HEMATOLOGICAL ISSUES IN ACUTE CARE: PART A - RBC DISORDERS

Dheeraj Reddy, MD

Objectives- Part A

- To understand how various blood cell types are produced from pluripotent hematopoietic stem cells and how hematopoiesis is regulated
- To appreciate the importance of a thorough history and physical exam in the diagnostic approach to hematologic abnormalities
- Basic interpretation of peripheral blood smear
- Approach to RBC disorders
  - Anemia
  - Polycythemia

Hematopoiesis

- Production of all types of blood cells including formation, development, and differentiation of all types of blood cells.
- $10^{11} - 10^{12}$ new blood cells are produced daily in our body to maintain steady state levels in the peripheral circulation
- All types of new blood cells are derived from “pluripotent stem cells”
Sites of Hematopoiesis in pre- and postnatal periods

MUCH SIMPLER!
Key Elements in History

- Weight loss
- Fever, night sweats (B symptoms)
- Fatigue, malaise, and lassitude
- Weakness
- Drugs and Chemicals Exposure
- Family History
- Sexual History
- Lumps and Bumps
- Bone Pain
- Skin rash/pruritus
- Surgical History

Key Elements in Physical Exam

LYMPH NODES
Other Laboratory Investigations

- ESR (Erythrocyte Sedimentation Rate)
- Iron studies; ferritin, transferrin, TIBC, serum iron
- WBC count including differential count, neutrophil segment count
- Platelet count
- PT/INR, aPTT

Peripheral Blood Smears

- Cell size
- Hb content
- Anisocytosis- pronounced variations in size of RBC
- Poikilocytosis- different RBC shapes in blood smear
- Polychromasia
- Gives clues to specific disorders

Normal peripheral blood smear

Severe Iron deficiency anemia

- Anemia
- Polycythemia Vera

Myelofibrosis

- Tear drop shaped cells, nucleated cells

Thalassemia

- Target cells
Case #1

- 70 year old female presents to the Emergency Department with worsening epigastric pain, easy fatigability and dizziness. She has dyspnea on exertion after ambulating 30 feet.
- Past Medical Hx: SLE diagnosed in her 20s (symptom free per her account), Osteoarthritis of knees
- Past Surgical Hx: nil
- Social Hx: non smoker, no etoh use
- Review of Systems: 2 episodes of loose dark tarry stools approximately a week ago. No chest pain
- Current Medications: Ibuprofen 600mg PO TID for arthritis pain.

Physical Exam Findings

- Vitals – Afebrile, HR: 117, Supine BP: 115/80 Standing BP: 93/60. BMI 19.6. Pulse ox sat; 95% on 2L O2
- General; Thin female
- HEENT: MM Pallor. No Jaundice. No petechiae
- CVS: Flow murmur over Left 3rd intercostal space
- Lungs: CTAB
- Abdomen: No Splenomegaly or Hepatomegaly
- Lymph nodes; No Lymphadenopathy
- Neurological: No focal deficits
- Nails
Physical Exam Findings

Spoon nail

Labs and Diagnostic Data

<table>
<thead>
<tr>
<th>CBC</th>
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</thead>
<tbody>
<tr>
<td>7.2</td>
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<td>23</td>
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<td>382</td>
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<table>
<thead>
<tr>
<th>BMP</th>
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<tbody>
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<td>144</td>
<td>106</td>
<td>20</td>
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</tr>
<tr>
<td>4.1</td>
<td>25</td>
<td>0.93</td>
<td></td>
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</tbody>
</table>

Peripheral Blood Smear

Microcytic and hypochromic red cells, note central pallor
What is your Diagnosis?

A  Anemia of chronic disease
B  Hemolytic Anemia
C  Iron deficiency
D  Sickle Cell Anemia

Definition

- Reduced hemoglobin concentration and hematocrit. Red blood cell (RBC) number below normal level.
- Decrease in the amount RBC or hemoglobin in the blood → Lowered ability of the blood to carry oxygen.
- Anemia – The World Health Organisation defines anemia as a hemoglobin level < 13g/dL in men and 12g/dL in women.
- Anemia – a major sign of an underlying disease
  - Infections
  - Chronic Medical Conditions; e.g. Rheumatoid Arthritis, Chronic kidney disease, Endocrinopathies, Chronic Liver Disease
  - New diagnosis of Cancer
  - Lymphoproliferative disorders (CLL, B cell neoplasm)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>14–18 g/dL, 12–16 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>40–52%, 37–48%</td>
</tr>
<tr>
<td>Erythrocyte count</td>
<td>4.3–5.7 × 10^6/μL, 3.9–5.3 × 10^6/μL</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>85–98 fl</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>28–34 pg</td>
</tr>
<tr>
<td>MCH concentration</td>
<td>32–37 g/dL</td>
</tr>
<tr>
<td>Erythrocyte diameter</td>
<td>6.8–7.3 μm</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0.3–1.5%</td>
</tr>
</tbody>
</table>

* Indices vary with age, gender and pregnancy
### Elements of Erythropoiesis

1. Erythropoeitin production
2. Iron, Folate, B12 availability
3. Proliferative capacity of the bone marrow
4. Effective maturation of red cell precursors

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Hemoglobin g/dL</th>
<th>Hematocrit %</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>Childhood</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>Adolescence</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Adult man</td>
<td>16 (±2)</td>
<td>47 (±6)</td>
</tr>
<tr>
<td>Adult woman (menstruating)</td>
<td>13 (±2)</td>
<td>45 (±6)</td>
</tr>
<tr>
<td>Adult woman (postmenopausal)</td>
<td>14 (±2)</td>
<td>42 (±6)</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>12 (±2)</td>
<td>37 (±6)</td>
</tr>
</tbody>
</table>
Reticulocyte count and RPI

- A reliable measure of red cell production
- Patient’s reticulocyte is compared with expected reticulocyte counts
- In established anemia, reticulocyte count of less than two-three times is an indication of inadequate marrow response
- Reticulocyte production index; can use websites like MDCalc

\[
RPI = \frac{\text{ReticCount} \times \text{Hemoglobin(observe)}}{\text{NormalHemoglobin}} \times 0.5
\]
Maturation disorders

- Features:
  - Anemia with low reticulocyte count
  - Macro or microcytosis on smear
  - Abnormal red-cell indices

- Two categories:
  - Macrocytic – nuclear abnormalities
  - Microcytic – cytoplasmic abnormalities

- Ineffective erythropoiesis due to destruction in marrow
- Bone marrow shows erythroid hyperplasia

Maturation disorders

- Nuclear maturation disorders:
  - Folate or Vitamin B12 deficiency, drug damage (methotrexate), myelodysplasia
  - Alcohol causes macrocytosis with variable degree of anemia due to folate deficiency

- Cytoplasmic maturation disorders:
  - Severe iron deficiency, thalassaemias
    - Iron deficiency: Low reticulocyte index, microcytosis, Serum iron profile can be used to differentiate from anemia of chronic disease

Iron Metabolism

- Intake
- Resorption: upper small bowel
- Transport: transferrin bound iron < 1%
- Functional iron: hemoglobin 90% → ferritin hemosiderin 20%
- Iron stores: whole-body iron 2-4 g
Causes of Iron Deficiency Anemia

- Chronic blood loss
  - Uterine e.g. menorrhagia/postmenopausal bleeding
  - Gastrointestinal, e.g. Peptic Ulcer Disease, Esophageal varices, Hiatal hernia, Malignancy (stomach, colorectal) Angiodysplasia, Colitis, Diverticulosis, Hemorrhoids
- Increased demands
  - Growth
  - Pregnancy
- Malabsorption
  - Postgastrectomy
  - Gluten-induced enteropathy
  - Autoimmune gastritis

Further Labs and Diagnostic Data

- Mean corpuscular volume: 55 fl (80-100 fl)
- Reticulocyte count: 0.4% of erythrocytes (0.5%-1.5% of erythrocytes)
- Iron 18 μg/dL (60-160 μg/dL)
- Total iron-binding capacity 517 μg/dL (250-460 μg/dL)
- Ferritin 2.2 ng/mL (15-200 ng/mL)
- Transferrin saturation 12% (20%-50%)

Principles of treating iron deficiency anemia

- Ferrous salts:
  - Ferrous sulfate – 65 mg elemental iron/tablet (Least expensive), most commonly used 325 mg three times daily, preferably taken 1 hour before meals.
  - Ferrous fumarate – 106 mg elemental iron/tablet
  - Ferrous gluconate – 28 to 36 mg iron/tablet
- Recommended oral daily dose for Rx iron deficiency in adults is in the range of 150 to 200 mg/day of elemental iron
- Factors that inhibit the absorption of iron salts
  - Antacids/H2 receptor blockers/proton pump inhibitors (two hours before, or four hours after ingestion)
  - Calcium-containing foods and beverages/calcium supplements
  - Antibiotics (quinolones, tetracycline)
  - Ingestion with cereals, dietary fiber, tea, coffee, eggs, or milk
Several months of therapy are needed to replenish body iron stores.

The most frequent cause of failure of iron therapy is patient noncompliance. Many patients cannot tolerate oral iron due to GI side effects.

Parenteral iron replacement
- Iron dextran: recommend test dose first due to risk of anaphylaxis
- Sodium ferric gluconate (Ferrlecit®)
- Iron sucrose (Venofer®)
- Ferumoxytol, a carbohydrate-coated iron oxide (Feraheme®)

Back to our patient!
- The patient has just received transfusion of 2 units packed red blood cells, prior to endoscopy;
- An EGD (esophagogastroduodenoscopy) revealed a small non bleeding duodenal ulcer.
- She is admitted to the hospital for IV infusion of PPI, monitoring of her clinical status

Should this patient be transfused Red Blood Cell products??
Principles for Transfusion Indication

- Restrictive policy of transfusion at a Hb concentration of 7 to 8 g/dL.
- Indication for transfusion is based on clinical symptoms and individual assessment.
- Asymptomatic blood loss → not necessarily an indication for transfusion.
- In acute blood loss → Hemoglobin < 8.0 g/dL.
- Chronic anemia → lower levels of hemoglobin (6–8 g/dL) are generally tolerated.
- Patients with coronary heart disease or risk of cerebral ischemia → Hemoglobin < 8 g/dL.
- Specific conditions (perioperative, pre-chemoRx) may require RBC transfusion support prophylactically.
  - One unit of red cells typically raises Hb concentration by approximately 1 g/dL (10 g/l).
  - Each milliliter of packed erythrocytes contains about 1 mg of iron.

36 hours later.....

The patient starts complaining of high grade fevers and has chills. When you evaluate this patient she has 8 blankets on. She complains of an excruciating headache and lumbar pain.

A Foley Catheter shows some blood tinged urine.

Temp: 40.1°C RR: 17, BP: 100/75, HR 135 (sinus)

o/e: HEENT; scleral icterus, bilateral CVA tenderness on palpation of lumbar spine.
Laboratory Tests

CBC

<table>
<thead>
<tr>
<th>Value</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>5.8</td>
<td>5.5 – 7.5</td>
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<td>8.6</td>
<td>7 – 10</td>
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</table>

BMP

<table>
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<tr>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>131</td>
<td>100 – 300</td>
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<tr>
<td>99</td>
<td>50 – 150</td>
</tr>
<tr>
<td>23</td>
<td>10 – 20</td>
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</tbody>
</table>

- Reticulocyte count: 6% (normal 0.5 to 1.5%) RPI 3.5
- LFTs were obtained to evaluate the jaundice
- AST/ALT normal. Total bilirubin 7.5mg/dL → Direct 1.2mg/dL (WNL) Indirect 6.3 (↑)

What is going on!!??

- Retransfusion
  - Immunologic
    - Hemolytic; Fever; Non-hemolytic; Allergic; Anaphylactic; Transfusion Reaction of Acute Lung Injury (TRALI)
  - Nonimmunologic
    - Hemolytic (Physical or Chemical destruction of RBC); Circulatory overload; Air embolus; Hypocalcemia; Hypothermia

Transfusion Reactions

1. Acute (<24 hours) Transfusion Reactions - Immunologic
   - Hemolytic; Fever; Non-hemolytic; Allergic; Anaphylactic; Transfusion Reaction of Acute Lung Injury (TRALI)

2. Acute Transfusion Reactions - Nonimmunologic
   - Hemolytic (Physical or Chemical destruction of RBC); Circulatory overload; Air embolus; Hypocalcemia; Hypothermia

3. Delayed (>24 Hours) Transfusion Reaction - Immunologic
   - Hemolytic; Graft vs. Host Disease; Posttransfusion Purpura

4. Delayed Transfusion Reactions - Nonimmunologic
   - Iron Overload

5. Infectious Complications of Blood Transfusion
**Hemolytic Anemia**

- Anemia caused by erythrocytic destruction characterized by decreased erythrocyte survival
- Red cell production indices > 2.5
- Polychromatophilic macrocytes on smear
- Red cells indices: Normocytic to Macrocytic due to increased reticulocytes

**Classification of Hemolytic Anemia**

**Corpuscular Hemolytic Anemia (Erythrocyte Defects)**
- Chronic Hemolysis
  - Hereditary membrane defects
    - Spherocytosis, Elliptocytosis
  - Hereditary enzyme defects
    - Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)
  - Stem cell defects
    - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Defects in hemoglobin synthesis
    - Sickle cell anemia and other hemoglobinopathies
    - Thalassemia

**Extracorpuscular Hemolytic Anemia (Extraerythrocytic Defects)**
- Acute Hemolysis
  - Immunohemolytic anemia
    - Warm antibody autoimmune hemolytic anemia (AIHA)
    - Cold antibody autoimmune hemolytic anemia (AIHA)
  - Microangiopathic hemolytic anemia
    - Thrombotic thrombocytopenic purpura (TTP)/Hemolytic-uremic syndrome (HUS)
  - Hemolysis due to erythrocyte damage
    - Traumatic hemolysis (after cardiac valve replacement, march hemoglobinuria)
    - Chemically induced hemolysis
    - Thermal hemolysis (burns)
    - Infection-associated hemolytic anemia
    - Drug-induced hemolysis
Further workup

- LDH ↑, haptoglobin ↓ highly suggestive of hemolysis.
- Coombs’ test: direct (detection of erythrocyte-adherent antibodies) or indirect (detection of serum antibodies) → should be sent in all suspected cases of post transfusion hemolysis.
- Blood group
- Peripheral blood smear
- Viral serology (including parvovirus B19), mycoplasma

Delayed Hemolytic Transfusion Reaction

- Clinical presentation > 24 h
- Due to secondary immune responses following re-exposure to a given red cell antigen
- Ab most commonly involved – Rh, Kidd, Duffy and Kell
- No clinical signs of red cell destruction but positive DAT
- Rarely fatal

Investigation of suspected hemolytic reactions

- Report all transfusion reactions to blood bank
- Send the following lab investigations:
  - Immediate post transfusion blood samples for:
    - Repeat ABO & Rh (D) grouping
    - Repeat antibody screen and crossmatch
    - Direct antiglobulin test/Coombs Test
    - Complete blood count (CBC)
    - Plasma hemoglobin
    - Coagulation screen → PT/INR aPTT.
    - BMP
    - Liver function tests (bilirubin, ALT and AST)
    - Blood culture in special blood culture bottles
    - Specimen of patient’s first urine following reaction
Back to our patient

- Supportive treatment. IVF, correct electrolytes
- Blood bank reports that the patient has Antibodies to the U antigen.
- The U antigen (originally named “Universal”) is a high incidence antigen, occurring in more than 99.9% of the population.
- U negative RBCs can be found in people of African descent.
- Exposure to U + blood has been associated with both hemolytic transfusion reactions

Risk of Blood Transfusion

- Infection
- Transfusion related
  - ABO Incompatible
  - Acute Lung Injury (TRALI)
  - Anaphylaxis
  - Circulatory Overload
- Total

  - 5:10,000
  - 3:10,000
  - 1:12,000
  - 1:10,000
  - 1:150,000
  - 1:10,000
  - 8:10,000

Transfusion Reactions

- Symptoms
  - Chest tightness
  - SOB
  - Chills
  - Back pain
  - Hypotension
  - Burning at I.V.
Other Transfusion Reactions

- **Allergic**
  - IgA deficient individuals (1:550)
  - Can result in anaphylaxis

- **Febrile**
  - Bacterial contamination
  - Secondary to developing HLA Abs to contaminating (donor) leukocytes

TRALI

- Noncardiogenic pulmonary edema temporarily related to the transfusion of (plasma-containing) blood products, due to the presence of leukocyte antibodies in transfused products.
- Symptoms include dyspnea, cough, and fever
  - Onset 1-6 hours after transfusion
  - Bilateral pulmonary infiltrates
- Risk factors: cardiac disease and hematologic malignancy predisposing inflammatory condition present in the OR or in critical care setting.
- Rx: Supportive.

Transfusion Reactions Management

- Stop transfusion
- Notify Blood Bank, follow protocol as per your institution.
- Start IVF to avoid hypotension, shock, renal failure
- If oliguric (late phase) then may need fluid restriction and lytes monitoring
- Prevention: Leukocyte reduction/Irradiation in high risk patients.
Case#2

- 79 year old male with Past Medical History of Type 2 DM, hypothyroidism, chronic kidney disease stage 3, dyslipidemia presents to the hospital with worsening dyspnea.
- He is found to have a right lower lobe pneumonia. Treatment for Community Acquired Pneumonia is initiated.
- His admission labs are as follows:

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<thead>
<tr>
<th>CBC</th>
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<tbody>
<tr>
<td></td>
<td>9.2</td>
<td>13.6</td>
</tr>
<tr>
<td>MCV</td>
<td>132</td>
<td>26</td>
</tr>
</tbody>
</table>

| BMP | 134 | 105 | 66 | 4.9 | 19 | 2.51 |

- MCV: 85 fl (80-100 fl)
- Reticulocyte count: 0.5% of erythrocytes (0.5%-1.5% of erythrocytes) RPI 2.1
- Iron: 45 µg/dl (60-160 µg/dl)
- Total iron-binding capacity: 200 µg/dl (250-460 µg/dl)
- Ferritin: 225 ng/mL (15-200 ng/mL)
- Transferrin saturation 15% (20%-50%)

Anemia of chronic disease

- Common normochromic or mildly hypochromic anemia, occurring in patients with different inflammatory and malignant diseases.
Hypoproliferative anemias

- 75% of all anemias
- Absolute or relative bone marrow failure
- Causes:
  - Mild to moderate iron deficiency
  - Inflammation
  - Marrow damage
  - Ineffective EPO production (impaired renal function, IL-1, hypothyroidism, diabetes mellitus, myeloma)
  - Normocytic normochromic, occasionally microcytic hypochromic
Hypoproliferative anemias

- Investigations:
  - Serum Iron, Serum Ferritin, TIBC
  - BMP to assess creatinine
  - Thyroid function
  - Bone Marrow biopsy/aspiration

### Anemia of chronic Disease vs. Iron deficiency anemia

<table>
<thead>
<tr>
<th></th>
<th>Anemia of chronic Disease</th>
<th>Iron deficiency anemia</th>
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<tbody>
<tr>
<td>Serum Iron</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>TIBC</td>
<td>Normal/Low</td>
<td>High</td>
</tr>
<tr>
<td>Transferrin Saturation</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Serum Ferritin</td>
<td>Normal/High</td>
<td>Low</td>
</tr>
</tbody>
</table>

**CASE 1: Iron deficiency Anemia**

- Mean corpuscular volume: 55 fL (80-100 fL)
- Reticulocyte count: 0.4% of erythrocytes (0.5%-1.5% of erythrocytes)
- Iron 18 µg/dL (60-160 µg/dL)
- Total iron-binding capacity: 517 µg/dL (250-460 µg/dL)
- Ferritin: 2.2 ng/mL (15-200 ng/mL)
- Transferrin saturation: 12% (20%-50%)

**CASE 2: Anemia of chronic disease**

- MCV: 85 fL (80-100 fL)
- Reticulocyte count: 0.5% of erythrocytes (0.5%-1.5% of erythrocytes)
- Iron: 45 µg/dL (60-160 µg/dL)
- Total iron-binding capacity: 200 µg/dL (250-460 µg/dL)
- Ferritin: 225 ng/mL (15-200 ng/mL)
- Transferrin saturation: 15% (20%-50%)

**CASE 3**

- 85 year old female with history of Type 2 DM, nursing home resident presents to your clinic for weight loss, poor oral intake, lower extremity parasthesias, and gait abnormalities.
- Medications: lisinopril, metformin, and aspirin
- Vitals: temperature 98.0 °F; blood pressure 127/74 mm Hg, pulse rate 97/min, and respiration rate 12/min.
- Mucous membranes are pale.
- Neurologic examination;
  - Impaired vibratory sense and proprioception in the toes and fingers.
  - Monofilament testing for foot sensation is intact.
  - Gait: wide based.
### Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>Reticulocyte count</td>
<td>0.8%</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>106 fL</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>80 pg/mL</td>
</tr>
<tr>
<td>Folate</td>
<td>172 ng/mL</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>470 U/L</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>Macrocytic erythrocytes, poikilocytosis, anisocytosis, hypersegmented granulocytes.</td>
</tr>
</tbody>
</table>

### Neurologic signs/symptoms of Vitamin B12 deficiency

- In advanced cases, funicular myelosis: neuropathy caused by symmetrical damage of the posterior columns of the spinal cord, the corticospinal tract and peripheral nerves.
- Motor abnormalities: mainly affecting the lower extremities
- Staggering gait
- Ataxia
- Spastic paresis
- Impaired vision
- Psychiatric disorders.
- Dementia

Most frequent cause: pernicious anemia (80% of cases): autoimmune atrophic gastritis with antibodies against gastric parietal cells (90% of cases) and/or antibodies against intrinsic factor (50% of cases)

- Achlorhydria, intrinsic factor deficiency
- Decreased vitamin B12 resorption in the terminal ileum
- Insufficient vitamin B12 uptake (strict vegetarians, alcoholics)
- Postoperatively (gastric resection, resection of the terminal ileum, blind loop syndrome)
- Vitamin B12 malabsorption, rare (Crohn's disease, scleroderma, amyloidosis)
- Infections / parasites (fish tapeworm, bacterial gastrointestinal infections)
- Medications: chronic metformin use, chronic ranitidine use.
Diagnostic Investigations
- B12 levels, Folate levels
- Evaluation of specific metabolic intermediates (eg, methylmalonate and homocysteine) which can accumulate in these deficiencies
- Peripheral Blood Smear
- Anemia of Vitamin B12 deficiency can be reversed with folate therapy; it is important to rule out Vitamin B12 deficiency before treating patients with folate—the neurologic status may deteriorate in such patients despite improvement in anemia

Treatment

<table>
<thead>
<tr>
<th>ROUTE OF ADMINISTRATION B-12</th>
<th>INITIAL DOSAGE</th>
<th>MAINTENANCE DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1,000 to 2,000 mcg per day for 1 to 2 weeks</td>
<td>1,000 mcg per day for life</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>1000 mcg q daily for one week, then 1000 mcg every week for four weeks</td>
<td>1,000 mcg q monthly</td>
</tr>
</tbody>
</table>

Folic acid (1 to 5 mg/day orally) for one to four months, or until complete hematologic recovery occurs.

Case #4
A 21-year-old African American man, travelling from NYC presents to the ED in Denver, CO complaining of pleuritic chest pain and bilateral lower extremity pain.
VS 101°F RR 29 Normal blood pressure, and slight tachycardia of 100 bpm. O2: 92% on 2L
Lung examination: bronchial breath sounds and egophony in the right lung base.
Extremities: tenderness on palpation of his extremities. Decreased ROM of bilateral hips
Lab: WBC 16.5K, 6% reticulocyte counts Hb 7.7 Hct 23
Sickle Cell Disease

- An inherited disease of red blood cells
- Affects hemoglobin
- Polymerization of hemoglobin leads to a cascade of effects decreasing blood flow
- Tissue hypoxia causes acute and chronic damage
- Infection, dehydration, and acidosis can exacerbate and cause crises.
Normal Vs. Sickle Red Cells

Normal
- Disc-Shaped
- Deformable
- Life span of 120 days

Sickle
- Sickle-Shaped
- Rigid
- Lives for 20 days or less

Hemolysis and Vaso-occlusion

Hemolytic Anemia:
The anemia in SCD is caused by red cell destruction, or hemolysis. The production of red cells by the bone marrow increases dramatically, but is unable to keep pace with the destruction.

Vaso-occlusion:
Rigid sickle shaped cells fail to move through the small blood vessels, blocking local blood flow to a microscopic region of tissue. Amplified many times, these episodes produce tissue hypoxia. The result is pain, and often damage to organs.

Acute Manifestations:
- Bacterial Sepsis or meningitis*
- Recurrent vaso-occlusive pain (dactylitis, musculoskeletal or abdominal pain)
- Splenic Sequestration*
- Aplastic Crisis*
- Acute Chest Syndrome*
- Stroke*
- Priapism
- Hematuria, including papillary necrosis

Chronic Manifestations:
- Anemia
- Jaundice
- Splenomegaly
- Eye disease (bleeding, retinal detachment)
- Proteinuria
- Cholelithiasis
- Delayed growth and sexual maturation
- Restrictive lung disease*
- Pulmonary Hypertension*
- Avascular necrosis
- Proliferative retinopathy
- Leg ulcers
- Transfusional hemosiderosis*

*Potential cause of mortality
**Sickle Cell Disease**

**SCD Genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell anemia (SS)</td>
<td>65%</td>
</tr>
<tr>
<td>Sickle Hb C disease (SC)</td>
<td>25%</td>
</tr>
<tr>
<td>Sickle S beta plus (Sβ⁺⁺ thalassemia)</td>
<td>8%</td>
</tr>
<tr>
<td>Sickle Beta zero (Sβ⁺⁻ thalassemia)</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Historical Distribution of Hemoglobin Variants**

Hemoglobin S

Hemoglobin C

Hemoglobin D

Hemoglobin E

Malarial Regions of Africa and Asia

Alpha thalassemia occurs in all these regions as well

**Prevalence/Incidence of SCD**

- In African-Americans the incidence of SCD is 1 in 375 for HbSS, 1 in 835 for HbSC and 1 in 1,667 for Sickle beta-thalassemia. In addition, 1 in 12 African-Americans are carriers for the disorder.

- In other U.S. populations, the prevalence of sickle cell disease is 1 in 58,000 Caucasians; 1 in 1,100 Hispanics (eastern states); 1 in 32,000 Hispanics (western states); 1 in 11,500 Asians; and 1 in 2,700 Native Americans.
Sickle Cell Pedigree

- Parents with sickle cell trait: hemoglobin AS
- Probability of child with hemoglobin AA: 25%
- Probability of child with sickle cell trait AS: 50%
- Probability of child with sickle cell disease SS: 25%

Chronic Complications

- Anemia/Jaundice
- Brain Damage/Stroke
- Kidney failure
- Decreased lung function
- Eye disease (bleeding, retinal detachment)
- Leg ulcers
- Chronic pain management

EMERGENT COMPLICATIONS OF SCD

- Acute painful crises
- Acute chest syndrome (ACS)
- Renal complications
- Stroke
- Osteonecrosis of the head of the femur/humerus
- Sickle sequestration in the liver
- Sickle sequestration in the spleen
- Leg ulcers
- Priapism
- Eye trauma (hyphema)
Fever and Infection

- Fever > 38.5°C (101°F) is an EMERGENCY
- Basic laboratory evaluation:
  - CBC with differential and reticulocyte count, blood, urine, and throat cultures, urinalysis, chest x-ray
- Indications for hospitalization & IV antibiotics:
  - Patient appears ill
  - Any temperature > 40°C
  - Abnormal laboratory values
- Start IV antibiotics IMMEDIATELY if clinically appears ill or temperature > 40°C (DO NOT WAIT FOR LABS)

PRESENTATION OF ACS

- New infiltrate
  - pleural effusion (56%)
AND...
- Chest pain, cough, tachypnea, or wheezing OR
- Fever > 38.5
- Drop in Hb (< 2g) and platelets (<175,000)

Differentiating Acute Chest Syndrome vs. Pneumonia in SCD

- Low yield of bacterial diagnosis, even with bronchoscopy and lavage.
- Involvement of basal lobes and bilateral
- Dramatic effect of exchange transfusion
- In SCD, but not in other patients, sickle cells are trapped on the alveoli wall, become deoxygenated and incapable of exiting.
Other characteristics of ACS

- Most common cause of death in SCD young adults in spite that it is treatable complication.
- Second most common cause of hospitalization.
- Preceded or followed by acute painful crises.
- After first ACS, repeat episodes are common.
- ACS can lead to pulmonary hypertension.

Etiology

- Fat embolism
  - Alveolar macrophages in 77% who had BAL
- Viral:
  - RSV, Parvo, Influenza, HSV, Echo, Rhino, CMV, EBV
- Atypical bacteria:
  - Mycoplasma, Atypical Mycoplasma, Chlamydia, Mycobacterium
- Bacteria:
- 23-62% unknown

FAT EMBOLI PRESENTATION

- The most severe form of ACS, with longer hospital stays and high mortality when misdiagnosed.
- Lower mean oxygen saturation
- Higher incidence of vaso-occlusive events
- Fat emboli originate in marrow undergo infarct/necrosis with release of a combination of fat and hemopoietic precursors into the circulation.
- Unique is the trapping of fat/cells in lung alveoli and sometimes the brain (confusion and mini-strokes/hypoxia by imaging)
- Frequently associated with sternal pain.
Treatment of ACS

- **Treatment:**
  - Analgesics
  - Broad-spectrum antibiotics
  - Bronchodilator and incentive spirometry
  - Simple or exchange transfusion
- **Simple:**
  - when blood deoxygenation is not getting worse fast.
- **Exchange transfusion:**
  - When O2 sat is 87 or lower and falling within 6 hrs.
  - When patient is confused (fat emboli).
  - When sternal pain is present (fat emboli).
- Bronchoscopy is recommended in patients with no response to initial therapy.

Priapism

- Commonly occurs in children and adolescents with SS or SC.

Treatment is difficult
- Opioid pain medication
- Intravenous fluids
- Aspiration and irrigation of the corpus cavernosum
- Surgery
- Blood Transfusions
- Impotence with severe disease or recurrent episodes.

Stroke

- Any acute neurologic symptom other than mild headache, even if transient, requires urgent evaluation.

- Intracranial hemorrhage
  - Common in adults than children.
- Sequela overt and “silent strokes”
- Paralysis overt stroke
- Neuropsychologic changes; both overt and silent strokes:
  - Visual-spatial impairment
  - Impaired memory
  - Poor impulse control

Treatment: Chronic transfusion therapy to maintain sickle hemoglobin at or below 30%.
Pain Management

Acute pain
- Hand-foot syndrome (dactylitis)
- Painful episodes: vasoocclusion
- Splenic sequestration
- Acute chest syndrome
- Cholelithiasis
- Priapism
- Avascular necrosis
- Right upper quadrant syndrome

Pain Management

Pain is an emergency
Hospital evaluation:
- Hydration: 1.5 times maintenance unless acute chest syndrome suspected
- Assess pain level and treat
  - Do not withhold opioids
  - Frequently reassess pain control
  - Assess for cause of pain/complications

Pain Management

Mild-moderate pain
- Acetaminophen
  - Hepatotoxic
- Non-steroidal anti-inflammatory agents (NSAIDs)
  - Contraindicated in patients with gastritis/ulcers and renal failure
  - Monitor renal function if used chronically

Moderate-severe pain
- Opioids are first-line treatment
- Morphine sulfate or hydromorphone
- May need PCA
Renal Disease
- Decreased ability to concentrate urine
- Decreased ability to excrete potassium
- Inability to lower urine pH normally
- Hematuria / papillary necrosis
- Proteinuria/Nephrotic syndrome
- 40% of SCD patients with nephrotic syndrome develop end-stage renal disease
- Risk factors for progressive renal failure
  - Anemia, proteinuria, hematuria

Gall Bladder and Liver
- Gall stones and biliary sludge
  - Monitor by ultrasound every 1-2 years
- Cholestasis
  - May progress, leading to bleeding disorders or liver failure
- Iron overload
  - Due to chronic transfusions
- Chronic hepatitis

Bone Disease Diagnosis and Treatment
- Avascular necrosis of hips and shoulders
  - Index of suspicion
    - Persistent hip or shoulder pain
    - Plain film or MRI
  - Treatment
    - Conservative
      - NSAID’s and 6 weeks of rest off affected limb
    - Physical therapy
- Osteomyelitis; most common cause of osteomyelitis in SCD is Salmonella species.
Leg Ulcers

- Occurs in about 25% of all hemoglobin SS patients
- Predominantly males
  - Incidence increased with
    - Age
    - Decreased hemoglobin
- Recurrence rate is ~ 75%

Chronic Management of SCD

- Pain lasting >3 to 6 months: Patients should receive comprehensive psychologic and clinical assessment. Ensure patients are on a PAIN CONTRACT.
- Treatment
  - Analgesics, opiates if necessary
  - Hydroxyurea daily
  - Folic Acid daily
  - Physical and occupational therapy

Case #4

- 59 yo male presents to ER with ataxia, dizziness and weakness that has lasted 12 hours. He has been experiencing blurry vision and headaches over the past few days as well. Additionally, he has been complaining of pruritus, especially after taking warm showers.
- a/e; VS all stable
- Skin- plethora (red), RLE swelling and warmth
- Abdomen- splenomegaly
- Neuro; ataxic gait, right lower extremity weakness. Ophthalmologic exam reveals- partial central retinal vein occlusion
Dx investigations:
- Right LE arterial thrombus on Doppler
- MRI → Posterior Circulation Infarct affecting cerebellum

CBC
- Hemoglobin: 21.2
- WBC: 7.3
- Platelets: 582

SMP
- Na: 140
- K: 100
- Cr: 20
- BUN: 4.4

Polycythemia Rubra Vera

- Primary neoplastic disorder in which bone marrow erythropoiesis is increased, usually accompanied by thrombocytosis +/− leukocytosis.
- Serum erythropoietin levels are low.
- JAK 2 mutation (>95% of cases of PRV)
- The JAK2 gene product is a tyrosine kinase that has a key role in signal transduction, and mutation has the effect of amplifying the growth promoting action of EPO.
- Need to distinguish from other causes of polycythemia.
### Clinical Features
- Occurs equally in males and females, typically over 55 years of age.
- Raised red cell mass and blood volume causes a ruddy complexion and conjunctival suffusion.
- Hyperviscosity leads to headaches and visual disturbance.
- Thrombosis caused by hyperviscosity and increased platelets.
- Excess histamine secretion from basophils and increased gastric acid and peptic ulcer disease, as well as pruritus, typically after a hot bath.
- Splenomegaly in 75% of patients.
- Gout increased cell turnover with uric acid production.

### Treatment
- Phlebotomy
- Aspirin for secondary prevention of stroke
- Allopurinol to prevent hyperuricemia
- Rx of thrombosis with anti-coagulation