Approach to Anemia

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Disclosures

• **Advisory Board**: Pfizer

• **Research**: Novartis, Esai, BMS, Daiichi Sankyo
By the end of this talk you will be able to:

1. State the 3 pathogenetic mechanisms of anemia and the 3 categories of anemia based on size of the red cell.

2. List and explain the 4 most important diagnostic tests for anemia.

3. Compare alternatives for iron supplementation.

4. Discuss indications and dosing considerations for erythropoietin in anemia management in the non-CKD population.

Hopefully, I know more.

Definitely, you know more.
Approach to anemia

Pathogenetic/kinetic approach

What is the *mechanism* of anemia?

Clinical/MCV approach

What is the *cause* of anemia?

https://www.google.ca/search?q=small+medium+large
https://www.google.ca/search?q=bone+marrow+making+blood+cells
https://www.google.ca/search?q=bone+marrow+making+blood+cells
Pathogenetic approach

- There are only 3 mechanisms of anemia:
  1. Increased loss of red cells (ie. bleeding)
  2. Increased destruction of red cells (ie. hemolysis)
  3. Decreased production of red cells

- It’s all about the reticulocyte!
  - Young red cells, normally represent 0.5-2% of circulating red cells, mature over ~1 day, bigger than mature red cells
  - The “right thing” for the marrow to do in an anemic pt is make more reticulocytes

https://www.google.ca/search?site=&tbm=isch&q=reticulocyte&imgdii=MpgBqpZsVl_yAM%3A%3BMpgBqpZsVl_yAM%3A%3BVch-VAv9cqTzM%3A&imgrc=MpgBqpZsVl_yAM%3A
Pathogenetic approach

1. **Increased loss** of red cells (ie. bleed)
   - Bone marrow does the right thing

2. **Increased destruction** of red cells (ie. hemolysis)
   - Bone marrow does the right thing

3. **Decreased production** of red cells
   - Bone marrow **cannot do** the right thing

**Important to note that it is “inappropriate” for retics to be normal in an anemic patient**
What does the bone marrow need?

- **Nutrients**
  - Iron, B12, folate

- **Hormones**
  - Eg. Erythropoeitin

- **No infiltration**
  - Eg. myeloma

- **No failure**
  - Eg. aplastic anemia

- **No suppression**
  - Eg. chemotherapy

...to do the right thing in the face of anemia, ie. make reticulocytes!
Clinical approach

- Divides anemias into different groups based on the **size** of the red cell (mean corpuscular volume, **MCV**)
  1. Microcytic
  2. Normocytic
  3. Macrocytic

- Each group has an associated “list” of anemias
Clinical approach

Microcytic anemias

- Thalassemia
- Anemia of chronic disease (but more commonly normocytic)
- Iron deficiency
- (Lead poisoning, Sideroblastic anemia)

Microcytic anemias are pretty easy to figure out!

And almost never represent a bone marrow disorder.

https://www.google.ca/search?site=&tbm=isch&q=animal+long+tail&imgurl=kp07qfDrIL94YM%3A
Clinical approach

**Normocytic anemias**

- Bleeding*
- Hemolysis*
- Early iron deficiency
- Anemia of chronic disease
- Chronic kidney disease
- Bone marrow disorder**
  - Infiltration, eg. lymphoma
  - Failure, eg. myelodysplasia
  - Suppression, eg. chemotherapy

*Can be macrocytic if reticulocytes (big) quite high

**Can be macrocytic too
Before we do macrocytic anemias

- **What is megaloblastosis?**
  - Refers to certain morphologic abnormalities on blood smear
    - Hypersegmented neutrophils and large oval red cells
    - You will know if a patient has megaloblastic changes from the hematopathologist’s comment on blood smear
  - Indicates **defective DNA synthesis**
  - A very helpful finding because there are very few causes
    - B12 deficiency
    - Medications that interfere with DNA synthesis
Clinical approach

**Macrocytic anemias**

- “False macrocytosis”*  
  - Bleeding or hemolysis
- Megaloblastic
  - B12 (or folate) deficiency
  - Medications
- Nonmegaloblastic
  - Alcohol excess
  - Liver disease
  - Hypothyroidism
  - Bone marrow disorder**
    - Infiltration, failure, suppression

*Due to increased reticulocytes (big)

**In practical terms, the same list as for normocytic anemias**
Diagnostic testing
4 most important tests

1. **Reticulocyte count**
   - **If high:** mechanism is destruction or loss
   - **If not high:** inappropriate, means decreased production

2. **MCV**
   - Should then focus your testing on the right “list”

3. **WBC and platelet count**
   - If also low, more concerning for decreased production

4. **Blood smear**
   - Not always truly needed, eg. Fe deficiency
   - But can have very helpful clues, eg.
     - Megaloblastic changes for B12 deficiency

Another important “test”

- The old CBC!

- Very helpful in terms of diagnosis, eg.
  - Last week Hb was 140, now it is 60: **must be bleeding or hemolysis**
  - Hb has gradually drifted down from 125 to 105 over 2 years: more **suggestive of chronic problem** such as indolent bone marrow disorder

What next?

- Tailor testing based on clinical scenario & initial results

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>WBC &amp; pltS</th>
<th>Blood smear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy menstrual bleeding</td>
<td>Low or “normal”</td>
<td>Pencil cells</td>
</tr>
<tr>
<td>Jaundice &amp; fatigue</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Weight loss &amp; sweats</td>
<td>Low or “normal”</td>
<td>High</td>
</tr>
</tbody>
</table>

Iron deficiency? **Ferritin**

Hemolysis? **LDH, bilirubin, haptoglobin, direct antiglobulin test**

MDS? **BM Bx**
A word on bone marrow biopsies

- When faced with anemia, patients & physicians are often worried about **hematologic malignancies**

- Sometimes, appropriate to **proceed quickly to BM Bx**
  - Sick patient, eg. anorexia, weight loss, sweats
  - No obvious easy explanation, eg. iron deficiency
  - Low or “normal” reticulocyte count
  - Bicytopenia or pancytopenia
  - Abnormal cells, eg. blasts, lymphoma cells, dysplasia

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Ferritin...my pet peeve

- There is a widespread belief that ferritin, as an acute phase reactant, should not be tested in hospitalized pts.

- However, using BM Bx as gold standard in 259 older pts, the following LRs were derived:
  - Ferritin <18: LR 41.5
  - Ferritin >100: LR 0.13

- When interpreted appropriately, ferritin is still the best test for iron deficiency!

Selected topics in the treatment of anemia

1. A hematologist’s view of vitamin supplements
2. EPO in the non CKD population
3. Future treatments for ACD?
A motherhood statement

- Anemia always has an underlying cause

- The treatment of anemia is to treat the cause!
  - Myeloma: chemotherapy
  - Iron deficiency: stop bleeding & give Fe
  - Autoimmune hemolytic anemia: steroids
  - Etc, etc, etc
Vitamin supplements
Iron supplementation

1. Oral
   - Appropriate & adequate in most cases
   - Recall that oral iron absorption is poor (~10%), even when increased in iron deficiency (~30%)
   - **LOTS** of GI side effects, esp. constipation

2. Intravenous
   - Used for severe IDA, esp. if unable to tolerate oral iron

3. Intramuscular
   - **Never!** – unreliable, painful, stains skin
# The oral Fe supplements

Recommended daily dose – 150-200 mg

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Elemental Iron</th>
<th>Iron form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feramax</td>
<td>150 mg</td>
<td>Iron polysaccharide</td>
</tr>
<tr>
<td>Ferrous Fumarate (Palafer)</td>
<td>100 mg</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Ferrous Sulfate (generic)</td>
<td>65 mg</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Ferrous Sulfate (Slow Fe)</td>
<td>50 mg</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Ferrous Sulfate Elixer (Fer in sol)</td>
<td>44mg/tsp</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>35 mg</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Materna</td>
<td>27 mg</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Floradix</td>
<td>4 mg/tsp</td>
<td>Iron salts</td>
</tr>
<tr>
<td>Proferrin</td>
<td>11 mg heme iron</td>
<td>Heme iron</td>
</tr>
</tbody>
</table>

…and many more
Two clinical scenarios

1. “Pharmacist, my iron supplement is not working!”
   - May be using a supplement with little elemental iron
   - May **not** have iron deficiency anemia!

2. “Pharmacist, I increased my iron supplement to 3 times daily, it is not working & I have horrible constipation!”
   - There is some evidence that high & frequent doses of oral iron lead to **decreased** iron absorption
   - Due to increase in hepcidin - blocks iron absorption

The IV iron supplements

- IV iron “markedly” benefits selected people with severe IDA
- No formulation proven safer than others

<table>
<thead>
<tr>
<th>Product (brand name)</th>
<th>Approved indications</th>
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<tbody>
<tr>
<td>iron dextran</td>
<td>iron deficiency when oral iron inadequate</td>
</tr>
<tr>
<td>Dexiron</td>
<td></td>
</tr>
<tr>
<td>sodium ferric</td>
<td>iron deficiency anemia of hemodialysis</td>
</tr>
<tr>
<td>gluconate (Ferrlecit)</td>
<td></td>
</tr>
<tr>
<td>iron sucrose</td>
<td>iron deficiency anemia in CKD</td>
</tr>
<tr>
<td>Venofer</td>
<td></td>
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A brief love affair

Vancouver Coastal Health

ORDERS
COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS
IRON IV THERAPY FOR RENAL PATIENTS

☐ ferumoxytol (FERAHHEME)

Ferumoxytol is contraindicated in patients with any known history of drug allergies (including allergies to other IV iron preparations)

Give ferumoxytol 510 mg IV in sodium chloride 0.9% 50 mL infused over 15 minutes
B12 & folate supplementation

- Because **malabsorption** is a common cause of **B12** deficiency, **IM** B12 supplementation has long been considered standard & necessary
  - Eg. B12 1 mg IM daily X 5, then monthly
  - But high dose oral B12 is likely adequate (more later…)

- I cannot think of any interesting controversies regarding **folic acid** supplementation!
  - Eg. folic acid 0.4 - 1 mg PO daily

**BC Guidelines [Internet]. Vancouver: BC Medical Association; 2012 [updated 2013 May 1; cited 2016 Apr 18]. Available from: [http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12](http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12)**
Is oral B12 OK?

38 pts with B12 def randomized to B12 2 mg PO daily vs. B12 IM 1 mg X 9

- ¾ of pts thought to have malabsorption as cause of B12 def
- Similar results in study of 60 pts with more severe B12 def using 1 mg PO B12

- **High dose** oral B12 seems to be adequate, even if malabsorption
- **But**…not as initial repletion for severe B12 def, bad neuro symptoms, poor compliance

BC Guidelines [Internet]. Vancouver: BC Medical Association; 2012 [updated 2013 May 1; cited 2016 Apr 18]. Available from: [http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12](http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12)
EPO in non CKD populations

https://www.google.com/search?site=&tbm=isch&source=hp&biw=1920&bih=900&q=x&oq=x&gs_l=img.3..0l10.1636.1636.0.1894.1.1.0.0.0.0.73.73.1.1.0....0...1ac.1.64.img..0.1.72.QIZogB5DImo#tbm=isch&q=lance+armstrong&imgref=ar_HoceAWNszRM%3A
EPO for myelodysplasia

- **MDS** is a hematologic malignancy with bone marrow failure
  - A spectrum from indolent “lower risk” disease to aggressive “higher risk” disease (→ acute leukemia)
  - A huge burden of anemia & transfusion dependence

- **EPO (+/- G-CSF)** often tried in “lower risk” MDS
  - Not just “replacing” EPO as in CKD, but trying to improve faulty erythropoiesis
  - Endogenous EPO levels often normal or high in MDS

EPO + G-CSF in MDS

110 pts

- 1/3 pts respond to EPO
- 1/2 pts respond to EPO + G-CSF
- Responders enjoy a better QOL & longer survival

36%
No diff in OS, AML, QOL in all pts
But...longer OS & better QOL in responders

9.6%

46.6%

What is interesting?

1. **Giant doses** of EPO!
   - 150 U/kg/d = **73,500 U/wk**
   - In practice, we start 40,000 U once weekly & may escalate to 80,000 U once weekly

2. **Synergism** between EPO & G-CSF
   - Some red cell precursors express G-CSF receptor, G-CSF binding inhibits apoptosis

3. EPO use in MDS is an **exception to the ASH & ASCO recommendation to avoid EPO** in cancer pts not receiving myelosuppressive chemotherapy

EPO for Jehovah’s Witnesses

- JW's **decline blood products** based on a literal interpretation of the bible & belief that transfusion equates to the “eating of blood”
  - “But you must not eat meat that has lifeblood still in it”

- **EPO** is an option for the severely anemic JW pt

- No data on dosing but endogenous EPO expected to be already high & high doses often used
  - Eg. 40,000 U once weekly, 150 U/kg daily


Book of Genesis
The future for anemia of chronic disease (ACD)?
Treatment of ACD

- Although the principle of treatment of ACD is treat the underlying illness, this is often difficult
- Recall the role of hepcidin in ACD

Hepcidin blockade for ACD?

**CLINICAL TRIALS AND OBSERVATIONS**

Effect of the antihepcidin Spiegelmer lexaptepid on inflammation-induced decrease in serum iron in humans

![Graph showing the effect of E. Coli LPS injection on serum Fe levels in 24 volunteers; one group was given placebo and another was given lexaptepid. The y-axis represents Serum Fe levels, and the x-axis represents time after endotoxin administration (h). The graph shows a significant decrease in serum Fe levels with lexaptepid compared to placebo.](image)

- E. Coli LPS injected into 24 volunteers
- 30 min later, placebo or lexaptepid
Summary

1. Anemia should be approached via a combination of the pathogenetic and clinical approaches.

2. A few simple tests are needed to start the search for the cause of an anemia, subsequent testing is based on these results and the clinical scenario.

3. Some interesting issues in the treatment of anemia relate to the use of various vitamin supplements, growth factors for MDS & possibly hepcidin blockade for ACD in the future.
The star of the show

https://www.google.ca/search?site=&tbm=isch&q=reticulocyte&imgdii=MpgBqpZsVl_yAM%3A%3BMpgBqpZsVl_yAM%3A%3BVch-VAv9cqxBz_M%3A&imgref=MpgBqpZsVl_yAM%3A