Approach to Anemia

Franchot van Slot MD/PhD

Why Does It Matter?

• Prevalence of anemia
  – Up to 61% in men
  – Up to 41% in women
• Complicates many other diseases: CHF, CAD with increased mortality1,2
• Correction can dramatically improve quality of life3
• Mortality of anemia
  – Increased risk for all cause mortality (AUC) for Hgb <11 HR 2.49
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  – Increased risk for 1st hospitalization HR 2.36
  – Increased risk for all CV specific hospitalization HR 2.09
  – Culleton et al. Blood 2006; 107: 3842-3846
• Often indication of an occult problem e.g.:
  – Fe deficiency pointing to GI bleed, indicating GI mass
  – Anemia of Chronic Disease suggesting worse diagnosis

Traditional Approaches to Anemia Diagnosis:

Three main approaches:

Morphologic: differentiating cause based on rbc size. Typically leads to other distinguishing features such as hypo/hyperchromic, retic count/rdw, ferritin, etc.

Kinetic: Anemia results from one (or more) of three potential mechanisms:
  - Direct blood loss
  - Decreased rate of blood production
  - Increased rate of blood destruction

Shotgun: sending off a large array of lab tests with the hope that one will be abnormal and make diagnosis obvious
Problems with traditional approaches:

Morphologic:
- Algorithms are non-intuitive, easily forgotten
- Algorithms rarely get to the source of anemia quickly
- Algorithms often rely on piecemeal diagnostics
- MCV is often normal even in severe anemia (~60-70% of anemia workups in my experience)
- Different causes of anemia can counteract the effect on MCV, e.g. Fe-deficiency/B12 deficiency cause small/large MCV and average to normal
- Large differential remains after working through most algorithms
- MCV does not definitively rule in or rule out any diagnosis
- No guidance for next steps when algorithm breaks down
- Hypochromia (where part of the algorithm) is not easily assessed without looking at peripheral smear

Kinetic Approach:
- Typically requires larger number of lab tests to get to diagnosis
- Unnecessarily long evaluation and thought process employed for simple anemia cases
- Bone marrow biopsies may be over-utilized

Shotgun Approach:
- Very costly
- Many unnecessary tests to come to conclusion
- Multiple, competing results can confuse diagnosis, e.g. Fe-deficiency, vitamin deficiency can cause bone marrow suppression

An Intuitive Approach

Developed out of:
- dissatisfaction, inadequacy, and lack of clarity with traditional approaches
- the observation that diagnosis can usually be made rapidly, easily, and with minimal studies
- a hybridization of iron studies analysis and the kinetic approach

Brief Algorithm

Step 1. Fe studies (serum Fe, TIBC, ferritin)...

Step 2. Kitchen Sink Approach

Step 3. Cause-specific Investigations

...Along with history of course
Step 1. Iron Studies

Two most common causes of anemia:
- Iron deficiency anemia (IDA)
- Anemia of chronic disease (ACD)

Together, these account for ~70% of all anemia.

- IDA and ACD can usually be quickly identified (in their pure forms) with three lab tests:
  - Serum Fe
  - TIBC (and/or transferrin saturation)
  - Ferritin

- Starting with iron studies in algorithm:
  - Often allows for a rapid diagnosis
  - Dramatically reduces the number of tests necessary for most anemia diagnoses
  - Does not add an unnecessary step or lead to unnecessary tests because iron studies are likely to still be required for Step 2.

Serum Fe

- Total iron in the serum, bound and unbound
  - Relatively little free iron in serum: toxic, leads to free radical generation

- Multiple iron binding proteins in serum
  - Major iron binding protein is transferrin
  - Other iron binding proteins include:
    - Lactoferrin
    - Metalloproteinases

TIBC: Total Iron Binding Capacity

- The total complement of protein in the serum capable of binding iron
- Essentially an inverse measure of transferrin saturation. $\text{Transf Sat} = \frac{\text{serum Fe}}{\text{TIBC}}$
- transferrin accounts for major component of TIBC:
  - Most important iron pool
  - Highest rate of iron turnover
  - Glycoprotein
    - $2$ Fe bound for every transferrin molecule: $\text{apo} \text{transferrin} + \text{Fe} \rightarrow \text{transferrin}$

- TIBC is distinguished from UIBC (unsaturated iron binding capacity), the remaining sites capable of binding iron
Transferrin

- Major iron binding protein in blood.
  - Accounts for ~70% of iron binding in blood
  - Major transporter/trafficker of (Non-Hgb) Fe in blood
  - Transfers Fe to and from tissues

Ferritin

- Storage depot for Fe
- Intracellular, present in all cell types
- Accumulates in aggregates in tissues, called hemosiderin
- Reduces iron toxicity
- Apoferritin + Fe = ferritin
  - Ferritin in high concentration in liver, spleen, bone marrow
    - Hepatic/splenic damage may release ferritin into blood
- Acts as buffer between Fe deficiency and iron overload
- Upregulated in chronic disease, acute inflammation (acute phase reactant).
  - Teleologically, apoferritin binds Fe, limiting access to bacteria and preventing bacterial growth, septicemia

Typical Patterns

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Fe</th>
<th>Trans sat</th>
<th>TIBC</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe defic.</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>ACD</td>
<td>↓ to Nrl</td>
<td>↓ to Nrl</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

Typical Reference Ranges:
- serum Fe: 50-170ug/dl
- transferrin saturation: 15-50%
- TIBC: 250-370ug/dl
- ferritin: 15-250ug/dl
Diagnosis and Diagnosis

Fe deficiency - why is the patient iron deficient? 
- Poor intake/absorption? 
  - inadequate intake, rare in western society 
  - malabsorption syndromes, Crohn's dz, etc, more common causes 
  - Treatment: PO/IV Fe, Vitamin C, folate 
- Blood loss? 
  - far and away most common cause 
  - identifying source of blood loss is imperative 
  - stop source of blood loss, replace losses with Fe, Vit C, folate, transfusion if prudent

Anemia of Chronic Disease
- What is the chronic disease? Key question if non-obvious 
  - Treatment: reverse chronic disease if possible, consider erythropoietin injections 
  - do not give Fe unless also clearly Fe deficient: may unnecessarily increase iron stores without raising Hgb, leading to potential Fe toxicity

What if the source is still unclear?

~70% of anemia identified with first three lab tests. That leaves 30% other 
anemia may not fall neatly into Fe-deficiency, ACD categories: 
- inadequate degree of Fe defic. or ACD to explain degree of anemia 
- high serum Fe, low ferritin 
- high serum Fe, high ferritin: mixed picture 
- relatively normal Fe studies, but significant anemia 
- sudden development of anemia without major changes in iron studies 
- anemia in adults is typically polyfactorial

That's when I head to my kitchen sink model...

N. B. IDA and ACD can lead to/ be associated with degrees of bone marrow suppression of their own accord. 
Keep the importance of starting with Fe studies rather than immediate shotgun approach, which may add diagnoses unnecessarily

Kitchen Sink

Beyond just throwing the kitchen sink at the problem...
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Kitchen Sink Model of Anemia

Hematuria, upper/lower GI bleeds, trauma/bleeding, epistaxis, bruising, phlebotomy, surgery, parasites, etc.

Kitchen Sink Model of Anemia

Bone Marrow

Transfusion

rbc's
Kitchen Sink Model of Anemia

Sources of Problems

- Bone Marrow production of red blood cells: depends on:
  - adequate nutritional support: Fe, folate, B-12
  - ability to get out of the marrow: myelodysplastic syndromes, malignancy
  - adequate stimulation to production: erythropoietin
  - proper synthesis: thalassemias

- Hemolysis can be seen with:
  - structural rbc problems: spherocytosis, sickle cell, G6PD defic, spectrin abnormalities, etc
  - autoimmune attack: SLE, PNH, maternal-fetal, drug-induced
  - Drugs: direct toxic effect: osmotic agents, chemotherapeutics, antibiotics, etc.
  - Mechanical: vasculitis, mechanical heart valve, endocarditis
Kitchen Sink Model of Anemia

1. Bone Marrow
   - Hematuria, upper/lower GI bleeds, trauma/bleeding, epistaxis, bruising, phlebotomy, surgery, parasitism, etc.

2. Transfusion
   - Vampirism

3. Retimization
   - rbc's
   - Hemolysis

Diagnosis 1: Bone Marrow

Bone Marrow Problem:
   - Bone marrow produces reticulocytes.
   - Reticulocyte: immature rbc with endoplasmic reticulum, ribosomes, RNA remaining
   - Reticulocytes should be sig elevated in anemia.
   - Anemia due to bone marrow problem should lead to low or inappropriately normal reticulocyte count/index

   If reticulocytes low or normal, in face of anemia, suspect bone marrow suppression

   Then, why are retics low?
   - Epo level, especially in any renal disease (anemia of chronic kidney disease)
   - Myelodysplastic syndromes/myelofibrosis: check peripheral smear (heavily, anaemia), consider bone marrow biopsy
   - Vitamin deficiency: high MCV, inappropriately normal MCV
     - Check B12 (MCV > 114 highly assoc. with B12), folate,
     - Direct toxic effect: chemotherapy, EtOH, drugs
     - Viral: Parvovirus B19 – infects erythroid precursors

Reticulocyte Index

- Reticulocyte Index = reticulocyte count * Pt HCT/Nrl HCT. Nrl HCT=45

- Reticulocyte Index:
  - 1-2 Normal
  - <1 Decreased retic production
  - >2 Increased, compensatory production
Diagnosis 2. Hemolysis

- Check Tbil first (quick, usually free with a CMP), fractionate looking for indirect bili
- Tbil, ind bili elevation in hemolysis (bilirubin is breakdown product of heme moieties)
- Check UA for blood without red cells (if red cells are present suggests GU bleeding source)
- either due to free hgb in urine or myoglobin (rhabdo)
- Consider LDH (released from rbcs with hemolysis or haptoglobin, elevated LDH, reduced haptoglobin strongly indicative of hemolysis
- Consider Epo (compensatory rxn to blood loss)
- Consider autoimmune causes
- history is key: rash, renal failure, joint pain
- consider AKA for SLE, Direct/Indirect Coombs
- recent transfusion?
- peripheral smear (e.g. schistocytes for TTP)
- Structural defects/high defects?
  - personal history: associated pain, bruising, association with food, meds
  - family history
  - peripheral smear, SPEP (serum protein electrophoresis)
- Mechanical causes?
  - prosthetic heart valve
  - endocarditis
  - hemodialysis
- Drugs- consider antibiotics, chemotherapy, directly toxic agents.
  - removal of offending agent should clarify diagnosis

Diagnosis 3. Direct blood loss

Blood loss

- History, obviously, is key
- Guaiac, EGD/colonoscopy
- U/A
- Consider CT scan for occult bleed
- stool studies for O+P
- menorrhagia
- phlebotomy
- look for two small holes in the neck region

Brief Algorithm

Step 1. Clear Diagnosis?

NO

YES

Step 2. Kitchen Sink Approach

Step 3. Cause-specific Investigations
Algorithm Step 3. Specific Investigations

- Fe-deficiency anemia requires seeking a source of blood loss
- Anemia of chronic disease requires an attempt at diagnosing the chronic disease
- Investigating the cause of bone marrow suppression is essential:
  - adequate nutritional support: Fe, folate, B-12
  - ability to get out of the marrow: myelodysplastic syndromes, malignancy
  - proper synthesis: thalassemias
- Identifying the cause of hemolysis is critical:
  - structural rbc problems: spherocytosis, sickle cell, thalassemia G6PD defic, spectrin abnormalities, etc.
  - splenic sequestration: thalassemias
  - autoimmune attack: SLE, PNH, maternal-fetal, drug-induced, transfusion rxn
- drugs: direct toxic effect: osmotic agents, chemotherapeutics, antibiotics, etc.
  - mechanical: vasculitis, mechanical heart valve, endocarditis

Diagnosis 4. Combined blood loss, blood gain: Undeadism

Pre-exposure
- More difficult diagnosis: very rare
- Diagnosis only formally possible at autopsy
- Otherwise, diagnosis of undadism
- Edta to blood transport mechanism requires additional study
- Characterized by classical syndromes
  - prodrome demonstrates neck rash, wounds
  - severe pallor, alternating with flushing
  - personality disorder NOS
  - circadian rhythm shifts
  - photosensitivity
  - highly contagious
  - photosensitive skin
  - photosensitive night
  - high fever, night sweats
  - vasoconstriction
  - photosensitive skin
  - high fever, night sweats
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Conclusion

- Typically only a few tests are necessary to make a diagnosis
- Progression to diagnosis is systematic, intuitive
- "Shotgun" labs increase cost, confuse diagnosis and are unnecessary when a reasoned approach is used
- Determining the cause of anemia is critically important:
  - many diseases may remain subclinical otherwise
  - diagnosis of anemia provides clues to general medical condition
  - treatment varies markedly depending on cause of anemia
  - treating an assumed cause of anemia (without a true diagnosis) can have very negative consequences (complications of transfusion, iron infusion), missed diagnosis of autoimmune disorder, malignancy
  - allows for quarantine of contagious syndromes (e.g., nosferatu)