Iron Deficiency in Primary Care
An Overview

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Scale of the Problem

- Incidence
  - 760,000 people (>18yrs) at risk of anaemia
    - 2011 – 2012 (Australian Bureau of Statistics)
  - Incidence rises rapidly with age
  - Prevalence of Iron Deficiency ~20% in women under 50 yrs

Who’s at Risk?

- Children (LBW, Prem, Pre school)
- Adolescents
- Menstruating women, Pregnancy, Breastfeeding
- Blood donors
- Endurance athletes
- Disadvantaged – refugees, indigenous persons
- Elderly in aged care facilities
- Restrictive diets
- Malabsorption disorders - Coeliac, gastric alteration surgery
- Chronic disease – Heart failure, inflammatory bowel disease, renal failure
- Medication use - PPI, ACEI

Consequences

Outcomes

- Anaemia
- Economic - Loss of productivity, work absences
- Mortality, morbidity
- Hospitalisation and length of stay
- Contributes to level of renal insufficiency and ejection fraction (GFR – Cardio Renal Syndrome)

- Common symptoms
  - Fatigue
  - Pale
  - Trouble concentrating
  - Sleep disruption

Under-recognised symptoms of iron deficiency

- Sleep apnoea and other sleep disturbances
- Restless leg syndrome
- Depression
- Cognition disturbances
- Impaired learning and concentration
- Thermoregulation issues
- Some association noted in ADHD

Diagnosis/Definition

- Iron deficiency
  - Absolute –Ferritin <30 (variable definitions)
  - Functional – inadequate utilisation of iron though stores may be apparently normal because of high hepcidin
- Anaemia (WHO definitions)
  - Hb <130 in males
  - Hb < 120 in females
  - Hb < 100 in pregnancy and preschool children

Myth 1: Iron deficiency is not common

Myth 2: Iron deficiency without anaemia is not a problem

Myth 3: A normal Ferritin excludes iron deficiency
Tests to order

- FBC - consider HB, MCV, film comments, RDW
- Iron studies - ferritin, transferrin, Transferrin Saturation (T sat), Serum iron
- CRP
- ?Soluble Transferrin Receptor (sTfR)
- ??Hepcidin

Interpreting Pathology Results

- Beware of comment on forms
- Understanding iron metabolism, the role of hepcidin
- Contextual factors are important
- “Consider the 4 rules of interpretation”

Pathology Results

4 Rules

Rule 1: Ignore the comment on lab results!
Rule 2: Serum Iron levels should be drawn fasting & without oral iron supplements
Rule 3: Transferrin is the HIGH level that is probably accurate
Rule 4: Trust all LOW level measurements as accurate.

Outside influences that can activate the acute phase reactant capability of iron indices will alter them UP/HIGHER, and make them ineffective as a honest reflection of iron status.

IRON METABOLISM

Iron compartments

Hepcidin

- Key regulator of the entry of iron into the circulation
- Inhibits iron transport by binding to the iron export channel ferroportin on basolateral surface of gut enterocytes and the cell membrane of reticuloendothelial cells (macrophages)
- Ferroportin inhibition stops entry of iron to circulation and release from macrophages
- Hepcidin secretion by the liver is controlled by iron stores within macrophages, inflammation, hypoxia, and erythropoiesis
- Measuring hepcidin would be of benefit to establish optimal treatment
- CRP surrogate for hepcidin
**Iron Study Interpretation Table**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Haemoglobin</th>
<th>MCV</th>
<th>MCH</th>
<th>Ferritin</th>
<th>Transferrin Saturation</th>
<th>Serum Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional iron deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Iron deficiency anaemia (IDA)</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Anaemia of chronic disease or inflammation (ACD)</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>IDA and ACD</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>'Normal' or increased</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Iron refractory IDA (IRIDA)</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Investigations - Simplified approach**

- A cause must be ascribed when ID or IDA is diagnosed
- Further investigations depend on context
- The anaemia algorithm

**A. All patients**

- History and examination
- Review medications
- Coeliac screen
- UA/MSU (1% will have renal tract malignancy)
- Renal function
- FOBT is not useful

**B. Male and Post-menopausal Women**

- GI investigations
- Younger men?

**C. Pre-menopausal Women**

- GI investigations for higher risk
- Persistent ID after empirical treatment
D. The Pre-operative Patient

- Patient Blood Management
- Check iron and Hb levels on patients with expected significant blood loss at surgery
- Optimise iron and Hb prior to surgery

Myth 6: The surgeon/hospital will arrange preoperative screening of HB/iron

National PBM Collaborative Sites

When to Refer

- Other haematological disorders
- Further GI investigations
- Failure to respond to treatment
- Multifactorial reasons for ID

Treatment - Oral

- How much
- What preparations
- How to take
- Intolerance

Why oral iron is frequently the wrong choice

- Compliance in how/when to take oral
  - 80% of those prescribed oral iron do not take it properly
- Requires 3-6 months to fill stores and enhance RBC production
- Not recommended for patients taking acid reducing medication OTC or by script
- Trial: 6 weeks without interference from other agents may raise H&H to adequate levels
  - BUT will not fill iron storage tank
Oral iron – instructions on use

- Take on empty stomach: In-between meals (1-1/2 hour before or after meal)
- Do not take at same time as other medication or supplements
- Do not take any acid reducing agents around the time of the iron dose (1-1/2 hr apart, and then discourage)
- Take with water. No tea, coffee or calcium enriched liquids
- Advise starting on stool softener at same time oral regime starts

NOTE: If diarrhea starts within first 24-48 hours of starting iron source reduce dose by 50% It continues, discontinue iron source and call MD.

Outcomes of treatment

- Induce reticulocytosis within days
- Raise serum hemoglobin by 10–20 g/L every 2 weeks (ideal)
- Review at 6 week intervals

Treatment- Intramuscular

- Not recommended
- Staining
- Painful
- Delayed adverse events
- Multiple visits

Myth 7: Intramuscular iron is a good first option for treatment

Treatment - intravenous

- Preparations - polymaltose, sucrose, carboxymaltose
- Not all are the same
- Indications

Myth 8: Intravenous iron is dangerous and can’t administered in general practice

Indications for IV iron therapy in iron deficiency anaemia (IDA)

- "Oral iron failure": Intolerance, non adherence or poor response
- Intestinal malabsorption (e.g., inflammatory bowel disease, gastric paresis, surgical weight loss bypass)
- Ongoing iron (i.e., blood) losses that exceed absorptive capacity
- Chronic renal impairment or cardiac failure
- Receiving concomitant erythropoietin-stimulating agent therapy, ACE’s or ARB’s
- A clinical need for a rapid iron supply
  i.e., in patients where optimisation of erythropoietic response is important to prevent physiological compromise or need of transfusion
- Pregnancy (beyond the first trimester and Hb <110) – for indications refer guidelines

IV Iron in Australia

- Intravenous Iron
  - Iron Polymaltose (iron dextrin – Ferrum H/Ferrosig)
    - $4.00 per 100 mg
    - suitable for TDI up to 2500 mg over 5-6 hours (or accelerated infusion)
  - Iron Sucrose (Venofer)
    - $13.00 per 100mg
    - multiple 100-200 mg doses or larger 500mg dose (no more than 1000mg in one week before being reassessed)
    - licensed and PBS listed for renal dialysis setting (Australia only)
  - Ferric Carboxymaltose (Ferinject)
    - $30.00 per 100mg
    - Up to 1000 mg (20mg/kg) over 15 minutes
    - Repeated at least a week later
    - PBS listed from 1st of June 2014
Ferric Carboxymaltose

- Hypersensitivity
  - Serious anaphylactic/anaphylactoid reactions 0.1% (2/1775)
  - 0.1% of patients receiving a comparator
  - Potentially associated hypersensitivity reactions including pruritus, rash, urticarial, wheezing, hypotension in 1.5%
  - 1.5% in comparator
  - In larger pooled data base (FDA) rates of hypersensitivity were 0.9% (42/5272)
  - 0.8% (37/4239) all comparators

Hypophosphatemia

- Little evidence that moderate decrease in blood phosphorus has significant clinical consequences
  - exception being ventilated patients
  - aggressive iv phosphate replacement is unnecessary
- Severe hypophosphatemia
  - associated with significant morbidity in hospitalised patients
  - generally recommended that patients with severe chronic hypophosphatemia (<1.0 mg/dL (0.3 mmol/l)) be treated
  - intravenous repletion may be considered, especially for patients who have clinical sequelae of hypophosphatemia


Some Practical Experience - The Belmont I.V Clinic

% Referrals

Outcomes, n=319

- Ferritin (average)
  - Pre infusion 16
  - 6 weeks post infusion 161

- Hb (average)
  - Pre infusion 116 g/dl
  - 6 weeks post infusion 132 g/dl
Safety - Adverse Events n=211

- Nil - 153
- Mild - 57
- Severe – 1

Summary

- ID is common
- A cause for ID/IDA must be determined
- Investigations can occur concurrently with treatment
- Request iron studies and beware of interpretation
- Oral is mainstay of therapy
- IV can be administered safely and effectively in primary care

Good Resources

- IDA app – App store
- Youtube:
  - Leahy M - Iron Metabolism: https://www.youtube.com/watch?v=Zii0RNMJ4FI
  - Leahy M – Understanding investigations: https://www.youtube.com/watch?v=2G_ORGsQX9I
  - Gallagher – Iron therapy: https://www.youtube.com/watch?v=MnAX3iaTzoQ