Iron Deficiency Anaemia

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OVERVIEW

• Background and Epidemiology

• Iron metabolism

• Aetiology

• Assessment and Diagnosis

• Management
BACKGROUND AND EPIDEMIOLOGY

• Varies globally
• Iron deficiency most common cause of anaemia
• Scant data available in Australia
  • 10% of females of adolescent and/or childbearing age
  • <1% of males of the same age range
• Higher prevalence
  • women of childbearing age
  • children
  • individuals living in low- and middle-income countries
  • pregnancy
  • elderly
Why is iron important?
IRON METABOLISM

• Total body iron 3-4 g
  • Haemoglobin in circulating RBCs – Approx 2 g
  • Storage in the form of ferritin or haemosiderin in bone marrow, liver and spleen
    ~ 0.8 to 1 g (men); approximately 0.4 to 0.5 g (women)
  • Iron-containing proteins (myoglobin, cytochromes) ~ 400 mg
  • Plasma iron bound to transferrin – 3 to 7 mg

• Daily requirements
  • Males – 1 mg
  • Women of reproductive age – 2-3 mg
  • Pregnancy – 3-4 mg
Iron metabolism - Source of Iron

- Normal diet provides 15mg/day
- Haem (meat) and non-haem iron (vegetable and cereal)
- 10-20% of ingested iron is absorbed, haem > non-haem
- Absorbed in the reduced form
- Ascorbate increases absorption
- Phytates (cereals and legumes), Tannates (tea), antacid and calcium reduce absorption
IRON METABOLISM

• Mainly absorbed in the duodenum and proximal jejunum
• Transported in plasma by Transferrin
• Transferrin measured by quantifying iron binding sites available = TIBC
• TIBC normally 1/3 saturated under normal physiological conditions
• Transferrin-iron complex endocytosed by erythroblast
• Iron incorporated into Hb
• Also involved in iron recycling when red cells senesce
Iron metabolism

- Iron absorption is regulated by demands of the body
- Upregulated in iron deficiency and increased erythropoiesis
- Physiological losses
  - 1mg daily
  - Sweating
  - Epidermal shedding
  - Menstruation, 1mg/day
  - Pregnancy/Lactation, 1000mg
AETIOLOGY

• Iron loss or requirements exceed absorption
• Usually multifactorial
• Major causes include decreased dietary intake, reduced absorption and blood loss
• Dietary causes unlikely in developed countries unless deliberate
  • vegetarian, ‘tea-toast’ in elderly
• Reduced absorption
  • Coeliac disease, atrophic gastritis (autoimmune), Helicobacter
  • Bariatric and gastric surgery, reduced area for absorption and reduced gastric acid
  • Rare inherited disorders in absorption
AETIOLOGY

- Overt or Occult blood loss
- GI causes
  - PUD
  - Oesophagitis
  - Varices
  - Hiatus hernia
  - Malignancy
  - Vascular lesions, angiodyplasia
  - Colitis
  - NSAID-related
  - Exercise-induced (‘sports anaemia’)
  - Parasites (e.g. hookworm)
Assessment

• Non-GI causes
  • Menorrhagia
  • Haematuria
  • Haemoptysis
  • Bleeding disorder
  • Urinary/pulmonary hemosiderosis
  • (intravascular haemolysis)
  • Frequent blood donation (250mg iron/unit)
Diagnosis

• Clinical features usually due to anaemia
• May also be present in severely reduced iron stores and extremely low serum ferritin who are not anaemic
• Fatigue, weakness, headache, reduced exercise capacity
• Exertional dyspnoea, vertigo, angina
• Pica – craving for bizarre substances (earth, clay, ice, starch)
• Restless Leg Syndrome
Pallor

Dry or rough skin

Atrophic glossitis with loss of tongue papillae, which may be accompanied by tongue pain or dry mouth

Cheilosis (also called angular cheilitis)

Koilonychia (spoon nails)

Oesophageal web, dysphagia (eg, Plummer-Vinson or Patterson-Kelly syndrome; rare)

Alopecia (rare) in especially severe cases
Biochemistry

- Serum iron
  - measures circulating iron bound to the transport protein transferrin
  - low in iron deficiency as well as in anaemia of chronic inflammation
  - fluctuates with dietary intake and normal diurnal variation
- By itself, low serum iron is not diagnostic of any condition but must be evaluated in light of other tests such as transferrin and ferritin
- Serum transferrin (TIBC) – circulating transport protein for iron
  - increased in iron deficiency
- Transferrin saturation – ratio of serum iron to TIBC
  - lower transferrin saturation in iron deficiency
FERRITIN

- Circulating iron storage protein that is increased in proportion to body iron stores
- Low ferritin level (e.g., <15 ng/mL [<15 mcg/L]) is highly specific for iron deficiency
- Acute phase reactant, increase independently of iron status in disorders associated with inflammation, infection, liver disease, heart failure and malignancy
- Higher ferritin level may be ‘falsely normal’
- Soluble transferrin receptor (sTfR) and sTfR-ferritin index – Circulating transferrin receptor or serum transferrin receptor
- Concentration in serum is directly proportional to erythropoietic rate and inversely proportional to tissue iron availability, similar to serum transferrin
- Iron-deficient patients generally have increased levels of sTfR
- Not used in routine practice but can be helpful in complex cases
- Major advantage of sTfR is that it reflects overall erythropoiesis - increased in iron deficiency
### 3 Interpreting laboratory blood test results to assess iron status*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Haemoglobin</th>
<th>Mean cell volume and mean cell haemoglobin</th>
<th>Serum ferritin µg/L</th>
<th>Transferrin or total iron binding capacity</th>
<th>Transferrin saturation†</th>
<th>Soluble transferrin receptor</th>
<th>Serum iron‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue iron deficiency without anaemia</td>
<td>Normal</td>
<td>Normal or low</td>
<td>&lt;15–30</td>
<td>Normal or high</td>
<td>Low-normal or low</td>
<td>High-normal or high</td>
<td>Low</td>
</tr>
<tr>
<td>Iron deficiency anaemia (IDA)</td>
<td>Low</td>
<td>Low (or normal in early IDA)</td>
<td>&lt;15–30 adult &lt;10–12 child</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Anaemia of chronic disease or inflammation</td>
<td>Low</td>
<td>Normal (may be mildly low)</td>
<td>Normal or elevated (elevated ferritin does not imply elevated iron stores)</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>IDA with coexistent chronic disease or inflammation</td>
<td>Low</td>
<td>Low</td>
<td>Low or normal, but usually &lt;60-100 µg/L</td>
<td>Normal or high</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Thalassaemia minor (or normal)</td>
<td>Low</td>
<td>Low (or normal)</td>
<td>Normal or elevated (correlates with body iron stores)</td>
<td>Normal</td>
<td>Normal or elevated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Iron overload</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated (correlates with body iron stores)</td>
<td>Normal to low</td>
<td>High</td>
<td>Normal to elevated</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* Compared with laboratory reference range for age, sex and gestation if applicable. † Ideally performed on fasting morning sample. ‡ Serum iron is markedly labile with a significant diurnal variation, is low in both iron deficiency and inflammation, and should not be used to diagnose iron deficiency. § Includes β-thalassaemia minor and single or two alpha gene deletion thalassaemia minor. A thalassaemic condition and iron deficiency may coexist, particularly in pregnancy.
MANAGEMENT

• Depends on cause
• Replacement options
• Dietary therapy, increased intake and minimising inhibitors
• Oral therapies
• Parenteral iron therapy
• Choice dependent on number of factors
  • acuity and severity of anaemia
  • costs
  • availability of different iron replacement products
  • tolerability
• Investigate underlying cause
4 Commercially available forms of iron therapy in Australia suitable for the treatment of iron deficiency anaemia (IDA)*

Dosing is based on elemental iron content. To avoid confusion, clinicians should write the name of the oral preparation(s) recommended for the patient to take to the pharmacist. Ingestion of even a small amount of iron can be fatal in infants and young children: patients should be advised to keep iron supplements out of reach of children and never give their child an adult dose.

<table>
<thead>
<tr>
<th>Name of preparation (company)</th>
<th>Formulation</th>
<th>Elemental iron content</th>
<th>Other active ingredients</th>
<th>Relative cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral formulations for adults‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FERRO-GRADUMET (Abbott Australasia)</td>
<td>Ferrous sulfate 325 mg Controlled-release tablets</td>
<td>105 mg</td>
<td>Nil</td>
<td>MIMS: $6.56 per 30 tablets 22 cents per tablet</td>
</tr>
<tr>
<td>FERROGRAD C (Abbott Australasia)</td>
<td>Ferrous sulfate 325 mg Controlled-release tablets</td>
<td>105 mg</td>
<td>Vitamin C 500 mg</td>
<td>MIMS: $8.16 per 30 tablets 27 cents per tablet</td>
</tr>
<tr>
<td>FGF (Abbott Australasia)</td>
<td>Ferrous sulfate 250 mg Controlled-release tablets</td>
<td>80 mg</td>
<td>Folic acid 300 µg</td>
<td>MIMS: $3.92 per 30 tablets 13 cents per tablet</td>
</tr>
<tr>
<td>FEFOL iron and folate supplement (Pharmacare Laboratories)</td>
<td>Ferrous sulfate 270 mg Controlled-release capsules</td>
<td>87 mg</td>
<td>Folic acid 300 µg</td>
<td>MIMS: $9.95 per 30 tablets 33 cents per tablet</td>
</tr>
<tr>
<td>FERRO-F-TAB (AFT Pharmaceuticals)</td>
<td>Ferrous fumarate 310 mg Non-controlled-release tablets</td>
<td>100 mg</td>
<td>Folic acid 350 µg</td>
<td>PBS: $12.79 per 60 tablets 21 cents per tablet</td>
</tr>
<tr>
<td><strong>Oral formulation for children§ (or adults‡ requiring a liquid)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FERRO-LIQUID (AFT Pharmaceuticals)</td>
<td>Ferrous sulphate Oral liquid 150 mg/5 ml</td>
<td>30 mg/5 ml</td>
<td>Nil</td>
<td>PBS: $19.35 per 250mL bottle</td>
</tr>
<tr>
<td><strong>Intravenous formulations¶</strong>††‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FERRUM H (Aspen Pharmacare)</td>
<td>Iron polymaltose</td>
<td>100 mg ampoules</td>
<td>Nil</td>
<td>PBS: $50.36 per 5 ampoules</td>
</tr>
<tr>
<td>FERROSIG (Sigma Pharmaceuticals)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENOFER¶‡ (Aspen Pharmacare)</td>
<td>Iron sucrose</td>
<td>100 mg ampoules</td>
<td>Nil</td>
<td>PBS: $139.48 per 5 ampoules</td>
</tr>
</tbody>
</table>
Oral Therapies

- 100-200mg elemental iron per day
- Hb increase by 20g/L every 3 weeks
- Oral iron eliminates the potential for infusion reactions and/or anaphylaxis
- Iron generally should not be given with food
- Phosphates, phytates and tannates in foods may bind iron and impair its absorption
- Taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fibre, tea, coffee and eggs
- Medications that reduce gastric acid (antacids, histamine receptor blockers, proton pump inhibitors) may impair iron absorption
- Iron given two hours before or four hours after ingestion of antacids
- Side effects include metallic taste, nausea, flatulence, constipation, diarrhoea, epigastric distress and/or vomiting
IV THERAPIES

• Side effects, non-compliance or intolerant of oral iron
• Ongoing iron/blood loss that exceeds absorptive capacity (e.g. heavy uterine bleeding, mucosal telangiectasias)
• Anatomic or physiologic condition that interferes with oral iron absorption (e.g. inflammatory bowel disease)
• Coexisting inflammatory state that interferes with iron homeostasis
• Previously used Iron Polymaltose (Ferrum H, Ferrosig)
• New preparation available
  • Iron carboxymaltose (Ferinject)
  • 15 minute infusion
  • side effects (1%) include headache, nausea, abdominal pain, rash, constipation, diarrhoea, injection site reaction
  • hypophosphataemia
• Standard method for calculating total iron deficit is the Ganzoni Equation

• Total Iron Deficit (mg) =
  Weight {kg} x (Target Hb – Actual Hb {g/L}/10) x 2.4 + 500

• Irrespective of body weight, generally give 1000mg
OVERT OR OCCULT GI CAUSE

- Coeliac serology
- Endoscopy
- Small bowel capsule endoscopy for obscure cause/lesion
- Treatment of lesion
- Follow up of iron studies
Case series
Case Scenario 1

• 68 year old retired gentleman
• Referred for abdominal bloating, bouts of diarrhoea

• Background
  • HTN
  • NIDDM
  • Hypercholesterolaemia
  • Ankylosing spondylitis; Naproxyn
  • GORD

• Non-smoker, minimal ETOH
• Well-balanced diet, not vegetarian
CASE 1

- Recurrent iron deficiency dating back 2013
- Colonoscopy 2013 – diverticulosis
- Current ferritin 18, haemoglobin 120
- Gastroscopy - normal
- Colonoscopy – minor TI ulcers, focal non-specific inflammation on TI biopsies
- Small bowel pillcam – multiple non-bleeding ulcers
Case 1
- Negative ancillary markers for IBD
- Normal CRP
- No supporting features on biopsies from colonoscopy
- NSAID-induced small bowel ulceration
Case Scenario 2

- 65 year old gentleman
- Symptomatic new-onset iron deficiency with anaemia
- Fatigue
- Haemoglobin 102, down from 148 over 4 months
- Microcytic (MCV 72) and hypochromic (MCH 20)
- Ferritin 7

Background
- NIDDM, Diabex
- Gout, Zyloprim
- Non-smoker and nil ETOH
• No overt GI bleeding
• No abdominal pain or change in bowel habit
• Minimal dietary iron, not vegetarian
• Normal coeliac serology
• Gastroscopy
  • mild diffuse erosive gastritis and duodenitis
  • small shallow duodenal ulcer

• Gastric and small bowel biopsies – Helicobacter
Case 2

- Colonoscopy – small benign polyp
- Ferinject
- Nexium HP7 for 1 week
- Normal Urea breath test following therapy
- Ferritin and Hb normalised
- No pillcam required
CASE SCENARIO 3

- 48 year old female
- First reviewed for severe iron deficiency anaemia
- Ferritin undetectable
- Hb 93 g/L

Background
- Nil NSAIDs or anticoagulation
- Sleeve gastrectomy
- Diabetes
- Menorrhagia for past few years
Case 3

- Nil overt GI bleeding
- Nil change in bowel habit
- Nil abdominal pain
- Weight loss from gastric sleeve
- Gastroscopy and colonoscopy for occult lesion
- Gastroscopy
  - Normal sleeve stomach otherwise normal
- Colonoscopy
  - Multiple aphthous ulcers in terminal ileum
  - Biopsies: non-specific active inflammatory changes
- Small bowel pillcam (Sep 2015)
  - multiple ulcers throughout the jejunum and ileum
  - erythema and active bleeding
Commenced on Pentasa 4g Imuran 50mg and Budesonide 9mg daily

• Ferinject

• Progress pillcam (Aug 2016)
  • Optimal 5-ASA and Mercaptopurine
  • Iron replete
  • No active bleeding
  • Multiple ileal ulcers
  • Jejunum normal

• Went on to have anti-TNF
Case Scenario 4

• 60 year old female
• First seen 2012
• Refractory iron deficiency anaemia
  • Multiple iron injections and blood transfusions
  • Nil melaena or blood described
  • Long term aspirin
• Previous gastroscopies and colonoscopies, nil capsule
  • Helicobacter gastritis
  • Poor bowel preparation at colonoscopies
  • Melaena in right colon
Case 4

- Obesity, NIDDM, HTN, IHD, AMI, CVA, NAFLD, OSA and OA
- Chronic renal impairment
  - ESRF creatinine 300
  - Diabetes and HTN
  - Dialysis and Aranesp
- Gastroscopy and colonoscopy repeated
- Gastroscopy
  - short segment Barretts
- Colonoscopy
  - few non-bleeding polyps
  - three non-bleeding caecal angiodysplastic lesions treated with APC
- Small bowel pillcam
  - Multiple angioectasia in proximal jejunum
  - Two also noted in caecal pole
  - Two actively bleeding
  - Small bowel enteroscopy – APC to lesions
Case 4

• Persistent anaemia
  • repeat colonoscopy
  • aspirin ceased

• Colonoscopy
  • 4x medium-sized angioectasia – APC
  • aspirin recommenced
  • well for 6 months and Hb normalised

• NSTEMI over Christmas

• Ticagrelor

• Recurrence of anaemia, Hb 64
  • iron and blood replacement
  • melaena
• Repeat capsule
  • duodenal and jejunal angioectasia
  • actively bleeding
  • melaena in distal ileum
  • repeat balloon enteroscopy and APC treatment
  • aspirin monotherapy
• Repeat gastroscopy and colonoscopy
  • several polyps
  • duodenal angioectasia – APC
• Hb stabilised
• Repeat enteroscopy 6 months later - normal
**Take Home Message**

- Iron deficiency is common and important
- Interpretation of iron studies
- Wide differentials including GI causes
- Overt vs occult – investigations
- Importance of endoscopy and small bowel pillcam in diagnostic algorithm
- Management dependent on cause
- Choice of replenishment
Thank you