due to dilution.

Route of administration:

- **Subcutaneous versus intravenous ESAs**
- When given subcutaneously, the serum half life of epoetin is extended, allowing for more efficient receptor binding and a greater erythropoietic effect.
- patient discomfort

Dosing:

- **Initial dose:**
- Epoetin alfa for a hemodialysis patient would be 2,000–3,000 units three times per week, and for a peritoneal dialysis patient 6,000 units once per week.
- Darbepoetin alfa would be approximately 25 mcg once weekly for a hemodialysis patient or 60 mcg every 2 weeks for a patient on peritoneal dialysis.
- Excessiv rapid rise in the hemoglobin level >> worsening of hypertension.

Initial response and plateau effect:

- During the initiation phase of therapy, hemoglobin should be checked every 1–2 weeks, and the ESA dose adjusted as needed.
- Plateau Response: Iron deficiency?
- Once the target level of hemoglobin has been reached, the hemoglobin should be checked every 2–4
- weeks

EPO…

- Most patients will be responsive, with hemoglobin values consistently >10 g/ dL (100 g/L), and an epoetin dose of <5,000 units three times per week.
- Relative resistance to therapy >> fully evaluation for causes of ESA hypo response (Iron deficiency, Infection?)

Side effects of ESA therapy.

- **Worsening of hypertension.**
- This is a common problem
- **Risk factors**: preexisting hypertension, rapid increase in hemoglobin, presence of dysfunctional native kidneys, and severe anemia prior to treatment.
- Various antihypertensive, including long-acting calcium channel blockers, are effective

Side effects of ESA …

- **Seizures:** Uncommon, During periods of rapidly increasing hemoglobin in association with hypertension.
- **Graft clotting.** Increased risk of thrombosis when the hemoglobin
- is raised to the 11–12 g/dL (110–120 g/L) range?
- The impact of higher hemoglobin levels is controversial.
- Substantial hemo-concentration during or after the hemodialysis treatment?

Side effects of ESA …

- **Stroke.** The risk of stroke has been increased in some of the randomized trials of ESAs where a relatively high Hgb.

- **Effect on *Kt/V.*** During dialysis, urea is removed from both
- red cells and plasma, and so urea clearance and Kt/V-urea
- are not affected by an increase in the Hgb.
- Creatinine and phosphorus are removed from the plasma only during passage of blood through the dialyzer, and as the Hgb is increased, at any given blood flow rate, the plasma flow rate
- and creatinine and phosphorus clearances will be proportionately
- reduced.

Causes of decreased response to ESA therapy:

- **Iron deficiency:** rapid utilization of iron to support erythropoiesis, blood loss
- **Blood loss:** very difficult to maintain
- iron stores in hemodialysis patients using oral iron supplements only.
- Losses in peritoneal dialysis patients are substantially less, and these patients can often be maintained on oral iron therapy.

Causes of decreased response …

- **Functional iron deficiency:**
- After the intravenous injection of ESA, there is an increase in the rate of erythropoiesis that leads to a greater immediate need for iron. In this setting, iron deficiency may occur even in the face of normal body iron stores. This phenomenon has been termed “functional iron deficiency.”

Causes of decreased response …

- **Inflammation (reticuloendothelial blockade):**
- Occult inflammation >> Increase in serum hepcidin concentrations >> reduced intestinal iron absorption >> diminished availability of iron in storage tissues.
- **Poor absorption of dietary iron**