APPROACHES TO ANEMIA

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Anemia-

- Most common hematologic disorder
- Evaluation should be orderly

Questions to ask

- Timing - new, old, rapidity of onset
- Isolated - only anemia, or other cell lines
- Size of cells -
  - Dividing anemia into MCV subtypes provides an easy way to subcategorize the various anemias into diagnostic groups
- Could also subgroup by bone marrow response (i.e. reticulocytosis)

Microcytosis

- Iron deficiency
- Thalassemia –usually trait in the adult population
  - Beta and alpha
- Lead toxicity
- Rare:
  - Copper or zinc deficiency
  - Sideroblastic disease
    - Myelodysplastic or drug induced
    - Anemia of Chronic Disease – usually normocytic

Case #1:

- 45 year old woman comes in for fatigue. Routine CBC shows Hgb 10/Hct=30/MCV=75; Fe/TIBC=250/550 (%saturation = 45%)
  - Most likely diagnosis is
    - Anemia of chronic disease
    - Thalassemia
    - Iron deficiency anemia
    - Hemochromatosis

IRON DEFICIENCY

- Iron deficiency
  - Most common form of anemia
  - Microcytic
    - R/o thalassemia, lead toxicity
  - Symptoms:
    - Related to degree of anemia
      - Fatigue, dyspnea, headaches, tachycardia, chest pain
    - Pica, restless leg syndrome, glossitis/cheilosis

IRON DEFICIENCY

- ETIOLOGY
  - DIET – in general most people get enough in their diet
    - Only need 5-10 mg/day
    - Heme iron (meat) has greater bioavailibility than non-heme iron
  - Decreased Absorption:
    - Achlorhydria
    - H. pylori infection
    - Celiac disease
      - Celiac disease should be sought if no other obvious gi source found
      - 4% Caucasians with unexplained IDA have Celiac disease (much lower in non Caucasians)
        - Clin GastroentHepat 2013; 11:801
    - Gastric bypass – becoming a much more prominent cause of malabsorption.

Causes of Iron Deficiency

- Blood loss
  - GI
  - Menstruation (1mg/day)
  - Pregnancy/Delivery - @1,000mg
  - Rarer causes:
    - Pulmonary hemosiderosis
    - Blood donors
    - Dialysis
  - In general, iron deficiency in men/post-menopausal women MANDATES gi evaluation

IRON DEFICIENCY ANEMIA

- DISTINGUISHING IRON DEFICIENCY FROM ANEMIA OF CHRONIC DISEASE

	IRON DEF.	ACD
SERUM IRON*	+/-	+/-
TIBC	HIGH	LOW
%SAT	LOW/VAR	NORMAL/VAR
FERRITIN**	LOW/VAR	HIGH
FEP***	HIGH (>100)	NORMAL
sTfR****	HIGH	NORMAL
BONE MARROW	ABSENT STORES	ABUNDANT

- *SERUM IRON REFLECTS IRON IN BLOOD AT THAT MOMENT IN TIME
- ** FERRITIN CAN BE ELEVATED IN INFLAMMATORY STATES
- *** FREE ERYTHROCYTE PROTOPORHYRIN
- **** SERUM TRANSFERRIN RECEPTOR

TREATMENT - ORAL

- Iron supplementation
  - Dietary repletion quite difficult once deficient
    - 3oz liver= 7.5mg iron; spinach=2.5mg etc
  - Oral Supplementation –
    - Usually try this first
      - Lower cost, ease of administration, can be given long term
      - Issues with GI tolerance, Adherence, Absorption
  - **Oral supplements:**
    - Ferrous Gluconate - 36mg elemental iron
    - Ferrous Sulfate - 60mg elemental iron
    - Ferrous Polysaccharide - 150mg
    - Ferrous Fumarate - 33mg elemental iron

TREATMENT - ORAL

- Oral Supplements:
  - **Aim for 60-120mg elemental iron <u>every other</u> day**
  - Recent data suggests QOD dosing enhances absorption
    - Stoffel et al; Lancet Haematology 10/2017
  - Better tolerance/adherence
  - Paradoxically higher doses/daily use may increase Hepcidin levels which decreases GI absorption

Treat for 6 weeks after MCV normalizes or Ferritin over 50 (do not stop for normal HTrct/Hgb)

- Exception is if you want to determine if bleeding source stopped

Treatment, Intravenous

- **Parenteral Treatments –**
  - **Useful for poor tolerance, chronic blood loss, poor absorption**
  - **Newer formulations much safer than in the past**

- **Can calculate total amount needed**
  - **BW(in kg) x (14-current Hgb) x 2.145**
  - **Usually use @1,000mg on average**

- **IV formulations:**
  - Iron Sucrose – 200-300mg/dose (4-5 doses needed)
  - Ferumoxytol -@510mg /dose or 1010mg/dose (1-2 doses total)
  - Ferric Carboxymaltose – 750mg doses x2; or 15mg/kg (low BW)
  - Choice based on cost, pharmacy and patient convenience

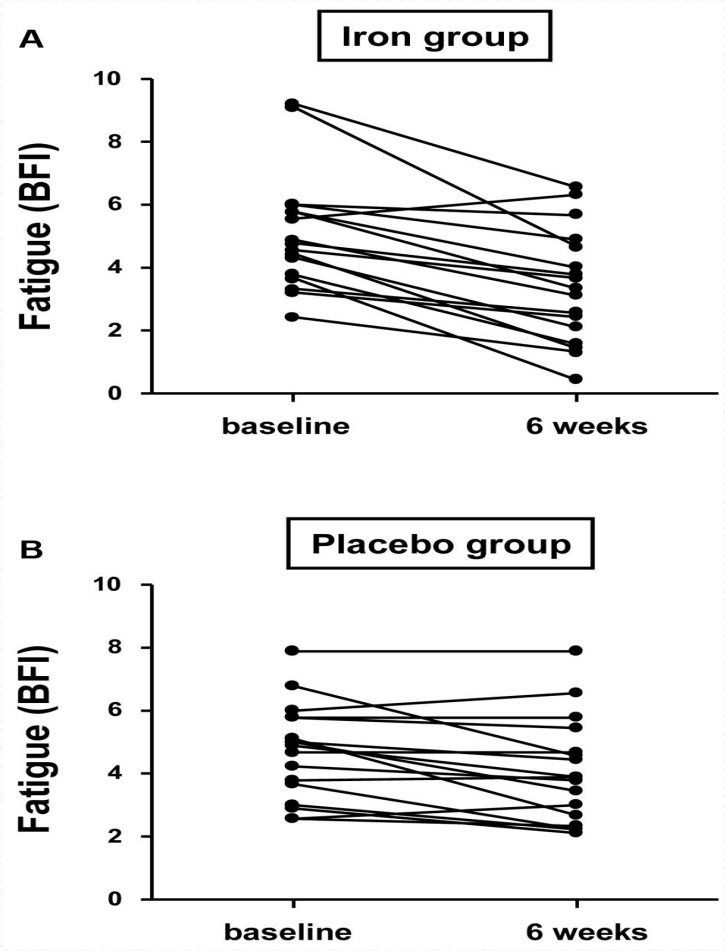
Iron supplementation and heart failure

- **Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency:** ***Stefan D. Anker, M.D., Ph.D., et al for the FAIR-HF Trial Investigators; NEJM, November 17,2009***
- ***Confirm-HF trial- Ferric Carboxymaltose in symptomatic patients with heart failure;*** ***Ponikowski, et al.*** Eur Heart J.2015 Mar 14;36(11):657-68.
  - Patients with Ferritin<100 or % saturation<20, but not necessarily anemic
  - Marked improvement in Patient global assessment/Functional capacity after IV infusion of iron (Ferric carboxymaltose) vs. placebo
  - Not related to degree of anemia

Fatigue and low Ferritin

Blood, 2011. Krayenbuehl, et al. 118:3222-3227

Am J. Hematology 2016. Sharma et al. 91(10); 973



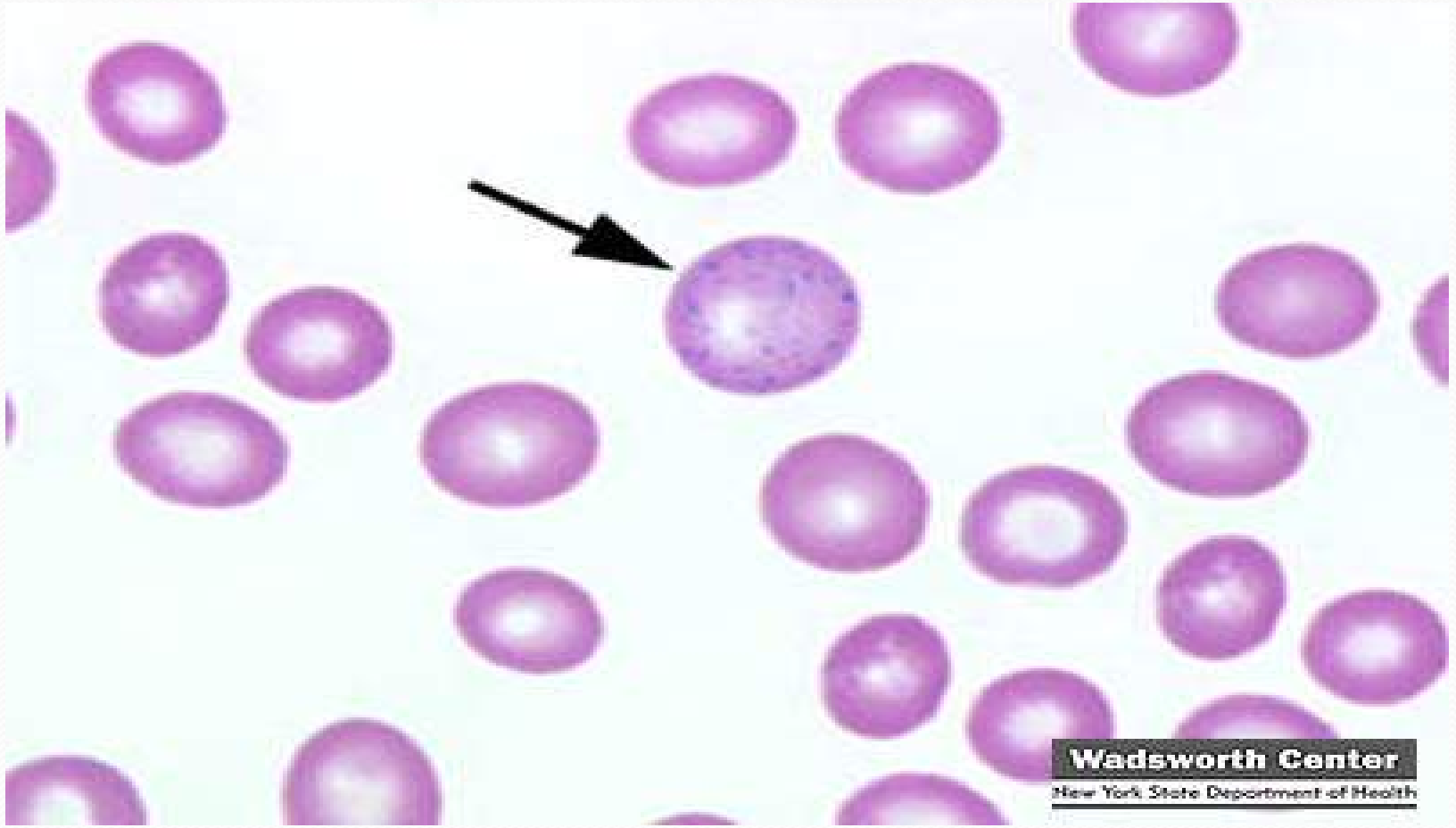
Case #2

- 35 year old Chinese woman comes to you for prenatal counseling. Her Hgb=11 with an MCV=62. Iron studies are normal. Hgb electrophoresis is normal. The most likely diagnosis is:
  - Iron deficiency anemia with surreptitious iron intake
  - Beta Thalassemia trait
  - Anemia of Chronic Disease
  - Alpha Thalassemia trait

Thalassemia

- Thalassemia -
  - Look for old CBCs - if MCV normal in the past then not likely thalassemia
  - MCV markedly reduced out of proportion to degree of anemia
    - Mentzer index (MCV:RBC <13)
  - Basophilic stippling
    - Ribosomal precipitates

Basophilic Stippling



Thalassemia

- Beta-Thalassemia
  - Mediterranean background
  - Hemoglobin electrophoresis -
    - Elevated A2
- Alpha-Thalassemia
  - African/Asian background
  - 4 genes so can have silent carrier
  - Not seen with Hemoglobin electrophoresis
  - Issues for fetal genetics, particularly in Asian families
    - Silent carrier + alpha trait= alpha thalassemia

Lead Toxicity

- Declining MCV over time
- Basophilic stippling
- Neurologic findings
- Not very common in adult population in US
- Exposure history important
  - Contractors/rehab old houses; traditional remedies; glazed pottery

Macrocytic Anemia - causes

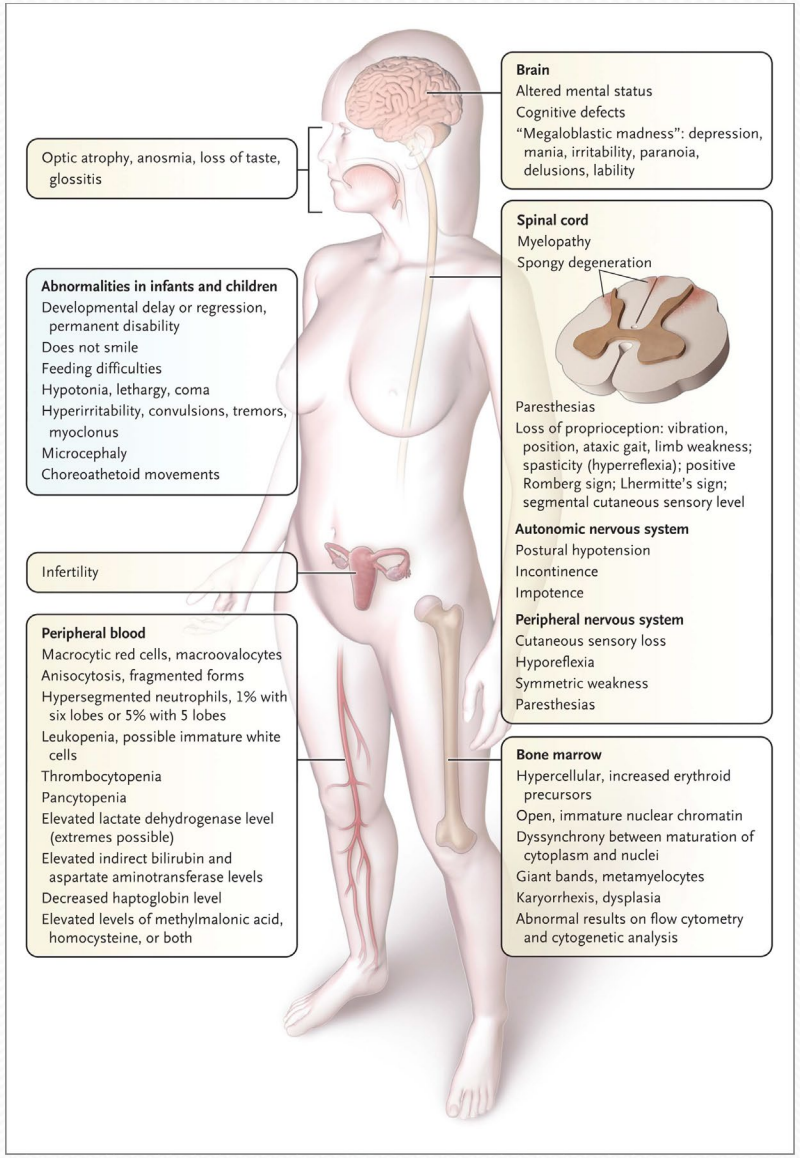
- B12/ Folate deficiency
- Hemolysis
- Myeloma
- Liver disease
- Toxin
  - Chemotherapy, drugs, alcohol
- Hypothyroidism
- Myelodysplastic syndrome, Leukemia

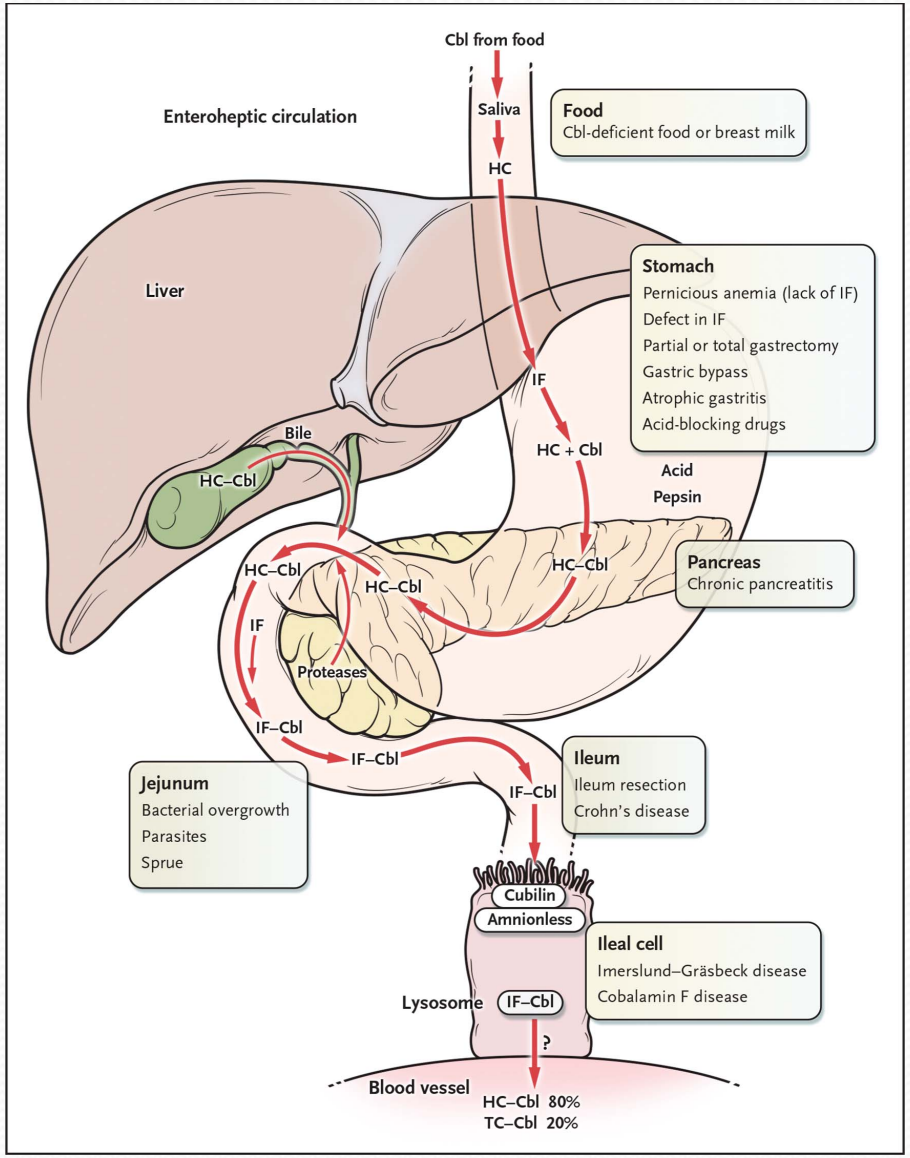
Case #3

- 68 year old man comes in complaining of fatigue, as well as some tingling in his toes. CBC shows a Hgb=9, Hct=27; MCV=108; B12=280 (nml 225-450); Folic acid =10 (nml >2.5)
- What is the best test to order next?
  - Schilling Test
  - Coomb's test
  - Methylmalonic Acid
  - Reticulocyte count
  - Homocysteine level

B12 deficiency

- Associated with neuropathy, pancytopenia, dementia/change in mental status
- Absorption depends upon acidic gastric environment, intrinsic factor and functioning terminal ileum
  - Deficiency caused by
    - pernicious anemia
    - atrophic gastritis
    - Malabsorption – bacterial overgrowth, Celiac disease, IBD,etc
    - Metformin - @6% incidence with chronic use
  - Stabler, S: NEJM: 368; 149-160, January 10,2013

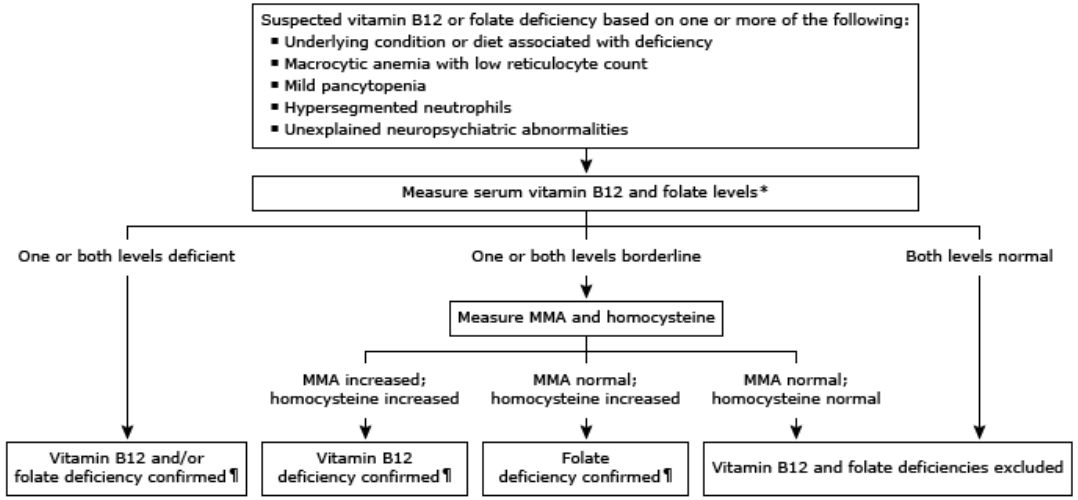

Optic atrophy, anosmia, loss of taste, glossitis
Abnormalities in infants and children
Developmental delay or regression, permanent disability
Does not smile
Feeding difficulties
Hypotonia, lethargy, coma
Hyperirritability, convulsions, tremors, myoclonus
Microcephaly
Choreoathetoid movements
Infertility
Peripheral blood
Macrocytic red cells, macroovalocytes
Anisocytosis, fragmented forms
Hypersegmented neutrophils, 1% with six lobes or 5% with 5 lobes
Leukopenia, possible immature white cells
Thrombocytopenia
Pancytopenia
Elevated lactate dehydrogenase level (extremes possible)
Elevated indirect bilirubin and aspartate aminotransferase levels
Decreased haptoglobin level
Elevated levels of methylmalonic acid, homocysteine, or both
Brain
Altered mental status
Cognitive defects
"Megaloblastic madness": depression, mania, irritability, paranoia, delusions, lability
Spinal cord
Myelopathy
Spongy degeneration
Paresthesias
Loss of proprioception: vibration, position, ataxic gait, limb weakness; spasticity (hyperreflexia); positive Romberg sign; Lhermitte's sign; segmental cutaneous sensory level
Autonomic nervous system
Postural hypotension
Incontinence
Impotence
Peripheral nervous system
Cutaneous sensory loss
Hyporeflexia
Symmetric weakness
Paresthesias
Bone marrow
Hypercellular, increased erythroid precursors
Open, immature nuclear chromatin
Dyssynchrony between maturation of cytoplasm and nuclei
Giant bands, metamyelocytes
Karyorrhexis, dysplasia
Abnormal results on flow cytometry and cytogenetic analysis


Cbl from food
Enteroheptic circulation
Saliva
HC
Food
Cbl-deficient food or breast milk
Liver
Stomach
Pernicious anemia (lack of IF)
Defect in IF
Partial or total gastrectomy
Gastric bypass
Atrophic gastritis
Acid-blocking drugs
IF
HC + Cbl
Acid
Pepsin
Bile
HC–Cbl
HC–Cbl
HC–Cbl
HC–Cbl
Pancreas
Chronic pancreatitis
IF
Proteases
IF–Cbl
IF–Cbl
IF–Cbl
Jejunum
Bacterial overgrowth
Parasites
Sprue
Ileum
Ileum resection
Crohn's disease
Cubilin
Amnionless
Ileal cell
Imerslund–Gräsbeck disease
Cobalamin F disease
Lysosome
IF–Cbl
?
Blood vessel
HC–Cbl 80%
TC–Cbl 20%

Diagnosing B12 Deficiency

- B12 levels highly variable
  - 50% false positives/negative rates
    - Variation in automated assays, binding to haptocorrin, interaction with intrinsic factor antibodies
- Methylmalonic acid, homocysteine levels may be of greater value when B12 levels are indeterminate or contradict clinical symptoms.

Diagnostic testing for suspected vitamin B12 or folate deficiency



UpToDate topics on vitamin B12 and folate deficiency discuss the presenting findings, diagnostic approach, differential diagnosis, and treatment in more detail, as well as additional post-diagnostic testing for the underlying causes of these deficiencies. This algorithm should not substitute for clinical judgment. Refer to laboratory-specific lower limits of normal.

- Typical values for vitamin B12 are as follows:
  - Deficient: <200 pg/mL
  - Borderline: 200 to 300 pg/mL
  - Normal: >300 pg/mL
- Typical values for folate are as follows:
  - Deficient: <2 ng/mL
  - Borderline: 2 to 4 ng/mL
  - Normal: >4 ng/mL

MMA: methylmalonic acid; RBC: red blood cell.

* Folate testing may be omitted if diet and gastrointestinal anatomy and function are normal. If dietary folate deficiency is suspected in a patient who has recently received a normal meal, RBC folate should be measured instead of serum folate. If one level is deficient and the other is borderline, then it may be necessary to follow more than one diagnostic path (eg, if folate is deficient and vitamin B12 is borderline, then folate deficiency may be confirmed but MMA and homocysteine testing may be required to determine vitamin B12 status). Another alternative in this setting would be to administer both vitamins.

¶ Additional testing may be appropriate. Examples include testing of MMA and homocysteine levels to further support a diagnosis of vitamin B12 deficiency; testing for autoantibodies to intrinsic factor if there is vitamin B12 deficiency not attributable to a known gastrointestinal condition; or screening endoscopy for malignancy in individuals with newly diagnosed pernicious anemia.

UpToDate®

B12 DEFICIENCY - Evaluation

- Pernicious Anemia
  - Parietal cell/ Intrinsic factor antibodies
  - Evaluate for autoimmune thyroid dysfunction
- Atrophic Gastritis
  - High gastrin levels, low pepsinogen
- Consider endoscopy to r/o occult malignancy
  - Higher risk for gastric cancer, carcinoid (2 fold higher risk adenocarcinoma; 11 fold higher risk carcinoid
    - Clin Gastro Hepatol, 2015
- Malabsorption
  - Schilling tests no longer done
  - Consider testing for celiac disease, inflammatory bowel disease in appropriate clinical setting

Treatment of B12

- Oral replacement often as effective as IV/SQ
  - 1,000 - 2000mcg (2mg)/day
  - Mass absorption doesn't require IF/acidic environment (<1% of normal process)
    - Cochrane Database Syst Review March 15, 2018
- Severe deficiency –
  - Parenteral replacement
    - 1,000mcg weekly x 4, then monthly

Folic Acid Deficiency

Increased requirements:

Pregnancy, hemolysis (sickle cell), hemodialysis, desquamating skin disorders

Malabsorption

Gastric bypass, Celiac disease, Sprue

Medications – often through reduction in Dihydrofolate reductase

Methotrexate

Trimethoprim

Phentoin, Valproate

Hemolysis

- Elevated retics, LDH, Bilirubin
- Low haptoglobin
  - Laboratory measures unbound haptoglobin
- Utilize Coomb's test to distinguish immune (extra-vascular) from non-immune (intravascular)

Coomb's positive hemolysis

- IgG:
  - Drug
  - Autoimmune
  - Lymphoproliferative
  - Idiopathic
- IgM:
  - Infectious
    - Mononucleosis
    - Mycoplasma
  - Lymphoproliferative
  - Idiopathic

Coomb's negative

- Microangiopathic process (Acquired)
  - DIC
  - TTP/HUS
- Inherited:
  - G6PD -
    - Heinze bodies
  - Sickle Cell
  - Hereditary spherocytosis

Case #4

- 85 year old woman comes in to the office for routine evaluation. You notice that over the past 3 years her Hgb has dropped slowly down to 10, with an MCV=110; WBC=3.5 and Platelets=120,000. Her B12 and Folic acid are completely normal. She feels entirely well except for slight fatigue and easy bruising. The most likely diagnosis is:
  - B12 deficiency
  - Hemolysis
  - Myelodysplasia
  - Alcohol ingestion

Myelodysplasia

- Primary bone marrow disorder
  - Refractory anemia, sideroblastic anemia, evolving leukemias
- Other cell lines usually involved
- Very common in the elderly
  - Seen in >5% over the age of 80
- Bone marrow diagnostic -
  - Frequent cytogenetic abnormalities

Other Macrocytic Anemias

- Myeloma
  - Secondary to Rouleaux formation
- Liver disease
- Toxin -
  - Cytotoxic drugs, alcohol, Dilantin, etc
- Hypothyroidism

Evaluation of Macrocytic Anemia

- Evaluate for B12/Folate deficiency
- Check IPEP, reticulocyte, TSH, LFTs
- Review history for drug/toxin exposure (ETOH!)
- If the above non-diagnostic -
  - Bone Marrow biopsy with cytogenetics

Normocytic Anemia

- Anemia of chronic disease
- Renal dysfunction
- Recent blood loss
- Mixed deficiencies
  - Look for wide RDW (could have both macrocytosis and microcytosis!)

Anemia of Chronic Disease

- Can be normocytic or mildly microcytic
- Poor mobilization of iron stores
  - Secondary to elevated mediators of inflammation
  - IL-6 increases hepcidin which leads to decreased ferroportin. This leads to decreased absorption from intestines and blocked release of iron from bone marrow stores
- Elevated Ferritin, ESR, CRP
- Elevated Hepcidin levels (not routinely obtained)
- Bone marrow diagnostic
  - Excess iron stores without sideroblasts

Renal Disease

- Ineffective Erythropoietin production
- Doesn't always correlate with serum creatinine levels
- Correct erythropoietin level for degree of anemia
- Treat with Erythropoietin injections
  - If Hgb<10, and EGFR<50
  - Beware higher levels and increased risk for stroke

Key Points/Next Steps

- Evaluation of anemia should be orderly
  - Can use MCV as a means to categorize types of anemia
  - Microcytic vs. Macrocytic vs. Normocytic
- Iron deficiency should prompt search for cause of iron loss
- Consider unusual reasons for malabsorption
  - Gastric bypass; Celiac disease
- Next Steps –
  - Utilize MCV in patients with puzzling anemia
  - Don't hesitate to call the hematologist if something doesn't fit

Conclusion

- “Before I came here I was confused about this subject, but now having heard your lecture I am still confused, but at a higher level”.

  - Enrico Fermi, Nobel Laureate, 1938