CancerCare Manitoba
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Blood Disorders Day 2018

FOR Health Professionals

B12 and Iron Supplementation

A Story of Timeless Wisdom

as told to Luke Kristjanson by Yoda Zarychanski

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

Presenters: Ryan Zarychanski and Mark Kristjanson

FINANCIAL DISCLOSURE RELEVANT TO THIS PRESENTATION:

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Learning Objectives

1. Identify clinical scenarios where iron or B_{12} supplementation is warranted
2. Appreciate efficacy and safety of iron and 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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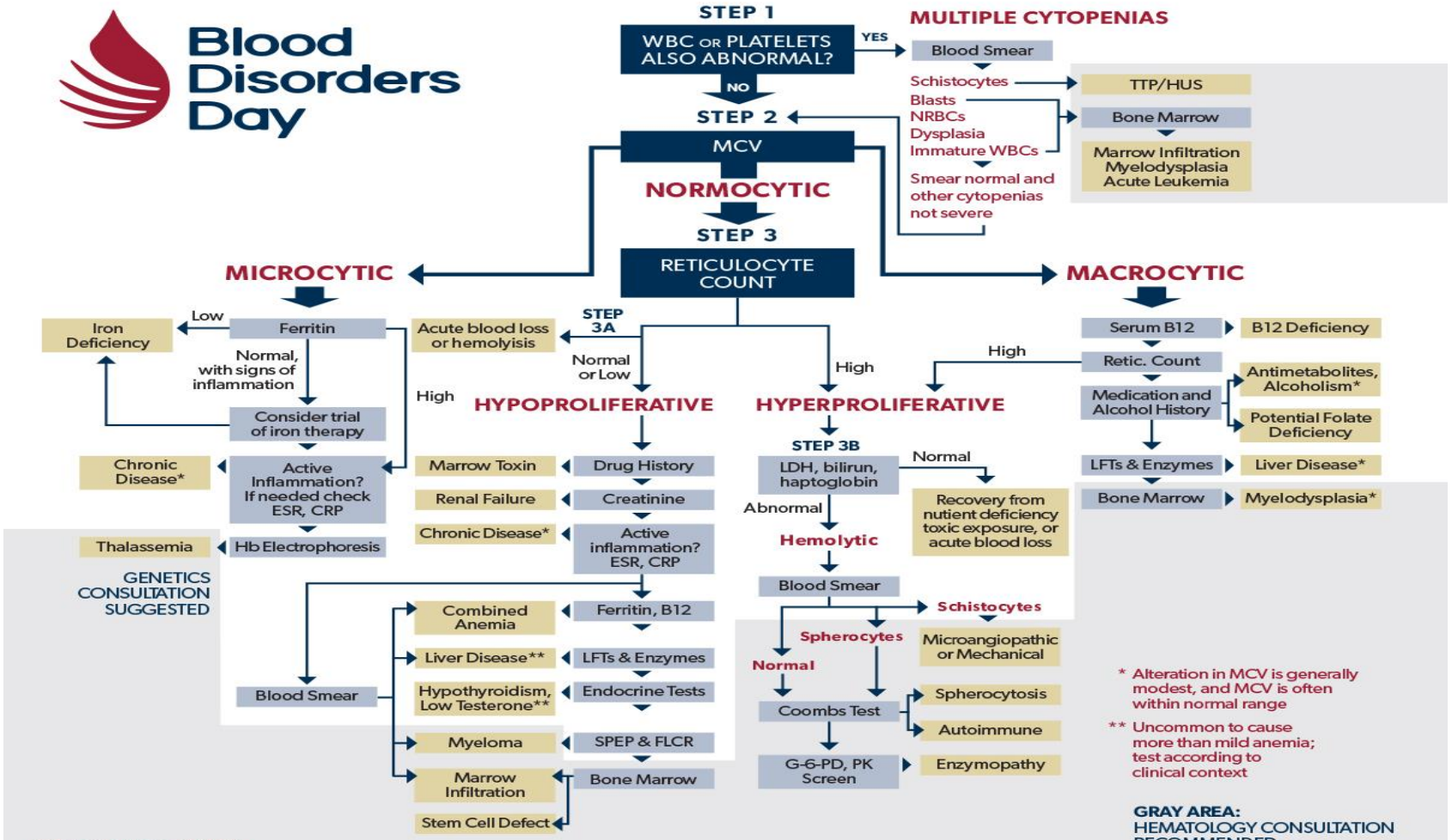

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B_{12} 130 (normal >180 pmol/L)

TSH and LFTs normal

Ferritin 110 (normal)

B_{12} (Cobalamin) Deficiency

Diagnosis: B_{12} deficiency

- B_{12} 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

B_{12} (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

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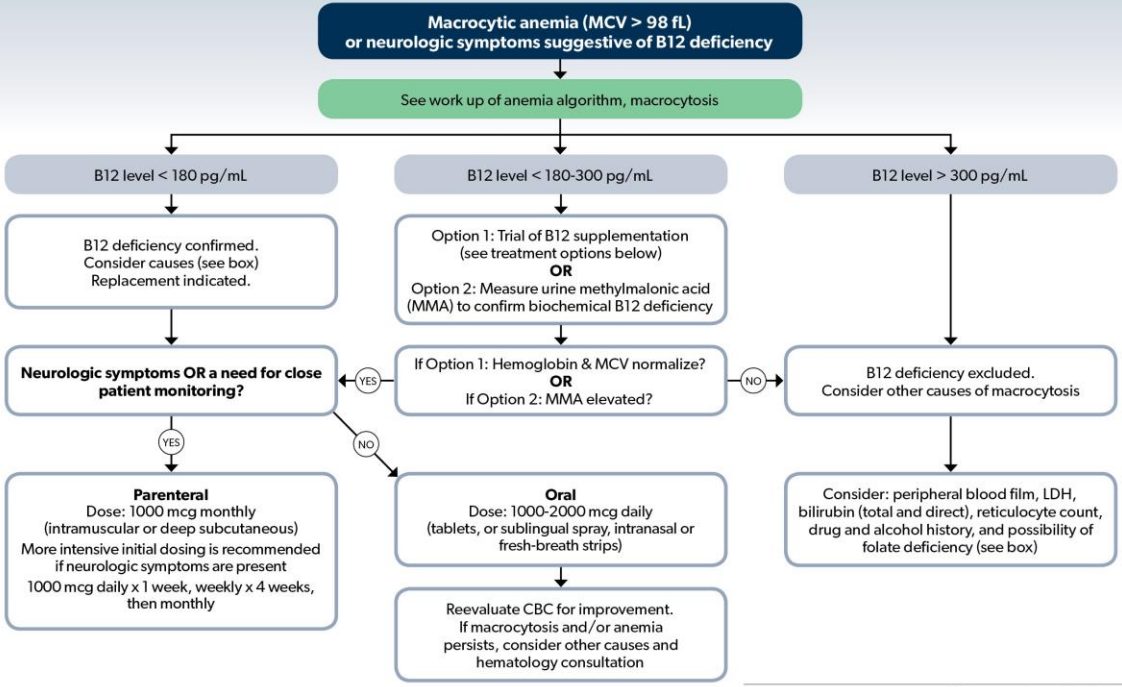
Vitamin B12 Deficiency



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

Causes of vitamin B12 deficiency

Gastric
» Pernicious anemia (autoantibodies)
» Gastrectomy/bariatric surgery
» Gastritis

Pancreatitis

Pancreatic insufficiency

Strict vegan diet

Small bowel disease
» Malabsorption syndrome
» Ileal resection or bypass
» Inflammatory bowel disease
» Celiac disease
» Bacterial overgrowth
» Blind loop
» Fish tapeworm

Agents that impair B12 absorption
» Biguanides (e.g. metformin)
» Proton pump inhibitors
» Histamine-2 receptor antagonists
» Nitrous oxide gas

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

Butler C, Vadal-Alaball J, Cannings-John R, McCaddon A, Hood K, Papaioannou P, Mcdowell I *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_{12}

	Parenteral	Oral
Pro	Compliance easily monitored Venue for close follow for patients who need this	Inexpensive Does not require a visit to a health practitioner Strips: freshen your breath while replacing B_{12}!
Con	Increased heath care costs Painful Not ideal for anticoagulated patients	Requires consistent compliance of the patient

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:

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

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

Now what?

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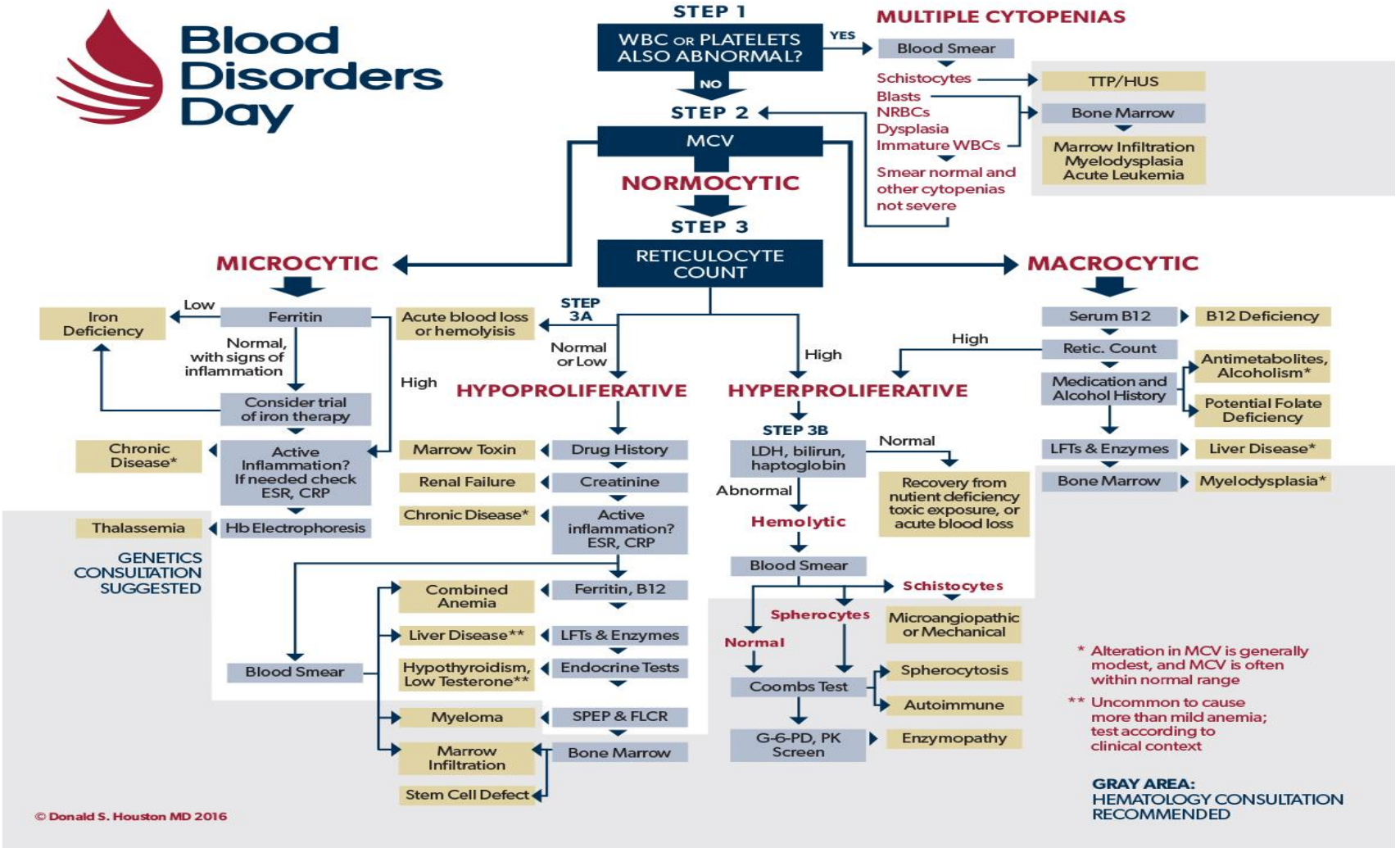
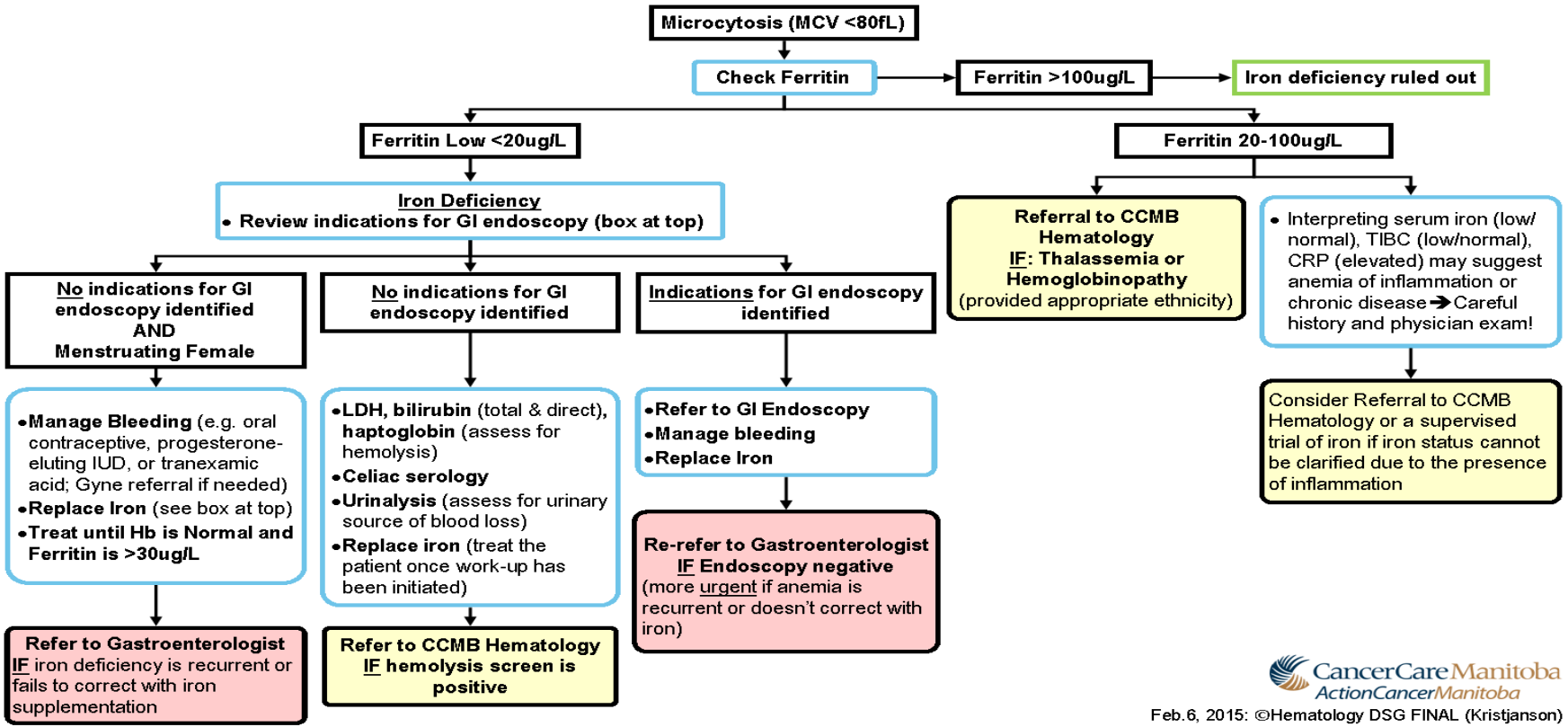


Work-Up of IRON DEFICIENCY ANEMIA in ADULTS

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, gluconate, or fumarate or iron polysaccharide in doses that provide 150-200mg of elemental iron per day (e.g. ferrous sulfate 300mg TID)



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Feb.6, 2015: ©Hematology DSG FINAL (Kristjanson)

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)

Recommended first line

Unproven claims of increased GI tolerability

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

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 another[3]

**Recommend NOT using sustained-release capsules

- very poorly absorbed

[3] Cancelo-Hidalgo MJ et al. Tolerability of different oral iron supplements: a systematic review. *Curr Med Res Opin*. 2013;29(4):291.

Iron dosing strategies

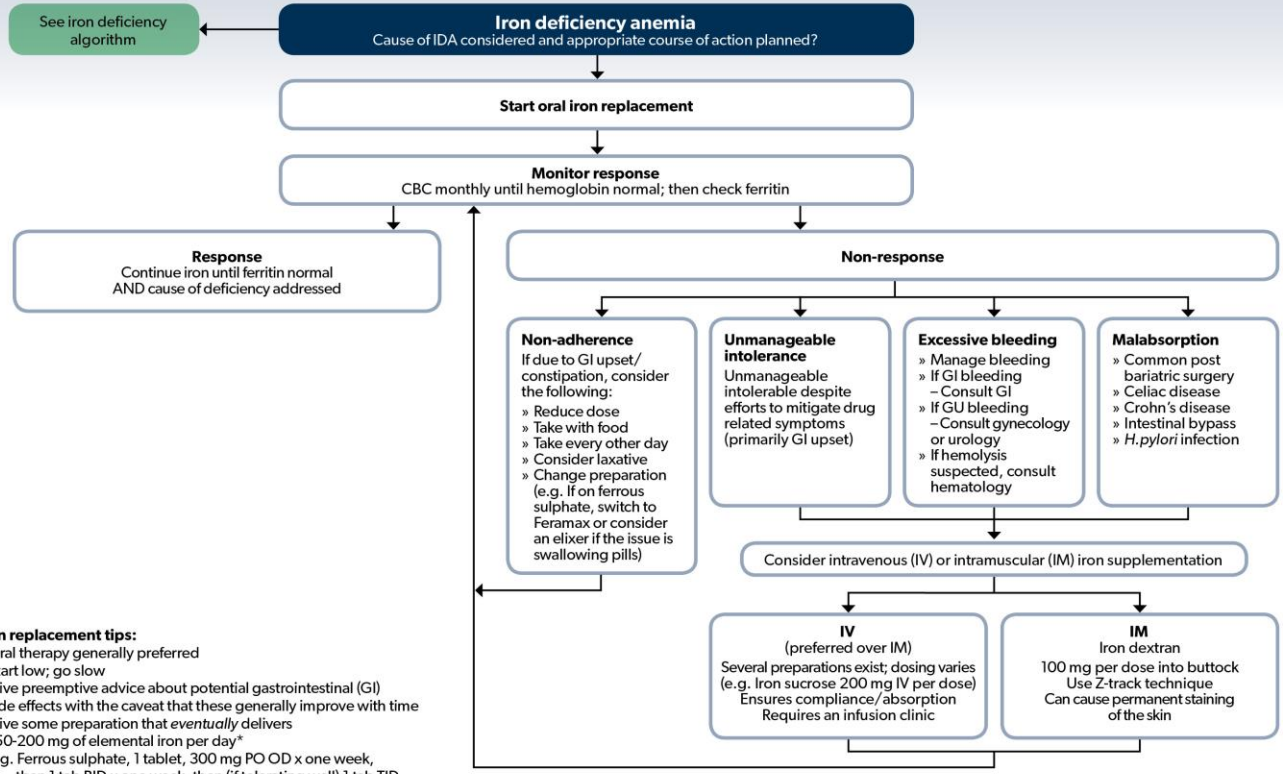
The optimal dosing strategy hasn't been adequately studied

- 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 intolerence and reduced absorption

Iron Replacement



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

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

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/fumerate
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

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Thank you

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