Iron deficiency anaemia in IBD

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Outline

• Epidemiology
• Terminology
• Basic science
  – Iron homeostasis
  – Bowel mucosal injury
• Clinical features
• Diagnosis
• Treatment
Introduction

• Anaemia is the commonest EIM
• Found more in hospitalized and newly diagnosed patients
• Iron deficiency most prevalent cause of anaemia
• More common in Crohn’s than UC
• Must be diagnosed and treated early
Table 3.2  **Global anaemia prevalence and number of individuals affected**

<table>
<thead>
<tr>
<th>Population group</th>
<th>Prevalence of anaemia</th>
<th>Population affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent</td>
<td>95% CI</td>
</tr>
<tr>
<td>Preschool-age children</td>
<td>47.4</td>
<td>45.7–49.1</td>
</tr>
<tr>
<td>School-age children</td>
<td>25.4</td>
<td>19.9–30.9</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>41.8</td>
<td>39.9–43.8</td>
</tr>
<tr>
<td>Non-pregnant women</td>
<td>30.2</td>
<td>28.7–31.6</td>
</tr>
<tr>
<td>Men</td>
<td>12.7</td>
<td>8.6–16.9</td>
</tr>
<tr>
<td>Elderly</td>
<td>23.9</td>
<td>18.3–29.4</td>
</tr>
<tr>
<td><strong>Total population</strong></td>
<td>24.8</td>
<td>22.9–26.7</td>
</tr>
</tbody>
</table>
Anaemia definition

- Children 6 months to <5 years: 11 g/dL
- Children 5 to <12 years: 11.5 g/dL
- Children 12 to <15 years: 12 g/dL
- Non-pregnant women: 12 g/dL
- Pregnant women: 11 g/dL
- Men ≥15 years: 13 g/dL
Iron restricted erythropoeisis

• Absolute iron deficiency
  – Reduced Iron stores

• Functional iron deficiency
  – Insufficient iron available for erythropoeisis despite normal or elevated iron levels
    • Anaemia of chronic disease
    • Erythropoesis stimulating agents
Iron homeostasis

- About 20-25mg iron needed daily for haem synthesis
- 1-2mg of that acquired from diet
- Remainder recycled from senescent RBC
- No active Iron excretion - concentration must be regulated at site of absorption
- 1-2mg obligatory loss daily
Mechanism of Anaemia in IBD

- Blood loss from ulcerated mucosal surfaces
- Anaemia of chronic diseases-Hepcidin
- Nutritional deficiencies
- Resection
- Medications
Effect of inflammation
Clinical features

- May be symptomatic in the absence of anaemia
- Impaired quality of life
- Cognitive, motor and behavioural impairment
- Increase in pregnancy complications
Diagnosing IDA in IBD

• Basic laboratory screening
  – FBC
  – Ferritin
    • Without inflammation: <30μg
    • With inflammation: <100μg
  – Transferrin: <20%
  – CRP
  – Reticulocytes
Diagnosing IDA in IBD

- **Hb <12 g/dL♀ - <13 g/dL ♂**
  
  - **Transferrin saturation <20%**
  
    - Ferritin <30 μg/L + MCH <27 pg → IDA
    - Ferritin 30-100 μg/L → ACD + ID
    - Ferritin >100 μg/L → ACD
Differentiating IDA from ACD

• Soluble transferrin receptor level
  – Not affected by chronic inflammation
  – High in IDA
• sTfR/Log Ferritin index

• For functional anaemia:
  – Percentage of hypochromic cell index
  – Reticulocyte haemoglobin
  – Zinc protoporphyrin
Therapeutic goals

• Treat underlying disease
• Normalise haemoglobin
• Replenish stores: Ferritin >100µg up to 400µg
• Avoid the need for transfusion
• Improve quality of life
Oral treatment

• Ferrous formulations: FeSO$_4$, Fumarate, gluconate
• Inexpensive and convenient to take
• Unfavourable side effect profile- up to 70%
• Food content may decrease/increase uptake
• Ferric form: Ferric polymaltose
Ferric formulation

• Complex between Ferric iron and Maltose
• Can be effective in patients who have failed or are intolerant to Ferrous
  – No interaction with food components
  – Does not induce ROS
• Can be an alternative to IV iron
• Commonest S/E: Gastrointestinal upset
Effects of Iron on inflammation

• Iron is a key growth and virulence factor for microbes
• Formation of a hydroxyl free radical which mediates tissue injury
• Activation of NFκβ
• Impaired intracellular killing of pathogens by macrophages
Is there evidence for adverse effects

• Oldenburg et al
• IL 10-/- vs. Wild type mice given oral and rectal iron
• Increase in pro-inflammatory cytokines
• No significant increase in histological inflammation
In humans...

- Silva et al: IDA in IBD and non-IBD
- 57 Patients invited, 10 lost to follow up
- Disease severity before and after treatment
- Results
  - 12 (26%) were intolerant
  - 2 IBD patients (6%) had disease relapse
  - No significant increase in disease related markers
  - No significant increase in ROS in rectal biopsies
Table 3. Responses to oral iron therapy for 4 weeks in patients with anaemia due to ulcerative colitis, Crohn's disease, active IBD and non-IBD causes

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis (n = 14)</th>
<th>Crohn's disease (n = 19)</th>
<th>Active IBD (n = 7)</th>
<th>Non-IBD (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before iron</td>
<td>After iron</td>
<td>P-value</td>
<td>Before iron</td>
</tr>
<tr>
<td>Simple Colitis Clinical</td>
<td>3.5 (2.6)</td>
<td>5 (3.2)</td>
<td>0.014*</td>
<td>-</td>
</tr>
<tr>
<td>Activity Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvey-Bradshaw Index</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.1 (1.7)</td>
</tr>
<tr>
<td>IBDQ (score/224)</td>
<td>164 (12)</td>
<td>175 (9)</td>
<td>0.016*</td>
<td>177 (36)</td>
</tr>
<tr>
<td>Non-IBD Symptom Score</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.3 (1.9)</td>
<td>12.7 (1.0)</td>
<td>0.004*</td>
<td>10.0 (1.6)</td>
</tr>
<tr>
<td>Ferritin (mcg/L)</td>
<td>5 (8)</td>
<td>25 (26)</td>
<td>0.002*</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Platelets (×10^9/L)</td>
<td>320 (95)</td>
<td>280 (121)</td>
<td>0.04*</td>
<td>338 (162)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>21 (35)</td>
<td>17 (41)</td>
<td>0.052</td>
<td>40 (30)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>5 (4)</td>
<td>7 (19)</td>
<td>0.063</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>44 (6)</td>
<td>43 (3)</td>
<td>0.91</td>
<td>38 (8)</td>
</tr>
</tbody>
</table>
Use of oral Iron in IBD

• Can be used for mild anaemia (Hb>10)
• Elemental Iron doses of up to 100mg
  – e.g. Approx 65mg in 200mg FeSO4
• Disease must be quiescent
• Aim for Ferritin >100μg/L
• Check levels after 4 weeks
• Continue for 6 months after Hb normalization
Iron refractory IDA (IRIDA)

- Defective gene TMPRSS6 that controls Matriptase 2
- Uninhibited Hepcidin production
- Low MCV, MCH, % transferrin saturation and normal-low Ferritin
- Can check TSAT/Hepcidin ratio
- May respond to IV iron
Intravenous Iron

• Previously associated with severe S/E
• Preferred route for supplementation in IBD
• Can be used for
  – Moderate to Severe anaemia –Hb <10
  – Intolerance to oral Iron or inadequate response
• Disadvantages
  – High cost
  – Infusion reactions, Hypophosphatemia
Formulations available

- Iron Sucrose- Venofer®
- Iron dextran- Cosmofer®
- Iron Isomaltoside 1000- Monofer®
- Ferric Carboxymaltose- Ferinject®
- Iron gluconate- Ferrlecit®
- Ferumoxytol- Rienso®
Characteristics of different iron formulations

<table>
<thead>
<tr>
<th>Iron Preparation</th>
<th>Molecular Weight (kDa)</th>
<th>Carbohydrate Shell</th>
<th>Complex Stability</th>
<th>Maximum Approved Single Dose</th>
<th>Maximum total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran, low molecular weight</td>
<td>73</td>
<td>Dextran (branched polysaccharide)</td>
<td>High</td>
<td>200 mg (&lt;30 min)</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>43</td>
<td>Sucrose (disaccharide)</td>
<td>Moderate</td>
<td>200 mg (≥30 min)</td>
<td>7 mg/kg (300 mg in some countries)</td>
</tr>
<tr>
<td>Iron gluconate</td>
<td>37</td>
<td>Gluconate (monosaccharide)</td>
<td>Low</td>
<td>62.5 mg (5–10 min)</td>
<td>62.5 mg (125 mg in some countries)</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>150</td>
<td>Carboxymaltose (branched polysaccharide)</td>
<td>High</td>
<td>1000 mg (≥15 min)</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>Iron isomaltoside 1000</td>
<td>150</td>
<td>Isomaltoside (linear oligosaccharide)</td>
<td>High</td>
<td>1000 mg (≥15 min)</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>Ferumoxytol*</td>
<td>721</td>
<td>Polyglucose sorbitol carboxymethylether</td>
<td>High</td>
<td>510 mg (≤1 min)</td>
<td>510 mg</td>
</tr>
</tbody>
</table>
## Determining dose

<table>
<thead>
<tr>
<th>Haemoglobin (g/dL)</th>
<th>Weight &lt;70kg</th>
<th>Weight &gt;70kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-12 (Women)</td>
<td>1000mg</td>
<td>1500mg</td>
</tr>
<tr>
<td>10-13 (Men)</td>
<td>1000mg</td>
<td>1500mg</td>
</tr>
<tr>
<td>7-10</td>
<td>1500mg</td>
<td>2000mg</td>
</tr>
</tbody>
</table>
Frequency of monitoring

– Pts in clinical remission or mild disease can be screened every 6-12 months
– Outpatients with active disease-3 monthly
– Not recommended to repeat iron parameters at least 4 weeks after infusion
– Aim for Ferritin >400μg/L
– Re-treat when Ferritin drops <100μg or Hb drops
Blood transfusion

• The need depends on
  – The rate of bleeding
  – Haemodynamic instability
  – Co-morbidities
  – Haemoglobin level—may be considered if below 7g/dL

• Seldom used in IBD
Take home messages

• Anaemia in IBD should be investigated and treated
• IDA often co-exists with anaemia of chronic disease
• Oral iron for mild anaemia and quiescent disease
• Intravenous iron for severe anaemia
References


- Ole Haagen Nielsen, Mark Ainsworth, Mehmet Coskun, Gunter Weiss. Management of Iron-Deficiency anaemia in Inflammatory Bowel Disease. Medicine 2015; 94 (23) e963
- Christoph Gasche et al. Ferric Maltol is Effective in Correcting Iron Deficiency Anaemia in patients with Inflammatory Bowel Disease: Results From a Phase 111 Clinical Trial Programme. Inflammatory bowel Disease 2015; 21: 579-588
- Blazevic A et al. Severe hypophosphaetemia after intravenous iron administration. The journal of medicine 2014; 72:49-53