ANEMIA IN THE PRE-SURGICAL PATIENT

Recognition, Diagnosis, and Management

New Insights and Concepts for the Primary Care Provider

“Anemia is a significant and modifiable risk factor for increased perioperative morbidity and mortality and should be diagnosed and treated before elective surgery.” - Irwin Gross MD, Medical Director, Patient Blood Management, Transfusion Services, Eastern Maine Medical Center, Bangor, ME
What is the unmet need in surgical patients?

Anemia is epidemic – a common complication of common diseases

• 30-60% of patients with rheumatoid arthritis
• 30-80% of patients with inflammatory bowel disease
• 30-50% of patients with chronic heart failure
• 20-40% of diabetics without overt renal failure
• 40-60% of patients with chronic kidney disease

All of these are related to iron absorption and metabolism.

Why care (more) about anemia?

Anemia is a significant modifiable risk factor in surgical patients

Prevalence of undiagnosed anemia

At least 1/3 of patients undergoing non-emergent surgical procedures have potentially treatable anemia.¹

Anemia increases perioperative morbidity and mortality

A large retrospective study of almost 8000 non-cardiac surgical patients found that the prevalence of preoperative anemia was almost 40%. Preoperative anemia was associated with a nearly five-fold increase in the odds of post-operative mortality.²

Even mild preoperative anemia (Hb 10-12 g/dL in women; 10-13 g/dL in men), is independently associated with a 41% increased risk of mortality and a 31% increase in morbidity in patients undergoing major non-cardiac surgery. Perioperative transfusion is associated with an additional increase in morbidity and mortality.³

Preoperative anemia is the most frequent predictor of perioperative transfusion⁴

A systematic review of 62 studies shows that preoperative anemia is the most frequent predictor of perioperative transfusion. Other factors include advancing age, female gender, and small body size.
Preoperative anemia diagnosis and treatment improves patient outcomes

• Improves readiness for surgery
• Reduces transfusion risk in the perioperative period
• Reduces anemia and transfusion associated morbidity and mortality
• Helps identify co-morbidities
• Effective clinical management of anemia improves patient outcomes in chronic diseases e.g., chronic heart failure, chronic kidney disease, inflammatory bowel disease, rheumatoid arthritis, etc.
• Anemia may be an indicator of an undiagnosed underlying disease process e.g., iron deficiency suggesting occult malignancy

What laboratory tests are needed for a pre-surgical anemia evaluation?

Goals of preoperative anemia laboratory test algorithm

• Allow diagnosis of common causes of anemia
• Avoid the need for patients to return for another blood sample
  • Draw CBC and sample for additional testing to “hold” for additional tests if needed
• Eliminate unnecessary lab studies

<table>
<thead>
<tr>
<th>First Tier Laboratory Tests</th>
</tr>
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<tbody>
<tr>
<td>Complete Blood Count (CBC)</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
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</table>
  • Absolute reticulocyte count
  • Reticulocyte hemoglobin content if available (a functional measure of iron status)
| Vitamin B12                 |
| Folate                      |
### First Tier Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
</tr>
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<tbody>
<tr>
<td>Iron Studies</td>
</tr>
<tr>
<td>• Transferrin Saturation</td>
</tr>
<tr>
<td>• Ferritin</td>
</tr>
<tr>
<td>• Iron</td>
</tr>
<tr>
<td>• Iron Binding Capacity</td>
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<tr>
<td>Serum Creatinine</td>
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</table>

### Second Tier Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>Thyroid Stimulating Hormone (TSH)</td>
</tr>
<tr>
<td>Direct Antiglobulin Test</td>
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<tr>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>Soluble Transferrin Receptor</td>
</tr>
<tr>
<td>Methyl Malonic Acid</td>
</tr>
<tr>
<td>Serum Protein Electrophoresis</td>
</tr>
<tr>
<td>Erythropoietin</td>
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<tr>
<td>Haptoglobin</td>
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PREOPERATIVE ANEMIA MANAGEMENT ALGORITHM

1. **Hgb is less than 13**
   - **Yes**: MCV less than or equal to 105
   - **No**

2. **MCV less than or equal to 105**
   - **Yes**: Add testing for vitamin B12 if MCV greater than or equal to 90 plus reticulocyte count, creatinine and folate
   - **No**

3. **Ferritin less than 100 ng/ml**?
   - **Yes**: Consider IV iron therapy.
   - **No**: Ferritin less than 100 ng/ml?
     - **Yes**: Consistent with iron deficiency. Consider possible sources of chronic blood loss, malabsorption, dietary deficiency, medications.
     - **No**: TSat less than 20%?
       - **Yes**: Consistent with anemia of inflammation (functional iron deficiency) or combined anemia of inflammation and iron deficiency.
       - **No**: Creatinine greater than 1.3 mg/dl or eGFR less than 60 ml/min?
         - **Yes**: Possible anemia of chronic kidney disease.
         - **No**: Consider DAT, haptoglobin, LDH to rule out hemolysis if elevated reticulocyte count. Consider acute blood loss if elevated reticulocyte count. Consider Hematology consult to rule out plasma cell dyscrasia or other primary marrow process if clinically indicated.

4. **Reticulocyte count, iron, iron binding capacity, ferritin, creatinine**
   - **Yes**: If transferrin saturation (TSat) greater than 20% and ferritin greater than 100 ng/ml and MCV less than 80 consider thalassemia or hemoglobinopathy.
   - **No**

5. **Reticulocyte count elevated**
   - **Yes**: Vitamin B12 less than or equal to 300?
     - **Yes**: Probable Vitamin B12 Deficiency.
     - **No**: Consider Vitamin B12 supplements.
   - **No**: Is there associated leucopenia, thrombocytopenia or ovalocytosis?
     - **Yes**: Consider hematology consult to rule out Myelodysplasia (MDS).
     - **No**: Consider Pre-op ESA treatment with appropriate iron supplementation.

6. **TSat less than 20%?**
   - **Yes**: Folate 1 mg daily
   - **No**

7. **Is folate less than 3.3 ng/ml**?
   - **Yes**: Rule out acute blood loss. Consider tests for hemolysis: direct anti-globulin test (DAT), LDH, Haptoglobin, Bilirubin. Consider Hematology consult.
   - **No**
Notes to Preoperative Anemia Management Algorithm:

1. If absolute iron deficiency is detected and cause is unknown, gastroenterologist or other appropriate referral to rule out malignancy as a source of chronic blood loss is indicated.\(^8\)

2. If ferritin, iron saturation values, or both or other markers of iron-restricted erythropoiesis are inconclusive, further evaluation to rule out iron deficiency or iron sequestration due to inflammation/chronic disease may be necessary.\(^8\)

3. A therapeutic trial of oral iron therapy would confirm absolute iron deficiency but may be impractical in the presurgical patient. No response to iron therapy may not rule out absolute iron deficiency because of patient non-compliance, ongoing blood (iron) losses in excess of oral iron absorption, and/or diminished gastrointestinal absorption and transport of iron due to inflammation.\(^8\)

4. Anemia in the setting of decreased transferrin saturation (< 20%) in the setting of decreased glomerular filtration rate (GFR < 60) will often respond to intravenous iron. Referral to a nephrologist may be indicated.\(^8\)

5. Additionally, iron-restricted erythropoiesis due to iron sequestration, functional deficiency, or both must be considered.\(^8\)
What anemia treatment strategies should be considered for the anemic pre-surgical patient?

Correct nutritional deficiencies

**Iron therapy**

- Choice of therapy is based on:
  - Timescale before surgery
  - Tolerance of oral iron
  - Iron status
- Consider oral iron if:
  - Adequate time (2-4 months)
  - No ongoing blood loss
  - No inflammatory process or co-morbidity
  - Normal GFR
  - Patient is tolerant
  
  NOTE: Relatively slow iron repletion with a high incidence (30-40%) of gastrointestinal intolerance; co-morbid inflammatory states reduces iron uptake. Need to re-evaluate anemia studies 4 weeks before surgery to determine effectiveness.

- Intravenous iron is the most common intervention in pre-surgical anemia
  - Better tolerated and much faster than oral iron
  - Effective—even in inflammation
  - Less expensive than ESAs
- Vitamin B12
- Folate
- Erythropoiesis Stimulating Agents (ESA)
  - When nutritional anemia has been ruled out and/or corrected
  - Use conservatively, lowest dose and shortest administration time
  - Prescribe supplemental iron throughout the course of ESA therapy to optimize pre-surgical red blood cell production and minimize ESA-induced functional iron deficiency
  - ESA therapy combined with supplemental iron may reduce the subsequent need for blood transfusion

Treat comorbidities

Delay surgery if necessary to optimize surgical outcome and reduce transfusion risk
Note: Expected hemoglobin optimization response to anemia treatment

Most patients can expect to have a hemoglobin rise between 0.5g/dL- 1.0g/dL per week with use of IV iron and or ESA therapy as per prescribing information.

<table>
<thead>
<tr>
<th>Iron Dextran</th>
<th>Iron Sucrose</th>
<th>Ferric Gluconate</th>
<th>Ferumoxytol</th>
<th>Ferric Carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name(s)</td>
<td>InFeD (Sanofi Aventis)</td>
<td>Venofer (American Regent Inc)</td>
<td>Ferrlecit (Sanofi Aventis US)</td>
<td>Feraheme (AMAG Pharmaceuticals)</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Iron deficiency in patients whom oral administration is unsatisfactory or impossible.</td>
<td>Iron deficiency anemia in adult and pediatric patients with chronic kidney disease (CKD).</td>
<td>Iron deficiency anemia in adult and pediatric patients with chronic kidney disease (CKD).</td>
<td>Iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; or who have non-dialysis dependent chronic kidney disease.</td>
</tr>
<tr>
<td>Black Box Warning</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>IV injection</td>
<td>IV injection</td>
<td>IV injection</td>
<td>IV injection</td>
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<tr>
<td></td>
<td>IV infusion</td>
<td>IV infusion</td>
<td>IV infusion</td>
<td>IV Infusion</td>
</tr>
<tr>
<td></td>
<td>IM injection (not recommended)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum FDA Approved Single Dose</td>
<td>100mg</td>
<td>400 mg</td>
<td>125mg</td>
<td>510 mg</td>
</tr>
<tr>
<td>Dosing</td>
<td>Doses less than or equal to 300 mg, slow IV push at a rate not to exceed 50 mg/minute; or diluted in 100-250 ml normal saline. For administration of a 1000mg total dose infusion, the total calculated dose should be diluted in 500 ml (range of 250 to 1000 ml) of normal saline. After a test infusion, the solution may be infused over 1 or more hours.</td>
<td>100mg IVP over 2-5 minutes; 100 mg/100ml 0.9% NS over 15 minutes; 200 mg /250ml 0.9%NS over 2-4 hours for a TDI of 1,000mg over a 14-day period. 300 mg/250ml 0.9% NS infusion over 1.5 hours. 400 mg/250 ml 0.9% NS infusion over 2.5 hours.</td>
<td>Administer 125 mg diluted in 100 ml normal saline over 60 minutes daily for 5 doses maximum per week. May need to continue to a cumulative dose of 1 gram.</td>
<td>Up to 510mg IV push in 17 seconds. However, due to free iron with the rapid infusion, it is recommended that the 17 ml injection be given in 60-90 seconds. Intravenous infusion 510mg/50-200mL 0.9%NS or 5%Dextrose over at least 15 minutes. Observe patients for signs and symptoms of hypersensitivity during and after administration for at least 30 minutes and until clinically stable.</td>
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</table>
| † When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not <2 mg of iron per mL and administer over at least 15 minutes. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute.
Adopt concept of Patient Blood Management

“The timely application of evidence based medical and surgical concepts designed to manage anemia, optimize hemostasis, and minimize blood loss in order to improve patient outcomes.” - Society for the Advancement of Blood Management (SABM.org)
References


