2024 RBWH CANCER CARE SERVICES PRECEPTORSHIP
FOR GENERAL PRACTITIONERS

- **OVERVIEW OF IRON**
- **Dr Michelle Spanevello**

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Metro North Health | Queensland Government

OVERVIEW OF IRON

RBWH Cancer Care Preceptorships for GPs 2024

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OVERVIEW

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

IRON IN HUMANS

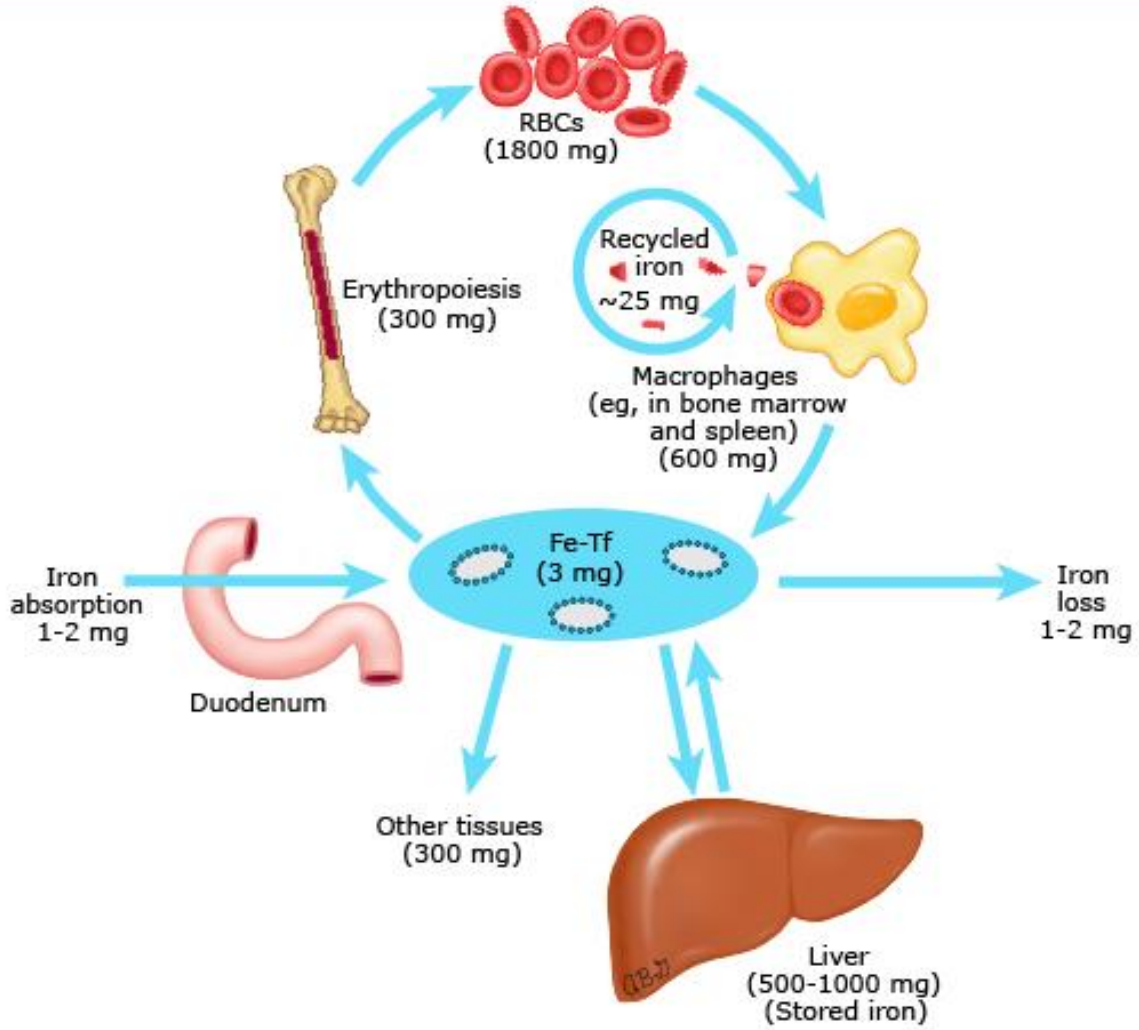
- Accounts from at least the 18th century report the presence of iron in blood
- Required for oxygen transport, energy production, DNA synthesis and cellular respiration
- Component of haemoglobin and myoglobin
- 3-5g iron in the average adult human
  - 60% in haemoglobin (2.0-2.5g)
  - 10% myoglobin,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

Chifman et al, Adv Exp Med Biol 2014

IRON METABOLISM BASICS

- Multi scale control system – processes from organism to subcellular
  - Hepcidin, ferroportin, iron regulatory proteins…..
- 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

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.

UpToDate®

IRON ABSORPTION

- Enterocyte uptake
  - Reduction
  - Non-heme iron (eggs, vegetables) – DMT1
  - Heme iron (fish, poultry and red meat – HCP1
- Within enterocyte
  - Heme Oxygenase 1 (HO-1)
- Enterocyte export
  - Ferroportin FPN1
  - Ferroxidase hephaestin HPE oxidation
- Plasma transport
  - Ceruloplasmin CP oxidation
  - Combines with apotransferrin in the plasma (transferrin = apotransferrin + 1-2 ferric ions)
- Excess intracellular iron stored in ferritin

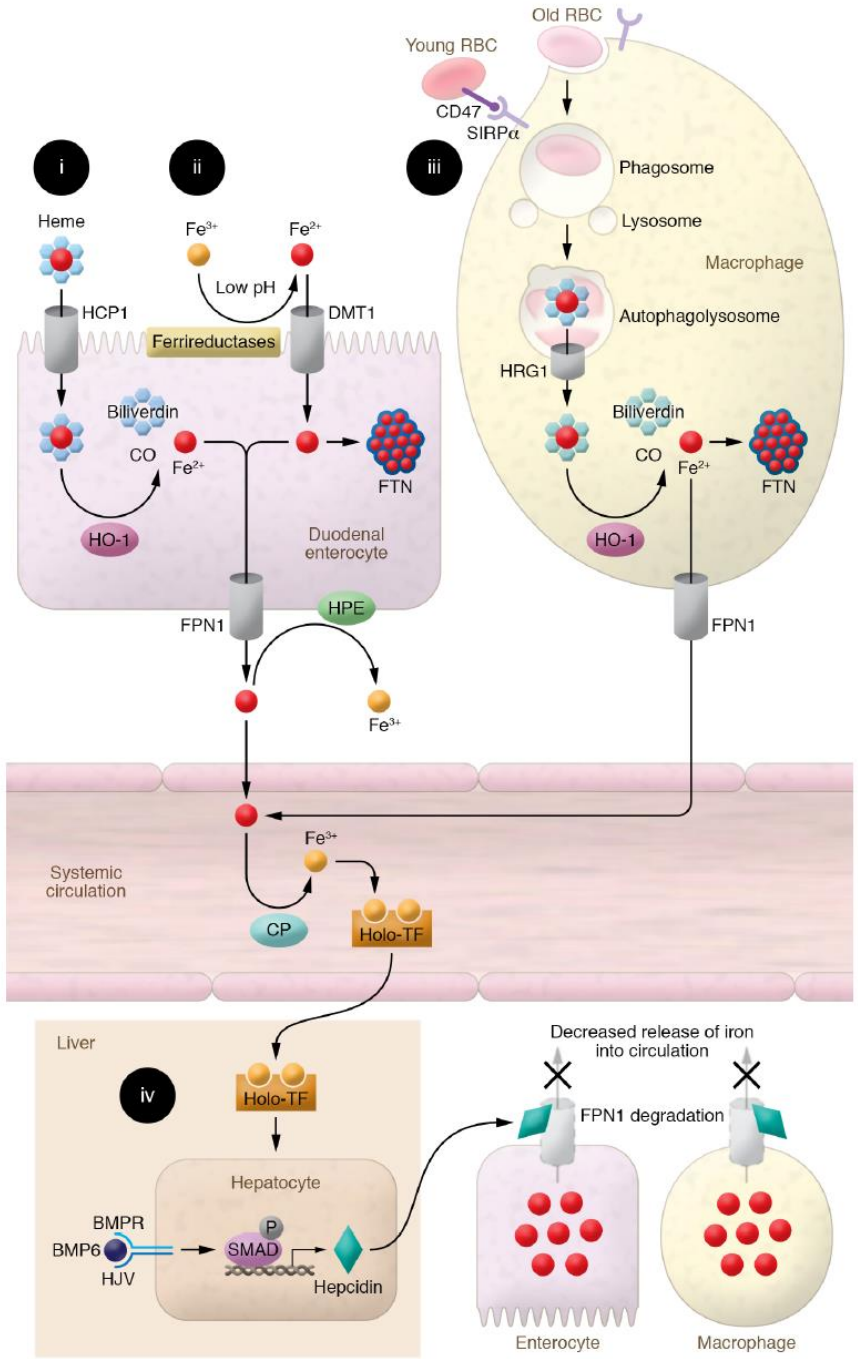


Figure 1. Depiction of the mechanism of systemic iron regulation. (i) Heme-bound iron is absorbed into duodenal enterocytes, possibly via HCP1. Enterocyte HO-1 releases iron from heme's porphyrin ring, producing Fe^{2+}, biliverdin, and carbon monoxide. Fe^{2+} iron is then exported into the circulation by FPN1. (ii) Absorbed Fe^{3+} is reduced to Fe^{2+} at the brush border by low pH and ferrireductases, enabling its transport by DMT1 into duodenal enterocytes. Fe^{2+} is either bound to FTN within the enterocyte, limiting the intracellular pool of free iron, or released into the circulation by FPN1, where it is oxidized to Fe^{3+} by hephaestin (HPE) and ceruloplasmin (CP) and bound to TF for transport. (iii) Macrophages identify senescent RBCs no longer expressing CD47 via SIRPα and recycle RBC iron through phagocytosis. Upon fusion of phagosomes with lysosomes, heme is released from hemoglobin and transported to the cytosol via HRG1. In the cytosol, heme-bound iron is extracted by HO-1 and exported by FPN1. Fe^{2+} is then oxidized to Fe^{3+} by CP and binds to TF for transport. (iv) When systemic iron levels are sufficiently replete, hepcidin is produced by the liver, binds to FPN1 on macrophages and enterocytes, and promotes its degradation. This prevents intestinal and macrophage iron release into the circulation. Binding of BMP6 to BMP receptor and its coreceptor HJV activates SMAD signaling and promotes transcription of hepcidin.

Koleini et al, J Clin Inv 2021

REGULATION OF IRON ABSORPTION

- Hepcidin (produced by the liver) is a ***negative*** regulator of intestinal iron absorption and release of recycled iron from macrophages and stored iron from hepatocytes
  - Inhibited by testosterone, erythroferrone (ERFE, hormone from erythroblasts stimulated by erythropoietin), pregnancy
  - 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

Nemeth and Ganz, Annu Rev Med 2023

HEPCIDIN REGULATION

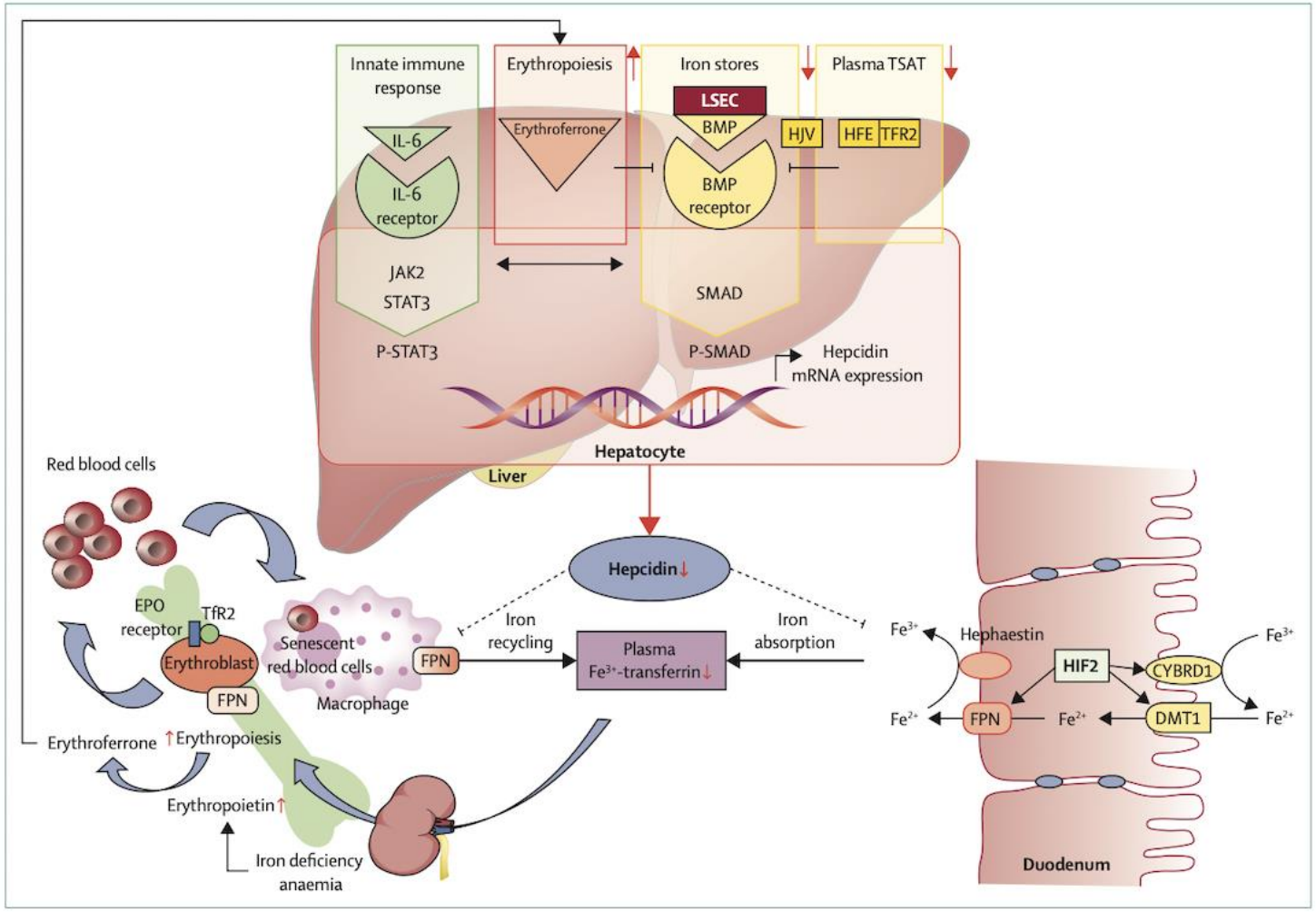


Figure 1: **Coordinated homoeostatic response to absolute and functional iron deficiency**
Red arrows refer to physiological stimuli (eg, absolute iron deficiency or increased erythropoiesis) that suppress hepcidin expression. During absolute iron deficiency, decreased circulating transferrin saturation and liver iron storage suppress hepcidin transcription via reduced BMP-SMAD signalling (yellow pathway). As a consequence, duodenal and macrophage FPN proteins are stabilised, facilitating dietary iron absorption in duodenal enterocytes and release of iron from macrophages of the reticuloendothelial system, thereby increasing iron concentrations in the plasma. Additionally, reduced iron concentration in duodenal enterocytes is sensed by the iron-dependent prolyl hydroxylase domain enzymes that increase stability of the transcription factor HIF-2, which regulates transcription of apical (CYBRD1 and DMT1) and basolateral (FPN) iron transport machinery. During iron deficiency, in most cell types the IRP/IRE system stabilises mRNAs of proteins crucial for iron uptake (eg, TfR1 and DMT1) and suppresses the synthesis of proteins involved in the storage (ferritin), utilisation (cytoplasmic and mitochondrial iron-containing proteins), and export (FPN) of iron. In functional iron deficiency, inflammation increases hepatic hepcidin expression via IL6-JAK2-STAT3 signalling (green pathway), causing reduced FPN abundance and function on cells, depriving the plasma of iron. In response to iron deficiency anaemia, the kidney produces erythropoietin, which stimulates erythropoiesis. Erythroblast erythropoietin sensitivity can be modulated by TfR2. In absolute iron deficiency, erythroblasts and erythrocytes donate iron through FPN-mediated iron export. Increased erythropoiesis (eg, during recovery from anaemia) causes secretion of erythroferrone, which suppresses hepatic hepcidin expression via inhibition of BMP-SMAD signalling (red pathway). LSEC=liver sinusoidal endothelial cell. P=phosphorylated. TSAT=transferrin saturation.

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

QUESTION: IRON STUDIES

A patient's iron studies results are

Serum Iron	8	umol/L	(10-30)
Transferrin	3.1	g/L	(1.9-3.1)
TIBC	75	umol/L	(41-77)
Transferrin Saturation	11	%	(20-45)
Ferritin	70	ug/L	(30-300)

Which is the correct answer below?

A. This shows an inflammatory pattern
B. A concurrent CRP would be useful
C. There is likely iron deficiency
D. All of the above

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Which is the correct answer below?

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IRON STUDIES INTERPRETATION

	Iron umol/L	Tf g/L	TIBC umol/L	TSat %	Ferritin ug/L	sTfR mg/L
Normal	~ 10-30	~ 2.1-3.8	~45-70	~ 15-45	~ 15-300	2-5mg/L
Iron deficiency	↓	↑	↑	↓	↓ <30 <20	↑
Iron deficiency likely (acute phase)	↓	↓ or N	↓ or N	N or ↓	N but < 100 (<60 in children)	↑
Acute phase	↓	↓	↓	↓	↑	Normal
Anaemia of Chronic Disease	↓	↓	↓	↓	>100	Normal

RCPA Manual, Melbourne Haematology

CAUSES OF IRON DEFICIENCY

Reduced intake

- Vegetarian/vegan

Poor absorption

- Coeliac disease, atrophic gastritis, IBD, H.pylori infection, impaired gastric acid secretion, 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, bleeding disorders, vascular malformations eg HHT

CASE: BF

- 18 yo F
- Significant fatigue
- Iron deficiency for nearly 12 months
- Irregular periods
- No abdominal symptoms, eats well, non-vegetarian
- Maltofer – nausea, constipation, nonadherence
- Yasmin added 6 months ago

QUESTION: BF

Results

- Hb 126 g/L (115-160), MCV 82 fL (80-98)
- Ferritin 6 umol/L (25-290), TIBC 89 umol/L (45-70)

This is a case of

A. Iron deficiency anaemia
B. Latent Iron Deficiency
C. Functional Iron Deficiency
D. Iron replete status

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This is a case of

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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 (pacophagia), 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

QUESTION: INDICATIONS TO TREAT

Which of these patients should be recommended supplementation?

A. Iron deficiency anaemia
B. Restless leg syndrome with ferritin 50
C. Symptomatic heart failure (EF < 40%) with ferritin 80
D. All of the above

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Which of these patients should be recommended supplementation?

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- 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

Soppi et al 2018 Clin Case Reports

IRON SUPPLEMENTATION

- Oral
- Parenteral

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 / phytates
- 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)

CASE: PM - CKD

- 75 yo M
- OSA on CPAP, T2DM, Obesity, Recurrent TIA/CVA, CKD on darbepoietin
- Usual haemoglobin 100-110
- Referred with worsening anaemia Hb 90-100
- Results Hb 93, Ferritin 63, TSat 24%
- Investigations non-contributory
- BMAT excluded MDS
- Regular bookings for ongoing iron infusions

CUMULATIVE FULL BLOOD EXAMINATION

Date	18/02/20	23/04/20	17/11/20		25/02/21		
Time	10:30	11:41	08:25		07:29		
Lab No	74541697	74544367	27747713		28977985		
Hb	93	104	109		108	g/L	(125-180)
RCC	2.8	3.2	3.4		3.2	x10 ^12 /L	(3.8-6.0)
Hct	0.28	0.31	0.34		0.33		(0.34-0.52)
MCV	99	98	101		102	fL	(80-98)
MCH	33	33	33		34	pg	(27-35)
Plats	245	217	215		217	x10 ^9 /L	(150-450)
WCC	7.2	7.4	6.5		5.7	x10 ^9 /L	(4.0-11.0)
Neuts	4.2	4.5	3.3	45 %	2.6	x10 ^9 /L	(2.0-7.5)
Lymphs	2.1	1.9	2.0	39 %	2.2	x10 ^9 /L	(1.1-4.0)
Monos	0.6	0.6	0.7	9 %	0.5	x10 ^9 /L	(0.2-1.0)
Eos	0.29	0.30	0.46	6 %	0.34	x10 ^9 /L	(0.04-0.40)
Basos	0.00	0.07	0.07	1 %	0.06	x10 ^9 /L	(< 0.21)
Retics		61				x10 ^9 /L	

PBS LISTED IRON INFUSIONS

Iron polymaltose (Ferrosig, FerrumH)

Inpatient

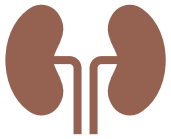
SL: Iron deficiency due to chronic haemolysis

(DPMQ $33.89 for 500mg)

Ferric carboxymaltose (Ferinject)

Outpatient preferred

(DPMQ $300.19 for 1000mg)



Ferric derisomaltose (Monofer)

Paediatric and renal patients, previous reaction

(DPMQ $285.60 for 1000mg)

Iron sucrose (Venofer)

Renal patients on ESA with previous reaction

SL: Iron deficiency due to chronic haemolysis

(DPMQ $39.53 for 500mg)

IRON INFUSION COMPARISON

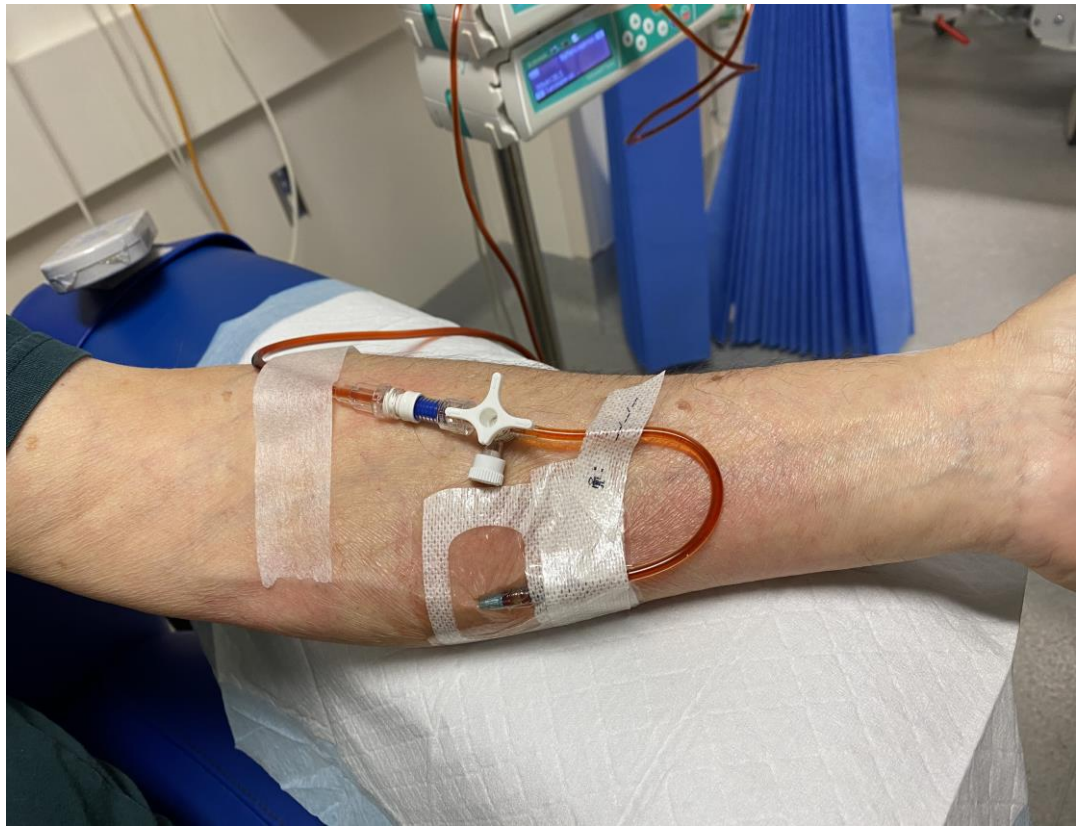
	Iron Polymaltose (slow)	Iron Polymaltose (rapid)	Ferric Carboxymaltose	Ferric Derisomaltose	Iron sucrose
Concentration	100mg/2ml	100mg/2ml	500mg/10ml	500mg/5ml	100mg/5ml
Presentation	2ml ampoules	2ml ampoules	2ml or 10ml vial		5ml ampoule
Order	1500mg in N/Saline (500ml)	1500mg in N/Saline (250ml)	1000mg 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 (1st dose) 20mins after completion (subsequent)	Baseline q5m during 15m and 30m after completion (1st dose) 20mins after completion (subsequent)	Dialysis observations
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	Over 15mins (1ml per minute)
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)	1000mg	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 1st 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

PROCESS

- Discontinue oral iron (up to 7 days prior and for 5 days following)
- Consent
- Dosing – Ganzoni's formula
  - Iron deficit(mg) = iron depot(mg)+ [(target Hb-actual Hb(g/L) x weight(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

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



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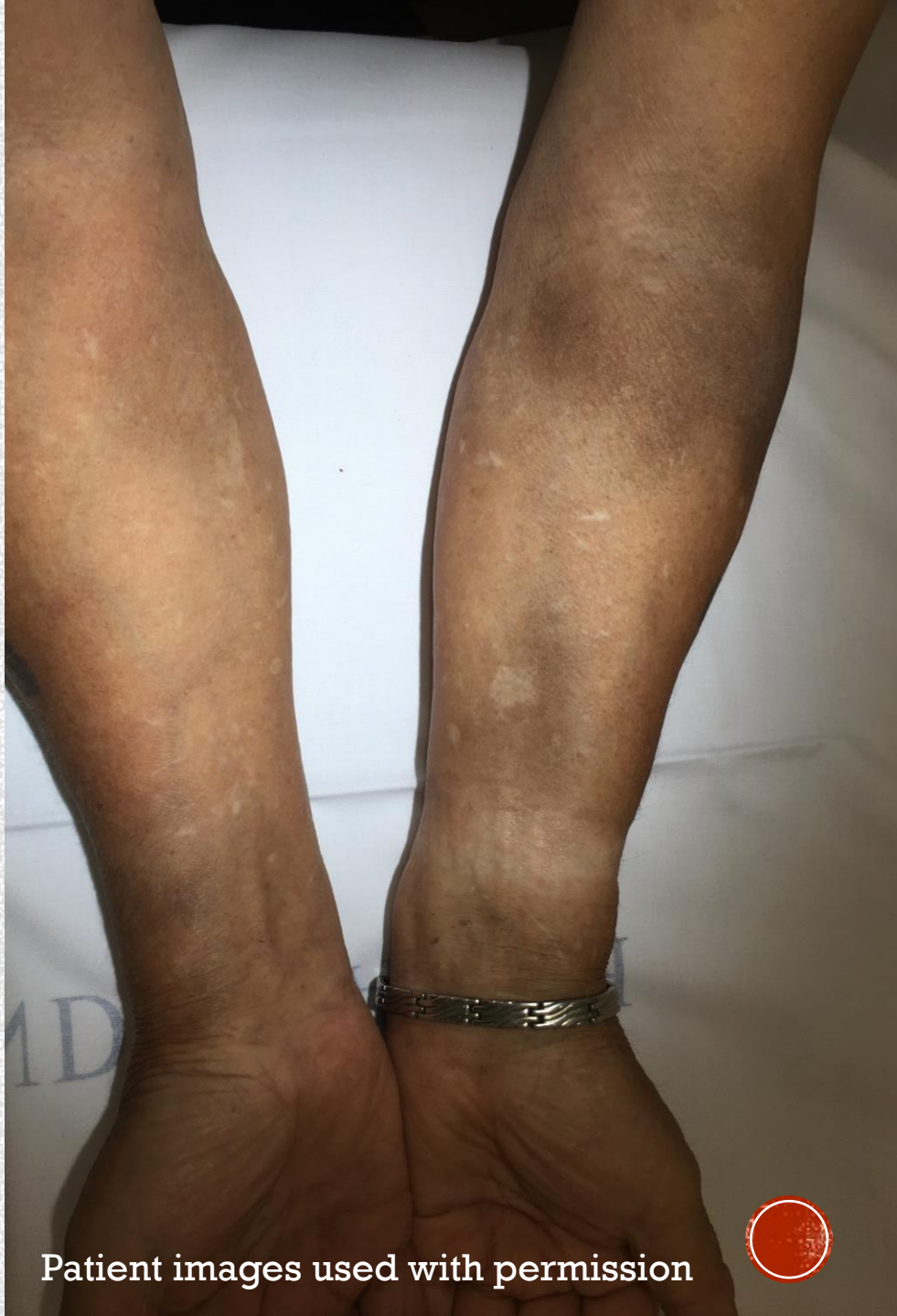
ADVERSE REACTIONS

- 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, hypophosphataemia, distant skin discolouration

Van Doren and Auerbach, Hematology 2023



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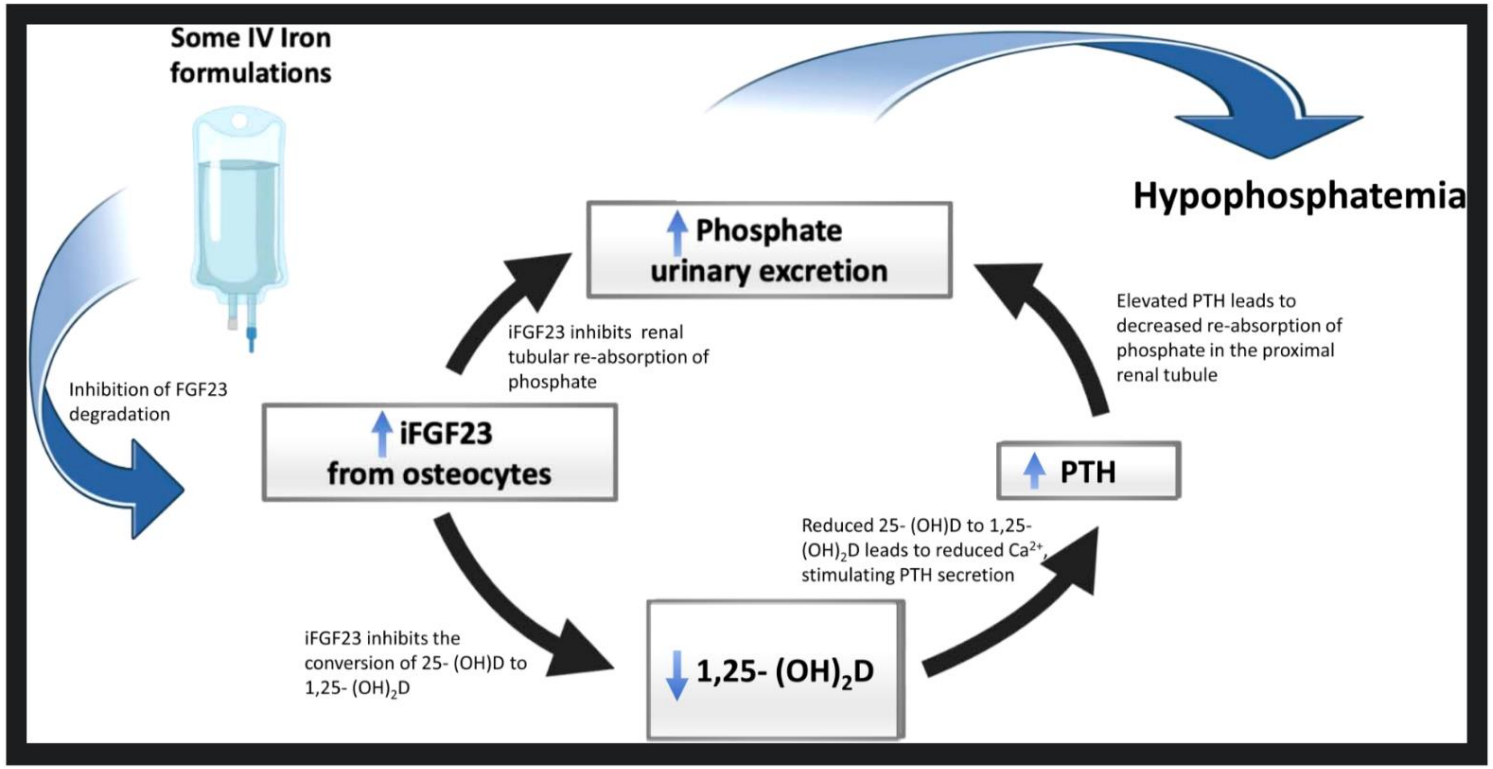
HYPOPHOSPHATAEMIA

- Ferric carboxymaltose
- Vitamin D deficiency
- Hypocalcaemia
- Hypophosphataemia
- Elevated PTH
- Prolonged supraphysiological ferritin
- Stacked infusions
- High doses
- Bariatric surgery
- (Renal insufficiency relatively protective)

Figure 4.



Mechanism of treatment-emergent hypophosphatemia. Following the administration of some intravenous iron formulations is a sharp rise in the plasma iFGF23, triggering a pathophysiological cascade of renal phosphate wasting, calcitriol deficiency, and secondary hyperparathyroidism. This frequently culminates in hypophosphatemia even after iFGF23 levels have normalized. PTH, parathyroid hormone.

Ifie et al, EDM 2019; Boots and Quax, Drug Safety 2022; Van Doren and Auerbach, Hematology 2023

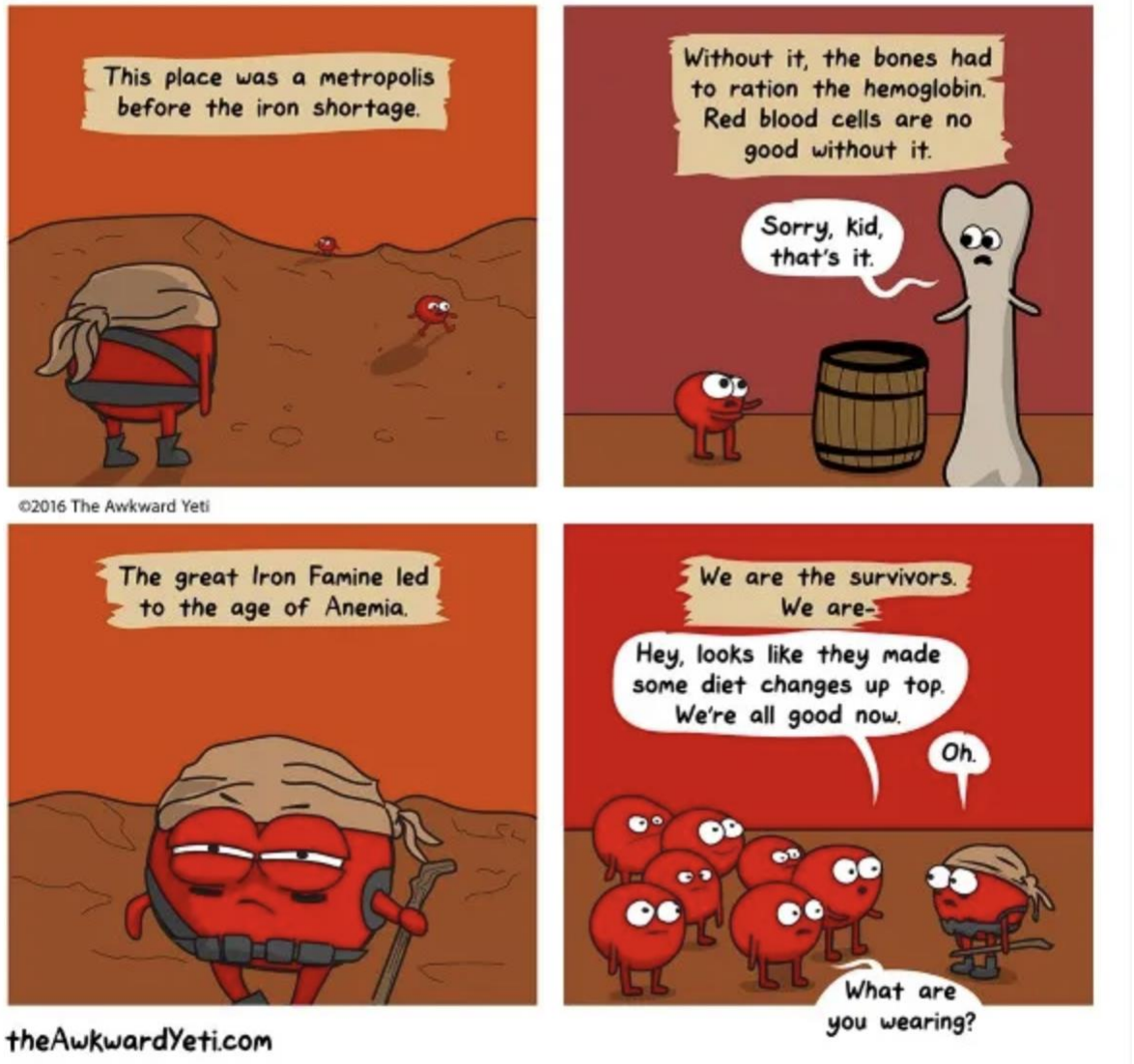
REFERRALS AND RESOURCES

Referral Processes

- Local GPs
- Outpatient based services
  - General medical units
  - Haematology
  - Gastroenterology
  - Cardiology
  - Renal
- Perioperative Services
  - Obstetric / Gynaecology (WNS)
  - Colorectal / Orthopedic

Resources

- managing-my-iron-factsheet.pdf (blood.gov.au)
- Fit For Surgery: Managing Iron Deficiency Anaemia | National Blood Authority
- iron-product-choice-and-dose-calculation20052016.pdf (blood.gov.au) (Appendix 3)
- Treating iron deficiency anaemia | Lifeblood
- ARCLB Oral iron choices for adults



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  - www.blood.gov.au/iron-product-choice-and-dose-calculation-guide-adults
- PBS Website accessed 17/7/2024
- MN policy – Intravenous iron therapy (total dose) – Adult patients 2022
- MN Policy – Iron supplementation Indication Flow Chart 2020
- Articles include
  - Elstrott et al, Eur J Hematol 2020
  - Gafter-Gavili et al, Acta Haematol 2019
  - Pena-Rosas et al, Cochrane 2016
  - Pasricha et al, Lancet 2021
- Uptodate images
- Patient images used with permission
- ESC guidelines, FERRIC-HF, AFFIRM, FAIR-HF, RIDE-CRT, CONFIRM
- PIVOTAL, DRIVE, NICE, KDOQI guideline
- RCPA Manual, Melbourne Haematology