Chapter 121 – Anemia, Polycythemia, and White Blood Cell Disorders

Episode overview

1. Outline the important aspects of the history and physical for clinically severe and non-emergent anemia
2. List 6 causes of rapid intravascular red blood cell destruction
3. List the admission criteria for nonemergent anemia
4. Classify the anemias according to MCV
5. What is the differential diagnosis of normocytic anemia?
6. What are the 3 different types of thalassemia?
7. What is the underlying pathophysiology of sideroblastic anemia? List causes of sideroblastic anemia
8. List 3 causes of B12 deficiency) and 3 causes of folate deficiency
9. List 3 drugs that can cause aplastic anemia
10. List 4 intrinsic and 4 extrinsic causes of hemolytic anemia
11. List two RBC enzyme deficiencies. How do they typically present?
12. What is the pathophysiology of G6PD? What triggers G6PD symptoms?
13. List 5 drugs that cause hemolysis in G6PD
14. List 5 causes and 4 drugs of autoimmune hemolytic anemia
15. Describe what to look for on history and physical exam in consideration of hemolytic anemia. What are at least 6 lab tests diagnostic for hemolysis?
16. What are the laboratory differences between intravascular and extravascular hemolysis? Which types of hemolytic anemia tend to be intravascular? Which are extravascular?
17. What is the pathophysiology of sickle cell disease?
18. Which presentations of sickle cell disease are associated with a sudden decrease in hemoglobin?
19. List potential end-organ complications of sickle cell disease by system
20. Describe the management of a sickle cell pain crisis
21. Describe the management of a sickle cell chest crisis
22. List 5 complications of sickle cell disease and their management
23. List 5 causes of apparent and secondary polycythemia
24. How might polycythemia present in the ED? What are the types of polycythemia? How is this condition managed?
25. List 6 causes of leukocytosis and 3 causes of lymphocytosis
26. List 5 causes of neutrophilia + 5 causes of lymphocytosis
27. How to approach neutropenia in children?

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1. How do you calculate the oxygen content of blood?
2. Which situations shift the oxygen-dissociation curve to the left? To the right? What is the significance of a leftward shift?
3. List 6 causes of anemia from ↓production (review question)
4. List 4 causes of MAHA (review question)
5. What organ damage is seen in sickle cell disease (table 112.8)
6. What is leukostasis?
7. How is neutropenia with fever managed?
8. Which type of leukemia would be most likely in the following pts and why might they present to the ED?
   1. 20-year-old with Downs syndrome
   2. Previously healthy 28-year-old
   3. 70-year-old with chest pain noted to have increased LNs

[1] Outline the important aspects of the history and physical for clinically severe and non-emergent anemia

Refer to boxes 112.2 and 112.3 for the important aspects of the history and physical for clinically severe and non-emergent anemia

**Clinically Severe Anemia**

**General History**
- Out-of-hospital status, therapy, response to therapy?
- Bleeding diathesis?
- Any previous blood transfusions?
- Any underlying disease?
- Current meds, any platelet inhibitors

**Trauma History**
- Nature and time of injury
- Estimated blood loss

**Non-trauma History**
- Skin: petechiae, bruising
- Respiratory: hemoptysis, epistaxis
- Gastrointestinal: hematemesis, hematochezia, melena, peptic ulcer
- Genitourinary: LMP, menorrhagia (bleeding in-between expected periods), metrorrhagia (excessive bleeding during periods), hematuria

**Physical Exam**
- Serial Vital signs (including orthostatic vitals), level/content of consciousness
- Skin: pallor (conjunctival, palmar creases highest LHR), diaphoresis, jaundice, cyanosis, purpura/bruising, petechiae, penetrating wounds
- CVS: murmurs, S3, S4
- Abdomen: big spleen, tender abdomen, rectal/pelvic exam, masses, stool hemoglobin testing.

**Nonemergent Anemia**

**History**
- Symptoms of anemia (chest pain, dyspnea, decreased exercise tolerance, weakness, fatigue, syncope)
- Bleeding diathesis
- Possible sites of blood loss (resp, GI, GU, Skin)
- Dietary history
- Drug use/Toxin exposure, ALCOHOL??
- Racial background (Mediterranean?) / Family history
Underlying diseases

Physical Exam

Similar to emergent case exam - maybe look at the fundi for hemorrhage, check some nodes, assess neurologic positional and vibratory sense?

[2] List 6 causes of rapid intravascular red blood cell destruction

Refer to box 112.1 for causes of rapid intravascular red blood cell destruction

Causes of rapid intravascular red blood cell destruction:

- Mechanical hemolysis associated with DIC
- Massive burns
- Toxins (poisonous venom, brown recluse spiders, cobras!)
- Infection (Malaria, clostridium, mycoplasma/mononucleosis leading to cold agglutinin hemolysis)
- G6PD deficiency with oxidative stress (ate a fava bean!)
- ABO incompatibility transfusion reaction
- Paroxysmal nocturnal hemoglobinuria exacerbated by transfusion
- Immune complex hemolysis (e.g., quinidine)

[3] List the admission criteria for non-emergent anemia

Refer to box 112.4 for admission criteria for nonemergent anemia

Admissions criteria for nonemergent anemia:

- Developing cardiac symptoms (chest pain, SOB, altered LOC)
- Initial unexplained Hb <80 or hematocrit <30%
- Difficulty obtaining outpatient care when Hb significantly low or major comorbidity

[4] Classify the anemias according to MCV

Refer to box 112.5 for classification of anemias according to MCV

Microcytic (low MCV, hypochromic)

- Thalassemia
- Anemia of chronic disease
- Iron deficiency
- Lead poisoning
- Sideroblastic anemia

Normocytic (normal MCV)

- Primary bone marrow problem: aplastic anemia, myeloid metaplasia with myelofibrosis, myelophthisic anemia
- Secondary to underlying disease: hypothyroid, hypoadrenal, hypopituitary, uremia, chronic inflammation, liver disease

Macrocytic (high MCV)

- Vit B12 deficiency / Folate deficiency
- Liver disease
- Hypothyroidism

[6] What are the 3 different types of thalassemia?

- Homozygous beta-chain thalassemia (Thalassemia major)
  Mediterranean, severe anemia, most common single gene disorder
- Heterozygous beta-chain thalassemia (Thalassemia minor)
  Mild anemia, mostly asymptomatic
- Alpha-thalassemia
  Wide spectrum of manifestation, viable forms in Asian/Afro-Americans

[7] What is the underlying pathophysiology of sideroblastic anemia? List causes of sideroblastic anemia

Pathophysiology:
Defect in porphyrin synthesis causes impaired Hb production leading to excess iron deposited in mitochondria of RBC precursors → poor erythropoiesis (anemia)

Causes of Sideroblastic Anemia:
Primary: Rare sex-linked form and idiopathic in elderly with refractory anemia
Secondary: Toxins, Hemolytic/megaloblastic anemia, infections, carcinoma, leukemia, rheumatoid arthritis, lead poisoning, and alcohol abuse

[8] List 3 causes of B12 deficiency and 3 causes of folate deficiency

Refer to box 112.7 for causes of Vitamin B12 deficiency
- Inadequate dietary intake (total vegan, chronic alcoholism),
- Inadequate absorption (pernicious gastrectomy/anemia, abnormal ileum),
- Inadequate use (enzyme deficiency, abnormal vitamin B12 binding protein)

Refer to box 112.6 for causes of Folate deficiency:
- Inadequate dietary intake,
- Inadequate absorption (Celiac sprue, blind loop syndrome, phenytoin or barbiturates),
- Inadequate use (metabolic block caused by methotrexate, etc.),
- Increased requirement (pregnancy, poor erythropoiesis, hemolytic anemia, chronic blood loss, lymphoproliferative diseases)

[9] List 3 drugs that can cause aplastic anemia

Refer to table 112.6 for drugs or chemicals that can cause aplastic anemia
- Chloramphenicol (61% relative incidence)
- Phenytoin (19%)
- Anticonvulsants (4%)
[10] List 4 intrinsic and 4 extrinsic causes of hemolytic anemia

Refer to box 112.8 for intrinsic and extrinsic causes of hemolytic anemia

Intrinsic Causes of Hemolytic Anemia

- Enzyme defect (pyruvate kinase deficiency, G6PD deficiency)
- Membrane defect (spherocytosis, elliptostomatocytosis, paroxysmal nocturnal hemoglobinuria)
- Hemoglobin defect (Thalassemias, hemoglobin M, unstable hemoglobin, sickle cell)

Extrinsic Causes of Hemolytic Anemia

- Immunologic (allo or autoantibodies)
- Mechanical (Microangiopathic hemolytic anemias (MAHA), prosthetic HVs)
- Environmental (Drugs, toxins, infections, thermal)
- Abnormal sequestration – hypersplenism

[11] List two RBC enzyme deficiencies. How do they typically present?

1) Pyruvate kinase deficiency – presents as hemolytic jaundice around infancy
2) G6PD deficiency – presents as acute hemolytic episode 24-48 hours after ingestion of oxidant drug/material


Deficiency of an enzyme in the early steps of glycolysis (glucose-6-phosphate dehydrogenase) means there isn’t sufficient NADPH produced from glycolysis to maintain reduced glutathione, an essential molecule in protecting Hb from oxidative stress. Hb are then extra vulnerable to any ingested oxidant!!

[13] List 5 drugs that cause hemolysis in G6PD

Refer to box 112.9 for drugs that cause hemolysis in G6PD

- Analgesics (aspirin, acetanilide)
- Antimalarials (Primaquine, quinacrine, quinine)
- Nitrofurans
- Sulfa drugs
- Miscellaneous (FAVA beans, methylene blue, phenylhydralazine)

[14] List 5 causes and 4 drugs of autoimmune hemolytic anemia

Refer to boxes 112.10 and 112.11 for disease causing AHA and drugs causing AHA

Diseases causing AHA:

- Neoplasms (CLL, CML, lymphoma, myeloma, thymoma, ovarian teratoma)
- Collagen vascular disease (SLE, RA, periarteritis nodosa)
Infections (Mycoplasma, syphilis, malaria, Bartonella, viruses – CMV, mono, coxsackie)

Miscellaneous (thyroid d/o, ulcerative colitis, drug immune reactions)

Drugs causing AHA:
- Quinidine
- Sulfa drugs
- Penicillin dosages >20 million units/day
- D-methyldopa + L-dopa
- Cephalosporins at dosages >4g/day

Describe what to look for on hx and physical exam in consideration for hemolytic anemia; What are at least 6 lab tests diagnostic for hemolysis?

Refer to box 112.12 for pertinent history and physical exam findings with hemolytic anemia

History: alteration of urine colour, association with new drugs, cold, sleep, ethnic background, family history of anemia or jaundice, drug or toxin exposure, diseases associated with hemolysis (SLE, renal disease lymphoma, mono, prosthetic HVs)

Physical: jaundice (scleral icterus), hepatosplenomegaly, ulcerations, enlarged lymph nodes

Refer to box 112.13 for diagnostic lab tests for hemolysis
- Peripheral blood smear
- Corrected retic index
- Haptoglobin (low=hemolysis)
- Plasma free Hb
- LDH level (high=hemolysis)
- Fractionated bilirubin
- Direct/indirect Coombs test

What are the laboratory differences between intravascular and extravascular hemolysis?

Extravascular – peripheral smear will have specific RBC morphologies suggesting etiology (bite cells, sickle cells, spherocytes, spur cells, Howell-Jolly bodies, etc.)

Intravascular – peripheral smear will predominantly show schistocytes (RBC fragments)

Which types of hemolytic anemia tend to be intravascular? Which are extravascular?

Extravascular – enzyme/membrane/hemoglobin defects, autoimmune hemolysis, toxins, hypersplenism
Intravascular – MAHA (DIC, TTP, HUS), transfusion reactions, sepsis, heat injury, paroxysmal nocturnal hemoglobinuria

[18] What is the pathophysiology of sickle cell disease?

Abnormal allele at gene loci for Hb beta chain relates to a single amino acid change within the beta chain and a resultant Hb chain with abnormal tertiary structure (sickled). Sickle RBCs are less deformable, increase blood viscosity, and tend to be sequestered more readily within the spleen. This pathologic process leads to vaso-occlusive crises, chronic hemolysis, and end-organ injury.

[19] Which presentations of sickle cell disease are associated with a sudden decrease in hemoglobin?

The hemolysis phenotype… genetically indeterminable from vaso-occlusive phenotype. Unknown why some present with hemolysis while others present with acute pain.

[20] List potential end-organ complications of sickle cell disease by system

- Skin – stasis ulcer
- CNS – CVA
- Eye – retinal hemorrhage, retinopathy
- Cardiac – CHF
- Pulmonary – PE, infarct, infection
- Vascular – occlusive phenomenon ANYWHERE
- Liver – infarct, transfusion-related hepatitis, hepatic sequestration, cholestasis
- Gallbladder – increased bilirubin gallstone production
- Spleen – acute sequestration
- Urinary – hematuria, hyposthenuria
- Genital – decreased fertility, impotence, priapism
- Skeletal – bone infarcts, osteomyelitis, aseptic necrosis
- Placenta – insufficiency with fetal wastage
- Leukocytes – relative immunodeficiency
- Erythrocytes – chronic hemolysis

[21] Describe the management of a sickle cell pain crisis

Acute: analgesia (patient dependent/directed) with opioids +/- NSAIDS
Chronic: Hydroxyurea reduces pain crisis frequency in adults with >3 pain crises / year
Cure: bone marrow transplantation (up to 90% disease-free survival rates)
[22] Describe the management of a sickle cell chest crisis

Supportive management with judicious rehydration, analgesia, incentive spirometry, maintain good oxygenation/ventilation, and empiric antibiotics (similar coverage for CAP)

[23] List 3 complications of sickle cell disease and their management

1) **Acute stroke**: exchange transfusion, tPA use in this setting is the same as for acute non-hemorrhagic stroke without sickle cell disease
2) **Acute splenic sequestration**: exchange transfusion, IV antibiotics against Staphylococcus and encapsulated organisms (Pneumococcus, H. influenza, Salmonella)
3) **Acute chest syndrome**: exchange transfusion + supportive management

[24] List some causes of secondary polycythemia

Refer to box 112.14 for causes of secondary polycythemia

*Appropriate response to tissue hypoxia states*: congenital heart disease with R-to-L shunt, pulmonary disease, carboxyhemoglobin, high-altitude acclimatization, hemoglobinopathies with high oxygen affinity

*Inappropriate erythropoiesis production states*: renal carcinomas, uterine fibroids, hepatoma of adrenal origin, cerebellar hemangioma, congenital overproduction, pure erythrocytosis, AIDS

[25] How might polycythemia present in the ED? What are the types of polycythemia? How is this condition managed?

*Presentation*: may vary from mild headaches to full-blown hypervolemia (vertigo, blurred vision, severe headache), hyperviscosity (venous thrombosis), and platelet dysfunction (epistaxis, spontaneous bruising, GI bleeding)

*Types of PV* – **Apparent** (dehydration, cigarette smoking), **Primary** (myeloproliferative disorder), and **Secondary** (carcinomas increasing erythropoietin, other conditions, see Q24)

*Management*: phlebotomy (500ml removed and replaced with equal amount saline). Final goal for hematocrit is <55%. ASA 81mg daily has been shown to prevent thrombotic complications (acute and chronic treatment)

[26] List 6 causes of leukocytosis and 3 causes of lymphocytosis

Refer to box 113.1 for causes of leukocytosis and lymphocytosis

*Causes of leukocytosis (increased WBC count)*

- Primary: myeloproliferative disorders (CML, PV), hereditary neutrophilia
Secondary: Infection, tissue necrosis (cancer, burns, infarctions), metabolic disorders (DKA, thyrotoxicosis, uremia), stress (exercise, pain, surgery, hypoxia, seizures, trauma), drugs (epinephrine, corticosteroids, lithium, cocaine), lab error

Causes of lymphocytosis (increased lymphocytes)
Viral (mono, rubeola, rubella, varicella, toxoplasmosis), CLL, autoimmune diseases, graft rejection, immunizations

[27] How to approach neutropenia in children?

- Determine absolute neutrophil count (ANC)
- Consider etiology: decreased production, increased destruction, or sequestration.
- Patient more susceptible to infections. Therefore, anyone with FEVER and low ANC warrants full radiographic and direct examination for potential infectious sources and cultures obtained for sputum, urine, and blood
- Early involvement of appropriate specialties
- Empiric antibiotics

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[1] How do you calculate the oxygen content of blood?

Content in blood depends on the saturation level of hemoglobin plus the amount of O2 dissolved in the blood based on partial pressures of O2:

\[ \text{CaO}_2 = (\text{Hb} \times 1.34 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.0031) \]

Where 1g of normal Hb carries 1.36 mL of O2

[2] Which situations shift the oxygen-dissociation curve to the left? To the right? What is the significance of a leftward shift?

**Right Shift** = Hb has decreased affinity for O2 (gives it up more readily to the tissues)
- Increased CO2, increased acidity (decreased pH), increased 2,3-BPG, increased temperature
- Basically the environment of overworked, oxygen starved tissues yields a right shift toward Hb giving up more O2

**Left Shift** = Hb has increased affinity for O2 (Hb gives up less O2 to tissues)
- Opposite factors to above list

[3] List 6 causes of anemia from decreased production (review question)

1. Iron deficiency,
2. Vitamin B12/folate deficiency,
3. Aplastic anemia,
4. Myeloid metaplasia with myelofibrosis,
5. Hypoendocrine state,
6. Renal disease

[4] List 5 causes of MAHA (review question)

1. DIC,
2. TTP,
3. HUS,
4. Malignant hypertension,
5. Preeclampsia

[5] What organ damage is seen in sickle cell disease?

- Skin – stasis ulcer
- CNS – CVA
- Eye – retinal hemorrhage, retinopathy
- Cardiac – CHF
- Pulmonary – PE, infarct, infection
- Vascular – occlusive phenomenon ANYWHERE
- Liver – infarct, transfusion-related hepatitis, hepatic sequestration, cholestasis
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- Skeletal – bone infarcts, osteomyelitis, aseptic necrosis
- Placenta – insufficiency with fetal wastage
- Leukocytes – relative immunodeficiency
- Erythrocytes – chronic hemolysis

[6] What is leukostasis?

An extreme form of leukocytosis (WBC >100,000/microL). Characterized by abnormal intravascular WBC aggregation and clumping, seen predominantly in leukemia patients.

[7] How is neutropenia with fever managed?

- Source identification and control (with radiography and direct investigation)
- Empiric antibiotics and judicial fluids
- Early involvement of appropriate specialists (hemo-oncologist, ID, med oncology, etc.)
- Many patients on chemo have been given treatment protocols by their oncologist
[8] Which type of leukemia would be most likely in the following patients and why might they present to the ED?

1) **20-year-old with Downs syndrome**
   Increased risk (500x) for subtype of AML and 20x increased risk for ALL
   Usually presenting early in life with hepatosplenomegaly, jaundice, leukocytosis, lots of blast cells of peripheral blood smear, anemia, and vesicopapular rash/purpura.

2) **Previously healthy 28-year-old**
   Iron deficiency anemia is the most common cause of anemia among healthy young people (especially females and those on special minimalist diets or are vegan)
   Fatigue, light-headedness, weakness, severe menstrual flow, hypochromic/low MCV anemia with poikilocytes on smear.

3) **70-year-old with chest pain noted to have increased LNs.**
   AML/CLL, high risk for leukostasis, or VTE