Anemia

Greek – Anaimia
from: an + haima
No Blood

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Conflict of Interest

I have nothing to disclose
Learning Objectives

- Discuss the causes for Anemia.
- Discuss optimal therapies for Anemia.
- Discuss failure of therapy in Anemia and its management.
## Normal values for red blood cell parameters in men and women

<table>
<thead>
<tr>
<th>Red cell parameter</th>
<th>Adult men</th>
<th>Adult women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>15.7 ± 1.7</td>
<td>13.8 ± 1.5</td>
</tr>
<tr>
<td>Hematocrit, percent</td>
<td>46.0 ± 4.0</td>
<td>40.0 ± 4.0</td>
</tr>
<tr>
<td>RBC count, million/microL</td>
<td>5.2 ± 0.7</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>Reticulocytes, percent</td>
<td>1.6 ± 0.5</td>
<td>1.4 ± 0.5</td>
</tr>
<tr>
<td>Mean corpuscular volume, fl</td>
<td></td>
<td>88.0 ± 8.0</td>
</tr>
<tr>
<td>Mean cell hemoglobin, pg/RBC</td>
<td></td>
<td>30.4 ± 2.8</td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration, g/dL of RBC</td>
<td></td>
<td>34.4 ± 1.1</td>
</tr>
<tr>
<td>Red cell volume distribution width, percent (RDW)</td>
<td></td>
<td>13.1 ± 1.4</td>
</tr>
</tbody>
</table>

Values are mean ± 2 standard deviations.

RBC: red blood cell.

High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

*Courtesy of Carola von Kapff, SH (ASCP).*
Anemia

- Decrease in concentration of red cells or hemoglobin

- Therefore, O$_2$ carrying capacity decreasing
Signs and Symptoms 1

- Symptoms affected by speed of onset
- Asymptomatic in mild cases
- Fatigue, dyspnea especially after exercise
- Angina, TIA unmasked by anemia
- Hgb < 7.5 g% results in increased cardiac output leading to palpitations and cardiac failure in pts with poor cardiac reserve
Signs and Symptoms 2

- Dizziness and headache
- Difficulty in concentrating
- Feeling cold because of decreased blood flow to the skin
- Restless Leg Syndrome
- Abnormal menstruation
Physical Examination

- Pallor – conjunctival or palmar
- Tachycardia
- Hyperdynamic precordium
- Systolic murmur
- Venous hum over neck vessels
- Icterus
- Splenomegaly
- Leg ulcers
Turns out she's anaemic.
Approach to patient with anemia 1

- Family history eg SCD, Thalassemia, Spherocytosis
- Physical Examination
Approach to patient with anemia 2

The Big Question:

1. Do we have decreased production of RBC?
   or
2. Enhanced destruction of RBC?
   or
3. Blood loss?
Approach to patient with anemia 3

- CHECK STOOL FOR OCCULT BLOOD LOSS
- CBC
- MCV – incredibly important and useful
- Will help distinguish between Microcytic, Macrocytic and Normocytic Anemias
CRUEL RESIDENT STORIES
SETTING: 3AM ON A CALL NIGHT DURING INTERNSHIP

JESSICA, CAN I PRESENT MY PATIENT TO YOU?
FINE.

MR. SMITH IS A 56 YEAR OLD MAN WITH A HISTORY OF CEREBRAL PALSY AND SEVERE MENTAL RETARDATION, KIDNEY FAILURE, HEART FAILURE, CHRONIC ANEMIA WHO PRESENTS WITH PNEUMONIA AND SEPSIS.

IS THE ANEMIA MACROCYTIC OR MICROCYTIC?
UM... I'M NOT SURE...

HOW COULD YOU PRESENT A PATIENT TO ME WITHOUT KNOWING IF HIS CHRONIC ANEMIA IS MACROCYTIC OR MICROCYTIC??!
GET OUT AND COME BACK WHEN YOU HAVE MORE INFORMATION!

BUT, HE'S SEPTIC AND UNCONSCIOUS...
## Differential diagnosis of anemia in the adult

### Low mean corpuscular volume (microcytic anemia: MCV < 80 fl)
- Iron deficiency anemia
- Thalassemic disorders
- Anemia of inflammation/anemia of chronic disease (late; uncommon)
- Sideroblastic anemia (eg, congenital, lead, alcohol, drugs; uncommon)
- Copper deficiency, zinc poisoning (rare)

### Normal mean corpuscular volume (normocytic anemia: MCV 80 to 100 fl)
- Acute blood loss
- Iron deficiency anemia (early)
- Anemia of inflammation/anemia of chronic disease (eg, infection, inflammation, malignancy)
- Bone marrow suppression (may also be macrocytic)
- Bone marrow invasion (eg, leuкоerythroblastic blood picture)
- Acquired pure red blood cell aplasia
- Aplastic anemia
- Chronic renal insufficiency
- Endocrine dysfunction
  - Hypothyroidism (most commonly normocytic)
  - Hypopituitarism

### Increased mean corpuscular volume (macrocytic anemia: MCV > 100 fl)
- Ethanol abuse
- Folate deficiency
- Vitamin B12 deficiency
- Myelodysplastic syndromes
- Acute myeloid leukemias (eg, erythroleukemia)
- Reticulocytosis
  - Hemolytic anemia
  - Response to blood loss
  - Response to appropriate hematocrit (eg, iron, B12, folic acid)
- Drug-induced anemia (eg, Hydroxyurea, AZT, chemotherapeutic agents)
- Liver disease
- Hypothyroidism (less commonly macrocytic)
Microcytic Anemias

- Iron deficiency
- Thalassemia
- Sideroblastic anemia
Macrocytic Anemia

- Megablastic anemias - deficiencies of Vit B12 and/or Folate
- Liver disease particularly alcohol use
- Hypothyroidism
- Aplastic anemia
- Myelodysplastic syndromes
- HEMOLYTIC ANEMIAS - ?? Reticulocyte count
Normocytic Anemia 1

A. Secondary to other underlying diseases

- Anemia of chronic disease
  - Infection
  - Autoimmune diseases (RA)
  - Malignancy
- Anemia of Uremia (CKD)
- Anemia of Liver Disease
- Anemia of Endocrinopathy
Normocytic Anemia 2

B. Intrinsic bone marrow pathology

- Myelodysplastic syndromes
- Myeloid metaplasia
- Myelophthisisic anemia
- Aplastic anemia

Usually bone marrow biopsy required for diagnosis, particularly when more than one cell line is abnormal.
Teardrop-shaped red blood cells (dacrocyes)

This peripheral smear from a patient with bone marrow fibrosis shows numerous teardrop-shaped red cells (arrows). Note that the teardrops are pointed in several different directions, ruling out an artifact due to preparation of the smear.

Courtesy of Carola von Kapff, SH (ASCP).
Hemolytic Anemias

- Immunohemolytic anemias
  - Coomb’s test
- Microangiopathic hemolytic anemia
  - DIC
  - TTP/HUS
- Sickle Cell & Thalassemia syndromes
- Membrane pathology eg Spherocytosis
- Enzyme pathology eg G6PD deficiency
Iron Deficiency Anemia 1

Adult male and non-menstruating female WITH LOW MCV
“Yesterday we ran a CBC, a BUN, a liver profile, a CPK, an SGOT, an SGPT, all electrolytes, a glucose, a bunch more serum chemistries, a clotting time, cholesterol, and everything was normal. Today we ran another CBC and he’s anemic.”
Iron Deficiency Anemia 2

??? IRON STATUS ???
Iron Deficiency Anemia 3

- Iron saturation – beware of low TIBC
- Ferritin
- Iron stains on bone marrow aspirate
Iron Deficiency Anemia 4

- Pica
- Ice – pagophagia
- Starch – amylophagia
- Clay – geophagia
Iron Deficiency Anemia 5

If iron deficiency found, endoscopic examination is

OBLIGATORY!!!
Iron Deficiency Anemia 6

- Malignancy – colon or gastric
- Menorrhagia
- BARIATRIC SURGERY
- Peptic Ulcer Disease
- Celiac Disease
- Angiodysplasia
- Blood donation
- Vegans
Your iron is low, you need to eat your spinach.

But I don't like spinach!
Iron Deficiency Anemia 7

- Increased Fe utilization eg pregnancy and rapid growth
- Hemodialysis
- Hematuria
- Chronic hemoglobinuria – mechanical heart valves and PNH
Peripheral smear at two different magnifications from a patient with iron deficiency shows small (microcytic) red cells with a thin rim of pink hemoglobin (hypochromic); occasional "pencil" shaped cells are also present. Normal red cells are similar in size to the nucleus of a small lymphocyte (arrow) and central pallor should equal about one-third of its diameter; thus, many hypochromic and microcytic cells are present in this smear.
Peripheral smear shows multiple target cells which have an area of central density surrounded by a halo of pallor (arrows). These cells are characteristic of liver disease and certain hemoglobinopathies (most notably hemoglobin C disease).

*Courtesy of Carola von Kapff, SH (ASCP).*
Treatment of Iron Deficiency

- **Oral iron**
  - Fe sulfate vs gluconate
  - Problems with P.O. Iron
  - Side effects and absorption

- **Parenteral iron**
  - Indications
  - Administration
"Doctor told me to take plenty of iron."
"The red are for the illness, the blue are for the side effects of the red and the green are for the effects of the blue."
Megaloblastic Anemia 1

- Macrocytosis
- Anemia - $\uparrow$ MCV or $\downarrow$ MCV if also iron deficient
- Neuropsychiatric symptoms
  - Peripheral Neuropathy
  - Spinal cord degeneration
  - Memory loss
Megaloblastic Anemia 2

- Infertility and fetal loss
- Glossitis
- Methylmalonic acid & hemocysteine
- Hypersegmented neutrophils (5-6 lobes)
- Anti-Intrinsic Factor Antibodies
- Achlorhydria – EGD?
Hypersegmented neutrophil in megaloblastic anemia

Blood smear from a patient with megaloblastic anemia showing a neutrophil with an increased number of nuclear lobes. At least six discrete lobes are present; normal neutrophils have five lobes or fewer.

Courtesy of Stephen A. Landaw, MD, PhD.
Megaloblastic Anemia 3

- Gastric atrophy/Achlorhydria (Pernicious anemia classic picture)
- Bariatric surgery
- Gastrectomy
- Ileal resection
- Crohn’s Disease
Megaloblastic Anemia 4

- Bacterial overgrowth
- Zollinger-Ellison Syndrome \( \downarrow \) pH
- Pancreatic insufficiency
- Megadoses Vit C & PPI
- Pregnancy
- Nitrous Oxide
- Vegans
Macroovalocytes in vitamin B12 deficiency

Peripheral smear shows marked macroovalocytosis in a patient with vitamin B12 deficiency. In this case teardrop cells are an advanced form of macroovalocytes.

Courtesy of Stanley L Schrier, MD.
Treatment of Vit B12 deficiency

- IM shots daily → weekly → monthly (neuro symptoms)
- P.O. vs sublingual
- Treat with B12 before folate to avoid masking B12 deficiency by folate (folate will not treat neuro symptoms)
Folic Acid Deficiency

Serum level vs RBC level

- Macrocytosis
- Anemia
  - $\uparrow$ MCV or normal
  - $\downarrow$ if Fe deficient
- Similar neuropsychiatric symptoms to B12 deficiency
- Infertility and fetal loss
Causes of Folic Acid Deficiency 1
- Lack of fresh vegetables (Dr. Victor Herbert)
- Ethanol
- Celiac Disease
- Small bowel resections
- Crohn’s Disease
- Cytotoxic chemotherapy eg MTX
Macrocytic: Non-Megaloblastic

Example:
Alcoholism and bone marrow damage

I love alcohol!

*le martini*
Causes of Folic Acid Deficiency 2

- Antibiotics – Trimethoprim
- Diuretic – Triamterene
- Anticonvulsant – Phenytoin, Carbamazepine
- Increased Utilization
  - Pregnancy
  - Chronic hemolysis (SCD)
  - Hemodialysis
Treatment

Daily Folate – 1 mg
Hemolytic Anemias 1

- History (especially family history)
- Fatigue
- Jaundice
- Abdominal pain, gallstones (chronic hemolysis)
- Meds
- Travel (infection)
Hemolytic Anemias 2

- Vascular/Cardiac surgery
- Discolored urine
- FH – Jaundice/ gallbladder disease/ splenectomy/ hereditary anemia
Hemolytic Anemias – Physical Exam

- Pallor
- Tachycardia
- Jaundice
- Mechanical heart valve click
- Splenomegaly
Hemolytic Anemias – Intrinsic Causes

- Abnormal hemoglobin
  - SCD
  - Thalassemia
  - Unstable hemoglobin

- Abnormal membranes
  - Spherocytosis
  - Elliptocytosis
  - Hemolytic uremic syndrome
  - PNH

- Abnormal enzymes
  - G6PD deficiency
  - Pyruvate kinase
Hemolytic Anemias – Extrinsic Causes 1

- Immune
  - Autoimmune syndromes
  - Transfusion induced alloantibodies
Hemolytic Anemias – Extrinsic Causes 2

- Fragmentation/Physical Damage

- Heart valves
- DIC
- TTP
- HUS
- Hemodialysis
- Malignancy
- Burns
- Marathon/march hemoglobinuria
- Vasculitis
- Malignant HTN
- AV malformation

Presenter: Y. Haroon Ahmad, MD
Hemolytic Anemias – Extrinsic Causes 3

- Infections
  - Malaria
  - Babesiosis
  - Bartonella
  - Closridium

- Chemicals
  - Oxidants with G6PD def
  - Insect and snake venom
  - Lead

- Other causes
  - Hypersplenism
  - Liver disease
Malaria: Red cell containing intraerythrocytic ring forms (trophozoites)

Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows).

Courtesy of Carola von Kapff, SH (ASCP).
Babesia microti parasites in red blood cells

Panel A) Babesia microti[1]. This thin peripheral blood smear (Giemsa stain; x1000) shows Babesia microti. Several erythrocytes contain multiple parasites, including a diagnostic tetrad form (arrow).

Panel B) Malaria (for comparison)[2]. Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows).

Panel C) Normal[3]. High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of:
1. Harriet Provine
2. Carola von Kapff, SH (ASCP).
Peripheral blood smear in autoimmune hemolytic anemia (AIHA)

This peripheral blood smear from a patient with autoimmune hemolytic anemia (AIHA) due to a warm-reactive IgG antibody demonstrates the presence of many dark red small microspherocytes (red arrows) and larger spherocytes (black arrow) (x1000). Many large irregular blue-tinted red cells are also present, representing reticulocytes (blue arrows).

Illustration used with the permission of Elsevier Inc.
Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).
Helmet cells in microangiopathic hemolytic anemia

Peripheral smears from two patients with microangiopathic hemolytic anemia, showing a number of red cell fragments (ie, schistocytes), some of which take the form of combat (red arrow), bicycle (thick black arrow), or football (blue arrow) "helmets." Microspherocytes are also seen (thin black arrows), along with a nucleated red cell (green arrow).

Courtesy of Carola von Kapff, SH (ASCP).
Peripheral blood smear in hemoglobin SC disease

Peripheral blood smear from a patient with hemoglobin SC disease shows numerous target cells (red arrows), partially sickled "canoe" shaped erythrocytes (black arrows), and folded (Pita bread) red cells (blue arrows).

Courtesy of Carola von Kapff, SH (ASCP).
Peripheral smear in Heinz body hemolytic anemia showing Heinz bodies and bite cells

Split screen view of a peripheral smear from a patient with Heinz body hemolytic anemia. Left panel: red cells with characteristic bite-like deformity (arrows). Right panel: Heinz body preparation which reveals the denatured hemoglobin precipitates.

Courtesy of Carola von Kapff, SH (ASCP).
Approach to Hemolytic Anemias 1

- History and Physical Exam
- Coomb’s test
- PNH screen
- Hemoglobin electrophoresis
Polychromatophilia due to increased reticulocytes

Peripheral blood smear taken from a patient with increased reticulocytes. Unlike mature red cells (thin black arrows), which have central pallor and are the same size as the nucleus of a small lymphocyte (thick arrow), reticulocytes (blue arrows) are larger, have a blue tint, and lack central pallor because they are not biconcave discs. (Wright-Giemsa stain). 

Courtesy of Stanley Schrier, MD.
Approach to Hemolytic Anemias 2

- Physical damage
  - Schistocytes
  - Plasma Hgb
  - Urine hemosiderin

- Infection

- Membrane and enzyme defects – measure RBC enzymes and provocative tests
Treatment of Hemolytic Anemias

- Immunohemolytic anemias
  - Steroids
  - Gammadglobulin
  - Rituximab
  - Chemotherapy

- Therapies for other hemolytic anemias directed toward their individual causes
Hemolytic Anemias – Intrinsic Causes

- Abnormal hemoglobin
  - SCD
  - Thalassemia
  - Unstable hemoglobin

- Abnormal membranes
  - Spherocytosis
  - Elliptocytosis
  - Hemolytic uremic syndrome
  - PNH

- Abnormal enzymes
  - G6PD deficiency
  - Pyruvate kinase
Hemolytic Anemias – Extrinsic Causes 2

- Fragmentation/Physical Damage

- Heart valves
- DIC
- TTP
- HUS
- Hemodialysis
- Malignancy

- Burns
- Marathon/march hemoglobinuria
- Vasculitis
- Malignant HTN
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Hemolytic Anemias – Extrinsic Causes

- **Infections**
  - Malaria
  - Babesiosis
  - Bartonella
  - Clostridium

- **Chemicals**
  - Oxidants with G6PD def
  - Insect and snake venom
  - Lead

- **Other causes**
  - Hypersplenism
  - Liver disease

Presenter: Y. Haroon Ahmad, MD
This graph indicates the exponential relationship between serum erythropoietin levels (EPO, milliUnits/mL, logarithmic scale) and venous hematocrit (percent, linear scale) in normal and anemic subjects without renal or chronic diseases. EPO was assayed by either bioassay or radioimmunoassay.

Contact information

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• Call for anything (except pizza)