B12 and Iron Supplementation
A Story of Timeless Wisdom
as told to Luke Kristjanson by Yoda Zarychanski
Presenter Disclosure

Presenters: Ryan Zarychanski and Mark Kristjanson

FINANCIAL DISCLOSURE RELEVANT TO THIS PRESENTATION:

Grants/Research Support: None

Speaker bureau/Honoraria: None

Consulting fees: None
Learning Objectives

1. Identify clinical scenarios where iron or $\text{B}_{12}$ supplementation is warranted
2. Appreciate efficacy and safety of iron and $\text{B}_{12}$ prescribing options
3. Have an approach to monitor and discontinue therapy when treatment goals are met
4. Provide practical advice to increase compliance in patients taking iron supplements
Case 1:
72 yr. old female with rheumatoid arthritis and Type II diabetes
On methotrexate, rabeprazole, metformin, calcium supplements

- WBC $4.2 \times 10^9$/L
- Hb 116 g/L
- Hct .392
- MCV 108 fL
- RDW 12
- Plts $162 \times 10^9$/L
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$B_12$ 130 (normal >180 pmol/L)
TSH and LFTs normal
Ferritin 110 (normal)
B₁₂ (Cobalamin) Deficiency

Diagnosis: B₁₂ deficiency

• B₁₂ is essential for DNA replication, formation of blood cells and maintenance of the nervous system
• **Presentation:** Anemia, pancytopenia and/OR neurologic symptoms (dementia, memory loss, weakness, ataxia, parasthesia)
• **Causes:** Food malabsorption, autoimmune (pernicious anemia), bacterial overgrowth, Crohn’s disease, parasitic infection, vegan diet
• **Risk factors:** Increasing age, PPIs, metformin, bariatric surgery
B₁₂ (Cobalamin) Deficiency

✓ Patients might not have anemia
✓ Macrocytosis may be masked by iron deficiency or thalassemia

Diagnosis can be confirmed with elevated methylmalonic acid (MMA)
• Not routinely done
• Not needed unless patient unresponsive to treatment
• Threshold to treat is low
Vitamin B12 Deficiency

Macrocystic anemia (MCV > 98 fl) or neurologic symptoms suggestive of B12 deficiency

See work up of anemia algorithm, macrocytosis

B12 level < 180 pg/mL

B12 deficiency confirmed. Consider causes (see box) Replacement indicated.

B12 level < 180-300 pg/mL

Option 1: Trial of B12 supplementation (see treatment options below)
OR
Option 2: Measure urine methylmalonic acid (MMA) to confirm biochemical B12 deficiency

B12 level > 300 pg/mL

B12 deficiency excluded. Consider other causes of macrocytosis

Neurologic symptoms OR a need for close patient monitoring?

Yes

Parenteral
Dose: 1000 mcg monthly (intramuscular or deep subcutaneous)
More intensive initial dosing is recommended if neurologic symptoms are present 1000 mcg daily x 1 week, weekly x 4 weeks, then monthly

No

Oral
Dose: 1000-2000 mcg daily (tablets, or sublingual spray, intranasal or fresh-breed strips)

If Option 1: Hemoglobin & MCV normalize?
OR
If Option 2: MMA elevated?

Yes

Reevaluate CBC for improvement. If macrocytosis and/or anemia persists, consider other causes and hematology consultation

No

Consider: peripheral blood film, LDH, bilirubin (total and direct), reticulocyte count, drug and alcohol history, and possibility of folate deficiency (see box)

Causes of vitamin B12 deficiency
- Pernicious anemia (autoantibodies)
- Gastric bypass surgery
- Gastritis
- Pancreatitis
- Pancreatic insufficiency
- Strict vegan diet

Causes of Folate deficiency
- Malabsorption
- Celiac disease
- Inflammatory bowel disease
- Intestinal bypass
- Folate inhibition
- Methotrexate
- Dilantin
- Alcoholism

Patients with any of the above should receive folate supplementation. No need to measure folate level. NOTE: mandatory staple food fortification has eradicated dietary folate deficiency.
B$_{12}$ (Cobalamin) Deficiency

Need for metabolite testing:

- When B$_{12}$ deficiency is suspected but the B$_{12}$ levels are within the normal range
- ...and when perhaps treatment can’t be reliably initiated in the face of borderline results (200-300 pmol/L)
- When there is no biochemical response to B$_{12}$ supplementation (e.g. to exclude a metabolic deficiency...which can be due to reduced carrier proteins)
Treatment of B$_{12}$ Deficiency

**Parenteral** (intramuscular or deep subcutaneous)
- 1000 mcg monthly
  - More intensive initial dosing if neurologic symptoms are present
    - 1000 mcg daily x 1 week, weekly x 4 weeks, then monthly
- Duration: likely indefinite unless cause is reversible

**Oral** (tablets….also sublingual spray, intranasal and fresh-breath strips!)
- 1000-2000 mcg daily
  - Start parenterally if neurologic symptoms are present
  - Greater patient compliance required
- Duration: likely indefinite unless cause is reversible
Oral vs. Parenteral $B_{12}$

Oral vitamin $B_{12}$ versus intramuscular vitamin $B_{12}$ for the vitamin $B_{12}$ deficiency: a systematic review of randomized trials
Family Practice. 2006;23(3):279.

- Two randomized controlled trials
- Total n = 93; both trials unblinded
- Follow up duration: 90 days to 4 months
- Dose of oral $B_{12}$: 1000-2000 mcg
- Dose of IM $B_{12}$: 1000 mcg

Bottom line: Oral dosing of $B_{12}$ was good or better than intramuscular dosing
## Oral vs. Parenteral B<sub>12</sub>

<table>
<thead>
<tr>
<th></th>
<th>Parenteral</th>
<th>Oral</th>
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<tbody>
<tr>
<td><strong>Pro</strong></td>
<td>Compliance easily monitored</td>
<td>Inexpensive</td>
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<tr>
<td></td>
<td>Venue for close follow for patients who need this</td>
<td>Does not require a visit to a health practitioner</td>
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<tr>
<td><strong>Con</strong></td>
<td>Increased health care costs</td>
<td>Requires consistent compliance of the patient</td>
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<td></td>
<td>Painful</td>
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<td>Not ideal for anticoagulated patients</td>
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</table>
Case 2:

55 y.o. male. Past history of obesity. Gastric bypass surgery 2 years go. Presents with fatigue.

- WBC \(6.8 \times 10^9/L\)
- Hb 116 g/L
- Hct .392
- MCV 76 fL
- Plts \(162 \times 10^9/L\)
Case 2:

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- WBC $6.8 \times 10^9$/L
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Ferritin 15 mcg/L (normal 20-200)

Now what?
Work-Up of IRON DEFICIENCY ANEMIA in ADULTS

INDICATIONS FOR GI ENDOSCOPY: • Adult males • Post-menopausal females • Unexplained weight loss • Family history of GI cancer • Any associated GI Symptoms such as: Dysphagia, Odynophagia, Dyspepsia, Abdominal pain, Melena, Hematochezia, Tenesmus, Altered bowel habit.

IRON REPLACEMENT: a) Control Blood Loss; b) Warn patients of GI side effects and start slow; c) Ferrous sulfate, glunacate, or fumarate or iron polyasacharide in doses that provide 150-200mg of elemental iron per day (e.g. ferrous sulfate 300mg TID)

Microcytosis (MCV <80FL)

- Check Ferritin
  - Ferritin >100ug/L: Iron deficiency ruled out
  - Ferritin Low <20ug/L
    - Ferritin 20-100ug/L: Referral to CCMB Hematology
      - IF: Thalassemia or Hemoglobinopathy (provided appropriate ethnicity)

Iron Deficiency

- Review indications for GI endoscopy (box at top)

No indications for GI endoscopy identified AND Menstruating Female

- Manage Bleeding (e.g. oral contraceptive, progesterone-eluting IUD, or tranexamic acid. Gyne referral if needed)
- Replace Iron (see box at top)
- Treat until Hb is Normal and Ferritin is >30ug/L

No indications for GI endoscopy identified

- LDH, bilirubin (total & direct), haptoglobin (assess for hemolysis)
- Celiac serology
- Urinalysis (assess for urinary source of blood loss)
- Replace iron (treat the patient once work-up has been initiated)

Indications for GI endoscopy identified

- Refer to GI Endoscopy
  - Manage bleeding
  - Replace iron

Re-refer to Gastroenterologist

IF Endoscopy negative (more urgent if anemia is recurrent or doesn’t correct with iron)

Refer to Gastroenterologist

IF iron deficiency is recurrent or fails to correct with iron supplementation

Refer to CCMB Hematology

IF hemolysis screen is positive

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Iron Deficiency

**Symptoms:**
- Fatigue, pica, depression, headache, restless leg syndrome

**When to treat:**
- When iron deficiency is confirmed AND when causes have been considered
- Especially with anemia, but likely also if not anemic.
Treatment of Iron Deficiency

How I replace iron

1. Address underlying cause
2. Oral therapy generally preferred
3. Start low; go slow. Minimize GI side effects
4. Give some preparation that eventually delivers 150-200 mg of elemental iron per day
   - e.g. ferrous sulphate, 1 tablet, 300 mg PO TID
Treatment of Iron Deficiency

Maximizing success of oral iron replacement

• Warn possible GI side effects and communicate that these are not dangerous and nor allergic in nature
• Give pre-emptive advice about managing side effects, esp. constipation: increase fluid intake, fibre intake, stool softeners
• Reassure that side effects typically abate with ongoing administration
**Oral iron preparations (Full Replacement doses)**

<table>
<thead>
<tr>
<th>Recommended first line</th>
<th>Ferrous gluconate</th>
<th>~35 mg elemental iron /300 mg tab (target dose: 4-6 tabs per day)</th>
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</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>~60 mg elemental iron /300 mg tab (target dose: 2-3 tabs per day)</td>
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<tr>
<td>$10 /mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron fumarate</td>
<td>~108 mg elemental iron /300 mg tab (target dose: 1-2 tabs per day)</td>
<td></td>
</tr>
<tr>
<td>Ferrous sulphate elixir</td>
<td>44 mg elemental iron / 5 mL (target dose: 15-20 mL)</td>
<td></td>
</tr>
<tr>
<td>Polysaccharide iron complex (FeraMAX)</td>
<td>$22 /mo</td>
<td>150 mg elemental iron per capsule (dose is 1 capsule OD)</td>
</tr>
<tr>
<td>heme-iron polypeptide (Proferrin)</td>
<td>11 mg of elemental iron per tab</td>
<td></td>
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</table>

*Unproven claims of increased GI tolerability*
Which oral supplement is preferred?

Which one is most efficacious?
• The one with the most iron

Which one is best tolerated?
• The one with the least iron

There is no evidence that one preparation is more effective than another or has fewer side effects than another³

**Recommend NOT using sustained-release capsules
- very poorly absorbed

Iron dosing strategies

The optimal dosing strategy hasn’t been adequately studied

• Large doses or oral iron are known to be associated increased hepcidin concentration which can reduce absorption of subsequent doses

• Large/infrequent doses vs. Small/frequent doses ??
  • Requires further study...

**Reduced doses are frequently required in the elderly who have increased intolerance and reduced absorption
Iron Replacement

Iron deficiency anemia
Cause of IDA considered and appropriate course of action planned?

Start oral iron replacement

Monitor response
CBC monthly until hemoglobin normal; then check ferritin

Response
Continue iron until ferritin normal AND cause of deficiency addressed

Non-adherence
If due to GI upset/constipation, consider the following:
- Reduce dose
- Take with food
- Take every other day
- Consider laxative
- Change preparation (e.g., if on ferrous sulphate, switch to Ferrous or consider an elixir if the issue is swallowing pills)

Unmanageable intolerance
Unmanageable intolerance despite efforts to mitigate drug related symptoms (primarily GI upset)

Excessive bleeding
- Manage bleeding
  - If GI bleeding
    - Consult GI
    - If GU bleeding
      - Consult gynecology or urology
      - If hemolysis suspected, consult hematology

Consider intravenous (IV) or intramuscular (IM) iron supplementation

Malabsorption
- Common post bariatric surgery
- Celiac disease
- Crohn’s disease
- Intestinal bypass
- H. pylori infection

Iron replacement tips:
- Oral therapy generally preferred
- Start low; go slow
- Give preemptive advice about potential gastrointestinal (GI) side effects with the caveat that these generally improve with time
- Give some preparation that eventually delivers 150-200 mg of elemental iron per day
  - e.g., Ferrous sulphate, 1 tablet, 300 mg PO OD x one week, then 1 tab BID x one week, then (if tolerating well) 1 tab TID until deficiency corrected

* Suggested to start by taking iron before bed to reduce GI upset.
## Oral vs. Parenteral Iron

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>IM</th>
<th>IV</th>
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</thead>
<tbody>
<tr>
<td><strong>Pro</strong></td>
<td>Inexpensive ($5 – 25 /mo)</td>
<td>Can be administered in an outpatient clinic</td>
<td>Least associated GI side effects</td>
</tr>
<tr>
<td></td>
<td>Lowest risk of anaphylaxis</td>
<td>Reduced GI side effects compared to oral</td>
<td>Certain compliance</td>
</tr>
<tr>
<td></td>
<td>Does not require clinic visit</td>
<td>Malabsorption? Still works</td>
<td>Rapid correction of anemia</td>
</tr>
<tr>
<td></td>
<td>Lengthy Tx duration</td>
<td></td>
<td>Malabsorption? Still works</td>
</tr>
<tr>
<td><strong>Con</strong></td>
<td>Highest incidence of GI side effects</td>
<td>Painful injection</td>
<td>Iron dextran associated with anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Inadequate in the face of substantial bleeding</td>
<td>Can cause permanent staining of the skin</td>
<td>Requires 3-4 hr infusion/trip to centre</td>
</tr>
<tr>
<td></td>
<td>Requires consistent compliance of the patient</td>
<td>Requires a visit to a health practitioner</td>
<td>Patients can feel ill for after large doses</td>
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</table>

When to consider IM or IV therapy**?

• Intolerance to more than 1 oral regimen, even when ramping up slowly and taking with food
  - Try iron sulphate elixer EOD
• Malabsorption syndromes
• Patient with IBD
• Post gastric bypass surgery - Perhaps not ’banding’ alone
• Chronic kidney disease – on dialysis (standard of care)

**In almost all instances, try oral replacement first
The Deficient but Non-Anemic Patient

- Iron deficiency is highly prevalent: ~2 billion individuals
- Many are not anemic
- Do they require treatment?
  - Will treatment improve their fatigue or quality of life?
  - Will it enhance physical performance?
The Deficient but Non-Anemic Patient

Efficacy of iron replacement therapy on fatigue and work capacity in non-anemic adults with iron depletion: a systematic review of randomized trials
Houston BL, Hurrie D, Graham J, Perija B, Rimmer E, Abou-Setta AM, Bernstein CN, Houston DS, Zarychanski R. *BMJ Open*. 2018

- 18 randomized controlled trials
- Total n = 1162 individuals; mostly young health females
- Follow up duration: 90 days to 4 months
- Oral iron preparations studied in 14 trials
- Mean daily dose was 87 grams (elemental)

**Bottom line:** Iron supplementation reduced self reported fatigue, but didn’t really change measures of work capacity
Iron Preparations

First line

Second line options

Oral

Ferrous sulphate/gluconate/fumarate
FeraMAX (polysaccharide)
[Proferrin (heme-polypeptide)] 🙁

IM

Iron dextran (INFeD)
100 mg per dose into buttock
Use Z-track technique

IV

Iron sucrose
Carboxymaltose, gluconate,
Iron Dextran
Iron: Monitoring and duration of therapy

- Check retic count and evaluate for side effects in 2 weeks
- Check CBC every 1-2 months until CBC corrects
- If only iron deficiency (no other cause of anemia), on full treatment doses, the hemoglobin could increase by 10 g/L every week
- Once CBC is corrected follow the ferritin
- Continue replacement until the ferritin is consistently within the normal range (ie. ~50 to 100 mcg/L)
  - Usually another 3-6 months
  - Consider a lower ‘maintenance’ dose if there are ongoing issues with blood loss or malabsorption.
  - Check ferritin periodically to monitor response and limit toxicity
Take home messages

B12 supplementation:
• Consider MMA testing for equivocal B12 results:
• Oral replacement is as good as parenteral for most patients
• Monitor response to therapy rather than repeat B12 testing

Replacing iron:
• Oral supplementation is preferred
• Forewarn patients of GI side effects; start low; work up slowly
• Oral replacement is generally first line
• Continue iron until Ferritin is within normal range
Thank you

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