Introduction

• Anemia defined as Hgb <13 g/dL in men or <12 g/dL in women.

• Anemias are a group of diseases characterized by a decrease in either Hgb or RBCs resulting in reduced oxygen-carrying capacity of the blood.
Anemias can result from:
1. Inadequate RBC production,
2. Increased RBC destruction,
3. Accelerated loss of RBC mass, or
4. They can be a manifestation of a host of systemic disorders such as infection, chronic renal disease, or malignancy.
Since anemias are often a sign of underlying pathology a rapid diagnosis of the cause of the anemia is essential.

The highest prevalence is in women, African-Americans, the elderly, and low-income persons.

Anemias can be classified on the basis of the morphology of the RBCs, etiology, or pathophysiology.
<table>
<thead>
<tr>
<th>TABLE 99-1. Classification Systems for Anemias</th>
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<tbody>
<tr>
<td><strong>I. Morphology</strong></td>
</tr>
<tr>
<td>- Macrocytic anemias</td>
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<tr>
<td>- Megaloblastic anemia</td>
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<tr>
<td>- Vitamin B₁₂ deficiency</td>
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<tr>
<td>- Folic acid deficiency anemia</td>
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<tr>
<td>- Microcytic, hypochromic anemias</td>
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<tr>
<td>- Iron deficiency anemia</td>
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<tr>
<td>- Genetic anomaly</td>
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<tr>
<td>- Sickle cell anemia</td>
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<tr>
<td>- Thalassemia</td>
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<tr>
<td>- Other hemoglobinopathies (abnormal hemoglobins)</td>
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<tr>
<td><strong>Nomocytic anemias</strong></td>
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<tr>
<td>- Recent blood loss</td>
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<tr>
<td>- Hemolysis</td>
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<tr>
<td>- Bone marrow failure</td>
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<tr>
<td>- Anemia of chronic disease</td>
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<tr>
<td>- Renal failure</td>
</tr>
<tr>
<td>- Endocrine disorders</td>
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<tr>
<td>- Myeloplastic anemias</td>
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<tr>
<td><strong>II. Etiology</strong></td>
</tr>
<tr>
<td>- Deficiency</td>
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<tr>
<td>- Iron</td>
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<tr>
<td>- Vitamin B₁₂</td>
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<tr>
<td>- Folic acid</td>
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<tr>
<td>- Pyridoxine</td>
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<tr>
<td>- Central—caused by impaired bone marrow function</td>
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<tr>
<td>- Anemia of chronic disease</td>
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<td>- Anemia of the elderly</td>
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<tr>
<td>- Malignant bone marrow disorders</td>
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<tr>
<td>- Peripheral</td>
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<tr>
<td>- Bleeding (hemorrhage)</td>
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<tr>
<td>- Hemolysis (hemolytic anemias)</td>
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<tr>
<td><strong>III. Pathophysiology</strong></td>
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<tr>
<td>- Excessive blood loss</td>
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<tr>
<td>- Recent hemorrhage</td>
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<tr>
<td>- Trauma</td>
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<tr>
<td>- Peptic ulcer</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>- Gastritis</td>
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<td>- Hemorrhoids</td>
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<tr>
<td>- Chronic hemorrhage</td>
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<tr>
<td>- Vaginal bleeding</td>
</tr>
<tr>
<td>- Peptic ulcer</td>
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<tr>
<td>- Intestinal parasites</td>
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<tr>
<td>- Aspirin and other nonsteroidal anti-inflammatory agents</td>
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<tr>
<td><strong>Excessive RBC destruction</strong></td>
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<tr>
<td>- Extracorpuscular (outside the cell) factors</td>
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<tr>
<td>- RBC antibodies</td>
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<tr>
<td>- Drugs</td>
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<tr>
<td>- Physical trauma to RBC (artificial valves)</td>
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<tr>
<td>- Excessive sequestration in the spleen</td>
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<tr>
<td><strong>Intracorpuscular factors</strong></td>
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<tr>
<td>- Heredity</td>
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<tr>
<td>- Disorders of hemoglobin synthesis</td>
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<tr>
<td><strong>Inadequate production of mature RBCs</strong></td>
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<tr>
<td>- Deficiency of nutrients (B₁₂, folic acid, iron, protein)</td>
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<tr>
<td>- Deficiency of erythroblasts</td>
</tr>
<tr>
<td>- Aplastic anemia</td>
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<tr>
<td>- Isolated (often transient) erythroblastopenia</td>
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<tr>
<td>- Folic acid antagonists</td>
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<tr>
<td>- Antibodies</td>
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<tr>
<td><strong>Conditions with infiltration of bone marrow</strong></td>
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<tr>
<td>- Lymphoma</td>
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<tr>
<td>- Leukemia</td>
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<tr>
<td>- Myelofibrosis</td>
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<tr>
<td>- Carcinoma</td>
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<tr>
<td><strong>Endocrine abnormalities</strong></td>
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<tr>
<td>- Hypothyroidism</td>
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<tr>
<td>- Adrenal insufficiency</td>
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<td>- Pituitary insufficiency</td>
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<tr>
<td><strong>Chronic renal disease</strong></td>
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<td><strong>Chronic inflammatory disease</strong></td>
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<td><strong>Granulomatous diseases</strong></td>
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<td><strong>Collagen vascular diseases</strong></td>
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<td><strong>Hepatic disease</strong></td>
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</table>
Diagnosis of Anemia

- History, physical examination and lab test are utilized in the evaluation of the anemic patient.
- The work-up determines if the patient is bleeding, if there is evidence for increased RBC destruction, if the bone marrow is suppressed, or if the patient is iron deficient and if so why.
- A previous abnormal blood exam may suggest a congenital problem.
• Occupation, social habits, travel history, and diet are all important in identifying causes of anemia.

• Information about concurrent nonhematologic disease states and a drug ingestion history are essential when evaluating the cause of the anemia.

• Past history of blood transfusions, liver disease, and exposure to toxic chemicals should also be obtained.
Presentation of Anemia

- Patients may be asymptomatic or have vague complaints.
- Patients with vitamin B12 deficiency may develop neurologic consequences.
- In anemia of chronic diseases the signs and symptoms of the underlying disorder often overshadow those of the anemia.
Symptoms

1. Decreased exercise tolerance,
2. Fatigue,
3. Dizziness,
4. Irritability,
5. Weakness,
6. Palpitations,
7. Vertigo,
8. SOB,
9. Chest pain,
10. Numbness and paresthesias
Signs

1. Tachycardia,
2. Pale appearance,
3. Decreased mental acuity,
4. Increased intensity of some cardiac valvular murmurs,
5. Diminished vibratory sense.
Lab Tests

- Hgb, Hct, and RBC indices may remain normal early in the disease and then decrease as the anemia progresses, low serum iron in IDA and ACD, ferritin levels are low in IDA and normal to increased in ACD, high TIBC in IDA, low TIBC in ACD, MCV elevated in vitamin B12 deficiency and folate deficiency, Vitamin B12 and folate levels are low in their respective types of anemia, homocysteine elevated in vitamin B12 deficiency and folate deficiency, methylmalonic acid elevated in vitamin B12 deficiency.
Other Tests

• Schilling test determines deficiency in intrinsic factor, bone marrow testing with iron staining can indicate low iron levels in IDA and an abundance of iron in ACD.
Anemia of rapid onset is most likely to present with cardiorespiratory symptoms such as tachycardia, palpitations, angina, hypotension, light-headedness, and breathlessness due to decreased oxygen delivery to tissues or from hypovolemia in those with acute bleeding.

With severe intravascular blood volume loss, peripheral vasoconstriction and central vasodilation preserve blood flow to vital organs.
• Over time systemic small vessel dilation increases tissue oxygenation.
• Vascular compensation results in decreased systemic vascular resistance, increased cardiac output, and tachycardia.
• With acute hemolysis and fall in RBC mass, there is some decrease in blood volume, but not in plasma volume.
• If the onset is more chronic the presenting symptoms may include fatigue, weakness, headache, symptoms of heart failure, vertigo, faintness, sensitivity to cold, pallor, and loss of skin tone.

• Traditional anemia signs such as pallor have limited sensitivity and specificity and may be misinterpreted.

• In chronic bleeding there is time for equilibration with extravascular space and total blood volume will remain normal.
Some of these physiologic effects, such as effects on respiratory function demonstrated by measurements of maximal oxygen consumption, may serve as end points of clinical benefit of treating anemia.

Manifestations of IDA include glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice).
These symptoms usually do not appear until the Hgb concentration falls below 8 or 9 g/dL.

IDA has negative effects on psychomotor and mental development in infants, children, and adolescents.

Maternal IDA can result in low birth weight infants and preterm delivery.
Patients with vitamin B12 deficiency may be pale and mildly icteric, and they may develop gastric mucosal atrophy.

Neurologic findings in vitamin B12 deficiency which often precede hematologic findings may be partly due to the impairment of the conversion of homocysteine to methionine.

Neurologic findings are found in 75% to 95% of individuals with clinically apparent vitamin B12 deficiency.

The occurrence of neurologic findings is inversely correlated with the degree of anemia.
• The neurologic findings include numbness and paresthesias as the earliest findings, then peripheral neuropathy, ataxia, diminished vibratory sense, increased deep tendon reflexes, decreased proprioception, imbalance, and demyelination of the dorsal columns and corticospinal tract develop.

• Psychiatric findings include irritability, personality changes, memory impairment, dementia, depression, and infrequently, psychosis.

• Other reported symptoms include glossitis, muscle weakness, dysphagia, and anorexia.
• Symptoms associated with folate deficiency are similar to those seen in patients with vitamin B12 deficiency with the absence of neurologic symptoms.

• Although the symptoms of anemia will improve with folate replacement and a partial hematologic response will occur the neurologic manifestations of vitamin B12 deficiency will not be reversed with folic acid replacement therapy and consequently may become irreversible if not treated.
• The initial lab evaluation of anemia involves CBC, including RBC indices; a reticulocyte index; examination of a peripheral blood smear; and examination of a stool sample for occult blood.

• The results from the preliminary evaluation determine the need for other studies.

• Anemia is present in males if the Hct is less than 41% or the Hgb is less than 13 g/dL, while females have a Hct less than 36% or a Hgb less than 12 g/dL.
<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range (y)</th>
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<tbody>
<tr>
<td></td>
<td>2-6</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.5-15.5</td>
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<tr>
<td></td>
<td>F 12.0-16.0</td>
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<tr>
<td>Hematocrit (%)</td>
<td>34-40</td>
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<td></td>
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<tr>
<td>MCV (fL)</td>
<td>75-87</td>
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<tr>
<td>MCHC (%)</td>
<td>—</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>24-30</td>
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<tr>
<td>RBC (million/mm³)</td>
<td>3.9-5.3</td>
</tr>
<tr>
<td>Reticulocyte count, absolute (%)</td>
<td></td>
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<tr>
<td>Serum iron (mcg/dL)</td>
<td>50-120</td>
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<td></td>
<td></td>
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<tr>
<td>TIBC (mcg/dL)</td>
<td>250-400</td>
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<tr>
<td>RDW (%)</td>
<td>11-16</td>
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<tr>
<td>Ferritin (ng/mL)</td>
<td>7-140</td>
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<td></td>
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<tr>
<td>Folate (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ (pg/mL)</td>
<td>100-900*</td>
</tr>
<tr>
<td>Erythropoietin (mU/mL)</td>
<td></td>
</tr>
</tbody>
</table>

*Varies by assay method.

F, female; M, male; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RDW, red blood cell distribution; TIBC, total iron-binding capacity.
Iron Deficiency Anemia (IDA)

- It is the most common nutritional deficiency in developing and developed countries and it is estimated that over 500 million people worldwide have IDA.
- Prevalence is 1% to 2% in adults.
- It results from prolonged negative iron balance or failure to meet increased physiologic iron need.
- The speed of iron deficiency development depends on an individual's initial iron stores and balance between iron absorption and loss.
• Multiple etiologic factors are usually involved but largely related to dietary factors.
• Other causes of include chronic illnesses, RA, and malabsorptive syndromes.
• Situations that increase the demand for iron are frequent blood donations, endurance sports, menstruation, pregnancy and lactation, infancy, and adolescence.
• In pregnant women guidelines recommend low-dose iron supplements (30 mg/day) to be initiated at the woman’s first prenatal visit for the primary prevention of IDA.
• Cause of IDA must be considered a consequence of blood loss until proven otherwise.
• More than 50% of adults with IDA have some form of gastrointestinal bleeding.
• Blood loss may occur as a result of many disorders like trauma, hemorrhoids, peptic ulcers, gastritis, gastrointestinal malignancies, diverticular disease, copious menstrual flow, nosebleeds, or postpartum bleeding.
• Diseases contributing to the development of IDA include various malignancies, usually in the GIT and renal disease.
• Medication history, specifically about use of recent or past iron or hematinics, alcohol, corticosteroids, aspirin, and NSAIDs is a vital part of the history.
• Other possible causes of hypochromic, microcytic anemia include ACD, thalassemia, sideroblastic anemia, and heavy metal (mostly lead) poisoning.
Patients with a past medical history significant for IDA should be periodically re-evaluated for iron deficiency.
Pathophysiology

- Iron is vital to the function of all cells and iron containing enzymes such as the mitochondria’s cytochrome system.
- Without iron, cells lose their capacity for electron transport and energy metabolism.
- IDA is associated with abnormal neurotransmitter function and altered immunologic and inflammatory defenses.
- This is because in addition to iron’s role in oxygen transport and delivery, iron is a cofactor for oxidative metabolism, dopamine and DNA synthesis, and free radical function in neutrophils.
Cont’d

• The balance of iron metabolism is designed to conserve iron for reutilization.
• The margin between the amount of iron available for absorption and the body’s iron requirement is narrow for growing infants and female adults which explains why IDA prevalence is highest in these populations.
• Risk of iron deficiency is related to levels of iron loss, iron intake, iron absorption, and physiologic demands.
• Iron deficiency is usually the result of a long period of negative iron balance.
Manifestations of iron deficiency occur in several stages and three stages have been described: prelatent, latent, and IDA.

Prelatent refers to a reduction in iron stores without reduced serum iron levels, and can be assessed with serum ferritin measurement.

In this first stage, iron stores can be depleted without causing anemia.

The stores allow iron to be utilized when there is an increased need for Hgb synthesis.
• Once stores are depleted, there is still adequate iron from the daily RBC turnover for Hgb synthesis.
• Further iron losses would make the patient vulnerable to anemia development.
• Latent iron deficiency occurs when iron stores are depleted, but Hgb is above the lower limit of normal for the population, yet may be reduced for a given patient.
• This can be determined by serial CBC measurements.
Cont’d

• Findings would include reduced transferrin saturation and increased TIBC.
• IDA occurs when the Hgb falls to less than normal values.
• Deficiency progresses to the classic hypochromia and microcytosis of iron-deficient erythropoiesis.
Laboratory Findings

- Abnormal lab findings include low serum iron and ferritin levels and a high TIBC.
- The first apparent sign is the increased RDW, although it is not specific to IDA.
- In the early stages of the RBC size is not changed.
- Low ferritin concentration is the earliest and most sensitive indicator of iron deficiency.
- The Hgb, Hct, and RBC indices usually remain normal.
• The disadvantage of using ferritin to evaluate iron stores is that renal or liver disease, malignancies, infection, or inflammatory processes may elevate the measured values, and these values may not correlate with iron stores in the bone marrow.

• In the later stages Hgb and Hct fall below normal values, and a microcytic hypochromic anemia develops.

• Microcytosis may precede hypochromia as erythropoiesis is programmed to maintain normal Hgb concentration in deference to cell size.
• As a consequence even slightly abnormal Hgb and Hct levels may indicate significant depletion of iron stores and should not be ignored.

• In terms of RBC indices, MCV reduction occurs earlier in iron-deficient hematopoiesis than reduction in Hgb concentration.

• Transferrin saturation (i.e., serum iron level divided by the TIBC) is also useful in assessing IDA.
Low values likely indicate IDA although low serum transferrin saturation values may also be present in inflammatory disorders.

The TIBC usually helps to differentiate the diagnosis in these patients.

- TIBC > 400 mcg/dL suggests IDA
- TIBC < 200 mcg/dL usually represent inflammatory disease.

With continued progression of IDA anisocytosis occurs and poikilocytosis develops as seen on peripheral smear and indicated by increased RDW.
• In rare cases bone marrow examination can be performed to assess bone marrow iron stores.
• Bone marrow examination reveals absent iron stores in IDA.
• Documentation of decreased hemosiderin can confirm the diagnosis of IDA.
• In microcytic anemias due to all other causes iron stores are detectable.
Treatment

• The severity and cause of IDA determines the approach to treatment.
• Treatment is focused on replenishing iron stores.
• Since iron deficiency can be an early sign of other illnesses treatment of the underlying disease may aid in the correction of the iron deficiency.
Cont’d

- Treatment of IDA usually consists of dietary supplementation and administration of therapeutic iron preparations.
- Iron is poorly absorbed from vegetables, grain products, dairy products, and eggs.
- It is best absorbed from meat, fish, and poultry.
- Beverages have also been shown to affect iron absorption.
• It is recommended that meat, orange juice, and other ascorbic acid–rich foods be included in meals.
• Milk and tea should be consumed in moderation between meals.
• Oral administration of iron therapy with soluble Fe2+ iron salts is appropriate.
• Fe2+ sulfate, succinate, lactate, fumarate, glycine sulfate, glutamate, and gluconate are all about equally absorbed.
• The addition of copper, cobalt, molybdenum, or other minerals, as well as hematinsics provides no advantage but adds expense.
The carbonyl iron may be advantageous because of lower risk of death in cases of accidental overdose.

Iron is best absorbed in the reduced Fe$^{2+}$ form with maximal absorption occurring in the duodenum primarily due to the acidic medium of the stomach.

The presence of mucopolysaccharide chelator substances prevent the iron from precipitating and maintains the iron in a soluble form.
• In the alkaline environment of the small intestines iron tends to form insoluble complexes that are unavailable for absorption.

• SR iron preparations do not undergo sufficient dissolution until reaching the small intestines which significantly reduces iron absorption and can attenuate the hematinic effects.
• This is especially true when enteric-coated preparations are used in achlorhydric patients.

• The dose of iron replacement therapy depends on the patient’s ability to tolerate the administered iron.

• Tolerance of iron salts improves with a small initial dose and gradual escalation to the full dose.

• In patients with IDA, it is recommended to start with 200 mg of elemental iron daily in 2 or 3 divided doses to maximize tolerability.
• If patients cannot tolerate this daily dose of elemental iron, smaller amounts of elemental iron such as a single 325-mg tablet of Fe$^{2+}$ sulfate, is usually sufficient to replace iron stores, albeit at a slower rate.

• The percentage of iron absorbed decreases progressively as the dose increases but the absolute amount absorbed increases.

• Iron should be preferably administered at least 1 hour prior to meals, as food interferes with its absorption.
<table>
<thead>
<tr>
<th>Salt</th>
<th>Elemental Iron Percentage</th>
<th>Elemental Iron Provided</th>
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<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>20%</td>
<td>60–65 mg/324–325 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>18 mg iron/5 mL syrup</td>
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<tr>
<td></td>
<td></td>
<td>44 mg iron/5 mL elixir</td>
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<tr>
<td></td>
<td></td>
<td>15 mg iron/0.6 mL drop</td>
</tr>
<tr>
<td>Ferrous sulfate (exsiccated)</td>
<td>30%</td>
<td>65 mg/200 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>60 mg/187 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>50 mg/160 mg tablet</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>12%</td>
<td>36 mg/325 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>27 mg/240 mg tablet</td>
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<tr>
<td>Ferrous fumarate</td>
<td>33%</td>
<td>33 mg/100 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>63–66 mg/200 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>106 mg/324–325 mg tablet</td>
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<tr>
<td></td>
<td></td>
<td>15 mg/0.6 mL drop</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 mg/5 mL suspension</td>
</tr>
<tr>
<td>Polysaccharide iron complex</td>
<td>100%</td>
<td>150 mg capsule</td>
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<tr>
<td></td>
<td></td>
<td>50 mg tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/5 mL elixir</td>
</tr>
<tr>
<td>Carbonyl iron</td>
<td>100%</td>
<td>50 mg caplet</td>
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</tbody>
</table>
• Many patients experience nausea and diarrhea when iron is administered on an empty stomach.
• GIT side effects are usually dose-related and are similar among iron salts when equivalent amounts of elemental iron are administered.
• Administration of smaller amounts of iron with each dose may minimize these adverse effects.
Cont’d

• H2-blockers or proton pump inhibitors that reduce gastric acidity may impair iron absorption.

<table>
<thead>
<tr>
<th>Drugs that Decrease Iron Absorption</th>
<th>Object Drugs Affected by Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-, Mg-, and Ca⁺²-containing antacids</td>
<td>Levodopa ↓ (chelates with iron)</td>
</tr>
<tr>
<td>Tetracycline and doxycycline</td>
<td>Methyldopa ↓ (decreases efficacy of methyldopa)</td>
</tr>
<tr>
<td>H₂ antagonists</td>
<td>Levothyroxine ↓ (decreased efficacy of levothyroxine)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Penicillamine ↓ (chelates with iron)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Fluoroquinolones ↓ (forms ferric ion-quinolone complex)</td>
</tr>
<tr>
<td></td>
<td>Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt)</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate ↓ (decreases absorption)</td>
</tr>
</tbody>
</table>
• Adverse reactions consist of a dark discoloration of feces, constipation or diarrhea, nausea, and vomiting.
• Failure to develop at least some of these symptoms, even mildly, may indicate noncompliance.
• If these side effects become intolerable, the total daily dose may be decreased to 110 to 120 mg of elemental iron or the dose may be taken with meals.
Cont’d

• Administration of iron with meals reduces the amount of iron absorbed by more than one-half.

• Common causes of treatment failure include poor patient compliance, inability to absorb iron, incorrect diagnosis, continued bleeding, or a concurrent condition that blocks full reticulocyte response.

• Even when iron deficiency is present response may be impaired when a coexisting cause for anemia exists.
• Rarely patients may not be able to absorb iron, most often due to previous gastrectomy or celiac disease.

• Malabsorption can be ruled out by the iron test, in which plasma iron levels are determined at half-hour intervals for 2 hours following the administration of 50 mg of elemental iron as liquid Fe2+ sulfate.

• If plasma iron levels increase by more than 50 mcg during this time, absorption is satisfactory.
• Regardless of the form of oral therapy used, treatment must be continued 3 to 6 months after the anemia is resolved to allow for repletion of iron stores and to avoid relapse.
Parenteral Iron Therapy

- When there is iron malabsorption or intolerance to orally administered iron, or when long-term noncompliance is a problem, parenteral iron therapy is indicated.
- Patients with significant blood loss who refuse transfusions and in whom oral iron therapy is not possible may also require parenteral iron therapy.
- It does not lead to a quicker hematologic response than oral iron.
Currently three different parenteral iron preparations available:

1. Iron dextran,
2. Sodium ferric gluconate, and
3. Iron sucrose

They differ in their molecular size, degradation kinetics, bioavailability, and side-effect profiles.
Iron Dextran

- It have been associated with deaths due to anaphylactic reactions.
- Absorption and metabolism varies with the route and amount of drug given.
- Absorption of an IM dose occurs in two phases.
- In the first 72 hours it is absorbed primarily through the lymphatics into the left superior vena cava.
- A smaller amount is absorbed directly through the IM into the blood.
A second slower phase involves uptake of the iron dextran complex by macrophages, with subsequent transport through the lymphatics into the blood.

The macrophages phagocytize the iron dextran complex and cleave the dextran moiety, making free iron available to the body as circulating iron, transferrin-bound iron, or storage iron (ferritin and hemosiderin).
• It can remain within these cells for many months.
• 60% of an IM dose of is absorbed after 3 days and up to 90% is absorbed within 3 weeks.
• The remainder is absorbed slowly over several months or longer.
• When it is given IV its taken up immediately by the reticuloendothelial system.
Cont’d

- Small to intermediate IV doses (50 to 500 mg of elemental iron) can be cleared from the plasma within 3 days of administration.
- Larger IV doses (500 mg of elemental iron) are processed by the reticuloendothelial system at a constant rate of 10 to 20 mg/h.
- Large doses are associated with increased plasma concentrations for as long as 3 weeks.
• Package insert carries a black box warning regarding the risk of anaphylaxis and requires a test dose before administration.

• Methods of IV administration include multiple slow injections of undiluted iron dextran solution or an infusion of a diluted preparation.

• This latter method is often referred to as total dose infusion.
The IM form should be taken via Z-tract injection technique to minimize staining of the skin.

IM dose is limited to 2 mL (100 mg of iron), multiple injections are often required.

Daily IM doses should not exceed 25 mg in patients less than 5 kg, 50 mg in patients less than 10 kg, and 100 mg in all other patients.

Problems with IM administration include patient discomfort, sterile abscesses, tissue necrosis, or atrophy.
• Up to 30% of an administered dose remains physiologically unavailable.
• For these reasons the IV route is the preferred parenteral route of administration.
Adults + Children over 15 kg

• In patients with iron deficiency anemia:

\[
\text{Dose (mL)} = 0.0442 \times (\text{desired Hgb} - \text{observed Hgb}) \times \text{LBW} + (0.26 \times \text{LBW})
\]

\[
\text{LBW males} = 50 \text{ kg} + (2.3 \times \text{inches over 5 ft})
\]

\[
\text{LBW females} = 45.5 \text{ kg} + (2.3 \times \text{inches over 5 ft})
\]
Children 5–15 kg

• In patients with iron deficiency anemia:

\[
\text{Dose (mL)} = 0.0442 \times (\text{desired Hgb} - \text{observed Hgb}) \times W + (0.26 \times W)
\]
Cont’d

- In patients with anemia secondary to blood loss (hemorrhagic diathesis or long-term dialysis):

\[ \times \text{mg of iron} = \text{blood loss (ml)} \times \text{hematocrit (decimal fraction)} \]
The IV dose should not exceed 50 mg of iron per minute (1 mL/min).

All patients considered for an iron dextran injection receive a test dose of 25 mg IM or IV, or a 5- to 10-minute infusion of the diluted solution.

Patients should be observed for more than 1 hour for untoward reactions.

If an anaphylaxis-like reaction were to occur, it generally responds to IV epinephrine, diphenhydramine, and corticosteroids.
• Patients receiving total dose infusions can have the remaining solution infused during the next 2 to 6 hours if the test dose is tolerated.
• Total replacement doses of IV iron dextran have been given as a single dose, diluted in 250 to 1000 mL normal saline or 5% dextrose in water and infused over 4 to 6 hours.
• A test dose is still required.
• The ability to give a total dose infusion is a benefit of iron dextran over the other parenteral iron products.
• It is best utilized when smaller frequent doses of sodium ferric gluconate or iron sucrose are impractical such as with peritoneal dialysis.

• If the patient receives a total dose infusion, there is an increased possibility of adverse reactions such as arthralgias, myalgias, flushing, malaise, and fever.

• Other adverse reactions of iron dextran include staining of the skin, pain at the injection site, allergic reactions, and rarely anaphylaxis.
Cont’d

- Patients most likely to experience adverse effects with a history of allergies, asthma, or inflammatory diseases.
- Patients with pre-existing immune mediated diseases such as active RA or SLE are considered at high risk for adverse reactions because of their hyperreactive immune response capabilities.
Iron Sodium ferric gluconate

- It is a complex of iron bound to one gluconate and four sucrose molecules.
- The MWt is 289,000 to 440,000 daltons and it is available in an aqueous solution.
- There is no direct transfer of iron from the Fe3+ gluconate to the transferrin.
- It is taken up quickly by the reticuloendothelial system and has a half-life of about 1 hour in the bloodstream.
• It is supplied in 5-mg ampules containing 62.5 mg of elemental iron.
• It appears to produce fewer anaphylactic reactions than does iron dextran.
• Test dose of sodium ferric gluconate is not required.
• It is given as 2 mL IV (25 mg elemental iron) in 50 mL normal saline over 60 minutes.
It may be administered undiluted as a slow IV injection (up to 12.5 mg/min).

It is most commonly administered 10 mL IV (125 mg elemental iron) in 100 mL normal saline over 1 hour.

Hemodialysis patients require a minimum total of 1 g of elemental iron over 8 dialysis sessions to replete their stores.

Side effects include cramps, nausea, vomiting, flushing, hypotension, loin pain, intense upper gastric pain, rash, and pruritus.
Iron sucrose

• It is a polynuclear iron (III) hydroxide in sucrose complex with a MWt of about 34,000 to 60,000 daltons, and is available in 5-mL single-dose vials.
• Each vial contains 100 mg (20 mg/mL) of iron sucrose.
• Iron is released directly from the circulating iron sucrose to the transferrin, and is taken up in the reticuloendothelial system and metabolized.
The half-life is approximately 6 hours with a volume of distribution similar to that of iron dextran.

For adults on hemodialysis it is administered as IV dose of 100 mg one to three times per week to a total dose of 1000 mg in 10 doses.

It can be given IV directly into the dialysis line by slow injection (20 mg iron [1 mL] per minute) or infusion without the requirement for a test dose.
• For infusion, it needs to be diluted in normal saline (maximum 100 mL) immediately prior to use and infused over a minimum of 15 minutes.

• Injection should not be administered with oral iron preparations as it will reduce the absorption of oral iron.

• Adverse effects include leg cramps and hypotension.

• It is well tolerated, but with less-than-expected efficacy at maintaining Hgb levels above 11 g/dL and transferrin saturation above 25%.
• 50% of patients experienced serum ferritin levels greater than 1,100 ng/mL, suggesting iron overload.
• The reduced hematologic response and development of high serum ferritin levels may be due to oversaturation of transferrin and the release of free iron.
• Varying doses of iron sucrose may not produce these results.
• Overall, iron sucrose has been shown to be safe and efficacious.
Transfusions

• To manage anemia with blood transfusions is based on the evaluation of risks and benefits.
• This form of therapy requires extreme caution with existing cardiovascular compromise.
• Once Hct decreases to less than 30%, the oxygen-carrying capacity in older patients drops precipitously, predisposing them to ischemia.
• Tachycardia, angina, ischemic patterns on ECG, cerebrovascular insufficiency, postural hypotension, and prerenal azotemia are strong indications that transfusions are necessary to maintain the Hct above 30%.

• An exception to this treatment option relates to the patient who has developed low Hct values over extended time periods.

• These patients often demonstrate cardiac compromise after transfusion despite Hct levels in the 20s.
• Therapy in these patients should consist of iron therapy followed by transfusion only if necessary.
• They suggest 6 to 8 g/dL of Hgb as a threshold for treatment, with no benefit above 10 g/dL.
Evaluation of Therapeutic Outcomes

• Oral therapy would result in a modest reticulocytosis in 5 to 7 days, with an increase in Hgb at a rate of about 2 to 4 g/dL every 3 weeks until Hgb is normalized.
• When Hgb level approaches normal the rate of increase slows progressively.
• Hgb response of less than 2 g over a 3-week period is unacceptable and warrants further evaluation.
• If the patient does not develop reticulocytosis, it is necessary to re-evaluate the diagnosis or iron replacement therapy.
• Iron therapy should continue for a period sufficient for complete restoration of iron stores.
• Serum ferritin concentrations should return to the normal range prior to iron d/c.
• The time interval required to accomplish this goal varies, although at least 3 to 6 months of therapy is usually warranted.
• Patients with bleeding may require iron replacement therapy for only 1 month after correction of the underlying lesion, whereas patients with recurrent negative balances may require long-term treatment.

• This latter group may require as little as 30 to 60 mg of elemental iron daily.

• When large amounts of parenteral iron are administered, either by total dose infusion or by multiple IM or IV doses, the patient’s iron status should be closely monitored.
• Patients receiving regular IV iron should be monitored for clinical or laboratory evidence of iron toxicity or overload.
• Iron overload may be indicated by abnormal LFT, serum ferritin greater than 800 ng/mL or a transferrin saturation greater than 50%.
• Serum ferritin and transferrin saturation should be measured in the first week after doses of 100 to 200 mg, and at 2 weeks after larger IV iron doses.
Cont’d

• Hgb and Hct should be measured weekly, and serum iron and ferritin levels should be measured at least monthly.

• Serum iron values may be obtained reliably 48 hours after IV dosing.
Megaloblastic Anemias

• Macrocytic anemias are divided into megaloblastic and nonmegaloblastic anemias.
• Macrocytosis can happen due to vitamin B12 or folate as well as due to various drugs such as hydroxyurea, zidovudine, cytosine arabinoside, methotrexate, azathioprine, 6-mercaptopurine, or cladribine.
Other causes of macrocytosis include:

1. Shift to immature or stressed RBCs as seen in reticulocytosis, aplastic anemia, and pure RBC aplasia;
2. Primary bone marrow disorder such as myelodysplastic syndromes and large granular lymphocyte leukemia;
3. Lipid abnormalities as seen with liver disease, hypothyroidism, or hyperlipidemia, and lastly;
4. Unknown mechanisms resulting from alcohol abuse and multiple myeloma.
• Alcoholism is a common cause of macrocytosis
• 90% of alcoholics have macrocytosis prior to the appearance of an anemia.
• Even with adequate folate and vitamin B12 levels plus the absence of liver disease, patients may present with an alcohol-induced macrocytosis.
Vitamin B12 Deficiency Anemia

- Adult incidence of 100 per 1 million population and is slightly more common in women.

- The incidence may be underestimated due to the aging population and universal use of gastric acid-suppressing agents, as these agents may inhibit vitamin B12 absorption.

- Older adults have an estimated prevalence reaching 40%.
• The three major causes of vitamin B12 deficiency are inadequate intake, malabsorption syndromes, and inadequate utilization.

• Inadequate dietary consumption of vitamin B12 is rare.

• It usually occurs only in patients who are strict vegans and their breast-fed infants, chronic alcoholics, or elderly patients with a “tea and toast” diet due to financial limitations or poor dentition.
• Decreased absorption of vitamin B12 is seen in patients with pernicious anemia.
• It is caused by the absence of intrinsic factor.
• It is most commonly seen in Europeans of northern descent and African-Americans.
• A deficiency in intrinsic factor limits vitamin B12 absorption, but is rarely diagnosed in patients less than 35 years of age.
• 50% of deficiencies later in life is the inability of vitamin B12 to be cleaved and released from the proteins in food due to inadequate gastric acid production.

• Conditions leading to this phenomenon include subtotal gastrectomy, atrophic gastritis resulting in decreased acid pepsin production, and prolonged use of acid suppression therapy.
• Supplemental cobalamin is well absorbed in these individuals, as it is not protein bound.
• Treatment of *Helicobacter pylori* may improve vitamin B12 status, as it is a cause of chronic gastritis.
• Vitamin B12 deficiency may also result from overgrowth of bacteria in the bowel that utilizes vitamin B12, or from injury or removal of ileal receptor sites where vitamin B12 and the intrinsic factor complex are absorbed.
Cont’d

- Blind loop syndrome, Whipple’s disease, Zollinger-Ellison syndrome, tapeworm infestations, intestinal resections, tropical sprue, surgical resection of the ileus, pancreatic insufficiency, inflammatory bowel disease, advanced liver disease, tuberculosis, and Crohn’s disease may all contribute to the development of vitamin B12 deficiency.
Pathophysiology

• Vitamin B12 is necessary for DNA synthesis, is important in metabolic reactions involving folic acid, and is essential in maintaining the integrity of the neurologic system.

• It is water-soluble vitamin obtained exogenously by ingestion of meat, fish, poultry, dairy products, and fortified cereals.

• Body stores, which are found primarily in the liver, range from 2 to 5 mg.

• The recommended daily allowance is 2.4 mcg in adults and is slightly higher in pregnant or breast-feeding women.
• It takes several years for a vitamin B12 deficiency to develop following vitamin deprivation, due to efficient enterohepatic circulation of the vitamin.

• After the stomach’s acidic environment facilitates the breakdown of vitamin B12 bound to food, the vitamin B12 binds to the intrinsic factor released by the stomach’s parietal cells.
• The secretion of intrinsic factor generally corresponds to the release of hydrochloric acid and serves as a cell-directed carrier protein similar to transferrin for iron.

• This complex forms in the duodenum and allows for subsequent absorption of vitamin B12 in the terminal ileum.

• The cobalamin-intrinsic factor complex is taken up into the ileal mucosal cell, the intrinsic factor is discarded, and the cobalamin is transferred to transcobalamin II, which serves as a transport protein.
• This complex is secreted into the circulation and is taken up by the liver, bone marrow, and other cells.

• Transcobalamin II has a short half-life of 1 hour and is rapidly cleared from the blood.

• Consequently, most circulating cobalamin is bound to serum haptocorrins whose function is unknown.

• It should be noted that an alternate pathway for vitamin B12 absorption independent of intrinsic factor or an intact terminal ileum accounts for a small amount of vitamin B12 absorption.
• This alternate pathway involves passive diffusion and accounts for approximately 1% absorption of the ingested vitamin B12.

• Cobalamin is also a crucial cofactor in the conversion of homocysteine to methionine.

• When this reaction is impaired, folate metabolism is disturbed, resulting in folate-deficient tissues, and consequently, megaloblastic erythropoiesis.
Lab Findings

- Most patients have elevated MCV to 110 to 140 fL.
- Mild leukopenia and thrombocytopenia are often present.
- Advanced cases of vitamin B12 deficiency may result in pancytopenia.
- Blood smear demonstrates macrocytosis accompanied by hypersegmented polymorphonuclear leukocytes, oval macrocytes, anisocytosis, and poikilocytosis.
Cont’d

- LDH and indirect bilirubin levels may be elevated.
- Serum iron concentrations and transferrin saturation are usually elevated
- Low reticulocyte count, low serum vitamin B12 level (<100 pg/mL), and low Hct (sometimes as low as 10% to 15%).
- If a bone marrow biopsy reflect erythroid hyperplasia and megaloblastic changes in the cells of erythroid lineage.
• Measurement of MMA and homocysteine is useful as these parameters are often the first to change.

• Elevations in MMA are more specific for vitamin B12 deficiency.

• Elevated homocysteine can be indicative of either vitamin B12 or folic acid deficiency, but offers greater specificity for folate plasma levels.
• Vitamin B12 values of 200 to 300 pg/mL are suggestive of depletion, and the patient should undergo repeated testing in 1 to 3 months.

• A Schilling test may be performed to diagnose pernicious anemia,

• Antibody testing and serum gastrin levels also usefull.
The goals of treatment for vitamin B12 deficiency include:
1. Reversal of hematologic manifestations,
2. Replacement of body stores,
3. Prevention or reversal of neurologic manifestations.
• Early treatment to reverse any neurologic symptoms present as they may be irreversible if the deficiency is not detected for 6 to 12 months.

• Permanent disabilities may range from mild paresthesias and numbness to memory loss and outright psychosis.

• Any underlying etiology that is treatable, such as bacterial overgrowth, should be remedied.
• In rare cases the oral or parenteral administration of vitamin B12 is beneficial.
• Patients should also be counseled on the types of foods high in vitamin B12 content.
• Oral doses may be initiated at 1 to 2 mg daily for 1 to 2 weeks, followed by 1-mg daily, since doses less than 0.5 mg may result in variable absorption.
• The 1-mg cobalamin tablets are available as OTC.
• Contraindications to oral therapy include inability to take medications orally, diarrhea, or vomiting.

• Parenteral vitamin B12 regimen consists of daily injections of 1,000 mcg of cyanocobalamin for 1 week to saturate vitamin B12 stores in the body and to resolve clinical manifestations of the deficiency.

• Then it can be given weekly for 1 month and monthly thereafter for maintenance.
• Parenteral therapy is preferred for patients exhibiting neurologic symptoms until resolution of symptoms and hematologic indices, since the most rapid-acting therapy is necessary.

• If converting patients from the parenteral to the oral form of cobalamin, 1 mg of oral cobalamin daily can be initiated on the due date of the next injection.
• Vitamin B12 is available in an intranasal gel formulation.
• This is advantageous for patients who are homebound, have cognitive impairment, or are experiencing dysphagia.
• Intranasal administration should be avoided in patients with nasal diseases or those receiving medications intranasally in the same nostril.
Patients should avoid administering the gel 1 hour before or after the ingestion of hot foods or beverages, as cobalamin absorption may be impaired.

It should only be used for maintenance therapy once hematologic parameters have normalized.

Side effects include hyperuricemia and hypokalemia.

Rebound thrombocytosis may precipitate thrombotic events.
• Another side effect of vitamin B12 therapy is sodium retention in patients with compromised cardiovascular status.
• Rare cases of anaphylaxis with parenteral administration of cobalamin have been reported.
Evaluation of Therapeutic Outcomes

• Most patients respond rapidly to vitamin B12 therapy.
• If glossitis is present improvement is seen within 24 hours.
• Bone marrow becomes normoblastic after 24 hours, but is not evident in the plasma for another 7 days.
• Reticulocytosis is evident in 2 to 5 days and peaks around day 7.
• Hgb begins to rise after the first week and the leukocyte and platelet counts normalize after about 7 days.
• Hypersegmented neutrophils persist for about 2 weeks.
• CBC and a serum cobalamin level is usually drawn 1 to 2 months after the initiation of therapy and 3 to 6 months thereafter for surveillance monitoring.
• Homocysteine and MMA levels should be repeated 2 to 3 months after the initiation of replacement therapy to evaluate for normalization of levels, although levels begin to decrease in 1 to 2 weeks.
• Failure in these findings usually indicates an incorrect diagnosis or other factors contributing to the anemia such as iron deficiency or thalassemia trait.

• If permanent neurologic damage has resulted, progression should cease with replacement therapy.

• Demands for iron may be greater during the initiation of therapy as a result of increased erythropoiesis.
Folic Acid Deficiency Anemia

• Folic acid deficiency is one of the most common vitamin deficiencies in the US largely due to its association with excessive alcohol intake and pregnancy.

• Requirements for folate in pregnancy are about five times higher than normal daily requirements.

• Major causes of folic acid deficiency include inadequate intake, decreased absorption, hyperutilization, and inadequate utilization.
• It is associated with poor eating habits, it is common in elderly patients, alcoholics, food faddists, the poverty stricken, and those who are chronically ill or in demented states.

• Absorption may decrease in patients who have malabsorption syndromes or those who have received certain drugs.

• Alcohol also interferes with folic acid absorption.
• Hyperutilization of folic acid may occur when the rate of cellular division is increased as is seen during pregnancy; hemolytic anemia; myelofibrosis; malignancy; chronic inflammatory disorders such as Crohn’s disease, rheumatoid arthritis, or psoriasis; long-term dialysis; burn patients; and growth spurts seen in adolescence and infancy.
• This can lead to anemia, particularly when the daily intake of folate is borderline, resulting in inadequate replacement of folate stores.

• Drugs (e.g., sulfasalazine, TMX, and methotrexate) have been reported to cause a folic acid deficiency megaloblastic anemia.

• These drugs either interfere with folate absorption or inhibit the dihydrofolate reductase enzyme necessary for conversion of dihydrofolate to its active tetrahydrofolate form.
• Phenytoin may induce a megaloblastic anemia.

• The progression to overt megaloblastic anemia occurs in less than 1% of patients.

• Since folic acid doses as low as 1 mg/day may affect serum phenytoin levels, routine supplementation is not generally advised.
• This decline in phenytoin concentration is usually evidenced within the first 10 days and may diminish the phenytoin levels by 15% to 50%.
Pathophysiology

- Folic acid is a water-soluble vitamin readily destroyed by cooking or processing.
- It is necessary for the production of nucleic acids, proteins, amino acids, purines, and thymine, and hence DNA and RNA.
- It acts as a methyl donor to form methylcobalamin, which is used in the remethylation of homocysteine to methionine.
- Because humans are unable to synthesize total daily folate requirements, they depend on a dietary source of this vitamin.
• Major dietary sources of folate include fresh, green, leafy vegetables, citrus fruits, yeast, mushrooms, dairy products, and such animal organs as liver and kidney.

• Once absorbed, dietary folate must be converted to tetrahydrofolate through a cobalamin-dependent reaction in order to achieve its active state.

• Even though body demands for folate are high, owing to high rates of RBC synthesis and turnover, the minimum daily requirement is 50 to 100 mcg.
• Recommended daily allowance for folate is 400 mcg in nonpregnant females, 600 mcg for pregnant females, and 500 mcg for lactating females.

• Folate is distributed to the other tissues primarily via enterohepatic recirculation.

• The methylated form of folate is reabsorbed from the bile into the serum.

• As it enters the tissues it endures for the remaining life span of the cell.
Lab Findings

• Lab changes are similar to those seen in vitamin B12 deficiency except vitamin B12 levels are normal.
• Decreases in serum folate level (<3 ng/mL) within a few days of dietary folate limitations.
• The RBC folate level (<150 ng/mL).
• Serum folate levels are sensitive to short-term changes such as dietary restrictions or alcohol intake which may result in a short-term decline in serum levels with adequate tissue stores.
Cont’d

• 60% of patients with pernicious anemia have falsely low RBC folate levels.
• If serum or erythrocyte folate levels are borderline serum homocysteine is usually increased with a folic acid deficiency.
• If serum MMA levels are also elevated, vitamin B12 deficiency needs to be ruled out.
Treatment

• Therapy consists of the administration of exogenous folic acid to induce hematologic remission, replace body stores, and resolve signs and symptoms.
• In the majority of cases, 1 mg daily is sufficient to replace stores except in cases of deficiency due to malabsorption, in which case doses up to 5mg daily may be necessary.
• Synthetic folic acid is almost completely absorbed by the gastrointestinal tract and is converted to tetrahydrofolate without cobalamin.
• Therapy should continue for 4 months if the underlying cause of the deficiency can be identified and corrected.

• This treatment period allows a sufficient amount of time for all folate-deficient RBCs to be cleared from the circulation.

• Long-term folate administration may be necessary in chronic conditions associated with increased folate requirements as listed previously.

• It is also recommended that patients with a folic acid deficiency be placed on diets containing foods high in folate.
• Low-dose folate therapy (500 mcg daily) may be administered when anticonvulsant drugs produce a megaloblastic anemia and may make it unnecessary to discontinue the anticonvulsant.

• Adverse effects have not been rare.

• Although megaloblastic anemia during pregnancy is rare, the most common cause is folate deficiency.

• The condition usually manifests itself as an underweight, premature infant and suboptimal health for the mother.
• Folic acid supplementation (800 to 1,000 mcg daily) prior to conception and during pregnancy reduces the incidence of neural tube defects in the general population.

• Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg of folic acid daily.

• It has been suggested that supplementation with 10 mg of folic acid daily may reduce the incidence of cleft lip.
• It is clearly essential that women in their childbearing years maintain adequate folic acid intake.
Evaluation of Therapeutic Outcomes

- Symptomatic improvement evidenced by increased alertness, appetite, and cooperation, often takes place early during the course of treatment.

- Reticulocytosis occurs within 2 to 3 days and peaks within 5 to 8 days after beginning therapy.

- Hct begins to rise within 2 weeks and should reach normal levels within 2 months.
The MCV initially increases because of an increase in reticulocytes, but then gradually decreases to normal.