ANAEMIA AND ITS PRE-OPERATIVE MANAGEMENT

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Head of Research
UCL Institute of Human Health and Performance, and UCL Iron Collaboration
Plan

• Definition
• Prevalence
• How pre-op anaemia affects recovery from surgery
• Guidelines for treatment
• Treatment strategies
ANAEMIA

Hb concentration level below

- 13g/dl for men
- 12g/dl for women

(World Health Organisation, 1968; World Health Organisation, 2008)
Prevalence

• Affects 24.8% of the global population (World Health Organisation, 2008).

• Around 30% (ranging from 11% (Carson, 1996) to 76% (Cappell, 1992) of elective non-cardiac surgical patients are anaemic immediately prior to surgery (Dunne, 2002, Dunkelgrun, 2008, Musallam, 2011),

• Up to three quarters of those having newly diagnosed anaemia (Bierbaum, 1999).

• Around 28% (De, 2009) to 54.4% (Hung, 2011) of cardiac surgical patients are pre-operatively anaemic
<table>
<thead>
<tr>
<th></th>
<th><strong>Absolute iron deficiency (AID)</strong></th>
<th><strong>Anaemia of chronic disease (ACD)/Inflammation (AI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Depleted iron stores</td>
<td>Disruption of iron homeostasis initiated by a cytokine-mediated immune response</td>
</tr>
<tr>
<td></td>
<td>RBCs are small (microcytic) and pale (hypochromic)</td>
<td></td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Most common for gastro referral (iron deficiency, folate deficiency, vitamin B_{12} deficiency,)</td>
<td>Infections, cancer, autoimmune, chronic rejection after solid organ transplant, chronic kidney disease and inflammation</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Fatigue, tiredness, SOBOE, Difficulty concentrating</td>
<td>May be mild and may not notice</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>30% of anaemia cases in elective surgical patients (van Straten, 2009).</td>
<td>the most common anaemia of chronically ill and hospitalised patients (Weiss, 2002)</td>
</tr>
<tr>
<td><strong>Most powerful test</strong></td>
<td>Decreased ferritin; decreased MCV, Increased transferrin</td>
<td>Increased cytokine, Normal to increased ferritin</td>
</tr>
</tbody>
</table>

**Functional iron deficiency**

- Inadequate iron supply to meet demand despite normal or abundant iron stores
  - Normal or high ferritin levels
  - TSAT <20%
Normal amounts of RBCs

Anaemic
Increase RBC

Increase oxygen transport/delivery

Increased oxygen – more aerobic power (longer and harder body can work before exhausted)
Decrease RBC

Decrease oxygen transport/delivery

Decreased oxygen – less aerobic power

Increased metabolic demands (increased need to deliver sufficient oxygen)

AFFECT RECOVERY FROM SURGERY
Vascular surgery: Dunkelgrun, 2008
Retrospective study, n=1,211

Moderate pre-op anaemia: 2.3x more likely to have MACE at 30 day

Severe pre-op anaemia: 4.7x more likely to have 30-day MACEs
Rectal cancer surgery: van Halteren et al 2004
Registry analysis, n=144
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
<th>N</th>
<th>Methods</th>
<th>Risk factor/independent variable</th>
<th>Outcome/dependent variable</th>
<th>Difference</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Preoperative</td>
<td>2006/07</td>
<td>J Cardiothorac Vasc Anesth</td>
<td>4804</td>
<td>Prospective, observational, multicenter</td>
<td>Lowest preop. Hgb, EuroSCORE</td>
<td>Postop. morbidity and mortality</td>
<td>Worse</td>
<td>Renal and CNS outcome increased directly by low Hgb, cardiac outcome increased by association with comorbidity, comorbidity alters anemia tolerance</td>
</tr>
<tr>
<td>Kulier</td>
<td></td>
<td>Vasc Anesth 17:585</td>
<td></td>
<td></td>
<td>Preoperative anemia</td>
<td>Postop. mortality</td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Koch</td>
<td>2003</td>
<td>Lancet 359:1747</td>
<td>2059</td>
<td>Observational, multicenter</td>
<td>Preop. Hgb &lt;10 g/dl</td>
<td>Postop. mortality</td>
<td></td>
<td>Worse</td>
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<tr>
<td>Zindrou</td>
<td>2002</td>
<td>J Thorac Cardiovasc Surg</td>
<td>938</td>
<td>Observational, multicenter</td>
<td>Age/RBC volume</td>
<td>Postop morbidity</td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Ferraris</td>
<td>1996</td>
<td>JACC 28:1147</td>
<td>1567</td>
<td>Retrospective risk model</td>
<td>Preop. anemia</td>
<td>Postop. morbidity and mortality</td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Magovern</td>
<td>2006</td>
<td>Crit Care 10R: 58</td>
<td>54</td>
<td>RCT, prospective</td>
<td>Hct 20% compared with 25% during normothermic CPB</td>
<td>No difference in oxygen delivery and consumption, blood lactate clinical outcome</td>
<td></td>
<td>n very small</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>2006</td>
<td>J Thorac Cardiovasc Surg</td>
<td>688</td>
<td>Consecutive series, multicenter</td>
<td>Lowest Hct during CPB (&lt;24%)</td>
<td>Post-CPB renal injury</td>
<td>Worse</td>
<td>Elective, low risk, no preop. renal dysfunction</td>
</tr>
<tr>
<td>von Heymann</td>
<td>2005</td>
<td>Crit Care Med 33:1749</td>
<td>1475</td>
<td>Retrospective</td>
<td>In-hospital morbidity and mortality</td>
<td></td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Habib</td>
<td>2001</td>
<td>Ann Thorac Surg 71:769</td>
<td>8004</td>
<td>Prospective observational</td>
<td>Low output heart failure</td>
<td></td>
<td></td>
<td>Intraop. RBC transfusion and CPB independent risk factors</td>
</tr>
<tr>
<td>DeFoe</td>
<td>1997</td>
<td>Circulation 96: 1144</td>
<td>2738</td>
<td>Observational</td>
<td>Postop. mortality</td>
<td></td>
<td></td>
<td>Females and small body surface at risk for severe hemodilution on CPB</td>
</tr>
<tr>
<td>Surgenor</td>
<td>1999</td>
<td>Transfusion 39:1070</td>
<td>428</td>
<td>Consecutive, RCT</td>
<td>Postop. morbidity and mortality</td>
<td></td>
<td></td>
<td>Risk further increased by RBC transfusion &lt;17% for all patients &lt;14% for high-risk patients</td>
</tr>
<tr>
<td>Fang</td>
<td>1998</td>
<td>J Thorac Cardiovasc Surg</td>
<td>2202</td>
<td>Prospective, observational, multicenter</td>
<td>Postop. transfusion Hgb &lt;8 g/dl compared with Hgb &lt;9 g/dl and Hct &gt;34% at ICU entry</td>
<td>Postop. mortality</td>
<td></td>
<td>Postop. MI, severe left ventricular dysfunction</td>
</tr>
<tr>
<td>Postoperative</td>
<td>1999</td>
<td>Crit Care Med 26:225</td>
<td>8501</td>
<td>Retrospective</td>
<td>Postop. Hgb &lt; 10 g/dl</td>
<td></td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Bracey</td>
<td></td>
<td>Transfusion 39:1070</td>
<td></td>
<td></td>
<td>Postop. morbidity and mortality</td>
<td></td>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>Rady</td>
<td>1998</td>
<td>Crit Care Med 26:225</td>
<td>8501</td>
<td></td>
<td>Postop. Hgb &lt; 10 g/dl</td>
<td></td>
<td></td>
<td>Postop. mortality</td>
</tr>
</tbody>
</table>

Reproduced from [17,19,28,29,47,53,57,58,59].
Cardiac surgery: Hospital length of stay (number of days) in anaemic and non-anaemic patients

- Cladellas et al 2006
- Kulier et al 2007
- De Santo et al 2009

Statistics:
- p=0.002
- p<0.001
- p<0.001
Pre-op Hb and C-POMS summary score (morbidity)

Table: Median C-POMS summary score by quintile of Hb

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (&gt;14.6)</td>
<td>2 [1-4] 85</td>
<td>2 [1-3] 78</td>
<td>3 [1-4] 19</td>
<td>2.5 [1.5-3.1] 4</td>
<td>-1.71 (0.29)</td>
</tr>
</tbody>
</table>

P value <0.0001 0.007 0.28 0.67 <0.0001
P value (trend) <0.0001 0.001 0.16 0.15 <0.0001

Fig: C-POMS summary score by pre-operative anaemia

***p<0.0001 vs. non-anaemic; boxes show median and inter-quartile range; 95% range shown by bars

Lower Hb was independently associated with increased morbidity:
0.38 decrease in C-POMS summary score per 1SD increase in Hb p<0.0001
Anaemia associated with increased blood transfusion requirement.

Roger et al 2012: Weston Australia PBM system major gynaecological surgery, n=843

**Table 3** Blood transfusion and patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RBC transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Patient age &gt; 65 years</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Preoperative anaemia</td>
<td>26 (51%)</td>
</tr>
</tbody>
</table>

ASA class

<table>
<thead>
<tr>
<th>ASA class</th>
<th>RBC transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II</td>
<td>31 (61%)</td>
</tr>
<tr>
<td>III–V</td>
<td>20 (39%)</td>
</tr>
</tbody>
</table>

Prior chemotherapy

<table>
<thead>
<tr>
<th>Prior chemotherapy</th>
<th>RBC transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

Procedure type

<table>
<thead>
<tr>
<th>Procedure type</th>
<th>RBC transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal or laparoscopic</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Open abdominal procedures</td>
<td>47 (92%)</td>
</tr>
</tbody>
</table>

**Table 4** Adjusted analysis of blood transfusion and associated characteristics

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>5.74</td>
<td>3.07, 10.75</td>
<td></td>
</tr>
<tr>
<td>ASA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>1.00</td>
<td>–</td>
<td>0.056</td>
</tr>
<tr>
<td>III–V</td>
<td>1.80</td>
<td>0.88, 3.68</td>
<td></td>
</tr>
<tr>
<td>Procedure type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal or laparoscopic</td>
<td>1.00</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Open abdominal procedures</td>
<td>19.00</td>
<td>6.68, 54.00</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac surgery

Transfusion rate (%) in anaemic and non-anaemic patients (all p<0.001)

Proportion of red blood cell transfusions in pre-operatively anaemic and non-anaemic patients

Sanders et al, unpublished
Blood transfusions: poorer outcome

**Bursi et al 2009**
Vascular surgery, n=359
Incidence of 30-day death among patients who did and did not receive RBT

![Graph showing cumulative hazard over time for transfusion and no transfusion groups](image)

**Malone et al 2003,**
Trauma patients, n=15,534

**Table 4 Blood Transfusion and Risk for Mortality and ICU Admission**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blood Transfusion (n = 1,703)</th>
<th>No Blood Transfusion (n = 13,831)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>377 (22.1)</td>
<td>313 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death &lt; 24 h (%)</td>
<td>194 (11.4)</td>
<td>114 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission (%)</td>
<td>1,015 (59.6)</td>
<td>2,496 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS (mean ± SD)</td>
<td>17 ± 16</td>
<td>12 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (mean ± SD)</td>
<td>14 ± 16</td>
<td>3 ± 6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Statistical analysis: t test for continuous variables, $\chi^2$ for categorical variables, to evaluate differences between Blood Transfusion and No Blood Transfusion groups.

Transfusion associated with mortality (OR 2.83, 95%CI 1.82-4.40, p<0.001), ICU admission (OR 3.27, 95%CI 2.69-3.99, p=<0.001), ICU LOS (OR 4.37, 95%CI 2.79-5.94, p<0.001), hospital LOS (OR 6.26, 95%CI 5.78-6.74, p<0.001)
RBC transfusion and total morbidity after cardiac surgery

RBC transfusion requirements was independently associated with total morbidity: Transfusion associated with 1.28 increase in C-POMS summary score, p<0.0001.
Correction of pre-operative anaemia through non-transfusion
Delay surgery if the cause of anaemia is unclear (Goodnough, 2005, Beris, 2008).

Approx 30% patients pre-operatively anaemic

Pre-op anaemia associated with:
- increased mortality
- increased morbidity
- increased blood transfusion requirement

Blood transfusions associated with poorer outcome from surgery
Preoperative tests
The use of routine preoperative tests for elective surgery

Clinical Guideline 3
June 2003
Developed by the National Collaborating Centre for Acute Care
**Grade 1 surgery (minor)**

ASA Grade 2: adults with comorbidity from renal disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Age (years)</th>
<th>16 to 40</th>
<th>40 to 60</th>
<th>60 to 80</th>
<th>≥ 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ECG</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Full blood count</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Haemostasis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal function</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Random glucose</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blood gases</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Lung function</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- Chest X-ray may be considered if the patient has signs of other comorbidities often associated with renal disease, such as hypertension and coronary heart failure.
- Depending on the cause of renal disease (e.g., diabetes and hypertension).

**ASAw Grade 3: adults with comorbidity from renal disease**

<table>
<thead>
<tr>
<th>Test</th>
<th>Age (years)</th>
<th>16 to 40</th>
<th>40 to 60</th>
<th>60 to 80</th>
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<td>No</td>
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</tbody>
</table>

- Chest X-ray may be considered if the patient has signs of other comorbidities often associated with renal disease, such as hypertension and coronary heart failure.

**FBC only not recommended in:**

- Minor surgery ASA 1 children <16 yrs and adults <60yrs
- Grade 2 surgery (intermediate) ASA 1 children <16yrs and adults <40yrs

**Cardiovascular surgery**

**ASA Grade 1: children < 16 years**

<table>
<thead>
<tr>
<th>Test</th>
<th>Age (years)</th>
<th>&lt; 6 months</th>
<th>6 months to 12 months</th>
<th>1 to 5 years</th>
<th>5 to 12 years</th>
<th>&gt; 12 years</th>
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<tbody>
<tr>
<td>Chest X-ray</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
</tr>
</tbody>
</table>

- Dipstick urine testing in asymptomatic individuals is not recommended (UK National Screening Committee).

**ASA Grades**

Grade 1 Normal healthy patient (i.e. without any clinically important comorbidity and without a clinically significant past/present medical history).

Grade 2 Patient with mild systemic disease.

Grade 3 A patient with severe systemic disease but the disease is not a constant threat to life.

See pages 3-4 for more information.
NHS acute Trusts and Primary Care Trusts (PCTs) should ensure that there are adequate arrangements for the pre-operative assessment of patients. For planned surgery, the arrangements for pre-operative assessment should permit the diagnosis and correction of anaemia in advance of surgery and optimisation of haemostatic function peri-operatively (including discontinuation of anti-platelet drugs and haematological advice for patients on oral anticoagulation).
Enhanced recovery pathway illustrating which elements may/may not require investment and examples of potential investment and savings

**Informed decision making £+ £N**
- Pre-operative health and risk assessment £+ £N
- Patient information and expectation managed £N
- DX planning (DD) £N
- Pre-operative therapy instruction as appropriate £+ £N

**Pre-operative assessment (POA) clinic – POA nurses. Cardiopulmonary exercise testing, appropriate anaesthetic cover (should all be in place irrespective of enhanced recovery).**
- Pre-operative patient preparation eg therapy/treatment instruction.
- Joint school varies according to model pre-operative therapy instruction/advice is either brought forward as opposed to post operative or needs to be funded irrespective of ER.

**Planned mobilisation £N**
- Regular oral analgesia, paracetamol and NSAIDS £N
- Appropriate IV therapy £N
- No wound drains £−
- Catheters removed early £N

**Rapid hydration and nourishment £+**
- Avoidance of systematic opiate-based analgesia where appropriate £N

**Overall, more savings than cost implications per patient if LOS can be reduced by even as much as 2 days (£500 capacity releasing).**
- There may be increased costs for CHO energy drinks (see other box) circa £4 per patient.

---

**Referral from Primary Care**

- Optimising pre op health: haemoglobin levels £+ £N £−
- Pre-existing co-morbidities eg diabetes £+ £−

- £+ investment may be required such as blood test (FBC already routine, Hb1ac)
- additional PC clinic time or treatment to manage anaemia (iron supplements or IV iron but still less than the cost of a transfusion).

- £+ Investment may be required £N Neutral or repositioned £− Reduced costs or savings

**Admission**

- Admission on day £−
- Optimising fluid hydration £N
- CHO loading £+ £−
- Reduced starvation £N
- No/reduced oral bowel preparation (bowel surgery) £−

- CHO loading costs will vary off the shelf energy drinks less than a £1 each, buy same products through pharmacy £6 or more circa £4 per patient

**Pre-operative**

- Minimally invasive surgery £+ £−
- Use of transverse incisions (abdominal) £N £−
- No NG tube post surgery (bowel) £−
- Use of regional/LA with sedation £+ £−
- Epidural/spinal management £+ £−
- Optimised fluid management individualised goal directed fluid therapy £+ £−

- If a Doppler is used for goal directed fluid therapy, the cost is Doppler – £8,000, disposable probes are £50-£70 each.
- Technical equipment and training costs for surgery (laparoscopic) but part of national programmes and developing practice irrespective of ER.
- Regional anaesthesia may have increased drug costs eg more lignocaine ampoules.
- Spinal/epidurals are in use anyway irrespective of ER and there may be an increase in post operative management from pain care team.

**Intra-operative**

- DX on planned day £−
- Therapy support (stoma, physio) £+ £N
- 24 hour telephone follow up if required £+ £−

- Therapy support may be increased by only if there is not sufficient capacity to meet existing demand. Demand is not changing, therefore, any increase in cost is required irrespective of or if telephone follow up is provided in existing models, it has to come out of existing establishment. Cost of a mobile/dedicated phone number.

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The best therapy for pre-operative anaemia is the treatment of the underlying cause or disease and the restoration of Hb and iron indices to normal (Weiss, 2005, Goddard, 2011).

<table>
<thead>
<tr>
<th>Absolute iron deficiency (AID)</th>
<th>Anaemia of chronic disease (ACD)/Inflammation (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Disruption of iron homeostasis initiated by a cytokine-mediated immune response</td>
</tr>
<tr>
<td>Depleted iron stores</td>
<td></td>
</tr>
<tr>
<td>RBCs are small (microcytic)</td>
<td></td>
</tr>
<tr>
<td>and pale (hypochromic)</td>
<td></td>
</tr>
<tr>
<td>Cause</td>
<td>Infections, cancer, autoimmune, chronic rejection after solid organ transplant, chronic kidney disease and inflammation</td>
</tr>
<tr>
<td>Most common for gastro referral (iron deficiency, folate deficiency, vitamin B₁₂ deficiency,)</td>
<td></td>
</tr>
</tbody>
</table>
ACD

- Treatment of underlying disease
  - For example: Rheumatoid arthritis

- RBC transfusion for severe or life-threatening anaemia

- Iron therapy not indicated unless also have true iron deficiency

- Erythropoietic agents: overcorrection may be harmful

- NICE guidelines
CG114 Anaemia management in people with chronic kidney disease

### Diagnosis

**Is anaemia due to CKD?**
- Consider other causes if eGFR ≥ 60 ml/min/1.73m²

**Consider investigating and treating anaemia if:**
- Hb ≤ 11 g/dl
- Hb ≤ 10.5 g/dl in children under 2 years
- Symptoms attributable to anaemia develop

### Treatment

**Optimise iron status:**
- Before or when starting ESAs
- Before deciding whether to use ESAs in non-dialysis patients

**Iron correction should maintain**:  
- Serum ferritin > 200 μg/l  
- TSAT > 20% (unless ferritin > 800 μg/l)  
- %HRC < 6% (unless ferritin > 800 μg/l)

**Review iron dose:**
- When serum ferritin reaches 500 μg/l (should not rise above 800 μg/l)

### Maintenance

**Maintain iron levels**:  
- Serum ferritin 200–500 μg/l in both haemodialysis and non-haemodialysis patients and either  
  - TSAT > 20% (unless ferritin > 800 μg/l), or  
  - %HRC < 6% (unless ferritin > 800 μg/l)  
  (In practice likely to require i.v. iron)

**Monitor:**
- Iron status no earlier than 1 week after receiving i.v. iron and at intervals of 4 weeks to 3 months routinely  
- Hb every 2–4 weeks (induction phase) or 1–3 months (maintenance phase) during ESA therapy  
- Hb more actively after adjusting ESA dose  
- In clinical setting agreed with patient

**Adjust ESA dose and frequency:**
- If Hb above 11.5 g/dl or below 10.5 g/dl  
- Established rate of change in Hb, e.g. > 1 g/dl/month  
- Investigate cause of any unexpected change in Hb level

**Review ESA use:**
- If ESA trial, review effectiveness  
- Discuss continued use with all patients after an agreed interval

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**Iron doses**

*Correction: usually 600–1000 mg iron for adults or equivalent doses for children (single or divided dose depending on the preparation). Treat patients with functional iron deficiency with i.v. iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require i.v. iron. In appropriate circumstances, iron treatment can also be administered in the community.*

*Maintenance: dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–60 mg i.v. iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require i.v. iron.*
TA142 Epoetin alpha, epoetin beta and darbepoetin alpha for cancer treatment-induced anaemia

Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia

This guidance does not cover the use of erythropoietin analogues (epoetin alfa, epoetin beta and darbepoetin alfa) in the management of cancer-related anaemia that is not induced by cancer treatment (chemotherapy or radiotherapy).

During this appraisal the regulatory health authorities have conducted reviews into the safety of erythropoietin analogues. This guidance was produced taking the conclusions of those reviews into consideration, and should be read in conjunction with the reports published by the regulatory health authorities.

Guidance
1. Erythropoietin analogues are not recommended for routine use in the management of cancer treatment-induced anaemia, except in the circumstances described below.

2. Erythropoietin analogues are recommended in combination with intravenous iron as an option for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/100 ml or lower. The use of erythropoietin analogues does not preclude the use of existing approaches to the management of anaemia, including blood transfusion where necessary.

3. Erythropoietin analogues in combination with intravenous iron may be considered for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

4. In the circumstances outlined in 2 and 3, the erythropoietin analogue with the lowest acquisition cost should be used.

5. People who are currently being treated with erythropoietin analogues for the management of cancer treatment-related anaemia but who do not fulfil the criteria in 2 and 3 should have the option to continue their therapy until they and their specialists consider it appropriate to stop.

Implementation tools
NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA142).

- Costing statement explaining the resource impact of this guidance.

Further information
Ordering information
You can download the following documents from www.nice.org.uk/TA142:

- A quick reference guide (this document) — a summary of recommendations for healthcare professionals.
- ‘Understanding NICE guidance’ — information for patients and carers.
- The full guidance.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or ‘Understanding NICE guidance’, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1563 (quick reference guide)
- N1564 (‘Understanding NICE guidance’).
Management

- All patients should have iron supplementation both to correct anaemia and replenish body stores (B).

- Parenteral iron can be used when oral preparations are not tolerated (C).

- Blood transfusions should be reserved for patients with or at risk of cardiovascular instability due to the degree of their anaemia (C).

- Menstrual blood loss
- GI tract blood loss
- Malabsorption
- NSAIDs

IDA

Figure 2 An abbreviated flow chart of the treatment of iron deficiency anaemia (IDA). bd, twice a day; FBC, full blood count.

- Generally considered a safe, cheap and convenient method

- Pre-operative oral iron supplements taken between 2-5 weeks has been shown to increase pre-operative Hb levels (Okuyama, 2005)

- Initial rise is more rapid than with oral iron, rise in Hb at 12 wks is similar

- Oral iron for example, FeSO₄ 200 mg bd
  - Consider parenteral iron
  - Check FBC monthly

- FBC normal
  - Consider further investigation, and blood transfusion if anaemia is severe

- Continue iron for another 3 months

- Recheck FBC every 3 months for a year and then after a further year giving further iron as necessary

- Normal FBC maintained
  - No further action unless further symptoms

- No other patient known to have IDA

- Treat cause if possible

<table>
<thead>
<tr>
<th>IV iron product</th>
<th>Preparation</th>
<th>Maximum single dose (mg)</th>
<th>Duration of infusion</th>
<th>Test dose needed</th>
<th>Cost/10mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron sucrose</td>
<td>Complex ferric hydroxide with sucrose containing 2% (20mg/mL) of iron</td>
<td>200</td>
<td>1 hour</td>
<td>Yes</td>
<td>£18.70</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Complex of ferric hydroxide with dextran containing 5% (50mg/mL) of iron</td>
<td>1600</td>
<td>6 hours</td>
<td>Yes</td>
<td>£39.85</td>
</tr>
<tr>
<td>Iron Isomaltoside</td>
<td>Complex of ferric iron and isomaltoside containing 10% (100mg/mL) of iron</td>
<td>1600</td>
<td>1 hour</td>
<td>No</td>
<td>£169.50</td>
</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>Ferric carboxymaltose complex containing 5% (50mg/mL) of iron</td>
<td>1000</td>
<td>15 minutes</td>
<td>No</td>
<td>£95.50</td>
</tr>
</tbody>
</table>
The highest increase occurred 2 weeks after the start of iron therapy (Theusinger et al., 2007).

IV iron studies in orthopaedic, menorrhagia, abdominal hysterectomy, general surgical patients:
- Increase Hb
- Decrease RBC transfusions
- Increased ferritin levels

- Range of preparations, doses. Studies small numbers

Fig. 1. Changes of hemoglobin (A), ferritin (B), and erythropoietin (C) concentration over time. *P = 0.050, **P < 0.017, ***P < 0.001 versus start. iv = intravenous.
Figure 1  Percentage of iron-deficient chronic heart failure patients treated with ferric carboxymaltose or placebo reporting at least a minimally important difference in EQ-5D index score at each study time point [minimally important difference is the smallest index score change meaningful for health professionals, patients and other stakeholders, and is 0.074 (7.4%) for the EQ-5D index score].

Comin-Colet et al 2012. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a sub-analysis of the FAIR-HF study. EJH Advance access published January 31st
PREVENTT: (Preoperative intravenous iron to treat anaemia in major surgery)

A randomised double-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with anaemia undergoing major open abdominal surgery

Start recruiting patients: September 2013
Start recruiting sites now
Summary

• Pre-operatively identify anaemia and type: ACD/AI and/or IDA/FID
  
  Need to do iron studies

• Identify and treat cause of anaemia
  
  Delay surgery if necessary

• Treat anaemia
  
  Blood transfusion in life-threatening anaemia or at risk of cardiac instability
  ACD: ESA; iron therapy if also IDA
  IDA: Iron supplementation to replenish iron stores: oral or IV