Anemia: A Practical Approach

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Conflicts of Interest

Pfizer/Bristol Meyer Squibb
  Independent Review Committee
  Scientific Ad Boards
  Consultant

Abbott
  Consultant

Unum Therapeutics
  DSMB
Agenda

Prevalent causes of anemia

Hemolytic anemias

Anemia in the elderly
ANEMIA

WHO classification of anemia

- < 12 g/dl for females
- < 13 g/dl for males
- < 11 g/dl for pregnant females

Anemia is a result of:
- decreased production
- increased destruction
- loss
ANEMIA: key labs

Reticulocyte count

absolute retics, corrected absolute retics, reticulocyte production index: correct for hemoglobin level

MVC

Peripheral smear
ANEMIA: decreased production

- Nutrient deficiency
  - Iron
  - B12
  - Folate
  - Copper
- Erythropoietin deficiency
  - Decreased renal production
- Inflammation
  - Multiple interacting pathways
- Mutations
  - Congenital and acquired
Evaluation of anemia by retics and MCV

Reticulocyte Index

Low retic index
- Iron deficiency
- Anemia of inflammation
- Sideroblastic anemia
- Thalassemias
- Renal failure
- Aplastic anemia
- Hypothyroidism
- B12/folate deficiency
- MDS
- Alcohol liver disease

High retic index
- Hemolytic anemias
- Blood loss

MCV

Low MCV
- Low retic index

Normal MCV
- High retic index

High MCV
ANEMIA: iron deficiency

- Iron deficiency anemia affects > 1.2 billion people

- Multiple factors
  - Increased needs: children, pregnancy, breast feeding
  - Decreased intake: vegan, malnutrition
  - Increased loss: menses, chronic anticoagulation or asa/nsaid use, intestinal parasites

- Factors affecting iron absorption
  - Gastric pH: requires low pH to change iron to $\text{Fe}^{2+}$
    - Proton pump inhibitors, atrophic gastritis, H. pylori
  - Abnormalities in duodenum and proximal jejunum
    - Resection
    - Celiac disease
ANEMIA: iron

Hepcidin is the gatekeeper that regulates iron level in plasma.

Increased hepcidin prevents mobilization of iron from stores and decreases absorption.

Decreased hepcidin allows release from stores and increased absorption.

The iron cycle and adaption to iron deficiency.

Camashella NEJM 2015
## Iron deficiency anemia vs anemia of inflammation

<table>
<thead>
<tr>
<th></th>
<th>Iron deficiency</th>
<th>Anemia of Inflammation</th>
</tr>
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<tbody>
<tr>
<td>Serum Fe</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>TIBC</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>saturation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>Very low</td>
<td>Normal or High</td>
</tr>
</tbody>
</table>
ANEMIA: iron deficiency

- Indications for IV iron
  - Failure of oral therapy
  - Intolerance of oral iron
  - GI abnormalities affecting absorption
  - Need for rapid restoration of stores
  - Jehovah’s Witness with blood loss
  - Renal dialysis
  - Heart failure?
  - “bloodless” surgery
## ANEMIA: iron deficiency

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical Replacement Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-molecular-weight iron dextran</td>
<td>25 mg as test dose; if no adverse reaction within 1 hr, then 975 mg over 4–6 hr for total dose of 1000 mg</td>
</tr>
<tr>
<td>Ferric gluconate</td>
<td>125 mg over 1 hr; repeat in seven subsequent sessions for total dose of 1000 mg</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>200 mg over 15–60 min, 300 mg over 1.5 hr, or 500 mg over 4 hr; repeat in one to four subsequent sessions for total dose of 1000 mg</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>510 mg over 17 sec; repeat in 3–8 days for total dose of 1020 mg</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>750 mg over 15–30 min; repeat in 7 days for total dose of 1500 mg</td>
</tr>
</tbody>
</table>
ANEMIA: B12 deficiency

• Megaloblastic anemia and demyelinating neurologic disease

• Hallmark macrocytic anemia, hypersegmented polys, megaloblastic maturation features
  – Can also have leukopenia and thrombocytopenia

• Neurologic findings due to demyelination of multiple tracts, can precede anemia
  – Cervical and thoracic dorsal and lateral columns
  – Cranial and peripheral nerves
  – White matter
ANEMIA: B12 deficiency

• Labs to **detect** B12 deficiency
  – Serum B12
    • < 200 pg/ml high sensitivity for B12 deficiency
    • < 350 pg/ml can see increased MMA
  – methylmalonic acid: more sensitive and specific
  – homocysteine

• Labs to **determine** etiology
  – “pernicious” anemia = autoimmune gastritis
    • Anti-intrinsic factor Abs and anti-parietal cell Abs
  – Atrophic body gastritis
    • Elevated fasting serum gastrin > 100 pmol/
ANEMIA: B12 and folate deficiency
ANEMIA: gastric bypass surgery

• Multiple nutrient deficiencies
• Type of bypass affects absorption
• Roux-en-y results in most severe deficiencies of
  – B12
  – Iron
  – Copper
ANEMIA: folate deficiency

• Water soluble with limited storage
  – Poor dietary intake, EtOH, bowl disorders previously associated with deficiency

• In 1997 US wheat supply fortified with folic acid

• Resurgence of folate deficiency possibly due to keto diet and paleo diet
ANEMIA: increased destruction

• Due to factors that affect integrity of RBC
• Will focus on hemolytic processes

• **Classification**
  – Intrinsic vs extrinsic to RBC
  – Non-immune
  – Autoimmune
  – Alloimmune

• **Site of destruction**
  – Intravascular vs extravascular
Hemolytic anemias

• How do you know it is hemolytic?
  – Increased reticulocyte count and absolute retics
  – *Peripheral smear*: abnormal RBC morphology
  – Decreased haptoglobin
  – Increased LDH
  – Increased indirect bilirubin
  – *DAT*: negative or positive?
    • If positive what type of antibody
Intrinsic RBC abnormality

• **Inherited**, with rare exceptions
  (PNH, acquired alpha thal)

• **Mutations resulting in:**
  – Membrane/cytoskeleton component defect
  – Hemoglobininopathy
  – Decreased enzymatic/metabolic function
Extrinsic RBC abnormality

- Antibodies
- Hypersplenism
- Shear stress
- Oxidants
- Pathogens
  - Malaria
  - Babesiosis
  - Clostridium perfringens
G6PD deficiency

• Most common inherited enzyme defect
  – Multiple mutations, track with ethnicity
  – can not reduce NADP or subsequently glutathione

• X-linked
  – males more significantly affected

• Most patients asymptomatic

• Hemolytic crises linked to oxidative stress:
  – Infection
  – Drugs
  – Fava beans: Mediterranean variant only
  – Chemicals
  – Diabetic ketoacidosis
HS and HE

**Figure 10-3** Blood film – hereditary spherocytosis

**Figure 10-4** Hereditary elliptocytosis

Bunn & Lux, Chapter 10

An & Mohandas, British Journal of Haematology, 141, 367–375
HS and HE

• Treatment: varies with severity
  – “typical” HS and HE: mild to moderate anemia, increased bili, splenomegaly, erythroid hyperplasia
  – Severe and atypical forms rare, manifest from birth, can have life threatening hemolytic crises

• Splenectomy
  – Normalizes RBC lifespan, anemia and increased bili usually resolve, spherocytes persist
  – Treat with folate especially if hemolysis persists

• Gallstones
  – Pigmented stones common
Immune hemolytic anemia

- Autoimmune

- Alloimmune
  - Transfusion
  - HSCT
  - Maternal/fetal: Rh, Kell

- Drug induced
Autoimmune hemolytic anemia

- Warm autoimmune hemolytic anemia (WAIHA)
- Cold agglutinin syndrome (CAS)
- Paroxysmal cold hemoglobinuria (PCH)
  - Donath Landsteiner antibodies
- Mixed AIHA
- Atypical AIHA (DAT negative)
Direct Antiglobulin Test (Direct Coombs' Test).

Autoimmune hemolytic anemia

The diagram illustrates the complement pathway in autoimmune hemolytic anemia. The process begins with the formation of an antigen-antibody (IgG) complex, which triggers the classical pathway. This leads to the C1 complex, which activates the C2a and C4b fragments. The alternative pathway is activated, resulting in C3 convertase and C3 hydrolysis. C3b and C3a fragments are produced, with C3b cleaving C5 into C5a and C5b. The C5b, C6, C7, C8, and C9 together form the cyllindrical membrane attack complex, leading to cell swelling and bursting.
WAIHA

- Incidence: 1 to 2 cases/100,000 per year
- F > M
- Adults > children
- IgG pan-agglutinins, react with all cells
  - Ag target usually protein, often Rh but poorly defined
  - Extravascular hemolysis
- Primary (idiopathic)
- Secondary
  - CLL
  - Lymphomas and lymphoproliferative disorders
  - SLE
Hgb ↓
Retic ↑
LDH ↑
Bilirubin ↑
Haptoglobin ↓

DAT:
IgG +
C3d +/-
Warm AIHA

• **1<sup>st</sup> line treatment**
  – Steroids

• **2<sup>nd</sup> line**
  – rituximab
  – mycophenelate
  – sirolimus
  – IgG

• **3<sup>rd</sup> line**
  – azathioprine, cyclosporine, pulse dose IV cyclophosphamide

• **More**
  – High dose cyclophosphamide, auto-HSCT
Cold agglutinin syndromes: clinical features

- Symptoms and findings
  - Chronic anemia
  - Intravascular hemolysis
  - Hemoglobinuria, urine hemosiderin
  - Plasma hemoglobin
  - Acrocyanosis
Cold Agglutinin Syndromes: Diagnosis

- Hgb ↓
- Retic ↑
- LDH ↑
- Bilirubin ↑

**DAT:**
- IgG -
- C3d +

www.pathologystudent.com

Cold agglutinin titer
Etiology and treatment of primary cold agglutinin disease

Ulrich Jaeger Blood 2017;130:392-393
Anemia: the elderly

Stauder, Blood 2018
Anemia: the elderly

- Common finding, often vexing diagnostic challenge
- Anemia linked to worse outcomes in elderly patients and is a marker for mortality
- Same possible etiologies as in younger patients
  - Everything discussed so far
  - Decreased epo production and/or decreased marrow response
  - “inflammaging”
  - Non-hematopoietic malignancy
- But clonal processes need to be considered in patients with unexplained anemia
  - Molecular diagnostic techniques have spawned new classifications
Possible mechanisms of anemia in older adults

Reinhard Stauder et al. Blood 2018;131:505-514

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Anemia: the elderly

- Comprehensive lab testing should be performed
  - CBC, comprehensive metabolic panel, iron studies, B12, folate, ESR, CRP, EPO, TSH, SPEP, consider: haptoglobin, DAT, LDH, CAG titers

- If unrevealing, molecular diagnostic testing and marrow biopsy may be needed guided by severity of anemia and co-morbid disease
### Classification of anemias

<table>
<thead>
<tr>
<th>Condition</th>
<th>UA</th>
<th>ICUS-A</th>
<th>CCUS</th>
<th>IDUS</th>
<th>CHIP</th>
<th>MDS</th>
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<td>Low risk</td>
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<td>Cytopenia*</td>
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<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Dysplasia</td>
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<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<td>BM blasts, %</td>
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<td>&lt;5%</td>
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<td>&gt;20%</td>
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<td>Cytogenetic abnormalities</td>
<td>nd</td>
<td>−/+</td>
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<td>−/+</td>
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<td>Molecular aberrations</td>
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| Comment                    | Workup needed | Cytopenic patients | Noncytopenic patients | Classification of MDS is based on WHO definition |

**ICUS-A:** idiopathic cytopenia of unknown significance w/isolated anemia  
**CCUS:** clonal cytopenia of undermined significance  
**IDUS:** idiopathic dysplasia of undetermined significance  
**CHIP:** clonal hematopoiesis of indeterminant potential

Stauder Blood 2018
Anemia: the elderly

• Treatment is **supportive** based on degree of anemia and findings
  – Replace nutrients
  – Optimize renal and cardiac function and concomitant meds
  – Transfusion if present with severe symptomatic anemia
  – ESAs have worked in small studies, certainly overcome the inflammatory driven anemia and work in early stages of CCUS, IDUS, and MDS but side effects and burden of care need to be considered

• Treatments in **development** to target
  • Hepcidin
  • BMP6
  • hemojuvelin