Anemia: Nutritional Deficiencies

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JHUSOM
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A 44 yo social worker is referred to you for anemia. She is married, with teenage children, and has no history of bleeding, and no menorrhagia. She has been told as long as she can remember that she has low iron, became anemic with pregnancies but did not require transfusions. She has taken oral iron infrequently, last more than a year ago. Lately she has seen a sleep specialist and been fitted for CPAP, a cardiologist for dyspnea and is planning to see a pulmonologist because of dyspnea and exercise intolerance. ROS was noted for a non-restricted diet, and dramatic pagophagia. Exam is noted for a BMI of 33, pale mucous membranes, a systolic ejection murmur, spoon nails. ROS is remarkable for dramatic pagophagia and pica.
Blood counts and iron studies on our 42 yo female are listed below. How would you proceed with evaluating and managing this patient:

1) No further evaluation, treat orally
2) Treat orally and/or intravenously
3) Refer to GI for EGD, colonoscopy
4) Refer to GI for EGD, small bowel biopsies, celiac serologies
5) Treat intravenously, recommend a wheat-free diet

<table>
<thead>
<tr>
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<th>2008</th>
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<td>Hemoglobin</td>
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<tr>
<td>MCV</td>
<td>80</td>
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<tr>
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<td>533</td>
<td>476</td>
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<tr>
<td>% sat</td>
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<td>55</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Ferrritin</td>
<td>13</td>
<td>150</td>
<td>10</td>
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</table>
Iron Distribution in *Man*

- Hemoglobin (2500 mg)
- Ferritin, Hemosiderin (1000 mg)
- Myoglobin, Enzymes (500 mg)
- Transferrin 4 mg
Iron Absorption

- Food sources: 10 - 25 mg / day
- Absorbed in the brush border of the duodenum
- Most dietary iron is nonheme form, <5% bioavailability
- <10% dietary iron is heme form, >25% bioavailability
The iron cycle
Iron Storage

- Ferritin
  - multi-subunit protein
  - primarily intracellular
  - some in plasma

- Hemosiderin
  - insoluble form of ferritin
  - visible microscopically
Pathophysiology of Iron Deficiency

• Depletion of iron stores
• Iron becomes a limiting factor in heme biosynthesis
• Heme deficiency limits hemoglobin assembly
• Hemoglobin deficiency limits red cell production
• Red cells are small (microcytic, low MCV)
• Red cells are deficient in hemoglobin (hypochromic, low MCH)
Iron Losses

• Iron is closely conserved in humans
• <0.05% of iron is lost per day normally
• Very small amounts in urine, bile and sweat
• Cells shed from skin, intestinal and urinary tracts
• Menstrual blood loss
• Pregnancy, delivery and lactation
• Humans have NO physiologic means to excrete excess iron
Routes to Iron Deficiency

- Occult or overt GI losses, traumatic or surgical losses
- Failure to meet increased requirements
  - Rapid growth in infancy and adolescence
  - Menstruation, pregnancy, delivery
- Inadequate dietary source
  - Diet low in heme iron (vegans, impoverished)
- Malabsorption
  - Gastrointestinal disease or surgery (gastric failure, atrophic gastritis, gastric bypass, H. pylori)
  - Duodenal/small bowel malabsorptive disease
    - Celiac disease, lymphoma
- Chronic hemolysis
  - PNH, march hemoglobinuria
Symptoms and signs of IDA

• Anemia symptoms – fatigue, feeling cold, dyspnea on exertion, palpitations, tinnitus
• Pica - craving of nonfood substances
  – e.g., ice, dirt, clay, laundry starch, newspaper
• Glossitis - smooth tongue
• Angular stomatitis - cracking of corners of mouth
• Koilonychia - thin, brittle, spoon-shaped fingernails
• Blue sclerae
• Short term memory loss
• Restless legs
Sequential Changes in IDA

NORMAL

DEPLETED IRON STORES

IRON DEFICIENCY

IRON DEFICIENCY ANEMIA

FERRITIN

IRON SATURATION

MCV & Hb & Hct
Peripheral blood smear in IDA
Therapy of Iron Deficiency

• *Patient education*
• RBC transfusion
• Oral iron salts (FeSO₄)
• For malabsorbers (gastric bypass, celiac disease, Barrett’s, gastrectomy) or chronic bleeders (menorrhagia, angiodysplasia, Chrohn’s)
  – Injectable iron preparations (iron dextran, iron sucrose)
  – DOM infusion center
• Ascorbic acid increases oral iron absorption
• Phytates (cereal grains), tannins (tea) and antacid therapy inhibit oral iron absorption
Response to Iron Therapy

- Peak reticulocyte count 7 - 10 d.
- Increased Hb and Hct 14 - 21 d.
- Normal Hb and Hct 2 months
- Normal iron stores 4 - 5 months
ASH-SAP

• A 30 yo female presents with iron deficiency refractory to iron supplementation. She has been amenorrheic for the past year, and runs 30 miles a week. She denies other sources of blood loss, and denies GI symptoms of any sort. She is a vegetarian. Her BMI is 18, ferritin is undetectable, and hemoglobin is 11 gm/dl. Contributors to her current clinical picture include all of the following except:
  – A. female sex
  – B. vegetarian diet
  – C. undiagnosed celiac disease
  – D. long distance running
  – E  All of the above
A 37 year old previously healthy African American male is hospitalized for an illness characterized by high fevers, incapacitating polyarthritis and rash. He had laboratories consistent with marked inflammation including an erythrocyte sedimentation rate of greater than 100, and a C-reactive protein of greater than 40. In addition to his hemogram, the intern sends iron studies and based on those results, hemochromatosis gene testing:

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>WBC COUNT</td>
<td>36650</td>
<td>4500 – 11000</td>
</tr>
<tr>
<td>RBC COUNT</td>
<td>3.00</td>
<td>4.50 – 5.90</td>
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<tr>
<td>HEMOGLOBIN</td>
<td>9.1</td>
<td>13.9 – 16.3</td>
</tr>
<tr>
<td>PACKED CELL VOLUME</td>
<td>27.1</td>
<td>41.0 – 53.0</td>
</tr>
<tr>
<td>MCV</td>
<td>90.3</td>
<td>80.0 – 100.0</td>
</tr>
<tr>
<td>MC HEMOGLOBIN</td>
<td>30.3</td>
<td>26.0 – 34.0</td>
</tr>
<tr>
<td>MC HGB CONCENTRATION</td>
<td>33.6</td>
<td>31.0 – 37.0</td>
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<tr>
<td>RBC DISTRIBUTION WIDTH</td>
<td>12.9</td>
<td>11.5 – 14.5</td>
</tr>
<tr>
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<td>150 – 350</td>
</tr>
<tr>
<td>ABS RETIC COUNT</td>
<td>38.3</td>
<td>24.1 – 87.7</td>
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<tr>
<td>Serum iron</td>
<td>84</td>
<td>65-170 mcg/dL</td>
</tr>
<tr>
<td>Transferrin</td>
<td>136</td>
<td>200-400 mg/dL</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>170</td>
<td>250-450 mg/dL</td>
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<tr>
<td>% Saturation</td>
<td>49</td>
<td>20-55%</td>
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<tr>
<td>Ferritin</td>
<td>19,322</td>
<td>10-300 ng/mL</td>
</tr>
<tr>
<td>HFE genotype C282Y</td>
<td>Wild-type</td>
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The patient is given a course of prednisone and his rash, arthritis and fever resolve within weeks. At a follow up clinic visit his iron studies and hemogram are repeated. Did the patient suffer from iron overload? Was hemochromatosis gene testing indicated?

<table>
<thead>
<tr>
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<th>Patient in Hospital</th>
<th>Patient after 3 months of treatment</th>
<th>NORMAL RANGE</th>
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<tr>
<td>WBC COUNT</td>
<td>36650</td>
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<td>4500 – 11000</td>
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<td>RBC COUNT</td>
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<td>4.45</td>
<td>4.50 – 5.90</td>
</tr>
<tr>
<td>HEMOGLOBIN</td>
<td>9.1</td>
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<td>13.9 – 16.3</td>
</tr>
<tr>
<td>PACKED CELL VOLUME</td>
<td>27.1</td>
<td>42.5</td>
<td>41.0 – 53.0</td>
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<tr>
<td>MEAN CORPUSCULAR VOLUME</td>
<td>90.3</td>
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<td>80.0 – 100.0</td>
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<tr>
<td>MC HEMOGLOBIN</td>
<td>30.3</td>
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<td>26.0 – 34.0</td>
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<tr>
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<tr>
<td>PLATELET COUNT</td>
<td>443</td>
<td>397</td>
<td>150 – 350</td>
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<tr>
<td>SERUM IRON</td>
<td>84</td>
<td></td>
<td>65 – 170 mcg/dL</td>
</tr>
<tr>
<td>TRANSFERRIN</td>
<td>136</td>
<td></td>
<td>200 – 400 mg/dL</td>
</tr>
<tr>
<td>TOTAL IRON BINDING CAPACITY</td>
<td>170</td>
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<td>250 – 450 mg/dL</td>
</tr>
<tr>
<td>% SATURATION</td>
<td>49</td>
<td></td>
<td>20 – 55%</td>
</tr>
<tr>
<td>FERRITIN</td>
<td>19,322</td>
<td>213</td>
<td>10 – 300 ng/mL</td>
</tr>
</tbody>
</table>
Anemia of inflammation

- IL-6 and hepcidin
- Hypoferremia
- Impaired iron absorption
- Impaired iron release
Hepcidin in anemia of inflammation

Tomas Ganz, Blood 2003;102:873
IDA vs. Inflammation

<table>
<thead>
<tr>
<th></th>
<th>IDA</th>
<th>Inflammation</th>
<th>Both</th>
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<tbody>
<tr>
<td>Ferritin</td>
<td>↓</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>TIBC</td>
<td>↑</td>
<td>↓</td>
<td>?</td>
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</tbody>
</table>
A 50 year old African American female was brought to the emergency department by her daughter because of erratic behavior, personality changes, shortness of breath and ataxia. The patient was dismissed by her employer due to erratic behavior. Her medical history was remarkable for a history of hypothyroidism diagnosed many years ago, but otherwise was benign. Physical examination revealed a well nourished middle aged female in no acute distress. The patient was irritable and was vague in answering questions throughout the interview. Her neurologic exam was noted for intact cranial nerves II-XII. Her muscle strength was 5/5 bilaterally when tested in the supine position. She had intact sensation to light touch and pinprick, though markedly diminished proprioception. She was markedly ataxic and needed to steady herself on the wall for added support.

<table>
<thead>
<tr>
<th></th>
<th>50 YO FEMALE</th>
<th>NORMAL RANGE</th>
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</thead>
<tbody>
<tr>
<td>WBC COUNT</td>
<td>3120</td>
<td>4500 - 11000</td>
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<tr>
<td>RBC COUNT</td>
<td>1.92</td>
<td>4.50 – 5.90</td>
</tr>
<tr>
<td>HEMOGLOBIN</td>
<td>7.8</td>
<td>13.9 – 16.3</td>
</tr>
<tr>
<td>PACKED CELL VOLUME</td>
<td>22.7</td>
<td>41.0 – 53.0</td>
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<td>MEAN CORPUSCULAR VOLUME</td>
<td>118.2</td>
<td>80.0 – 100.0</td>
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<tr>
<td>MC HEMOGLOBIN</td>
<td>40.6</td>
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<tr>
<td>MC Hgb CONCENTRATION</td>
<td>34.4</td>
<td>31.0 – 37.0</td>
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<tr>
<td>RBC DISTRIBUTION WIDTH</td>
<td>20.0</td>
<td>11.5 – 14.5</td>
</tr>
<tr>
<td>PLATELET COUNT</td>
<td>123</td>
<td>150 – 350</td>
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<tr>
<td>NUCLEATED RBC NUMBER</td>
<td>20</td>
<td>0 – 12</td>
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<tr>
<td>RETICULOCYTE %</td>
<td>0.9</td>
<td>0.5-1.8</td>
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<td>ABS RETIC COUNT</td>
<td>13.4</td>
<td>24.1 – 87.7</td>
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</tbody>
</table>
Milestones in Vitamin Theory and Therapeutics

- 1907 scurvy in guinea pigs – Vitamin C 1932
- 1912 vitamin(e) theory postulated
- 1913 growth failure in rats – Vitamin A 1937
- 1918 rickets in puppies
- 1922 therapeutic insulin preparations derived from bovine pancreas
- 1926 liver feeding to pernicious anemia patients
- 1935 liver as an iron source
Pernicious Anemia

Megaloblastic anemia

Gastric atrophy

Neurologic degeneration
Pernicious Anemia - laboratory exam

- blood smear and bone marrow
- hemolysis (hyperbilirubinemia, LDH)
- thrombocytopenia, leukopenia
- elevated gastric pH
Study of Pernicious Anemia = B_{12} Identification

Responses to daily liver feeding supported the theory that a deficiency was the cause of PA.

Liver contained an “extrinsic factor” that could not be absorbed by PA patients due to loss of an “intrinsic factor” in their gastric secretions.

Identity of the extrinsic factor crystallized from liver, named vitamin B_{12} in 1948.
Vitamin B₁₂
Cobalamin
Coenzyme B₁₂

R = 5′-deoxyadenosyl, Me, OH, CN
Vitamin B₁₂

- synthesized only by microorganisms
- dietary sources include liver, glandular tissue, muscle, eggs, dairy products, seafood
- body stores are 2-5 mg, with the liver as the major storehouse
- daily needs are 2-5 ug, 0.1% of the stores
- B12 excreted in bile, extensive reabsorption via the enterohepatic circulation
Absorption of $B_{12}$ (Cbl) from food
Causes of $B_{12}$ Deficiency

**Common**

Malabsorption due to:

- Salivary gland dysfunction
- Loss of gastric function resulting in intrinsic factor deficiency and/or loss of gastric acid secretion
  - Autoimmune basis
  - Atrophic gastritis due to H. pylori
  - Gastrectomy
  - Ageing
  - H2 blockers
- Pancreatic disease
- Terminal ileum disease
  - sprue, inflammatory bowel disease
Causes of $B_{12}$ Deficiency

*rare to never*

- **Acquired deficiency states**
  - Inadequate ingestion
    - Vegans
    - Breast-fed infants of vegans
    - Breast-fed infants of B12 deficient mothers
- **Congenital deficiency states**
  - Transcobalamin II deficiency
  - Imerslund-Grasbeck syndrome
    - mutation of receptor for IF-B12
Measurement of serum $B_{12}$ is not fool-proof.
Serum $B_{12}$ - falsely normal intestinal bacterial overgrowth, liver disease, myeloid disorder.
Serum $B_{12}$ - falsely low pregnancy, lymphoid disorders, ageing, racial differences
Sensitivity of methylmalonic acid in B$_{12}$ deficiency
Vitamin B$_{12}$ mediates 2 reactions

- Methyl transfer
  - methylation of homocysteine to generate methionine
    - B12 is a cofactor, methyltetrahydrofolate supplies the methyl group (substrate)
    - B12 accelerates this reaction several thousand-fold
    - Tetrahydrofolate required for thymine and purine generation = crucial for rapidly dividing tissues
- Hydrogen transfer
  - generation of succinyl coA from methylmalonyl coA
  - crucial for myelin maintenance
Convergence of $\text{B}_{12}$ and Folic acid
Causes of hyperhomocysteinemia

- Cystathionine β-synthase ➞ > 200 mcmol/L
- B12 deficiency ➞ 20-241
- Folate deficiency ➞ 15-50
- Renal disease ➞ 17-20
- MTHFR gene polymorphisms ➞ 8-15
- Normal individuals ➞ 4-12
Folic Acid Overcomes Methylfolate Trap

Folic Acid

Dietary Folates
Many unanswered questions

- Variation in clinical presentation of B12 deficiency
  - Anemia and neurologic features – 30%
  - Anemia without neurologic symptoms – 50%
  - Predominantly neurologic presentations with very mild anemia or no anemia – 20%
- Basis of this variation in clinical phenotype?
  - Dietary methionine and folate stores, polymorphisms in enzymatic activity – hypothetical claims
You are involved in two other patients with B12 deficiency. One, an 8-month old patient, presented with severe developmental delay. The third, a 60 year old male, presented with anemia and no neurologic symptoms. Their hemograms and laboratories are presented below. What factors may account for the variability in their clinical presentations?

<table>
<thead>
<tr>
<th></th>
<th>50 YO FEMALE</th>
<th>8 MONTH OLD</th>
<th>60 YO MALE</th>
<th>NORMAL RANGE</th>
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<td>WBC COUNT</td>
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<td>2990</td>
<td>2620</td>
<td>4500 - 11000</td>
</tr>
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<td>RBC COUNT</td>
<td>1.92</td>
<td>2.20</td>
<td>1.55</td>
<td>4.50 – 5.90</td>
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<tr>
<td>HEMOGLOBIN</td>
<td>7.8</td>
<td>6.0</td>
<td>5.6</td>
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<td>22.7</td>
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<td>16.4</td>
<td>41.0 – 53.0</td>
</tr>
<tr>
<td>MEAN CORPUSCULAR VOLUME</td>
<td>118.2</td>
<td>83.0</td>
<td>106</td>
<td>80.0 – 100.0</td>
</tr>
<tr>
<td>MC HEMOGLOBIN</td>
<td>40.6</td>
<td>27.3</td>
<td>36.1</td>
<td>26.0 – 34.0</td>
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<tr>
<td>MC Hgb CONCENTRATION</td>
<td>34.4</td>
<td>32.0</td>
<td>34.1</td>
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<td>RBC DISTRIBUTION WIDTH</td>
<td>20.0</td>
<td>28.3</td>
<td>20.0</td>
<td>11.5 – 14.5</td>
</tr>
<tr>
<td>PLATELET COUNT</td>
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<td>91</td>
<td>140</td>
<td>150 – 350</td>
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<tr>
<td>NUCLEATED RBC NUMBER</td>
<td>20</td>
<td>50</td>
<td>20</td>
<td>0 - 12</td>
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<tr>
<td>RETICULOCYTE %</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.5-1.8</td>
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<tr>
<td>ABS RETIC COUNT</td>
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<td>16.9</td>
<td>10.4</td>
<td>24.1 – 87.7</td>
</tr>
<tr>
<td>Serum B12</td>
<td>72</td>
<td>&lt;45</td>
<td>65</td>
<td>200-900 pg/ml</td>
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<td>Homocysteine</td>
<td>241</td>
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<td>Methylmalonic acid</td>
<td>65,700</td>
<td>Not measured</td>
<td>2,463</td>
<td>90-279 nMol/L</td>
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<tr>
<td>Ferritin</td>
<td>454</td>
<td>257</td>
<td>270</td>
<td>10-300 ng/ml</td>
</tr>
</tbody>
</table>
Therapy for B12 malabsorption

- Identify and correct malabsorption
  - Celiac disease, lymphoma, Crohn’s, H.pylori
- Supplement
  - Oral - ? Passive transfer theory, requires monitoring
  - Parenteral – fool-proof (doctors and patients), inexpensive, effective, never toxic, preferred by patients
- Duration of therapy
  - Dependent on clinical scenario – long term most of the time
Forces at play in nutritional anemias

- Diseases change
  - Atrophic gastritis
- Infectious diseases evolve
  - H.pylori
- Treatments evolve
  - H2 blockers
- Nutritional status evolves
  - Food fortification, Nutritional lifestyle, Obesity, Wheat genetically modified
  - Populations change
    - Aging of the world
    - Racial makeup of the US population – genomic and cultural factors
- Diagnostic testing evolves