Iron therapy in General Practice
Oral and intravenous options with a focus on Patient Blood Management

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Features of iron deficiency

- Iron deficiency can exist in the absence of overt anaemia (ID 3 x more common than IDA)
- Serum ferritin is the most powerful marker of iron deficiency
- Early markers of iron deficiency are reduced MCH, MCV and MCHC
Ferritin, inflammation and iron stores

- Ferritin is an acute phase reactant and levels are elevated in those with inflammation, infection, liver disease and malignancy.
- Leads to misleadingly elevated ferritin levels in iron-deficient patients with co-existing systemic illness.
  - In the presence of inflammation ferritin levels can be increased up to 3 fold.
  - Ideal to check CRP if inflammation present or suspected, but confounder is that CRP may not be elevated in chronic setting.

Resources and guidelines

- BloodSafe e-learning
  - www.bloodsafelearning.org.au
    - Discusses investigation and management of ID and IDA and patient blood management principles.
- Patient Blood Management Guidelines
Pre-op anaemia in 28%
- 20% of those <65 yr old
- 31% of those 65-85 yr old
- 44% of those >85 yr old

Anaemic
- 23% MCH <27, 14% MCV <80

Non-anaemic
- 5.3% MCH <27, 2.4% MCV <80

Data care of Dr Kathryn Robinson
Is the patient anaemic? Hb <130 g/L (male) or Hb <120 g/L (female)

Preoperative tests
• Full blood count
• Iron studies including ferritin
• CRP and renal function

Preoperative haemoglobin assessment and optimisation template

This template is for patients undergoing procedures in which substantial blood loss is anticipated such as cardiac surgery, major orthopaedic, vascular and general surgery. Specific details, including reference ranges and therapies, may need adaptation for local needs, expertise or patient groups.

Table 2: Transfusion rates in admitted patients with pre-op anaemia compared to those without pre-op anaemia

<table>
<thead>
<tr>
<th></th>
<th>Anaemic</th>
<th>Non-anaemic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>92/141</td>
<td>122/331</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve</td>
<td>70/86</td>
<td>60/159</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colorectal (Left)</td>
<td>34/81</td>
<td>9/97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colorectal (Right)</td>
<td>43/105</td>
<td>3/59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>THA</td>
<td>13/64</td>
<td>14/146</td>
<td>0.04</td>
</tr>
<tr>
<td>TKA</td>
<td>14/61</td>
<td>7/174</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>265/538</td>
<td>215/966</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NO anaemia: Ferritin <100 mcg/L
• Consider iron therapy if anticipated postoperative Hb decrease is ≥30 g/L
• Determine cause and need for GI investigations if ferritin suggestive of iron deficiency <30 mcg/L

Is the patient anaemic? (Hb <130 g/L, male; Hb <120 g/L, female)

YES

Ferritin <30 mcg/L
• Consider clinical context
• Review iron status
• Consider iron metabolism

Ferritin 30–100 mcg/L
• Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
• Consider iron therapy

Raised Ferritin
• Consider clinical context
• Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
• Seek haematology advice

CRP

NO

Ferritin >100 mcg/L
• Evaluate possible causes based on clinical findings
• Discuss with gastroenterologist and their timing in relation to surgery
• Commence iron therapy

Possible iron deficiency
• Consider clinical context
• Discuss gastroenterologist regarding GI investigations and their timing in relation to surgery
• Commence iron therapy

Possible anaemia of chronic disease or inflammation, or other
• Consider clinical context
• Review iron status
• Consider iron metabolism
• Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
• Seek haematology advice

Fit for surgery: managing iron deficiency

Published in Health News and Evidence
Date published: 15 September 2015

Key points | Iron deficiency and anaemia | Managing anaemia: tests and treatments | Fit for surgery: the vital role of primary care | References

Summary

- Iron deficiency is common in Australia, affecting around one in 10 Australians. Iron deficiency and iron-deficiency anaemia should be viewed as serious but treatable medical conditions and patients with blood results indicating these conditions should be managed accordingly.
- For patients undergoing elective surgery, anaemia is a predictor of blood transfusion, which is associated with adverse outcomes including mortality. Preventing unnecessary exposure to blood products leads to improved clinical outcomes.
- Health professionals working in primary care are well placed to reduce patients’ exposure to blood products by engaging in patient blood management paradigms aimed at optimising patients’ own blood, in preference to transfusion. Identifying and treating anaemia and iron deficiency in patients who are planning surgery is a key aspect of this.
- The National Blood Authority and NPS MedicineWise have collaborated to produce a suite of support materials to help health professionals and consumers prepare for planned surgery.

Key points:

- Iron deficiency is common in Australia.
- Iron deficiency and iron-deficiency anaemia should be viewed as serious but treatable medical conditions.
- Patients undergoing elective surgery with anaemia are at risk of blood transfusion.
- Health professionals in primary care can reduce patients’ exposure to blood products.
- The National Blood Authority and NPS MedicineWise have collaborated to support health professionals and consumers.

Fit for Surgery
Fit for Life

Patient blood management improves patient outcomes by ensuring the care that patients receive is supported by an effective blood management service that allows planning, optimising resource use and reducing the need for blood transfusion.

One of the key areas where general practitioners can contribute to patient blood management is in the preparation of patients who are about to undergo elective surgery where blood loss is anticipated.

Ensuring patients are informed prior to surgery optimises this and can reduce the need for blood transfusion in patients who experience blood loss during surgery.

Anaemia and elective surgery

Anaemia and iron deficiency have been identified as a significant issue in patients who are undergoing elective surgery.

Studies have estimated anaemia to be present preoperatively in around one in five patients.

Patients with preoperative anaemia have other risks associated with surgery. One study found a 30% reduced in 30 day mortality, 10% reduced in 90 day mortality, and a 30% reduction in 30 day incidence associated with declining haematocrit.

Iron deficiency in the absence of anaemia is also a risk as it may impact an individual’s ability to respond to blood loss.

If anaemia is identified it is important that the underlying cause is determined. This algorithmists deals with decisions regarding therapy for anaemia and iron deficiency only.

Anaemia needs to be considered in all patients undergoing elective surgery where blood loss is anticipated.
Oral iron replacement therapy

- First line treatment for most patients with ID and IDA
  - Must be taken in appropriate doses and for sufficient duration
- Therapeutic adult dose of oral iron: 100-200 mg/day of elemental iron
  - Can be administered daily or in 2-3 divided doses to improve tolerability
  - Administration before food (acidic environment) aids absorption but if GI adverse effects administer with food
  - Ensure iron liquid administered via straw
- Multivitamin products contain insufficient iron to be of therapeutic value
  - Absorption of iron may be reduced due to interactions with other ingredients such as calcium
### Oral Preparations for Treatment of Iron Deficiency Anaemia (IDA) in Australia

<table>
<thead>
<tr>
<th>NAME (Manufacturer)</th>
<th>TABLET (Actual size)</th>
<th>FORMULATION</th>
<th>ELEMENTAL IRON CONTENT</th>
<th>OTHER ACTIVE INGREDIENTS</th>
<th>RELATIVE COST 2011 MMB ($/PBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERRO-GRADUSET (Abbott)</td>
<td>325 mg Ferrous Sulphate Controlled release tablet</td>
<td>105 mg</td>
<td>nil</td>
<td>6.56 30 tablets</td>
<td></td>
</tr>
<tr>
<td>FERRO-GRAD C (Abbott)</td>
<td>325 mg Ferrous Sulphate Controlled release tablet</td>
<td>105 mg</td>
<td>Ascorbic acid 500 mg</td>
<td>8.16 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Ferro-tab (AFT Pharmaceuticals)</td>
<td>310 mg Ferrous Fumarate Non-controlled release tablet</td>
<td>100 mg</td>
<td>Folic acid 350 mcg</td>
<td>$9.47 60 tablets PBS listed ($32.79)/2</td>
<td></td>
</tr>
<tr>
<td>FEFOL Iron &amp; Folate Supplement (Pharm-a-care)</td>
<td>270 mg Ferrous Sulphate Controlled release capsule</td>
<td>87.4 mg</td>
<td>Folic acid 300 mcg</td>
<td>$9.95 30 tablets</td>
<td></td>
</tr>
<tr>
<td>FGF (Abbott)</td>
<td>250 mg Ferrous Sulphate Controlled release tablet</td>
<td>80 mg</td>
<td>Folic acid 300 mcg</td>
<td>$3.92 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Ferro-tab (AFT Pharmaceuticals)</td>
<td>200mg Ferrous Fumarate Non-controlled release tablet</td>
<td>65.7 mg</td>
<td>nil</td>
<td>$8.95** 60 tablets PBS listed ($11.62)/2</td>
<td></td>
</tr>
<tr>
<td>FERRO-LIQUID (AFT Pharmaceuticals)</td>
<td>Ferrous Sulphate Oral liquid</td>
<td>30 mg/5 mL</td>
<td>nil</td>
<td>$19.00 250mL bottle PBS listed ($19.35)/2</td>
<td></td>
</tr>
</tbody>
</table>

Usual ADULT dose for IDA is around 100–200 mg elemental iron daily in divided doses (1–2 tablets per day of above preparations, ideally 1 hr before or 2 hrs after food). GI upset may be reduced by taking tablet with food or at night & increasing dose gradually. When a rapid increase in Hb is not required, intermittent dosing (1 tablet 2–3 times a week) or lower doses of iron (eg. 30–60 mg of elemental iron, increasing to twice daily or three times a day if tolerated) may reduce GI upset. Multivitamin-mineral supplements should not be used to treat IDA as iron content is low & absorption may be reduced.

*Australian Medicines Handbook 2011*
Oral iron polymaltose

- Treatment (and prevention in those at high risk) of iron deficiency in adults/adolescents where the use of ferrous iron supplements is not tolerated, or otherwise inappropriate.
- Rise in Hb significantly more rapid at 3 and 6 weeks with ferrous sulfate compared to oral iron polymaltose, similar after 12 weeks
  - If rapid rise in Hb required, preference is for other oral iron preparations
- Absorption greater if taken with food
- Lower rate of GI adverse effects
- Cost ++ compared to other preparations

Oral iron replacement therapy

- When therapeutic dose of iron is taken, anticipate a 20 g rise in Hb after about 3 weeks of therapy (approx 1 g/day)
  - Monitor Hb 3-4 weeks after starting therapy to assess response and compliance
- Once Hb has normalised it takes at least three months at a therapeutic dose of oral iron to replete total body iron stores
  - Important to advise patients of this and continue to check compliance and tolerability
  - If sub-therapeutic dose administered, may take 6-9 months to replete iron stores
- Two standard release preparations (Ferro-tab and Ferro-f-tab) which are able to halved and crushed
Tolerability of oral iron

- **80% of people able to tolerate oral iron**
- Gastrointestinal adverse effects most common
  - Upper GI adverse effects (e.g. nausea, reflux) tend to be dose related and may respond to
    - lower dose or alternate day dosing for first 2-4 weeks (noting that therapeutic response will be delayed),
    - bedtime dose
    - smaller dose more frequently
    - Take dose with meals (but may reduce absorption)
    - switch to a controlled release formulation, however these may have lower bioavailability
  - Lower GI adverse effects (e.g. constipation) tend not to be dose related and may require concomitant stool softener

### Drug Interactions with oral iron

<table>
<thead>
<tr>
<th>Class</th>
<th>Interaction with Iron</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetacycline antibiotics</td>
<td>Iron forms poorly soluble chelates with tetracyclines, reducing their absorption and antimicrobial activity. Tetracyclines also significantly reduce the absorption of oral iron.</td>
<td>Separate doses of oral iron and tetracycline antibiotics by as long as possible, at least 2 hours.</td>
</tr>
<tr>
<td>Quinolone antibiotics</td>
<td>Iron binds to quinolone antibiotics in the gastrointestinal tract, reducing the absorption and activity of the quinolone antibiotics.</td>
<td>Take the quinolone antibiotic dose at least 2 hours before oral iron.</td>
</tr>
<tr>
<td>Bisphosphonates (oral)</td>
<td>The bisphosphonates can form complexes with iron, resulting in a significant reduction in the absorption and activity of the bisphosphonate.</td>
<td>Recommendations vary slightly between bisphosphonate products. Take alendronate, ibandronate and risedronate at least 30 minutes before oral iron. Take cladribine at least one hour before oral iron, and etidronate at 45 minutes before oral iron.</td>
</tr>
<tr>
<td>Levodopa, carbipoda</td>
<td>Folic acid binds strongly to carbidopa and levodopa to form chelates complexes that are poorly absorbed. This may impair the control of Parkinson’s disease.</td>
<td>Separate the administration times of levodopa and carbidopa by as long as possible from oral iron.</td>
</tr>
<tr>
<td>Metyldopa</td>
<td>Ferric sulfate and ferric gluconate reduce the bioavailability of methyldopa, reducing its activity and interfering with blood pressure control.</td>
<td>Separate doses by at least 2 hours; monitor blood pressure and adjust methyldopa dose if necessary.</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Ferric sulfate and ferric tannate reduce the absorption of penicillamine (possibly by forming a chelate) and may reduce the activity of penicillamine.</td>
<td>Take oral iron at least 2 hours prior to penicillamine.</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Ferric sulfate decreases the absorption of thyroid hormones and may reduce their therapeutic effect. Other ferrous salts are likely to have a similar effect.</td>
<td>Allow 4–5 hours between administration of oral iron and thyroid hormones. Monitor for the signs of hypothyroidism, monitor thyroid function as necessary and increase thyroxine dose if indicated.</td>
</tr>
<tr>
<td>Proton Pump inhibitors (PPI)</td>
<td>Hypochlorhydria induced by PPIs may impair the absorption of oral iron and may retard clinical response to oral iron in patients with iron deficiency or iron deficiency anaemia.</td>
<td>If the interaction is suspected to be significantly interfering with response to oral iron, consider withdrawal of the PPI (only if clinically appropriate), or seek expert advice as to the need for administration of IV iron.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Large doses of calcium compounds (≥ 500 mg of elemental calcium) may form insoluble complexes with oral iron and reduce the absorption of oral iron.</td>
<td>Separate administration of calcium and oral iron products by several hours.</td>
</tr>
<tr>
<td>Aluminum hydroxide and magnesium salts (mattards)</td>
<td>Antacids may decrease the absorption of oral iron.</td>
<td>Separate administration of each product by as long as possible.</td>
</tr>
</tbody>
</table>

*Note: this list is not exhaustive. Please contact the Drug and Therapeutics Information Service (DATIS) for references.*
Iron replacement therapy in the presence of inflammation

- Oral iron absorption is poor in inflammation e.g. post surgery, infection
- In the presence of inflammation or when body iron stores are replete, hepcidin is upregulated and released from the liver.
  - Hepcidin is the ‘master regulator’ of iron metabolism
  - Hepcidin levels can remain elevated for several weeks post surgery
- Hepcidin reduces oral iron absorption from the gut and increases iron sequestration in the bone marrow and by reticuloendothelial macrophages.
IV Iron in Australia

- Iron polymaltose (Ferrum H/Ferrosig)
- Iron sucrose (Venofer)
- Ferric carboxymaltose (Ferinject)
Ferritin falsely elevated for up to 6 weeks post IV iron, Hb is the more reliable marker of early response.

Figure 2: Time course for serum ferritin changes.
Oral iron

Case 1
35 yo lady
Severe menorrhagia
Ferritin 7, Iron 3, Hb 100, MCV 80
- Immediate felt better on oral Fefol bd
- No side effects
Three months later
Ferritin 32, Iron 14, Hb 140, MCV 90

Iron infusion

• Who
• How
• Where
• $$$ How much
Iron infusion

- Who

Ferrinject is on the PBS as a general benefit
500mg x 2 plus 1 repeat

Available for any patient who is iron deficient and cannot tolerate oral iron
Iron infusion

All patients undergoing major surgery should have a ferritin >100

All patients with heart failure should have a ferritin > 100

Iron infusions at Chandlers Hill Surgery

- 50 patients in 12 months
- 45 female
- Age range 16 – 85
- Menorrhagia overwhelming majority
- Diet
- Chronic iron deficiency
- Warfarin
- Lapband, Coeliac, Colitis, Gastritis, CRF on EPO, Blood donor,
Iron infusion

Case 2
- 88 yo lady with PHx of collagenous colitis
- Two iron infusions at local hospital in last three years taking 4-6 hours, travel, prior specialist consults
- 2014 Ferritin 14; Hb 103

Iron infusion

Case 2
- Ferinject 500mg
- Slow IV push over 5 minutes

- Patient extremely happy
- No side effects

- Excellent response
Case 2

Iron infusion

Case 3

- 60 yo woman. PHx SLE. Feldene 20mg mane
- Hb 97, MCV 75, Ferritin 7
- Normal endoscopy and colonoscopy
- Oral iron for 3 months; Ferritin 21
Case 3
Iron infusion 1000mg over 15 minutes
No side effects
Ferritin 340, Hb 136

Iron Infusion

Case 4
• 50 yo blood donor
• PHx iron deficiency treated with oral iron “hated it”
• 2013 Hb 140; Ferritin 36
• 2014 Feeling tired, Hb 120 – elliptocytes, pencil cells, Ferritin 16
Iron infusion

Case 4
• Weight 100kg
• Target Hb 140
• Current Hb 120

• Calculation 1000mg IV infusion
• Side effects of muscle aches that night
Iron Infusion

- Saves patient’s time
- Patients love the GP being involved
- GPs doing a procedure
- GPs in control
- Teamwork with Practice Nurses

- Upskilling – IV cannulation, IV infusion
- Cost – no Medicare item number
Summary

• Consider ID and IDA management as an essential component of patient blood management and transfusion minimisation/avoidance.
• Oral iron replacement considered first line unless not tolerated, insufficient time pre-surgery, poor absorption or losses exceeding replacement.
• Intravenous iron therapy is an option and can be done in the primary care setting.