Supercharging the blood:
How GPs can help preoperative blood management

Dr Michael Leahy
Haematology
Royal Perth Hospital
Discussion topics

- Anaemia the problem
- Patient Blood Management
- Preoperative assessment
- Management
### Prevalence of preoperative anaemia in elective surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiac</td>
<td>30-40%</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>20-44%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>25-54%</td>
</tr>
<tr>
<td>Colorectal surgery</td>
<td>25-70%</td>
</tr>
<tr>
<td>Major gynaecological (Browning 2012)</td>
<td>17%</td>
</tr>
<tr>
<td>Vascular</td>
<td>33%</td>
</tr>
</tbody>
</table>

71% males and 56% females for cardiac & orthopaedic surgery were anaemic on admission.

Grey et al. Vox Sang 2011
The prevalence and impact of pre-admission and hospital-acquired anaemia

A retrospective cohort study of over 80,000 admissions to a tertiary hospital in Western Australia studied in-hospital anaemia between July 2010 and June 2015. The main outcome measures were in-hospital mortality and length of stay.

- 34% were anaemic prior to admission
- 57% were anaemic during their admission
- 35% of those not anaemic on admission developed hospital-acquired anaemia...
- resulting in over half being anaemic at some point during their hospital stay

Anaemia, even when mild, was associated with:
- Increased in-hospital mortality
  - Mild: 1.59 times higher (95% CI 1.36-1.86, p<0.001)
  - Moderate/Severe: 2.77 times higher (95% CI 2.32-3.30, p<0.001)

Increased length of stay in emergency and elective patients
- Emergency:
  - Mild: 1.52 times longer (95% CI 1.46-1.56, p<0.001)
  - Moderate/Severe: 2.18 times longer (95% CI 2.11-2.36, p<0.001)
- Elective:
  - Mild: 1.30 times longer (95% CI 1.21-1.41, p<0.001)
  - Moderate/Severe: 1.69 times longer (95% CI 1.55-1.83, p<0.001)

Independent of anaemia, transfusion was associated with:
- Increased in-hospital mortality: 2.23 times higher (95% CI 1.89-2.64, p<0.001)
- Increased length of stay: 1.31 times higher (95% CI 1.21-1.37, p<0.001)
Patient Blood Management: definition

“Patient blood management is an evidence-based bundle of care that optimizes medical and surgical patient outcomes by clinically managing and preserving a patient’s blood”

Leahy et al Transfusion 2017
Consensus definition developed at the International Foundation for Patient Blood Management International PBM Summit Melbourne Australia 2016
1st Pillar
Optimise patient’s own blood

2nd Pillar
Minimise blood loss & Bleeding

3rd Pillar
Harness & optimise physiological tolerance of anaemia

Hofmann: The Oncologist 2011

9/2011 PBM FHHS
Fremantle Hospital workshops in 2012 assist GPs to optimise patients for surgery

**Registration Form**

**Why nearly normal is not good enough when it comes to anaemia and iron deficiency in the patient referred for surgery**

- **Time:** 6:30 – 7:00pm – Registration, networking, light snacks and refreshments
- **7:00 – 9:15pm** interactive presentation/workshop

**Venue:** Seminar Room 1 University Club, UWA

Approved for RACGP 40 Category One Active Learning Module points (three modules) or Four Category Two points per module. Approved for ACRRM pro rata Core Points and pro rata Surgery MOPS. Full program details will be sent out prior to each event. To register please Fax back to Fremantle OP Network or Email: julie.skewton@fremantlenetwork.com.au. Enquiries to Julie Skewton, Tel: 9319 0555 / Mob: 040 487 5157

Please indicate the modules(s) you would like to attend:

**Module 1, Tuesday 15 May 2012**

*Why nearly normal is not good enough – why bother proactively managing anaemia or iron deficiency?*  
- Mr Shannon Farmer, Implementation Board, Patient Blood Management Project, WA Department of Health; Adjunct Research Fellow, School of Surgery, UWA

Clinical investigation and management of anaemia – Clinical Professor Michael Leaky, Haematologist, Fremantle Hospital

**Module 2, Wednesday 23 May 2012**

*How do we remove roadblocks to surgery for our referred patients?*  
- Optimising your patients for surgery – management of modifiable risk factors to prevent delays in being wait-listed – Dr Anton Van Niekerk, Pre Admission Anaesthetist, Fremantle Hospital

Practical nuts and bolts – Dr Monica Lacey, GP Liaison Fremantle Hospital

**Module 3, Thursday 31 May 2012**

*So what extra tricks and resources can we use to optimise iron stores?*  
- The what, how and when of iron supplementation – Ms Tandy-Sue Copeland, Senior Pharmacist, Fremantle Hospital

The more complicated patient – Ms Julie Tovey, Clinical Nurse Consultant Fremantle Hospital

Hospital and Ms Trudi Gallagher, State Patient Blood Management Coordinator
Questions to ask when referring patients for surgery?

..likely significant blood loss?

orthopaedic, GIT, gynaecology

preoperative assessment?

....history?

...basic investigations?

Anaemia, iron deficiency, renal failure?
History

- Tiredness, fatigue
- G I Tract symptoms and signs
- Menorrhagia
- Cardiac disease
- Haematuria or haemoglobinuria
Examination

- Pallor
- Koilonychia
- Cardiac murmurs
- Abdominal masses
- Splenomegaly
- Telangiectases
Co-morbidities

- Chronic inflammation
- Renal dysfunction
- Liver dysfunction
- Cardiac failure
- B12 and/or folate deficiency
- Iron deficiency
Clinical consequences of iron deficiency

- IDA correlates with reduced health-related QoL, treating IDA improves QoL

  - Impaired cognitive function
  - Hair loss
  - Dysepsnia
  - Chronic fatigue
  - Increased susceptibility to infection
  - Restless legs
  - Headache
  - Tachycardia
  - Nausea
  - Abnormal nail findings and hair loss

- Significant economic-burden on the individual and the whole population

TYPES OF IRON DEFICIENCY

- True iron deficiency
  - Low hepcidin state
- Functional iron deficiency – anaemia of chronic disease
  - High or “relatively high” hepcidin state
Hepcidin Regulation of Iron Uptake and Release

**Low hepcidin**
- Iron uptake
- Ferritin
- Iron-exporting cells (duodenal enterocytes, macrophages, hepatocytes)
- Iron release into plasma

**High hepcidin**
- Iron uptake
- Ferritin
- Hepcidin
- Iron release into plasma
### Table 6–5

**Iron studies in IDA versus anemia of chronic inflammation.**

<table>
<thead>
<tr>
<th></th>
<th>IDA</th>
<th>Anemia of chronic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>Decreased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Serum iron</td>
<td>Normal or decreased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Total iron binding capacity or transferring</td>
<td>Increased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>% iron saturation</td>
<td>Decreased (&lt;10%-15%)</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>MCV</td>
<td>Decreased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>RDW</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>sTfR/log ferritin ratio</td>
<td>&gt;2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepcidin (not currently clinically available)</td>
<td>Suppressed</td>
<td>Increased</td>
</tr>
</tbody>
</table>

- IDA = iron deficiency anemia; MCV = mean corpuscular volume; RDW = red blood cell distribution width; sTfR = serum–soluble transferrin receptor.
Criteria for diagnosis of iron deficiency in routine practice.

Iron deficiency in cancer

IDA

Absolute iron deficiency (no iron stores)
- Low hepcidin
- Ferritin < 100 ng/mL
- TSAT < 20%

Functional iron deficiency (iron stores +/-)
- High hepcidin
- Ferritin ≥ 100 ng/mL
- TSAT < 20%

% HYPO > 5%
CHr < 26 pg

Anaemia

**Preoperative GP Management:**

Using the wait time to investigate anaemia and iron deficiency and to optimise haemoglobin and iron stores.

This template is for patients referred to RPH undergoing procedures in which substantial blood loss is anticipated such as major orthopaedic, vascular, cardiac, urological and general surgery or for surgery for patients that are typically anaemic such as orthopaedic surgery.

**Recommended screening to accompany GP referral (results from ≤ 3 months prior to referral):**
- Full blood count & reticulocyte count – single cost when ordered together
- Iron studies including Ferritin
- CRP and Creatinine – single cost when ordered together
- U&Es and LFTs
- Vitamin B12 & Folate if indicated – single cost when ordered together
- Other investigations as appropriate depending on comorbidity

**Is the patient anaemic?**
- Hb <130 g/L (male) or
- Hb <120 g/L (female)

**Recommended clinical investigations based on Ferritin levels:**

- **Ferritin <30 mcg/L:**
  - Consider iron therapy if anticipated postoperative Hb decrease is ≥30 g/L
  - Determine cause and need for GI investigations if Ferritin is suggestive of iron deficiency <30 mcg/L

- **Ferritin 30–100 mcg/L:**
  - Evaluate possible causes based on clinical findings
  - Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
  - Commence iron therapy

- **Ferritin >100 mcg/L:**
  - Consider clinical context
  - Review renal function, MCV/MCH and blood film
  - Check B12/folate levels & reticulocyte count
  - Check liver and thyroid function
  - Seek haematology advice or, in the presence of chronic kidney disease, renal advice

**For clinical advice ring haematology registrar or haematologist on call**

‘Fit for Surgery’ (anaemia and iron deficiency specific)

Reduced likelihood of anaemia / iron deficiency delays to patient being wait listed for surgery.
Recommended screening to accompany GP surgery referral (results from ≤ 3 months prior to referral):

- Full blood count & reticulocyte count – *single cost when ordered together*
- Iron studies including Ferritin
- CRP and Creatinine – *single cost when ordered together*
- U&Es and LFTs
- Vitamin B12 & Folate if indicated – *single cost when ordered together*
- Other investigations as appropriate depending on comorbidity
Ferritin <30 mcg/L

- **Iron deficiency +/-anaemia**
  - Evaluate possible causes based on clinical findings
  - Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
  - Commence iron therapy
Possible iron deficiency
Ferritin 30-100mcg/L

• Consider clinical context
• Consider haematology advice or, in the presence of chronic kidney disease, renal advice
• Discuss with gastroenterologist regarding GI investigations and their timing in relation to surgery
• Commence iron therapy

- Transferrin Saturation <20% either absolute or functional iron deficiency
If Ferritin is 30 - 100mcg/L

- Consider iron therapy if anticipated postoperative blood loss is >2-3 units RBC i.e. Hb loss >30g/L
- Determine cause and need for GI investigations if Ferritin is suggestive of iron deficiency <30 mcg/L
Possible anaemia of chronic disease or inflammation, or other cause: Ferritin >100mcg/L

- Consider clinical context
- Review renal function, MCV/MCH and blood film
- Check B12/folate levels & reticulocyte count
- Check liver and thyroid function
- Seek haematology advice or, in the presence of chronic kidney disease, renal advice
- TSAT <20% consider absolute or functional iron deficiency
Treatment of iron deficiency

- Oral: if 3+ months to surgery and no significant comorbidities
- Intravenous: <3 months to surgery or if comorbidities
Anaemia is a contraindication for elective surgery.

Anaemia is a multiplier of disease that can increase your patient’s risk factors from other co-morbidities three - five fold.

Even mild anaemia can predispose your surgical patient to transfusion.

Iron deficiency with or without anaemia is also a risk factor that can predispose your surgical patient to post-operative anaemia and transfusion.

Paradoxically, both anaemia and transfusion are independently associated with organ injury and increased morbidity.

Anaemia and iron deficiency are modifiable risk factors.

Iron requirements are relative to the patient condition and proposed surgery.

Surgical patients with suboptimal iron stores (as defined by a Ferritin level < 100 mcg/L) in whom substantial blood loss is anticipated, should be treated with preoperative iron therapy.

In patients undergoing surgery, preoperative anaemia should be identified, evaluated and managed as early as possible to coordinate scheduling of surgery with optimisation of haemoglobin and iron stores.

Minimising RBC transfusion reduces morbidity, mortality, ICU length of stay and hospital length of stay.


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### 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>
</tr>
</thead>
<tbody>
<tr>
<td>FERRO-GRADUMET (Abbott)</td>
<td>![Image]</td>
<td>325 mg Ferrous Sulphate Controlled release tablet</td>
<td>105 mg</td>
</tr>
<tr>
<td>FERRO-GRAD C (Abbott)</td>
<td>![Image]</td>
<td>325 mg Ferrous Sulphate &amp; 650 mg Ascorbic Acid Controlled release tablet</td>
<td>105 mg</td>
</tr>
<tr>
<td>Ferro-tab (AFT Pharmaceuticals) PBS listed†</td>
<td>![Image]</td>
<td>310 mg Ferrous Fumarate &amp; 350 mg Folic Acid Non-controlled release tablet</td>
<td>100 mg</td>
</tr>
<tr>
<td>FEFOL Iron &amp; Folate Supplement (Pharm-a-care)</td>
<td>![Image]</td>
<td>270 mg Ferrous Sulphate &amp; 300 mg Folic Acid Controlled release capsule</td>
<td>87.4 mg</td>
</tr>
<tr>
<td>FGF (Abbott)</td>
<td>![Image]</td>
<td>250 mg Ferrous Sulphate &amp; 300 mg Folic Acid Controlled release tablet</td>
<td>80 mg</td>
</tr>
<tr>
<td>Ferro-tab (AFT Pharmaceuticals) PBS listed†</td>
<td>![Image]</td>
<td>200mg Ferrous Fumarate Non-controlled release tablet</td>
<td>65.7 mg</td>
</tr>
<tr>
<td>FERRO-LIQUID (AFT pharmaceuticals) PBS listed†</td>
<td>![Image]</td>
<td>Ferrous Sulphate Oral liquid</td>
<td>30 mg/5 ml</td>
</tr>
</tbody>
</table>

Many oral iron preparations contain too little iron to be effective. Multivitamin-mineral supplements should not be used to treat IDA as iron content is low & absorption may be reduced. **Usual ADULT dose for IDA is around 100-200 mg elemental iron daily in divided doses** (1-2 tablets per day of these 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 or lower doses of iron may also reduce GI upset. For example, 1 tablet 2-3 times a week or try Ferro-tabs or biminate liquid, 30-60 mg of elemental iron, increasing to twice daily or three times a day if tolerated. Around 3-6 months of oral iron is needed once Hb has normalised to replenish stores.

PTO
Maltofer iron polymaltose better tolerated?

100mg elemental iron per tablet

Maltofer®: Body-friendly iron

Maltofer® is an oral iron therapy for the treatment of dietary iron deficiency in adults and adolescents. Many people don't get enough iron from their diet, which can lead to low iron levels.

Maltofer® is an oral iron therapy which is clinically proven to correct iron levels, with fewer and milder side effects compared to ferrous iron supplements. That means less constipation, less nausea and an effective dose of iron. It's the kind of iron deficiency treatment many have been waiting for.

Maltofer® is now available in Australian pharmacies, with no prescription needed. Maltofer® is manufactured in Switzerland and is available in more than 80 countries around the globe.
CLINICAL EXAMPLE OF MUCOSAL BLOCK of oral iron

- Over a course of 1800mg (30 doses of 60 mg orally)
- Hb increases by more than 7g/L on alternate day dosing compared with daily dosing
- Alternate day dosing less side effects and more effective

Stoffel et al Lancet Haematol 2017;4:524-33
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

- Iron carboxymaltose  2010
- PBS $309 per 1000mg
- Up to 1000mg can be administered in 15 minutes
Dosing IV iron

Gazoni formula for iron deficit in mg:
[body weight in kg x (target Hb - actual Hb in g/dL) x 0.24 + 500]

<table>
<thead>
<tr>
<th>Hemoglobin level</th>
<th>&lt; 70 kg</th>
<th>&gt; 70 kg</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic iron deficiency without anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 g/dl (women)</td>
<td>500–1000 mg</td>
<td>500–1000 mg</td>
<td>ECCO 2015&lt;sup&gt;6&lt;/sup&gt; based on Favrat et al.&lt;sup&gt;33&lt;/sup&gt; and Evstatiev et al.&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt; 13 g/dl (men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–12 g/dl (women)</td>
<td>1000 mg</td>
<td>1500 mg</td>
<td>ECCO 2015&lt;sup&gt;6&lt;/sup&gt; based on the FERRIcor trial&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>10–13 g/dl (men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–10 g/dl</td>
<td>1500 mg</td>
<td>2000 mg</td>
<td>ECCO 2015&lt;sup&gt;6&lt;/sup&gt; based on the FERRIcor trial&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt; 7 g/dl</td>
<td>2000 mg</td>
<td>2500 mg</td>
<td>ECCO 2015&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ECCO, European Crohn’s and Colitis Organization.
Follow-up

- **Adequate response**
  
  assess at 4 weeks Hb increase by 20g/L after 3 weeks and to normal in 6-8 weeks

- **Poor response**
  
  Ferritin >100 mcg delays response
  Helicobacter and Coeliac disease, vitamin C,D ?
  Drugs: H2 antagonists  proton pump inhibitors

- Once iron corrected **re-assess every 3 months**
  
  for 1 year, then 6-12 monthly
  
  Substitute iron again if Ferritin <100 mcg/L, Hb below normal
Case Study One..

- Mrs Robson is a 42 year old mother of 7 children (aged between 18 months and 12 years).
- She has been short of breath on exertion for a few months and presents to the emergency department (ED) with chest pain.
- She has a low grade fever, productive cough with yellow sputum and chest pain on coughing, reproduced with chest wall pressure. Other vital signs are within normal limits and ECG and chest XRAY unremarkable.
- As she is being prepared for discharge home for a chest infection her FBC result came back at follows:

  - Hb 84 (115-155g/L)
  - WCC 11.8 (4 – 11 a 10/9/L)
  - Platelets 439 (150 – 400 x 10/9/L)
  - MCV 60.1 (80 – 98fl)
  - MCH 16.4 (27 – 33pg)
  - RDW 19.2 (11.5 – 15.5 %)
  - RCC 2.2 (3.5 - 5 x10¹²/L)

- Differential diagnosis?
- Iron studies
  - Transferrin Saturation 6% (15-45)
  - Ferritin 2 ug/l (15-45)

- Management ?
- Investigation ?
Case Study 2:

- Mrs S., a 65 yr old woman, arrives at pre admission clinic prior to a TKR (Total Knee Replacement) and has an FBC, U&E, Fe studies. History of rheumatoid arthritis controlled with weekly methotrexate.

- Hb 95g/L (135-180)
- WCC 5.3 $ \times 10^9$/L (4-11)
- Platelet 361 $\times 10^9$/L (150 – 400)
- RCC 2.1 $\times 10^{12}$/L (3.5-5.5)
- MCV 77 fl (80 – 100)
- MCH 26 pg (27 – 32.0)
- RDW 16.6 (9-15)
- Ferritin 120 ug/L (30 – 620)
- Transferrin Sat 14 % (20 – 45%)
- Creatinine 160 umol/L (60 – 110)
- eGFR 53 (>60 ml/min 1.73 per m2)

- How would you proceed?
Case study 3

67 yr male with NIDDM presents with SOBE and chest pain prior to hip surgery. He is pale and has a yellowish complexion

Hb 59g/L
MCV 120 fl (80-100)
RBC 1.8 x10^{12} (3.7-5.5)
WBC 3.2 /nl (4-11)
platelets 120/nl (150-400)
Reticulocytes 2% (2-4) 50/nl (90-140)

TSAT 60 % (15-45)
Ferritin 700 ug/L (30-350)
Bilirubin 30 umol/l (12-22)
ALT 50 U/L (45-150)
Alk Phosphatase 49 U/L (30-150)
LDH 800 U/L (<250)

Differential Diagnosis?
Confirmation?
Case Study 4

25 yr male with tiredness

Hb  110  (135-180g/L)  
HCT  0.45  (0.4-0.5)  
WCC  7.8  (4 – 11 a 10/9/L)  

Platelets 389 (150 – 400 x 10/9/L)

MCV 69 .0 ( 80 – 98fl)  
MCH 22.4 (27 – 33pg)  

RDW  19.2 (11.5 – 15.5 %)  
RCC  6.5 (3.5 - 5 x10^{12}/L)  

Iron studies  
Transferrin Saturation  48%  (15-45)  
Ferritin 250ug/l  (30-300)  

What is differential diagnosis? Confirmation?