Approach to Anemia & Nutritional Anemia

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Anemia theoretically is defined as a reduction in the red cell mass but practically as a reduction in the hemoglobin. Hemoglobin level of < 13 g/dL in adult males, <12 g/dL in non pregnant females and 11 g/dL in pregnant females of all races at the same altitude warrants investigations and management for anemia. (WHO)

Clinically for the purpose of management, anemia may be divided into there.

1. **Acute**: Recent onset arbitrarily taken as anemia occurring within 2 weeks.
   - Causes: hemolysis, overt blood loss, acute leukemias

2. **Sub-acute**: 2 weeks to 6 weeks
   - Causes: Occult blood loss, Low grade hemolysis, Leukemia, Increased requirement (demand), Infections, Collagen vascular disorders, Hypoplastic anemia, Drug induced

3. **Chronic**: more than 6 weeks
   - Causes: Nutritional Occult blood loss
   - Bone marrow infiltration Infections (parasitic or Otherwise)
   - Hypoplastic anemia

   Anemia of chronic disease (e.g. chronic renal disease, Chronic inflammation)MDS.

   Once anemia is confirmed by hemoglobin estimation, one of the initial investigations to be done is a **reticulocyte count**. The Normal reticulocyte count is 0.2 to 2%. Based on the reticulocyte count anemia can be classified into:

1. **Anemia with increased reticulocyte count**. This includes hemolytic anemia and its various causes and hemorrhage (mainly sub acute blood loss)

2. **Anemia with normal or decreased reticulocyte count**. This group is further divided according to the MCV (Mean corpuscular volume)
   - a) Normocytic normochromic MCV 80-90.
   - b) Microcytic anemia MCV < 80.
   - c) Macrocytic anemia MCV > 90

**Normocytic normochromic anemia**

(Hypoproliferative anemias)

This group is becoming the common type of anemia in India and includes

1. Aplastic anemia
2. Bone marrow infiltration e.g. leukemia, lymphoma
3. Marrow fibrosis like myelofibrosis (Primary or secondary)
4. Drugs damaging the marrow like those used for treatment of HIV
5. Anemia of chronic disease (ACD)
   - Secondary to chronic inflammatory diseases and other chronic diseases e.g. rheumatoid disease, cardiac failure.
6. Chronic renal failure. When erythropoiesis is reduced due to decrease in erythropoietin
7. Metabolic diseases like hypothyroidism.
8. Mild to moderate iron deficiency.

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Microcytic anemia
1. Severe iron deficiency anemia
2. Thalassemia
3. Sideroblastic anemia

Macrocytic anemia includes
1. Vit B12 deficiency
2. Folic acid deficiency
3. Combined deficiency
4. Refractory anemia MDS
5. Drug toxicity, Methotrexate, alkylating agents, alcohol.

Appropriate investigations should be carried out once the anemia is grouped to make a final specific diagnosis. For example if the anemia is grouped as macrocytic (i.e. MCV>90) then a serum B12 and folic acid levels would determine the cause in majority of cases. A bone marrow study will diagnose MDS (Myelodysplastic Syndrome). Drug history is also important.

Nutritional anemia:
Nutritional anemia rarely exists in a pure form. It exists in association with parasitic infestations, chronic blood loss or neoplastic disorders.

Common nutritional anemias in the order of frequency are
1. Iron deficiency anemia.
2. Combined deficiency (Diphoric anemia).
3. Folate deficiency.
4. B12 deficiency

Iron deficiency anemia (IDA)
Criteria for diagnosis:
Essential:
1. Anemia
2. Blood smear – hypochromic microcytic red cells. In many cases it may be associated with neutrophilia or thrombocytosis. Marked thrombocytosis (more than 4.5 L/cmm) may point to blood loss as the cause of iron deficiency anemia. In areas where thalassemia is present it should be excluded by appropriate tests (HbF, HbA2 estimation and Hemoglobin electrophoresis). In thalassemia the total RBC count will be normal or increased while in IDA it is usually decreased.

Confirmatory:
Demonstration of depletion of bone marrow iron (iron staining of a bone marrow smear)
Reduced serum Ferritin levels <12 ng/ml.
Serum iron and total iron binding capacity are not very specific and may be normal in the very early stages. S. iron will be low (<60 mg/dL) and TIBC will be elevated (>350 mg/dL).

More recent diagnostic tests include soluble serum trasferrin receptors and free erythrocyte zinc protoporphyrin which are increased in IDA (iron deficiency anemia).

Other tests: which may be helpful are
Red cell indices: Reduced MCV (less than 80) and MCHC with increased red cell distribution width (RDW-red cell distribution width- varying width of RBCs) are diagnostic of iron deficiency, while in thalassemia RBCs are of uniform width though the MCV is low.

Bone marrow examination: is done mainly to exclude other conditions causing anemia. Hyperplastic bone marrow is seen in Iron def. Anemia. (Erythroid hyperplasia)

Iron deficiency anemia may be the first sign of a more serious underlying disorder especially neoplastic disorders (common sites are lower GI tract and genito-urinary tract in the female).

Treatment:
Prophylactic treatment with iron is given for those at high risk of developing of iron deficiency. E.g.: pregnant and lactating women, low birth wt. or preterm infants.

Improvement of diet: Diet rich in iron content are meat, liver, jaggery, spinach, drumstick leaves, broccoli, grapes, onions and green leafy vegetable.

Therapeutic medicinal iron: oral route is to be preferred unless there is a contraindication.
Dose: Ferrous sulphate 300 mg tid. To be taken before food.
Duration: Once the Hb level has become normal iron has to be continued for 3-6 months for replenishing the iron stores. This is a very important clinical therapeutic point.

Oral Iron:

More than 120 iron preparations are available in the market. Due consideration has to be given before selecting a particular product. Please pay attention to the following.

1. Ferrous salts are better absorbed than ferric salts.
2. The amount of elemental iron varies among different products. For optimal hemoglobin synthesis 25 mg of elemental iron is needed per day. So we have to supply 100-180 mg of elemental iron/day, since iron absorption is only <20%. The drug should contain 30-100 mg of elemental iron to have fewer side effects.
3. Compound iron preparations: The addition of various minerals and B-Complex vitamins to iron preparations are unnecessary and it only increases the cost.
4. Sustained release preparations: have no therapeutic advantage over the standard preparations and should be avoided.
5. Vitamin C: Vitamin C in doses above 200 mg increases the absorption of iron by 30%, but the various preparations contain only 50-70 mg of Vitamin C and thus provide no advantage.
6. Docusate: Iron can cause constipation or diarrhea. So there is no rationale for combining docusate in the iron preparation.
7. Hemoglobin iron: this is banned in many of the developed countries. Majority of the preparations contain less than 2 gm of hemoglobin. Each gram of hemoglobin contains only 3 mg of iron. Even though hemoglobin iron is absorbed to the extent of 30% to provide 20-25 mg iron, 4-6 capsules has to be provided.

Dose of Elemental Iron (Oral) = 5 WD (5X WXD) (W = Weight in Kg, D = Deficiency of Hb in g%)

Parental Iron:

Total dose infusion: Indications:

1. When Hb in <5 g/dL.
2. Non compliance therapy.
3. GI. Intolerance to oral states.

Dose Calculation: Hemoglobin deficit (15-Hb) X weight in Kilogram X 2.3+ 1000 mg (male)
600 mg (female)-for the storage iron e.g. hemoglobin 5 grams in a 60 kilogram weight male Hemoglobin deficit 15 - 5 (10 grams) X 60 X 2.3 = 1380 mg + 1000 mg - male = 2380 mg.

1. Total dose of iron is calculated and Iron dextran (Infernon) is diluted in 500 ml of 5% glucose and is given slowly IV over a period of 3-4 hours under close medical supervision. Side effects include anaphylaxis, severe headache, thrombophlebitis, arthralgia and arthritis and local suppuration at injection site. Patient should be watched for 3-4 days for disabling arthralgias and reactions.

Alternatively iron can be given by deep IM injection: Total dose to be calculated and given in divided doses of 100 mg/day. Patient can develop a discoloration along the track of injection.

Iron dextran (Infernon) was the only parenteral iron that was available. Now newer compounds sodium Ferric gluconate (Globac 62.5 mg vials) and iron sucrose (Venofer or Ferri, 50 mg vials) are available. These intravenous preparations are very safe and anaphylaxis rare. Two vials (125 mg vials Globac or 100 mg Ferri) can be diluted in 0.9% normal saline (100 ml) and infused slowly over 60 minutes. If symptoms of chest pain, wheezing, fall in BP or other systemic signs develop, the infusion should be interrupted immediately. In patients with gastric disease or gastric surgery, special treatment with iron solution (elixirs) may be necessary since the retention capacity of stomach is reduced in these conditions. Good retention capacity is necessary for dissolving the shell of the iron tablet before the release of iron.

Response of oral therapy can vary according to the Erythropoietin stimulus and rate of absorption. If there is no response to oral iron, poor absorption, non compliance or a coexisting cause like folic acid
or B12 deficiency should be suspected. If iron deficiency persists it is worth while shifting to parenteral iron therapy since safer preparations are available now.

Packed red cell transfusion: Indication: severe anemia especially of rapid onset, anemia associated with cardiac failure or postural syncope.

Folic Acid Deficiency: Causes:
1. Dietary inadequacy (Folic acid is found in liver, green vegetables, sprouted pulses), alcoholics
2. Mal-absorption: (celiac disease, sprue)
3. Increase requirement: pregnancy, childhood, hemolysis,
4. Malignancies and prolonged dialysis,
5. Drugs (Dilantin, cotrimoxazole)

Clinical features: anemia, beefy tongue, glossitis, hyper-pigmentation.

Diagnosis: macrocytic red cells (MCV>100), Hyper segmented neutrophils (>5% with 5 lobes few cells with 6 lobes).

Confirmation: Red cell folate. Serum estimation is helpful. (Normal 2-14 mg/ml)

Optional: Bone marrow examination to assess severity and exclude other conditions – BM picture: Megaloblastic bone marrow.

Treatment
Oral folic acid is given in a dose of 5-15mg per day till anemia is corrected and continue for at least 4 months to make up for the storage (the duration depends on the underlying condition). Diet rich in folic acid should also be advised (liver, yeast, spinach, other greens and nuts)

Folic acid and neural tube defects:
There is a strong association between folate deficiency and neural tube defects. So those who are likely to become pregnant are advised to take folic acid and 0.4 mg/day 3 months prior to conception till the initial 12 weeks after conception.

B12 Deficiency: Pure form is not common

Causes:
1. Dietary
2. Mal-absorption
3. Blind loop syndrome
4. Total resection of stomach
5. Pernicious anemia - mal-absorption due to parietal cell and intrinsic factor antibodies

A special type of Vitamin B12 (cobalamin) deficiency is recently observed in people above the age 60 – 70 yrs. This is due to an inability to release the cobalamin from food substances like meat. Cobalamin in food is tightly bound to enzymes in meat and is split from these enzymes by hydrochloric acid. People above 70 years commonly have achlorhydria. These old people however retain the ability to absorb crystalline B12, the form commonly available in multivitamin tablets.

Diagnosis:
1. Circumstantial evidence
2. Clinical features (as mentioned for folate deficiency)
3. Lab findings as for folate deficiency.

Confirmatory: Serum B12 assays (N. value 200-600 pg/ml). Values below 100pg are diagnostic.

Management: Therapeutic

Parenteral B12 = Hydroxocobalamin 1 mg (1000 microgram) 1m/IV, daily, alternate days or once in three days X 6 injections should replace the body stores.

Patients needing maintenance (pernicious anemia or total resection of stomach or those with terminal ileal disease) may have to be supplied with monthly B12 injections life long- 500 – 1000mg/month.

Some experts have recommended the use of 0.1 mg oral crystalline cobalamin prophylaxis daily for people over the age of 65 yrs.