Iron Therapy

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Walsall Manor Hospital
CONFLICTS OF INTEREST

Vifor Pharma /Abbvie consultant on their advisory board.
Aims

1. Why is it important to understand it better?
2. Understanding Iron metabolism.
3. When Oral Iron Works and when it does not!
4. When to use PRCs and when not!
5. Does Chronic Inflammation has impact on Iron absorption and how?
6. When to use IV Iron?
7. Dose of IV Iron
8. Risk Vs Benefits of IV Iron

PATHWAY.
On a lighter note!
Understanding Iron Absorption/Metabolism.
Dietary Factors

Iron Rich Foods
- Red Meat
- Quinoa
- Shellfish (cooked @ 12 months+)
- Dried Fruits

Dark Leafy Greens
- Broccoli

Egg Yolks

Poultry

Legumes/Lentils

Vitamin C
- Vitamin C helps the body absorb iron more efficiently
- Broccoli
- Orange
- Berry
- Kiwi

Source: WholesomeBabyFoodGuide.com
Daily Recommended Iron Intake
Iron Absorption and Utilization
Iron Absorption

- Heme iron
- Nonheme iron
- Duodenal cytochrome B
- DMT1
- Mucosal ferritin
- Ferroportin 1
- Hepcidin
- Hephaestin
- Liver
- Blood
- Plasma transferrin
- Erythroid marrow

Lost by shedding of epithelial cells
Iron Excretion

Small quantities are excreted by desquamation of GI epithelial cells.

This is not dependent on Iron saturation.
Iron Replete state

body iron stores full:

regulation in duodenum:

absorbed iron bound to ferritin; lost from body when enterocyte dies
Iron Deficiency
Iron Deficiency State
CAUSES OF IRON DEFICIENCY
Causes of IDA

Systemic Inflammation
- Rheumatoid arthritis
- CKD
- COPD
- Connective tissue disorders

Dietary insufficiency
- CHF
- Coeliac disease
- GI infection
- Gut oedema
- Medications

Blood loss
- GI bleeding
- Peri-operative
- Haemodialysis

Malabsorption
- GI cancer
- Gastritis
- Inflammatory bowel disease
- Gastrectomy
THE SIZE OF THE CHALLENGE
IDA is the 6\textsuperscript{th} Most Common Cause of Potentially Avoidable Admissions in the Over 75yrs\textsuperscript{1}

\textbf{ACSC Conditions 75 and Over / 100,000 Population (National)}

1. Data on File, Harvey Walsh Ltd (Source: HES Data, England 2013/14)
Over 75yrs Health Episode Statistics
2013/2014

1. Data on File, Harvey Walsh Ltd (Source: HES Data, England 2013/14)
Cost to NHS!!

Non-Elective costs

- £12,500,000 (2013)
- £15,000,000 (2014)

Non-Elective costs
Length of stay - Under 75 years of age
Length of stay - Age - 80 years and above
Walsall Healthcare NHS Trust

What is the impact of IDA on bed capacity?

Number of bed days where patients have been coded as primary diagnosis of IDA

The Majority of this is attributed to the non-elective cohort
What does this mean?

Increased cost to the healthcare

Poor patient care

Source: King's Fund
Prevalence of Anaemia Older People

**US NHANES III**
- Anaemia in 11% of men & 10% of women ≥65 years; ~20% by age 80 years
- 20% due to iron deficiency; 24% due to anaemia of inflammation

**UK SACN 2010**
- Anaemia in 52% of men & 39% of women in institutions
- Anaemia in 13-38% of free-living adults ≥75 years
- ID in 12-14% of free-living women ≥75 years

**US Women’s Health and Ageing Studies**
- Anaemia in 13.3% of community-dwelling women ≥70 years
- ID in 5.8%
- IDA in 3.8%
- ID accounted for >1/4 of all anaemia

2. UK Scientific Advisory Committee on Nutrition 2010
HEPCIDIN
Hepcidin

- Hepcidin is understood to be the principal regulator of iron homeostasis.
- Peptide hormone produced by the liver.
- Acts to reduce iron uptake by enterocytes in the GI tract and block the release of iron from hepatocyte and macrophage stores.
- Levels are high when the body is iron replete and low when the body is iron deficient.
- Hepcidin is also an acute-phase reactant.
- Systemic inflammation, and co-morbid inflammatory conditions lead to the up-regulation of the hormone hepcidin which inhibits the utilisation of iron in the body.
Role of Systemic Inflammation

INFLAMMATION

body becomes full:
increased hepcidin secretion by liver

regulation in duodenum:
hepcidin binds to ferroportin
ferritin
ferroportin

absorbed iron bound to ferritin; lost from body when enterocyte dies
ferroportin degraded
IMPACT OF ANAEMIA ON COMORBIDITIES AND FUNCTION
Mortality

- Anaemia has been found to be significantly associated with increased mortality in community-dwelling elderly people,\textsuperscript{1,2,3} Nursing Home residents\textsuperscript{4,5} & hospitalized patients.\textsuperscript{5}

- Anaemia of inflammation has been shown to be significantly associated with increased mortality in community-dwelling, older, disabled women.\textsuperscript{6}

- Some evidence that improving Hb improves survival.\textsuperscript{5,7}

\begin{itemize}
\item 1. Izaks GJ et al. JAMA 1999;281:1714-7
\item 2. Zakai NA et al. Arch Intern Med 2005 24;165:2214-20
\item 7. Terrier B et al. QJM 2012;105:345-54
\end{itemize}
Frailty

• Anaemia significantly & independently associated with:
  – Frailty\(^1\)
  – Higher rate of disability, poor performance & reduced muscle strength\(^2\)
  – Decline in physical performance over time\(^3\)
  – Longer stay in hospital (25 v 13 days)\(^4\)

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Chronic Heart Failure
Chronic Heart Failure (CHF)

- Iron deficiency present in 35-50% of CHF patients.\(^1,2,3\)
- Iron deficiency independently associated with risk of death in patients with heart failure.\(^1,2,3\)
- IV iron treatment improves symptoms, functional class and exercise tolerance in patients with CHF.\(^4,5,6\)
- IV iron shown to reduce the risk of hospitalization due to worsening CHF.\(^6\)
- IV iron reduces BNP levels.\(^7\)

2. Okonko DO et al. J AM Coll Cardiol 2011;58:1241-51
CONFIRM-HF\textsuperscript{1}

A 52 week, placebo-controlled study to assess the effect of IV iron (Ferinject\textsuperscript{®}) on exercise capacity, symptoms, QoL and safety in patients with CHF and iron deficiency.

Ferinject\textsuperscript{®} significantly improved exercise capacity at week 24 vs placebo, with a significant and sustained improvement in 6MWT during 1 year.

Ferinject® significantly improved quality of life, measured by the Patient Global Assessment (PGA), fatigue scores and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores.¹

Ferinject® significantly improved NYHA class from week 24 onwards vs placebo.¹

Ferinject® was associated with a reduction in the risk of first hospitalisation due to worsening CHF.¹

TREATMENT OF IDA
Iron Therapy

**Enteral Iron Therapy**
First line
Cost Effective

**For How Long?**
Till Hb is back to normal and
3 months to replenish Iron Stores.

Ongoing loss of blood

Absorption of oral iron may be limited due to hypochlorhydria/achlorhydria or gut oedema.

Therapy with oral iron can take some time.

Oral iron is poorly tolerated which can lead to reduced compliance.

Up regulation of hepcidin

Limitations of Oral Iron Therapy
## Treatment Options for ID/IDA

<table>
<thead>
<tr>
<th></th>
<th>Oral iron</th>
<th>IV iron</th>
<th>Blood transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>High iron content</td>
<td>Essential in cases of cardiovascular instability&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Non-invasive</td>
<td>100% bioavailable</td>
<td>Replaces RBCs</td>
<td></td>
</tr>
<tr>
<td>Simple administration</td>
<td>Compliance</td>
<td>Compliance</td>
<td></td>
</tr>
<tr>
<td>Convenient</td>
<td>Fast acting&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Well tolerated&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerance</td>
<td>Potential adverse reactions</td>
<td>Potential transfusion reactions</td>
<td></td>
</tr>
<tr>
<td>Potential poor compliance</td>
<td>Invasive</td>
<td>Invasive</td>
<td></td>
</tr>
<tr>
<td>Risk of malabsorption in inflammatory conditions</td>
<td>Day case / inpatient</td>
<td>Day case / inpatient – secondary care input needed</td>
<td></td>
</tr>
<tr>
<td>Slower to increase haemoglobin vs IV iron&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Cost</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>Interactions with common oral drugs</td>
<td>Cost</td>
<td>Limited supply</td>
<td></td>
</tr>
<tr>
<td>Can delay investigative procedures, i.e. colonoscopies</td>
<td>Complex administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can only absorb 10-20mg a day&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Venofer&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Cosmofer&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Ferinject&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum single dose</strong></td>
<td>200mg</td>
<td>20mg/kg</td>
<td>20mg/kg, up to 1000mg</td>
</tr>
<tr>
<td></td>
<td>3x per wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test dose required</strong></td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td><strong>Infusion times</strong></td>
<td>30 mins</td>
<td>4-6 hours</td>
<td>≤500mg - 6 mins &gt;500mg - 15 mins</td>
</tr>
<tr>
<td><strong>Use in children</strong></td>
<td>×</td>
<td>≥14 years</td>
<td>≥14 years</td>
</tr>
<tr>
<td><strong>Use in pregnancy</strong></td>
<td>Not in 1&lt;sup&gt;st&lt;/sup&gt; trimester</td>
<td>Not in 1&lt;sup&gt;st&lt;/sup&gt; trimester</td>
<td>Not in 1&lt;sup&gt;st&lt;/sup&gt; trimester</td>
</tr>
<tr>
<td><strong>Use in breastfeeding</strong></td>
<td>✓</td>
<td>Not recommended</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Use with caution in asthma, eczema or other atopic allergy</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Use with caution in decompensated cirrhosis and hepatitis</strong></td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Use with caution in rheumatoid arthritis with active inflammation</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Acute renal failure</strong></td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Use with caution in patients with acute or chronic infection</strong></td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
</tbody>
</table>

<sup>1</sup> Venofer Summary of Product Characteristics  
<sup>2</sup> Cosmofer Summary of Product Characteristics  
<sup>3</sup> Monofer Summary of Product Characteristics  
<sup>4</sup> Rienso Summary of Product Characteristics  
<sup>5</sup> Ferinject Summary of Product Characteristics
IV Iron Treatment Effectiveness

• Bypasses the limitations of oral iron, as it circumvents the gut.

• Quickly restores both available iron and iron stores.

• High levels of iron in cells up-regulate ferroportin channels, partially overcoming the hepcidin block, allowing release of iron from macrophages.
Safety of IV Iron
Historic Concerns of Parenteral Irons

• Many clinicians have experience historically with High Molecular Weight (HMW) dextran iron preparations.

• The unacceptably high risk of dextran-based anaphylactic reactions led to withdrawal from the European Market.

• More recent parenteral iron preparations are considered to be better tolerated than the HMW dextran irons.
Cost Effectiveness
## Resource (1g)

<table>
<thead>
<tr>
<th></th>
<th>1g</th>
<th>Ferinfect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cosmofer</strong></td>
<td><strong>Drug Cost per gram</strong></td>
<td><strong>140.06</strong></td>
</tr>
<tr>
<td><strong>79.7</strong></td>
<td><strong>Drug Cost per dose</strong></td>
<td><strong>140.06</strong></td>
</tr>
<tr>
<td><strong>10201.6</strong></td>
<td><strong>Drug cost per 128 patients</strong></td>
<td><strong>17927.68</strong></td>
</tr>
<tr>
<td><strong>5</strong></td>
<td><strong>Chair time (hours)</strong></td>
<td><strong>1.25</strong></td>
</tr>
<tr>
<td><strong>277.75</strong></td>
<td><strong>Chair cost (@£55.55/hour) per dose</strong></td>
<td><strong>69.4375</strong></td>
</tr>
<tr>
<td><strong>35552</strong></td>
<td><strong>Chair cost per 128 patients</strong></td>
<td><strong>8888</strong></td>
</tr>
<tr>
<td><strong>70.4</strong></td>
<td><strong>Nurse Cost (@£14.08/hour) per dose</strong></td>
<td><strong>17.6</strong></td>
</tr>
<tr>
<td><strong>9011.2</strong></td>
<td><strong>Nurse cost per 128 patients</strong></td>
<td><strong>2252.8</strong></td>
</tr>
<tr>
<td><strong>54764.8</strong></td>
<td><strong>Total Annual Cost</strong></td>
<td><strong>29068.48</strong></td>
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<tr>
<td><strong>427.85</strong></td>
<td><strong>Per Patient Cost</strong></td>
<td><strong>227.0975</strong></td>
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<tr>
<td><strong>Total Saving</strong></td>
<td></td>
<td><strong>25696.32</strong></td>
</tr>
<tr>
<td><strong>37632</strong></td>
<td><strong>Total income 128 x SA04D @ £294</strong></td>
<td><strong>37632</strong></td>
</tr>
<tr>
<td><strong>-17132.8</strong></td>
<td><strong>Annual Cost -Annual Income (Trust Profit)</strong></td>
<td><strong>8563.52</strong></td>
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</tbody>
</table>
# Resource (1.5g)

<table>
<thead>
<tr>
<th></th>
<th>1.5g</th>
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<tbody>
<tr>
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</tr>
<tr>
<td><strong>Drug Cost per dose</strong></td>
<td>119.55</td>
<td>210.09</td>
</tr>
<tr>
<td><strong>Drug cost per 128 patients</strong></td>
<td>15302.4</td>
<td>26891.52</td>
</tr>
<tr>
<td><strong>Chair time (hours)</strong></td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Chair cost (@£55.55/hour) per dose</strong></td>
<td>277.75</td>
<td>138.875</td>
</tr>
<tr>
<td><strong>Chair cost per 128 patients</strong></td>
<td>35552</td>
<td>17776</td>
</tr>
<tr>
<td><strong>Nurse Cost (@£14.08/hour) per dose</strong></td>
<td>70.4</td>
<td>35.2</td>
</tr>
<tr>
<td><strong>Nurse cost per 128 patients</strong></td>
<td>9011.2</td>
<td>4505.6</td>
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<tr>
<td><strong>Total Annual Cost</strong></td>
<td><strong>59865.6</strong></td>
<td><strong>49173.12</strong></td>
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<tr>
<td><strong>Per Patient Cost</strong></td>
<td><strong>467.7</strong></td>
<td><strong>384.165</strong></td>
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<tr>
<td><strong>Total Saving</strong></td>
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<td><strong>10692.48</strong></td>
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<td><strong>Total income 128 x SA04D @ £294</strong></td>
<td><strong>37632</strong></td>
<td><strong>75264</strong></td>
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<tr>
<td><strong>Annual Cost -Annual Income (Trust Profit)</strong></td>
<td><strong>-22233.6</strong></td>
<td><strong>26090.88</strong></td>
</tr>
</tbody>
</table>
Case scenarios

• Medical
27, M known to have severe UC, presents with Anaemia.
Hb 79, MCV 63, Fer 12

What treatment?

• Medical/Ortho
• 84, M with fall. #NOF.
Hb 81
MCV 66
Fer 31

What Treatment?
Case scenarios

• 74, M presents with IDA, new diagnosis of CRC.
  Due to have right hemicolecotmy in 2 weeks?

• What treatment?

49, F with menorrhagia/DUB,
  Hb 84
  MCV/MCH – low
  Fer 4
  Due to have hysterectomy in 6 weeks?

What treatment?
Could we use Iron to minimize blood transfusions

**Medical**
Have a clear pathway of management of IDA, Improved access to IV Iron.

**Obstetric**
Early access to Iron therapy. Pathway

**Surgical**
**Emergency** - Probably not

**Elective** -
We can improve access to IV iron/Oral Iron to preoperative patients.
Pathway
Patients presents to A&E with symptoms of IDA or low Hb and symptoms attributed to underlying anaemia

Order bloods: FBC, U&E’s, LFT’s, ESR, Ferritin, B12, CRP, Folate.

Definition of Anaemia

WHO Hb threshold for anaemia
Males ≤ 130 g/l
Non pregnant Females ≤ 120 g/l

Ferritin <30: Highly suggestive of IDA. Initiation of iron therapy is recommended.

Ferritin 30-100: Possible IDA in presence of inflammation/raised CRP. Initiation of iron therapy is recommended.

Ferritin >100: IDA unlikely. Identify alternative cause of anaemia

Treatment Aims:
Restore Hb and Replenish Iron Stores
Diagnose and treat underlying cause
Hb <7

- Consider Blood Transfusion
  - a single unit transfusion to achieve a Hb of 7-8.
  - (Further test required for subsequent units.)
  - then replenish iron stores

Symptomatic +/- Decompensated

Y

- Consider IV iron
  - (See Appendix 1 for contraindications and special precautions)

N

Hb 7-9

Hb >9

Consider IV iron

(See Appendix 1 for contraindications and special precautions)

Calculate initial Ferinject dose for infusion over 15 minutes

Patients Weight (kg) | Initial Ferinject dose (mg) | Maximum volume of 0.9% sodium chloride (ml)
---------------------|-----------------------------|----------------------------------
35-50                | 500                         | 100                              |
>50                  | 1000                        | 250                              |

Monitor patients for adverse reactions for 30 minutes

Request GP to refer to Gastroenterology for diagnostic test to find underlying cause of IDA
Upper GI CNS Sam King Fax referral to 01922 656993
On a lighter note!

Guinness is good for you.
Thank You For Your Attention Any Questions?
Can Iron be Bad?
Carcinogen or not: Iron in the circulation

No effect of i.v. iron on 3-year progression-free survival in anemic patients with lymphoid malignancies.

In CRC mice - No influence on intestinal tumorigenesis, parenteral iron did not promote tumour formation.

Parenteral iron replenished splenic iron and significantly reduced inflammation in the colon without increasing hyperplastic lesions.

Iron s.c. in APC knockout CRC models did not promote intestinal tumorigenesis.
Carcinogen or not: Iron from the gut?

Murine CRC models – increased tumourigenesis in dietary iron
Gut iron chelators – reduce proliferation and cell cycle in vitro
But variable effects in vivo – perhaps due to host toxicity
So is Iron Bad?

Iron may be bad if delivered to the gut

Higher effect in vitro seen in genetically predisposed

IV iron has no effect
B-catenin/TCF binding generates multiple oncogenes via the activation of Wnt-signalling
APC mutations common in sporadic and familial CRC