

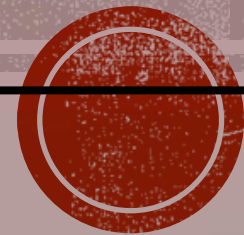
IRON INFUSIONS

Cancer Preceptorships for GPs 2021

Dr Michelle Spanevello, BPhy(Hons) MBBS(Hons) FRACP FRCPA

Senior Staff Specialist

Haematology





OVERVIEW

- Iron metabolism
- Iron deficiency
 - Definition
 - Iron studies
 - Causes
- Iron supplementation
- Iron infusions



IRON IN HUMANS

- Accounts from at least the 18th century of the presence of iron in blood
- Required for oxygen transport, energy production, DNA synthesis and cellular respiration
- Component of haemoglobin and myoglobin
- 3-5g iron in the average adult human
 - 60% in haemoglobin (2.0-2.5g)
 - 10% myoglobin, cytochromes, catalase (300-500mg)
 - 0.1-0.2% plasma transferrin-bound iron (3-4mg)
 - ~30% stored in hepatocytes and reticuloendothelial macrophages as ferritin, haemosiderin



IRON METABOLISM BASICS

- Multi scale control system – processes from organism to subcellular
- Tightly regulated as excess causes toxic radicals
- No active excretion mechanism known
 - 1-2mg per day lost in sweat, blood loss, intestinal epithelial loss, desquamation
- Haemoglobin synthesis requires 20-25mg/day
- Dietary absorption only 1-2mg/day – therefore recycling is an important part of metabolism
- Hepcidin, ferroportin, iron regulatory proteins.....

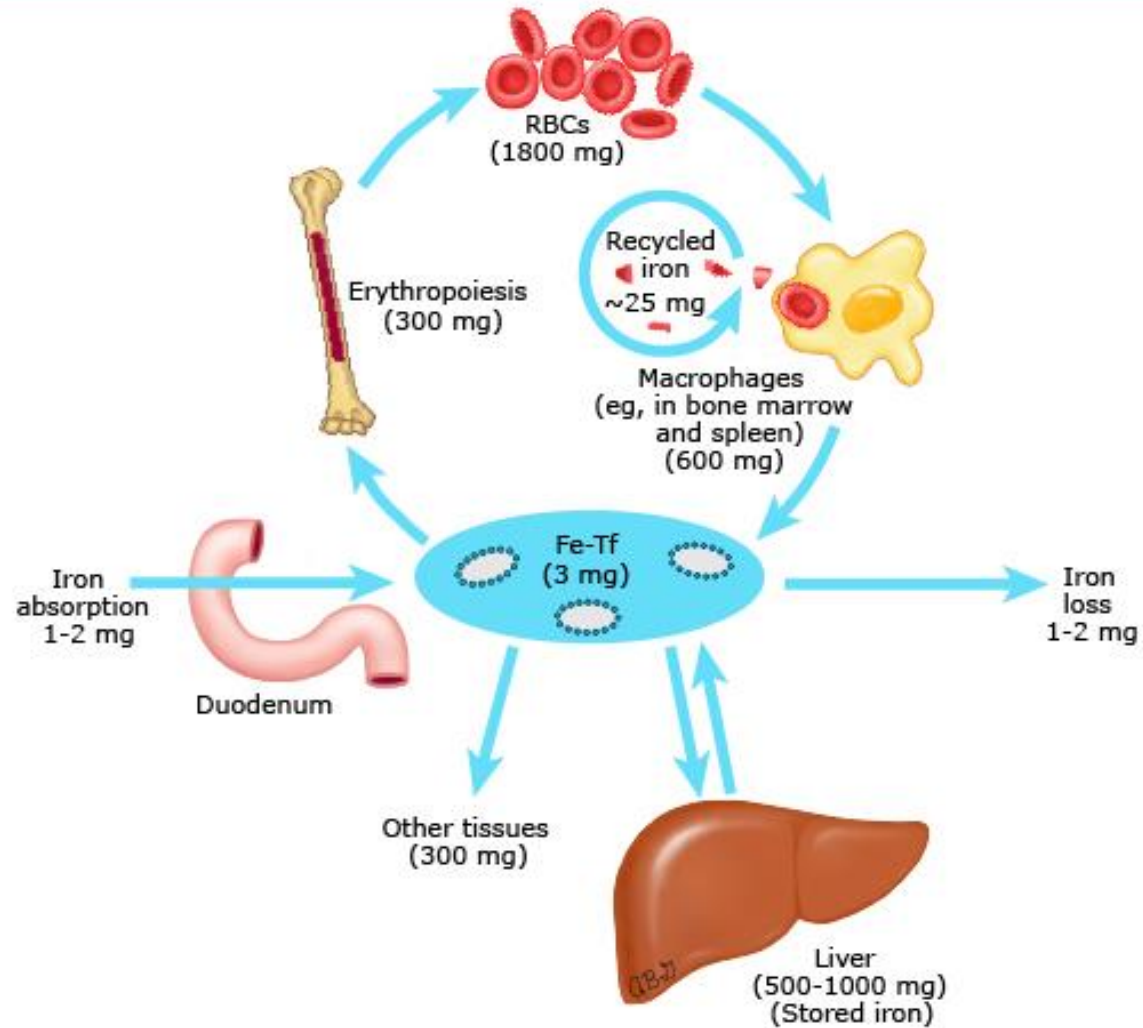


IRON ABSORPTION

- Non-heme iron (eggs, vegetables)
 - Ferrireductase (Cybrd1) reduces non-heme iron to Fe^{2+} then transported through the cellular membrane of duodenal enterocytes through DMT1
- Heme iron (fish, poultry and red meat, chelated form of Fe^{2+}) have higher bioavailability than non-heme iron but absorption not fully understood
 - Proteolytic digestion of myoglobin and haemoglobin, intestinal absorption of intact metalloprotein
- Ferric (Fe^{3+} , oxidized, soluble at pH 3) less well absorbed than ferrous (Fe^{2+} , reduced, soluble up to pH 7-8)
- Once absorbed, transported into cytosol and released by heme oxygenase 1
- Exported from enterocytes through ferroportin with ferroxidase hephaestin that oxidises Fe^{2+} to Fe^{3+}
- Transported by transferrin in the plasma
- Excess intracellular iron stored in ferritin



Regulation of iron absorption, transport, and homeostasis



Schematic showing iron homeostasis. Refer to UpToDate for details of the regulation of iron absorption, transport, and storage in the body.

RBCs: red blood cells; Fe-Tf: transferrin-bound iron, the major transport form in the body.



REGULATION OF IRON ABSORPTION

- Hepcidin (produced by the liver) is a negative regulator of intestinal iron absorption and release from macrophages
 - Inhibited by testosterone, erythroferrone (ERFE, hormone from erythroblasts stimulated by erythropoietin)
 - Increased by lipopolysaccharide, IL6 and IL1B seen in inflammation
- Ascorbic acid and meat sources enhance absorption of non-animal sources of iron (cereals, fruits, bread and vegetables)
- Tannates (teas), bran, calcium, soy, phosphates and phytates inhibit iron absorption



DIAGNOSING IRON DEFICIENCY

IRON STUDIES

- Serum iron (light absorbance)
- Transferrin (turbidimetric)
- TIBC = calculated using Tf or to get an indirect measure of transferrin, UIBC + iron
- Transferrin Saturation = calculated value of serum iron divided by total iron-binding capacity of available transferrin
- ➔ ▪ Ferritin (2 step immunoenzymatic assay) – in plasma apoferritin, non-iron containing, reflects overall iron storage generally (ferritin 1ug/L = 10mg stores)

Other tests

- sTfR (immunoturbidimetric) – not medicare rebatable
- ➔ ▪ Bone marrow iron staining – negative result can be seen with ferritin up to 100



IRON STUDIES INTERPRETATION

	Iron	Tf	TSat	Ferritin	sTfR
Normal	10-30	2.1-3.8	15-45	15-300 v	2-5mg/L v
Iron deficiency	↓	↑	↓	↓ <30 <20	↑
Iron deficiency likely (acute phase)	↓	↓ or N	N or ↓	N but < 100 (<60 in children)	↑
Acute phase	↓	↓	↓	↑	Normal
Anaemia of Chronic Disease	↓	↓	↓	>100	Normal



CAUSES OF IRON DEFICIENCY

Reduced intake

- Vegetarian/vegan

Poor absorption

- Coeliac disease, atrophic gastritis, H.pylori infection, bariatric surgery, PPI, IRIDA (TMPRSS6 mutation), SLC11A2 mutation (DMT1), ACD (iron sequestered in macrophages and absorption reduced), medications, obesity

Increased utilization

- Blood donations, pregnancy, lactation, adolescence, athletes and overtraining, erythropoietin/ESA, obesity

Blood loss

- GI bleeding, menstruation/menorrhagia, childbirth, haemolysis, GI parasites, haemodialysis, urinary / pulmonary haemosiderosis



DEFINITIONS IN IRON DEFICIENCY

- Affects predominantly childbearing women, children, individuals in low- and middle- income countries
- Iron deficiency without anaemia (latent iron deficiency)
 - Iron depletion, iron deficient erythropoiesis
 - Ferritin < 30 (<50)
 - Symptoms include fatigue, decreased exercise tolerance
- Iron deficiency anaemia
 - Low haemoglobin / haematocrit caused by low iron
 - Pica (pachophagia), restless legs syndrome, headache, exercise intolerance, exertional dyspnoea, weakness, hearing loss
- Absolute iron deficiency
 - Reduction / absence of storage iron
- Functional iron deficiency
 - Iron-restricted erythropoiesis – ACI/ACD, ESA





WHEN TO TREAT

Iron deficiency with anaemia (with Ix for causes): ferritin < 30, Hb <120-130

Symptomatic iron deficiency without anaemia: ferritin < 30 (<50)

Restless leg syndrome: ferritin < 75

Symptomatic heart failure (EF<40%): ferritin <100 OR 100-299 with TSat <20%

CKD: ferritin < 100 and TSat < 20%

CKD ND and anaemia: ferritin < 500, TSat < 30% (KDIGO)

CKD5-HD: ferritin < 200-500 or TSat <20

CKD on ESA: ferritin < 250-500, Tsat < 25-40%

Pregnancy: ferritin <30, Hb<110

Oral

Parenteral

**IRON
SUPPLEMENTATION**



ORAL IRON REPLACEMENT



Maltofer Syrup	Maltofer	Ferroliquid	Ferrograd C	Ferrograd	Ferrograd F	Ferro + Vit C	Fefol	Ferro-F	Ferro-tab
10mg/ml	100mg	6mg/ml	105mg	105mg	80mg	105mg	87.4mg	100mg	65.7mg



STRATEGIES FOR ORAL SUPPLEMENTATION

TOLERABILITY

- Intermittent dosing
- Divided doses
- Take dose at night
- Take with food
- Consider alternative formulation

ABSORPTION

- With vitamin C
- On empty stomach
- Avoid tea / coffee
- Review other meds eg PPI, calcium, antacids
- Intermittent dosing





**INDICATIONS FOR
INTRAVENOUS
IRON**

- Confirmed iron deficiency or IDA
- and one of**
- Demonstrated intolerance, non-compliance or lack of efficacy (3 month trial of oral iron, haemoglobin rise of 20g/L every 3 weeks)
 - Pregnancy (second and third trimester), postpartum
 - Intestinal malabsorption (eg coeliac)
 - Ongoing losses exceeding absorptive capacity
 - Need for rapid iron supply
 - Heart failure patients
 - Chronic renal impairment receiving ESA
 - Pre-operative optimization of anaemia (2 months)

ADVERSE REACTIONS

- Allergy/anaphylaxis
 - Wheezing, stridor, sweating, tachycardia, dyspnea, dizziness, hypotension, cardiac arrest
- Extravasation / Staining
 - Redness, swelling, taut skin, fluid leakage, coolness, blanching, numbness, tingling, skin discolouration
- Delayed symptoms
 - Vomiting, nausea, light headedness, metallic taste, myalgia/arthralgia, fever, diarrhea, chest pain/tightness, indigestion, fatigue, rash, headache, abdominal pain



PBS LISTED IRON INFUSIONS



Iron polymaltose (Ferrosig, FerrumH)

Inpatient (\$31.32 for 1000mg,
\$37.04)



Ferric carboxymaltose (Ferinject)

Outpatient preferred
(\$298.80 for 1000mg, \$41.30)



Ferric derisomaltose (Monofer)

Paediatric and renal patients,
previous reaction (\$298.80
for 1000mg, \$41.30)



Iron sucrose (Venofer)

Renal patients on ESA with
previous reaction (\$298.80
for 1000mg, \$41.30)



PROCESS

- Discontinue oral iron (up to 7 days prior and for 5 days following)
- Consent
- Dosing – Ganzoni’s formula
 - Iron deficit in mg = iron depot in mg + [(target Hb-actual Hb in g/L) x bodyweight in kg x 0.24]
 - Iron depot below 35kg = 15mg/kg, above 35kg = 500mg
- Fully equipped emergency trolley – EpiPen
- Cannulation – avoid sites of flexion, proximal to previous sites of failures, adequately secured and protected from movement
- Use infusion/extension set
- Monitor / Observations – baseline, during and for up to 1 hour post first infusion
- Review response – peak level 7 days, 4 weeks haemoglobin response, 3-6months for ongoing



IRON INFUSION COMPARISON

	Iron Polymaltose (slow)	Iron Polymaltose (rapid)	Ferric Carboxymaltose	Ferric Derisomaltose	Iron sucrose
	100mg/2ml	100mg/2ml	500mg/10ml	500mg/5ml	100mg/5ml
Order	1500mg in N/Saline (500ml)	1500mg in N/Saline (250ml)	1000mg in N/Saline (100-250ml)	Dilute to 100-500ml	Dilute to 100ml
Observations O2, temp, BP, pulse, RR, cannula site	Baseline q5mins x 15mins q15mins x 45mins q1h until 1h post completion	Baseline q5m x 15mins q15mins until 1h post completion	Baseline q5m during 15m and 30m after completion (1 st dose) 20mins after completion (subsequent)	Baseline q5m during 15m and 30m after completion (1 st dose) 20mins after completion (subsequent)	
Timing	50mg first hour (eg 17ml/hour x 1 hour) then increase to 120ml/hr 5 hour infusion	40ml/hr for 15 mins then increase to 250ml/hr	200-400ml/hr (over 15-30mins)	Over 20mins	
Equivalence to 100mg elemental iron	318mg (6.36ml)	318mg (6.36ml)	100mg (2ml)	100mg (1ml)	100mg (5ml)
Maximum dosing	2500mg	1500mg	1000mg per week (7.5mg/kg, ideally 1g q6m)		100mg tiw to 1000mg over 10 dialysis sessions
Note		NOT for HF NYHA 3/4, EF<30%, eGFR <15, risk of fluid overload	NOT in 1 st trimester pregnancy		For Renal patients on ESA with reaction to iron polymaltose
Storage			20-25deg Room temp 72h	20-25deg Room temp for up to 8h	< 25deg



FERRIC CARBOXYMALTOSE

- Infusion time 15-30mins
- Low volume
- Can remain at room temp for 72 hours
- Observations at baseline, q5m during infusion, then at 15m/30m post (1st dose), 20m post subsequent infusions



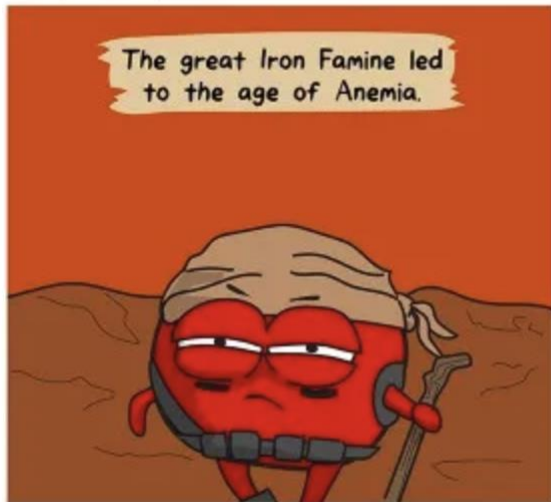
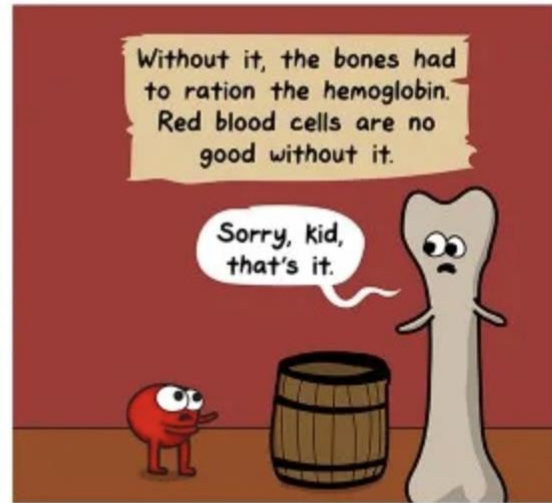
REFERRALS

- Local GPs
- Outpatient based services
 - General medical units
 - Haematology
 - Gastroenterology
 - Cardiology
 - Renal





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