Anemia in Pediatric Patients

50 Shades of Pale

Stefanos Intzes, MD
Ross Goshorn, MD
Pediatric Hematology/Oncology
Sacred Heart Children's Hospital

Objectives

• Review the definition of anemia
• Explore the life cycle of red blood cells
• Discuss the diagnosis of anemia
• Review case reports
• Explore blood transfusions and transfusion complications in pediatric patients

Anemia

• The reduction in red cell mass or blood hemoglobin concentrations

Disclosures

• Nothing to disclose

References

Nathan and Oski's Hematology of Infancy and Childhood 7th Edition: Table 10-1

https://www.youtube.com/watch?v=Jy7QDkK4BbM
Life Cycle of the Red Blood Cell

Red Cell Production

**Recipe:**

**Ingredients:**

- Erythrocytes
- Glutin
- Erythropoietin
- Folic Acid
- Vitamin B12
- Iron
- Folate
- Globin
- Heme

**Directions:**

Under the instruction of erythropoietin, gently combine all ingredients above within a happy healthy marrow space. Remove erythrocytes from the marrow just before they are fully matured.

These are reticulocytes. Reticulocytes will mature to regular red blood cells in the blood stream. Perfectly formed red blood cells will last ~120 days.

So your patient has Anemia..

**Figuring Out Anemia**

- **Size Matters: MCV (Mean Corpuscular Volume)**

<table>
<thead>
<tr>
<th>Small (Microcytic)</th>
<th>Average (Normocytic)</th>
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- **Age Matters with MCV**

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Microcytic Anemia

- Iron Deficiency
- Chronic Disease
- Thalassemia
- Lead Poisoning
- Sideroblastic anemia

Laboratory Evaluation for Microcytic Anemia

- CBC with differential with smear
- Reticulocyte count
- Serum Iron, Ferritin, TIBC
- Lead level
- CRP (C-Reactive Protein), but no ESR (Erythrocyte Sedimentation Rate)
- Newborn Screen Results

Laboratory Evaluation for Normocytic Anemia

- CBC with smear
- Reticulocyte count
- Labs that reveal red cell destruction
  - CMP
  - LDH
- Coombs (DAT)

Microcytic Anemia

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Figuring Out Anemia

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<td>Lead Poisoning</td>
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<td></td>
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Hemolysis:
- ↑ AST
- ↑ Total Bilirubin
- ↑ LDH
- Schistocytes

Direct Coombs test / Direct antiglobulin test

Blood sample from a patient with immune mediated hemolytic anemia: antibodies are shown attached to antigens on the RBC surface. The patient’s washed RBCs are incubated with anti-human antibodies (Coombs reagent). RBCs aggregate: anti-human antibodies from links between RBCs by binding to the human antibodies on the RBCs.
Figuring Out Anemia

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Laboratory Evaluation for Macrocytic Anemia

- CBC with differential with smear
- Reticulocyte counts (these guys are big)
- Folate and B12
- CMP
  - EtOH, Liver disease
- TSH/FT4

What can a CBC teach us?

- White Blood Cells: WBC 27.60 x 10^3/UL
- Red Blood Cells: RBC 2.88 x 10^6/UL
- Hemoglobin: HGB 8.6 G/DL
- Hematocrit: HCT 25.5%
- Mean Corpuscular Volume: MCV 88.5 FL
- Mean Cell Hemoglobin: MCH 29.9 PG
- Mean Cell Hemoglobin Concentration: MCHC 33.7 G/DL
- Segmented Neutrophils: SEG% 71.9%
- Lymphocytes: LYMPH% 10.7%
- Monocytes: MONO% 9.9%
- Eosinophils: EOS% 2.5%
- Basophils: BASO% 1.7%
- Absolute Neutrophil Count: ANC 20.76 x 10^3/UL
- Nucleated Red Blood Cells: NRBC 0%
- Absolute Nucleated Red Blood Cells: ABSOLUTE NRBC 0.00 10^3/L

Case 1

- History
  - 2 year old presents with pallor
  - Noted by relatives
  - He is irritable, only has 20 word vocabulary
  - Diet: 40 oz milk/ day
  - Enjoys consuming ice, and has been seen eating paper

- Physical Exam
  - Temp 99 F, HR 146; RR 24; BP 86/44
  - Patient is overweight, irritable,
  - HEENT: non-icteric
  - Skin: pale, non-jaundiced
  - CV: Tachycardic, flow, systolic murmur III/VI
  - Abd: Soft abdomen, no hepatosplenomegaly
  - Neuro: no deficits, but stays mostly in bed; does not speak in sentences, 10 word vocabulary
Differential diagnosis-microcytosis

- Iron deficiency anemia
- Thalassemia
- Chronic disease/ inflammation- consider Juvenile Idiopathic Arthritis
- Lead poisoning
- Sideroblastic anemia

Case 1- investigations

- Cbc
- Wbc
- hct
- MCV
- Retin
- Fei

Case 1-assessment/plan

- 2 y o with severe microcytic anemia
- Severe Iron deficiency anemia
- Treatment involves iron replacement
- PRBC transfusion vs iron
- Intravenous vs oral iron
- Dietary modifications- maximum milk intake 24 oz/day

Blood transfusion indications

- Depends on acuity of presentation (long standing)
- Hb <7 g/dL is relative indication
- Provision of increased oxygen-carrying capacity

Blood transfusion

- Packed PRBC- 250-300 mL
- Dose: 1 unit in adults increases the Hb by 1 g/dL; in children, 5mL/kg increase the Hb by 1 g/dL
- Acute blood loss necessitates rapid replacement with PRBC
- Chronic blood loss necessitates slow replacement, such as 5 mL/kg of PRBC transfused over 3-4 hours to prevent pulmonary edema

Blood transfusion

- Leukocyte-depleted PRBC
- Contain less than 10^7 leukocytes per unit
- Indication: reduction of the incidence of febrile reactions, CMV transmission, HLA alloimmunization, platelet transfusion refractoriness
- Irradiated PRBC reduce risk of transfusion-related GVHD
Blood transfusions

- Washed PRBCs
- Saline-suspended red cells 200-250 mL
- Indication is to support patients with severe or recurrent allergic reactions, including patients with IgA deficiency

Transfusion complications

- Adverse effects occur after 1-3% of transfusions
- Most common adverse event is alloimmunization to WBC or platelets
- Non-infectious serious hazards of transfusions are hemolytic transfusion reactions and transfusion related acute lung injury (TRALI)
- There is a 1/100,000 fatality rate

Transfusion complications

Immunologic

- Hemolysis- antibody in patient or donor
- Febrile non-hemolytic reaction- WBC in blood component
- TRALI- WBC or cytokine induced in blood component
- Allergic- proteins in plasma component, IgE from donor
- Anaphylactic
- GVHD

Non-immunologic

- Infectious- viral, bacterial, parasitic
- Circulatory overload- whole blood vs PRBC transfusion
- Citrate toxicity- anticoagulant
- Electrolyte imbalance- aged units
- Iron overload with chronic transfusion
- Embolism- air or particulate matter
- Arrhythmia- infusion of cold products

Iron Repletion

<table>
<thead>
<tr>
<th>Oral</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Ease of administration</td>
<td>Faster correction than with oral</td>
</tr>
<tr>
<td>Super Cheap</td>
<td>Ideal for malabsorption or GI blood loss or chronic renal disease</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Non-palatable formulations</td>
<td>IV access</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>Infusion reactions</td>
</tr>
<tr>
<td>Abdominal discomfort, constipation</td>
<td>Theoretical risks of infection and cardiovascular disease</td>
</tr>
<tr>
<td>Lengthy treatment course</td>
<td>Cost</td>
</tr>
</tbody>
</table>

Iron- calculation

- **Ganzoni Equation**

\[
\text{Total Iron Deficit} = \text{Weight (kg)} \times (\text{Target Hb} - \text{Actual Hb}) \times 2.4 + \text{Iron stores (mg)}
\]

iron stores: 500 if Weight > 35kg
15 mg/kg if Weight < 35kg
Case 2

Case 2 - history

- Previously healthy 12 y o boy presents with syncope
- He had been tired for the past month, noticed episodes of dizziness with standing
- Became short of breath and fainted during football game
- Has had intermittent fevers, rash, and excessive bruising
- Admits to having bone pain, but has been very active as well

Case 2 - physical exam

- Temp 101.2 F, HR 120, RR 18, BP 112/82
- Alert, anxious, in mild distress due to leg pain
- Pale, non-icteric, no jaundice; petechiae, ecchymoses present
- Firm lymphadenopathy to neck and inguinal regions
- Tachycardic, II/VI flow systolic murmur, good perfusion
- Mildly distended abdomen, with hepatosplenomegaly
- No neurologic deficits

Case 2 - investigations

- WBC 2300, 15% segs, 60% lymphocytes, 25% "atypical" lymphocytes; Hb 5.5 g/dL; Hct 16.1%, platelet count 23,000
- MCV 105 fL
- Chemistries: LDH 1083, K 5.1, Creatinine 1.8, Calcium 9, Phosphorus 10, uric acid 12.2
- INR 1.5
- Peripheral blood flow cytometry: blasts

Differential diagnosis - macrocytosis

- Vitamin B 12/ folate deficiency
- Myeloproliferative disease- leukemia/ myelodysplastic syndrome/ aplastic anemia
- Medication effect (eg sulfa)
- Hypothyroidism
- Liver disease
- Alcoholism

Case 2 assessment/plan

- 15 y o with acute lymphoblastic leukemia, pre B cell type
- Pancytopenia is fairly commonly seen at presentation, but isolated severe anemia with or without bone pain is encountered as well
Leukemia

- Clonal expansion and arrest at a specific stage of normal lymphoid or myeloid cell development
- Most common malignancy of childhood
- Acute Lymphoblastic Leukemia (ALL) accounts for 75% of all leukemia cases
- Acute Myeloblastic Leukemia (AML) accounts for 20% of all leukemia cases
- Peak incidence between 2 and 5 years of age
- Complications - metabolic derangements, tumor lysis syndrome, infectious complications, bleeding

Leukemia- incidence

http://www.curetoday.com/tumor/childhood/treatment/

Leukemia- treatment

- Chemotherapy is required, with intensity based on risk stratification status
- Risk is determined based on age, WBC count at presentation, cytogenetics, leukemia involvement of CNS or testes, response to therapy

Leukemia- cure rates

Case 3

- 7 y o female presents for evaluation of fatigue - long standing, but interfering with activity the last month
- Dyspnea with exertion
- Has always looked pale with intermittent scleral icterus and jaundice
- Had jaundice as a newborn, required phototherapy
- Also complains of intermittent bone pain
- Father had required splenectomy and cholecystectomy as a teenager for a “blood problem”
Case 3 - physical exam

• Temp 98.3°F, HR 84, RR 22, BP 107/53
• Thin, small for age, 10% for height and weight
• HEENT: scleral icterus, splaying of facial bones
• Skin: pale, slight jaundice
• CV: RRR, normal S1, S2, II/VI flow murmur
• Abd: soft, no hepatomegaly, spleen tip palpable at 2 cm below left costal margin
• Neuro: no deficits

Case 3 - investigations

• WBC 5,700, HB 8 g/dL, hct 24%, platelet count 258,000
• MCV 67.8 fl
• Retic 4.2%, blood smear with microcytosis, target cells
• Nucleated RBC
• Direct Coombs negative
• Haptoglobin < 10 mg/dL
• LDH 377 U/L (311 upper limit of normal)
• Ferritin 191 ng/mL (normal)
• Hemoglobin electrophoresis did not show abnormal hemoglobins but fetal Hb and Hb A were elevated

Case 3 - assessment/plan

• 7 yo with chronic hemolytic anemia and microcytosis and molecular testing confirmed diagnosis of beta-thalassemia
• Patients have chronic hemolytic anemia, with risk of splenomegaly due to being a site of destruction and also site of extramedullary hematopoiesis, cholecystitis due to development of bile stones, and bone changes related to increase in hematopoiesis
• With increase in age, particularly during puberty, anemia may worsen
• Chronic transfusion therapy is indicated to stop extramedullary hematopoiesis and to allow for normal development

Hemoglobin types

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Composition</th>
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<tbody>
<tr>
<td>Hb A</td>
<td>Adult</td>
<td>αβββ</td>
</tr>
<tr>
<td>Hb A2</td>
<td>Minor adult Hb</td>
<td>ααδδ</td>
</tr>
<tr>
<td>Hb F</td>
<td>Fetal Hb</td>
<td>ααγγ</td>
</tr>
<tr>
<td>Hb Barts</td>
<td>Abnormal Hb</td>
<td>γγγγ</td>
</tr>
<tr>
<td>Hb H</td>
<td>Abnormal Hb</td>
<td>βγγγ</td>
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Thalassemia

• Derived from Greek word for sea, as it is common in people from the Mediterranean Sea, but also involving Africa, Asia and is now found everywhere
• It is a quantitative disorder of hemoglobin, characterized by decreased production of normal globin chains, leading to ineffective RBC production and increased hemolysis
• Wide array of genetic defects causing quite diverse clinical presentations
• Clinical syndromes are divided into alpha- and beta-thalassemias depending on how many of their respective globin genes are mutated
Thalassemia

Globins in excess precipitate and damage the RBC membrane

Imbalance between alpha and beta globins

Decreased production of alpha or beta globins

Anemia/ Bone marrow expansion/ Increased iron absorption/ Extramedullary hematopoiesis

Thalassemia- Alpha

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Alpha genes</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>aa/aa</td>
<td>4</td>
<td>normal</td>
</tr>
<tr>
<td>aa/a-</td>
<td>3</td>
<td>Silent carrier</td>
</tr>
<tr>
<td>a-/a-</td>
<td>2</td>
<td>Thalassemia trait</td>
</tr>
<tr>
<td>a-/a</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>a/-</td>
<td>1</td>
<td>Hb H disease</td>
</tr>
<tr>
<td>a/-</td>
<td>0</td>
<td>Hydrops fetalis</td>
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Thalassemia- Beta

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<tr>
<td>β/β</td>
<td>Normal</td>
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<tr>
<td>β/β+</td>
<td>Beta thalassemia trait</td>
</tr>
<tr>
<td>β+/β</td>
<td>Beta thalassemia intermedia</td>
</tr>
<tr>
<td>β/β</td>
<td>Beta thalassemia major</td>
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Beta 0= no detectable beta chain synthesis
Beta ++ reduced beta chain synthesis

Thalassemia

- Thalassemia minor (trait): no therapy needed, but counseling is indicated as progeny may be affected by more severe type; prenatal testing is routine in countries with high incidence
- Iron deficiency anemia mimics alpha-thalassemia trait, and masks beta-thalassemia trait, so if iron studies do not support iron deficiency do not treat. These patients will always be borderline anemic and microcytic
- Thalassemia intermedia: some require intermittent transfusions, iron overload is a risk due to increased iron absorption
- Thalassemia major: cure is stem cell transplantation; chronic transfusion therapy is needed to alleviate symptomatic anemia, suppress hematopoiesis, prevent bony complications and decrease organomegaly, improve growth, development, quality of life
Conclusions

• Anemia definition varies according to age and gender
• Broad differential diagnosis includes bone marrow and non-bone marrow (systemic) illnesses
• Nutritional deficits affect many patients of all ages and are most common
• Consider thalassemia in patients whose anemia does not resolve

Questions

References

• Pediatric Hematology/ Oncology Review Course Syllabus, 2017, section on Hemoglobinopathies
• McCullough, JM Transfusion Medicine, Elsevier 2005
• Auerbach M., and H. Ballard, Clinical Use of Intravenous Iron: Administration, Efficacy, and Safety, ASH Hematology the Education Program, 2010
• Medicines.org, Ferinject® SPC (Summary of Product Characteristics)