RBC disorders 2
Anemia of diminished production

Ahmad T. Mansour, MD
• Iron deficiency anemia
• Anemia of chronic disease
• Megaloblastic anemia
• Others
  • anemia in liver disease
  • anemia in renal disease
  • aplastic anemia
  • myelophthisic anemia
1. All of the following can be found in iron deficiency anemia, except:
   A. Low ferritin
   B. Low serum iron
   C. Low TIBC
   D. Low transferrin saturation
   E. Low MCV
2. Anemia of chronic disease is caused by elevated levels of:
   A. Hepcidin
   B. Iron
   C. Ferritin
   D. B12
   E. neutrophils
3. All of the following are true regarding megaloblastic anemia, except:

   A. defective DNA synthesis, resulting in nuclear immaturity

   B. macrocytic anemia

   C. can be seen in the setting of pernicious anemia

   D. most common cause is nutritional deficiency of B12

   E. can be associated with neurological symptoms in the case of B12 deficiency.
4. The most common cause of anemia in patients with liver disease is:

A. Iron deficiency
B. Hypersplenism
C. Therapy related hemolytic anemia
D. Therapy related suppression of EPO receptor
E. Alcoholic-cirrhosis-induced folate deficiency
5. One of the following can cause myelophthysisic anemia:
   A. Tuberculosis
   B. B12 deficiency
   C. Folate deficiency
   D. Iron deficiency
   E. Anemia of chronic disease.
Iron: Distribution

- **Heme enzyme (<1%)**
- **Myoglobin (6%)**
- **Iron-sulfur clusters (<1%)**
- **Transport and storage forms (26%)**
  - hemoglobin (2.5 g)
  - myoglobin (0.15 g)
- **Heme proteins (~72%)**
- **Transport and storage proteins (~26%)**
  - transferrin (1.0 g)
  - serum ferritin (0.0001 g)
- **Iron–sulfur clusters (<1%)**
  - cofactors in the respiratory chain, other redox chains

- human body: 4–5 g iron (protein-bound)
• Transferrin is the major transport protein in plasma and is normally one third occupied.

• Plasma ferritin is derived largely from the storage pool of body iron; its levels correlate well with body iron stores, if total iron is decreased ferritin will be low, and vice versa.
• Iron balance is maintained through absorption, excretion is limited to 1-2mg/day through shedding of mucosal cells.
Iron deficiency anemia

- Deficiency of iron is the most common nutritional disorder in the world and results in clinical signs and symptoms that are mostly related to inadequate hemoglobin synthesis.
Iron deficiency can result from

- (1) dietary
- (2) impaired absorption,
- (3) increased requirement,
- (4) chronic blood loss.
Question time!!!

Which clinical scenario is more serious

- A 19 year old lady, with severe menorrhagia presenting with shortness of breath on exertion, fatigue, pallor and a hemoglobin of 7.6g/dl, low MCV
- A 79 year old asymptomatic gentleman who, on routine check up, was found to have a hemoglobin of 11g/dl and low MCV
Think of anemia as you think of fever!!!
pathogenesis

- Negative iron balance due to any reason
- Compensation by storage iron
- Progressive deficiency until complete depletion
- Anemia develops accompanied by low ferritin and low transferrin saturation
morphology
Clinical presentation

Symptoms and signs of anemia
Lab findings

- Low hemoglobin and hematocrit
- Low MCV
- Low MCH
- Low iron levels
- Low ferritin
- **High TIBC**
- **High RDW**
- Low hepcidin
- Low transferrin saturation
• Treat by iron supplementation and treating the underlying cause.
Anemia of chronic disease

- Anemia of chronic disease is impaired red cell production associated with **chronic diseases that produce systemic inflammation**

- The most common cause of **anemia among hospitalized** patients

- Examples include chronic microbial inflammation, autoimmune inflammation, and malignancy.
IL6 results in increased hepcidin
• Starves the EP cells of iron.

• Inhibits erythropoietin and subsequently decreases EP proliferation

• Possible immunologic role for hepcidin
Clinical presentation

- Mild anemia
- Signs and symptoms of underlying disease
Lab findings

- Low HB and Hct
- Can be hypochromic microcytic or normochromic normocytic.
- High ferritin and low TIBC (exactly opposite to iron deficiency anemia)
Megaloblastic anemia

Vitamin B12 or folate deficiency
Biochemical role of B12

Homocysteine → Methionine

MTHF → THF → Methylmalonyl CoA → Succinyl CoA

DNA synthesis → MMA

Lipid and carbohydrate synthesis
## Vitamin B<sub>12</sub> Deficiency

<table>
<thead>
<tr>
<th>Decreased Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate diet, vegetarianism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impaired Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic factor deficiency</td>
</tr>
<tr>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Gastrectomy</td>
</tr>
<tr>
<td>Malabsorption states</td>
</tr>
<tr>
<td>Diffuse intestinal disease (e.g., lymphoma, systemic sclerosis)</td>
</tr>
<tr>
<td>Ileal resection, ileitis</td>
</tr>
<tr>
<td>Competitive parasitic uptake</td>
</tr>
<tr>
<td>Fish tapeworm infestation</td>
</tr>
<tr>
<td>Bacterial overgrowth in blind loops and diverticula of bowel</td>
</tr>
</tbody>
</table>
Pernicious anemia

Autoimmune attack on gastric mucosa.

three types of antibodies

1-parietal canalicular antibodies

2-blocking antibodies

3-intrinsic factor–B12 complex

antibodies
Clinical manifestations

- Related to anemia similar to those found in folate deficiency
- Additionally, leukopenia with hypersegmented neutrophils can be seen
- Neurological symptoms:
  - Numbness
  - Unsteady gate
  - Loss of position sense
- Increase risk of malignancy in patient with pernicious anemia
Folate

FH₄ derivatives
(one-carbon donor pool)

One-carbon fragments used in synthesis of
Purines, methionine
dTMP

FH₄
(one-carbon acceptor)

One-carbon fragments derived from serine, FIGlu
<table>
<thead>
<tr>
<th>Folic Acid Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased Intake</strong></td>
</tr>
<tr>
<td>Inadequate diet, alcoholism, infancy</td>
</tr>
<tr>
<td>Impaired Absorption</td>
</tr>
<tr>
<td>Malabsorption states</td>
</tr>
<tr>
<td>Intrinsic intestinal disease</td>
</tr>
<tr>
<td>Anticonvulsants, oral contraceptives</td>
</tr>
<tr>
<td>Increased Loss</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td><strong>Increased Requirement</strong></td>
</tr>
<tr>
<td>Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis</td>
</tr>
<tr>
<td><strong>Impaired Utilization</strong></td>
</tr>
<tr>
<td>Folic acid antagonists</td>
</tr>
<tr>
<td><strong>Unresponsive to Vitamin B₁₂ or Folic Acid Therapy</strong></td>
</tr>
<tr>
<td>Metabolic Inhibitors of DNA Synthesis and/or Folate Metabolism (e.g., Methotrexate)</td>
</tr>
</tbody>
</table>
Clinical manifestations

- Nonspecific symptoms of anemia, weakness, fatigue…etc
- GI symptoms due to the effect on GI epithelial lining cells.
- NO neurological symptoms
- Diagnose by serum and RBC folate levels.
Anemia in liver disease

- Multiple etiologies:
  - Iron deficiency is the most common
  - Hypersplenism
  - Therapy related hemolytic anemia and suppression of EPO receptor
  - Alcoholic-cirrhosis-induced folate deficiency
Spur cells
Anemia of renal disease

- Related to decrease EPO production by the damaged kidney.
- High levels of inflammatory cytokines
- Hemolysis
- Chronic bleeding
- Folate deficiency in patients on dialysis.
ecchinocytes
Aplastic anemia refers to a syndrome of chronic primary hematopoietic failure and attendant pancytopenia (anemia, neutropenia, and thrombocytopenia)
<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Acquired stem cell defects</td>
</tr>
<tr>
<td></td>
<td>Immune mediated</td>
</tr>
<tr>
<td>Chemical Agents</td>
<td>Dose related</td>
</tr>
<tr>
<td></td>
<td>Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>Antimetabolites</td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Inorganic arsenicals</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td></td>
<td>Organic arsenicals</td>
</tr>
<tr>
<td></td>
<td>Methylphenylethylhydantoin</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Penicillamine</td>
</tr>
<tr>
<td></td>
<td>Gold salts</td>
</tr>
<tr>
<td>Physical Agents</td>
<td>Whole-body irradiation</td>
</tr>
<tr>
<td></td>
<td>Viral Infections</td>
</tr>
<tr>
<td></td>
<td>Hepatitis (unknown virus)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus infections</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus infections</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster (varicella zoster)</td>
</tr>
<tr>
<td>Inherited</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td></td>
<td>Telomerase defects</td>
</tr>
</tbody>
</table>
Pathogenesis of aplastic anemia

- Environmental insult (viruses, drugs, etc.)
- Genetically altered stem cells
  - Express new antigens
  - Reduced proliferative and differentiative capacity
- T-cell response
  - IFNγ
  - TNF
- Marrow aplasia
Morphology
Clinical features

• Any age with no gender predilection
• Stigmata of pancytopenia
• Normocytic and occasionally macrocytic anemia.
• No splenomegaly
• No increased reticulocyte count
• Bone marrow exam is a must for diagnosis
• Respond well to immunosuppressive therapy, BM transplantation is the treatment of choice with 5 year survival of more than 75%.
Myelophthisic anemia

Extensive infiltration of the marrow by tumors or other lesions.

• Metastatic cancer (lung, breast, prostate)
• Tuberculosis
• Lipid storage disorders
• Osteosclerosi

• Leukoerythroblastic reaction on peripheral blood.
1-tear drop RBC
2-immature erythroid precursor cell
3-immature myeloid cell
• Patients present with anemia and thrombocytopenia
• WBC are usually less affected.

• Treatment is directed at the underlying etiology.
1. All of the following can be found in iron deficiency anemia, except:

A. Low ferritin
B. Low serum iron
C. Low TIBC
D. Low transferrin saturation
E. Low MCV
2. Anemia of chronic disease is caused by elevated levels of:
   A. Hepcidin
   B. Iron
   C. Ferritin
   D. B12
   E. Neutrophils
3. All of the following are true regarding megaloblastic anemia, except:

   A. defective DNA synthesis, resulting in nuclear immaturity

   B. macrocytic anemia

   C. can be seen in the setting of pernicious anemia

   D. most common cause is nutritional deficiency of B12

   E. can be associated with neurological symptoms in the case of B12 deficiency.
4. The most common cause of anemia in patients with liver disease is:

A. Iron deficiency
B. Hypersplenism
C. Therapy related hemolytic anemia
D. Therapy related suppression of EPO receptor
E. Alcoholic-cirrhosis-induced folate deficiency
5. One of the following can cause myelophthisic anemia:

A. Tuberculosis
B. B12 deficiency
C. Folate deficiency
D. Iron deficiency
E. Anemia of chronic disease.
THANK YOU