Approach to Anemia

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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 mortality[1,2]
- Correction can dramatically improve quality of life[3]
- Mortality of anemia
  - Increased risk for all cause mortality HR 4.29
  - Increased risk for all cause mortality (ACM) for Hgb <11 HR 5.01
  - Increased risk for ACM after controlling for GFR HR 4.29
  - Increased risk for 1st hospitalization HR 2.16
  - Increased risk for all CV specific hospitalization HR 2.49
    - Culleton et al. Blood 2006; 107: 3842-3846
- Often indication of an occult problem e.g.:
  - Fe deficiency pointing to GIB, indicating GI mass
  - Anemia of Chronic Disease suggesting worse diagnosis

[1]Ezekowitz et al. Circulation. 2003;107:223.
[2]Corti et al. American Journal of Cardiology 1997; 79: 120-127
[3]Crawford et al. Cancer 2002; 95: 888–895,

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, ~50-75% of anemia workups in my experience
- -different causes of anemia can counteract effect on MCV,
  - e.g. Fe-defic/ B-12 defic 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) not easily assessed without looking at peripheral smear

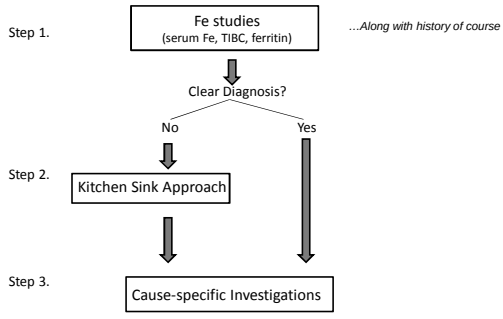
Kinetic Approach:
- -typically requires larger number of lab tests to get to diagnosis
- -unnecessarily long evaluation and thought process employed for simple anemia cases
- -Bone marrow biopsies may be over-utilized

Shotgun Approach:
- -very costly
- -many unnecessary tests to come to conclusion
- -multiple, competing results can confuse diagnosis , e.g. Fe-defic., 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. 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. Transf Sat = serum Fe/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 *apo*transferrin + Fe → 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

Condition	Serum Fe	Transf sat	TIBC	ferritin
Fe defic.	⇩	⇩	⇧⇧	⇩
ACD	⇩ to Nrl	⇩ to Nrl	⇩⇩	⇧⇧⇧

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 erythropoeitin injections
  - -do not give Fe unless also clearly Fe deficient: may unnecessarily increase iron stores without raising hgb, leading to potential Fe toxicity

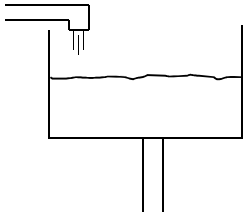
What if the source is still unclear?

~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. Hence 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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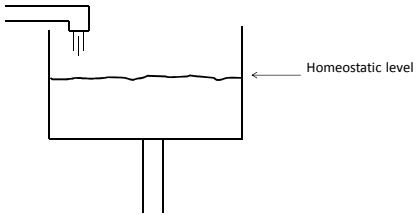
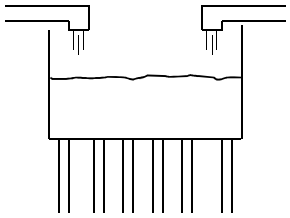


Beyond just throwing the kitchen sink at the problem…

Kitchen Sink Model of Anemia



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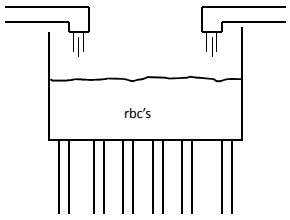

Hematuria, upper/lower GI bleeds, trauma/bleeding, epistaxis, bruising, phlebotomy, surgery, parasites, etc

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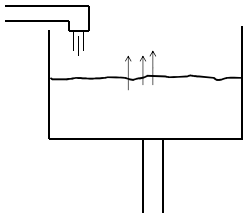

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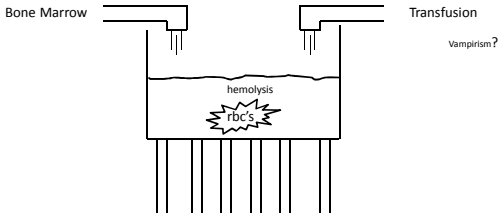


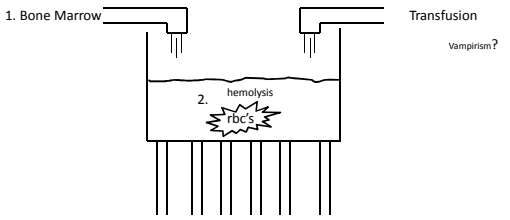
Hematuria, upper/lower GI bleeds, trauma/bleeding, epistaxis, bruising, phlebotomy, surgery, parasites, etc

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: thallassemias

-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



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

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.

-any 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 (teardrops, anisocytosis), consider bone marrow biopsy

-vitamin deficiency: High MCV, inappropriately normal MCV? Check B-12 (MCV > 114 highly assoc. with B-12), folate,

-direct toxic effect: chemotherapeutics, EtOH, drugs

-viral: Parvovirus B-19 – 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

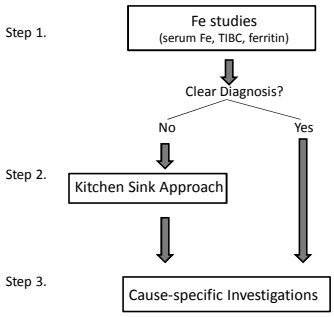
Diagnosis 2. Hemolysis

-Check Tbili first (quick, usually free with a CMP), fractionate looking for indirect bili
  -Tbili, Ind bili elevation in hemolysis (bilirubin is breakdown product of heme moiety)
-Check U/A 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 ANA for SLE, Direct/Indirect Coombs
  -recent transfusion?
  -peripheral smear (e.g. schistocytes for TTP)
-Structural defects/Hgb 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, chemotherapeutics, 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



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
- -adequate stimulation to production: erythropoietin
- -proper synthesis: thallassemias

-Identifying the cause of hemolysis is critical:
- -structural rbc problems: spherocytosis, sickle cell, thallassemia G6PD defic, spectrin abnormalities, etc
- -splenic sequestration: thallassemias
- -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

Post-exposure

-More difficult diagnosis: very rare
-Diagnosis only formally possible at autopsy
-Otherwise, diagnosis of exclusion
-PO to IV blood transport mechanism requires additional study
-Characterized by classical syndrome:
- -prodrome demonstrates neck rash, wounds
- -severe pallor, alternating with flushing
- -personality disorder NOS
- -circadian rhythm shifts
- -photosensitivity
- -highly contagious
- -hypothermia
- -conjunctivitis/iritis
- -hyperkinetic/ADHD vs bipolar
- -enlarged canines
- -significant thirst (possibly ADH mechanism)
- -anaphylaxis to garlic supplements, purified water
- -myocardial sensitivity to cellulose-containing products
- -not associated with decreased life span
- -apparently confers innate resistance to CHF, CAD, all cause mortality

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)