Preoperative Anemia and Anemia Management

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Disclosures

• Medical Advisory Committee, Strategic Healthcare Group
• No other disclosures or potential conflicts
Prevalence of Anemia

• Estimated prevalence of anemia in U.S. is (at least!) 3.5 million
• Previously undiagnosed anemia is common in elective surgical patients
• Most common underlying causes include:
  • iron deficiency
  • vitamin B12 deficiency
  • chronic kidney disease
  • other chronic inflammatory diseases
  • folate deficiency
  • Unexplained Anemia of the Elderly (UAE)
## Prevalence of Anemia in Surgery

<table>
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<th>Type of Surgery</th>
<th>Study</th>
<th>N</th>
<th>Prevalence of Anemia (%)</th>
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<td>Hip and knee replacements only</td>
<td>Gruson et al (2003)</td>
<td>395</td>
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<td>Andrews et al (1997)</td>
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<td>Bonnet et al (1997)</td>
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<td>Haljamae et al (1982)</td>
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<td>19</td>
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<td></td>
<td>Bierbaum (1999)</td>
<td>8561</td>
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<td>Halm et al (2004)</td>
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<td>Noncardiac</td>
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<td>Colorectal</td>
<td>M’Koma et al (1994)</td>
<td>32</td>
<td>22</td>
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<td></td>
<td>Cappell, Goldberg (1992)</td>
<td>315</td>
<td>Dukes A: 39.1&lt;br&gt;Dukes B &amp; C: 56.8&lt;br&gt;Dukes D: 75.8</td>
</tr>
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</table>

Preoperative Anemia: Prevalence and Outcomes

Anemia = Poorer Outcomes

• In a retrospective review of almost 8,000 consecutive non-cardiac surgical patients
  – Prevalence of anemia was almost 40%
    • Defined as Hgb < 12 g/dl for women; <13 g/dl for men
  – After adjustment for major confounders and elimination of patients who were transfused or who had severe anemia, *anemia was associated with increased mortality* (odds ratio, 2.29)

*Anesthesiology. 2009 Mar; 110(3):547-81*
Preoperative Hematocrit Levels and Postoperative Outcomes in Older Patients Undergoing Non-cardiac Surgery

- Retrospective cohort study of VA National Surgical Quality Improvement Database: 310,311 subjects, > 64 years who underwent non-cardiac surgery
- 30 day mortality and cardiac event rates increased by 1.6% for each 1% change in Hct
- Inflection point: below 39%

Therefore, pre-operative hemoglobin less than 13 g/dL associated with worse outcomes

Wu et al JAMA 2007;297:2481
Preoperative Anemia and Postoperative Outcomes in Non-cardiac Surgery

• ACS NISQIP Database study: 227,425 subjects, > 18 years; major non-cardiac surgery, excluding trauma
• 30% of patients were anemic
• Patients with even mild anemia (hgb 10 - 12g/dl in women; 10 - 13 g/dl in men experienced:
  – Higher 30 day adjusted mortality
  – Increased morbidity including cardiac, respiratory, urinary tract, wound events, sepsis and thromboembolism
• Perioperative transfusion also associated with increased morbidity and mortality
• Treatment of preoperative anemia should be strongly considered
• Transfusion is…”the least favorable option”

Musallam Lancet 2011;378:1396-407
Anemia and Risk of Perioperative Transfusion

• Systematic review of 62 studies
  – Most frequent predictor of transfusion was preoperative anemia
  – Additional predictors
    • older age
    • female gender
    • lower body mass
    • co-morbidities

Anemia and Risk of Perioperative Transfusion

Fig. 2. Probability of allogeneic transfusion only in knee and hip replacements unilateral, nonrevision, no erythropoietin. (x) Men; (□) women.

Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) Study

Transfusion 2003; 43: 459-69
Conclusions

Preoperative anemia is:

- common
- associated with increased risk of transfusion
  - Transfusion is associated with an increased risk of infection, increased length of stay and increased mortality
- associated with increased mortality independent of transfusion

Fortunately, anemia can be treated prior to elective surgery
The Case for Preoperative Anemia Management

Preoperative anemia management is an effective tool to:

• Improve a patient’s readiness for elective surgery
• Reduce the risk of allogeneic transfusion in the perioperative period
• Reduce morbidity (and mortality associated with preoperative anemia)
• Help identify co-morbidities
Elements of a Preoperative Anemia Management Program

• A preoperative anemia management program should be designed to:
  – Screen “at risk” elective surgical patients for anemia
  – Identify the common causes of anemia
  – Treat anemia in order to optimize preoperative hemoglobin
  – Identify patients with primary marrow pathology, less treatable forms of anemia or serious co-morbidities as a cause of their anemia, for referral to the appropriate specialist
  – Establish an infrastructure for an anemia clinic
Elements of a Preoperative Anemia Management Program

• Limited in scope – know when to:
  – Refer back to the PCP or a specialist
    • Unidentified source of chronic blood loss
    • Anemia secondary to previously unrecognized co-morbidity
  – Refer to hematologist for additional evaluation including marrow examination
    • Anemia where initial evaluation does not reveal cause
    • Anemia associated with abnormal cells in the peripheral smear
    • Anemia with leucopenia and/or thrombocytopenia
    • Hemolytic anemia
Elements of a Preoperative Anemia Management Program

- Method of identifying patients
  - Patients “enrolled” by the surgeons’ offices
    - Challenges to this approach
  - O.R. scheduling “event” for specified procedures
    - Potential for automatic referral using the EMR
  - Referrals by primary care providers
Establishing an Outpatient Anemia Clinic

• Develop a laboratory test algorithm – goals:
  – Diagnose common causes of anemia
  – Avoid need for patients to return for an additional blood sample except in a minority of cases
    • Chemistry tube to “hold” at the same time the CBC is drawn
  – Eliminate unnecessary lab studies - reflex protocols
    • CBC is performed (we prefer a CBC)
    • Additional studies are predicated on CBC (and other) results
    • May miss “latent” iron deficiency
Key Lab Tests for Anemia Evaluation

• **First Tier**
  – Complete blood count (CBC)
  – Reticulocyte count
    • Absolute reticulocyte count
    • Reticulocyte hemoglobin content, if available
  – Vitamin B12
  – Iron
  – Iron Binding Capacity, Transferrin Saturation
  – Ferritin
  – Creatinine

• **Second Tier**
  – Folate
  – TSH
  – Direct Antiglobulin Test
  – C-Reactive Protein
  – Soluble Transferrin Receptor
  – Methyl Malonic Acid
  – Serum Protein Electrophoresis
Hb<12 g dl\(^{-1}\) for females
Hb<13 g dl\(^{-1}\) for males

Evaluation necessary

Iron status?

SF<30 µg litre\(^{-1}\) and/or TSAT<20%
SF 30–100 µg litre\(^{-1}\) and/or TSAT<20%
SF>100 µg litre\(^{-1}\) and/or TSAT>20%

Rule out iron deficiency

Iron deficiency
Consider referral to gastroenterologist to rule out malignancy

Iron therapy
(i) Oral iron in divided doses
(ii) I.V. iron if intolerance to oral iron, gastrointestinal uptake problems (hepcidin), or short timeline before surgery

Serum creatinine
Glomerular filtration rate

Abnormal
Normal

Vitamin B\(_{12}\) and/or folic acid

Chronic kidney disease
Consider referral to nephrologist

Anaemia of chronic disease
No response

Erythropoiesis-stimulating agent therapy

Folic acid and/or vitamin B\(_{12}\) therapy

No action required

Evaluating the Patient

- Review the clinical history including the type of surgery (and the surgeon)
  - Expected surgical blood loss
  - Possible sources of recent blood loss
  - Clinical conditions associated with chronic anemia
  - Previous treatment for anemia
- Review the CBC and other laboratory results
  - Review abnormalities in WBC and platelets
- Make treatment decision
Some Logistics

- Reimbursement for use of ESAs and/or intravenous iron may be restricted by CMS coverage determinations (NCD or LCD)
- There may be a difference between the coverage determination and the “labeled” indications for the medication
Some Logistics

• Pre-printed order sets and treatment algorithms makes it easier and more efficient to manage patients
  – Include most common diagnoses with check boxes to ensure accurate documentation of medical necessity
  – Include most common treatment regimens and doses
Demographics and Diagnosis

Iron Replacement

ESA and Iron Maintenance

STEP 1: Enter demographics & diagnoses

Demographics
- **Weight:** [ ] kg (Provider: [ ] Date of Procedure: [ ])
- **Serum Creatinine:** [ ] mg/dL (Date: [ ])
- **Hemoglobin:** [ ] g/dL (Date: [ ])
- **Iron:** [ ] mg (Date: [ ])
- **Transferrin Saturation:** % (Date: [ ])

**Diagnoses for ESA Therapy**
- **Anemia unspecified (per-surgical):** [ ]
- **Anemia, deficiency specified:** [ ]
- **Anemia of chronic disease:** [ ]
- **Anemia of other chronic disease:** [ ]
- **Hepatocellular carcinoma (HCC):** [ ]
- **Hepatitis C, chronic with coma:** [ ]
- **Hepatitis C, chronic without coma:** [ ]
- **Hepatitis C, acute:** [ ]
- **Hepatitis C, viral:** [ ]
- **HIV Disease:** [ ]
- **Lupus Erythematosus:** [ ]
- **Systemic lupus erythematosus:** [ ]
- **Malignant neoplastic disease:** [ ]
- **Myelodysplastic Syndromes:** [ ]
- **Myelodysplastic Syndrome:** [ ]
- **Myelodysplastic Syndromes with Q:** [ ]
- **Myelodysplastic Syndromes without Q:** [ ]
- **Myelofibrosis with myeloid metaplasia:** [ ]

**Diagnoses for Iron Therapy**
- **Chemotherapy related anemia:** [ ]
- **Cytotoxic and mitotically active, unspecified:** [ ]
- **Iron deficiency anemia, unspecified:** [ ]
- **Iron deficiency anemia secondary chronic:** [ ]
- **Iron deficiency anemia, unspecified:** [ ]

STEP 2: Choose a treat

1. Does patient meet high criteria for
   - **Diagnosis of myelodysplasia & H:** [ ]
   - **Chemotherapy treatment & Hg:** [ ]
   - **Post-surgical patients & Hg:** [ ]

2. Ferritin < 100 mg/dL AND
   - Ferritin < 50 mg/dL AND

STEP 3: Sign all three pages

Page 1: Demographics and Diagnosis
Page 2: Iron Replacement
Page 3: ESA and Iron Maintenance
Some Logistics

- There should be clear communication back to the surgeon and to the primary care provider about the treatment plan
  - Can be done using template letters
  - If anemia is of undetermined etiology, severe, or requires delay of surgery, speak directly with the surgeon and PCP
Some Logistics

- CMS does **not** reimburse for pre-operative screening labs until 30 days prior to surgery
  - Ideal time to *screen* elective surgical patients undergoing a “high blood loss” procedure is as early as possible within the 30 day window
  - Patients with anemia between 10-13 g/dl can usually be managed within that 3-4 week window
  - More severe anemia may require more in-depth evaluation or more time
  - If a patient is known to have anemia or a co-morbidity associated with anemia, screen as early as possible
Treatment of the Patient with Preoperative Anemia

- Treatment options
  - Erythropoietic stimulating agents (ESA)
  - Intravenous iron
  - Enteric iron
  - Vitamin B12
  - Folate
  - Treatment of co-morbidities, e.g. hypothyroidism
  - Delay surgery and refer
ESAs in Treatment of Chronic Anemia and Perioperative Anemia
“Black Box” for Red Blood Cell Transfusion

WARNINGS: Increased mortality, increased risk of infection, increased risk of tumor progression or recurrence, risk of transfusion transmitted disease, circulatory overload, acute lung injury, thromboembolic events, transfusion related immunosuppression, acute allergic reactions and hemolytic transfusion reactions
Preoperative Epoetin in Major Elective Spine Surgery and Thromboprophylaxis

- RCT involving 680 patients randomized to 600 U/kg epoetin alfa weekly x 4 dose (days -21, -14, -7, and 0) vs. standard care
  - No baseline ultrasound scanning to exclude DVT
  - Only mechanical thromboprophylaxis allowed post-op
  - Doppler screening for DVT on day 4 or if symptomatic
    - Rate of all DVT (doppler plus symptomatic) was greater in the treatment group (4.7% vs. 2.1%)
    - Rate of **symptomatic** acute DVT was the same
  - Post-hoc analysis of combined PE and acute DVT identical in the two groups
  - Basis of recommendation for thromboprophylaxis

*Spine 2009; 34: 2479-85*
Cardiac and Vascular Surgery Excluded from Coverage

• 182 patients randomized to one of two dose regimens of EPO (150 or 300 units/kg) or placebo 5 days before, day of, and 2 days after CABG

• Trend toward increased mortality in the two treatment groups (p = .06)
  – 4 of the 5 deaths viewed a “possibly drug-related” due to thrombotic or vascular events
  – Two of the four deaths occurred > 3 months post-surgery
  – No deaths in the placebo group

• Basis for the FDA exclusion of CV surgery from perisurgical ESA

_D’Ambra Ann Thor Surg 1997;64:1886-93_
Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) – Created Doubts About Safety

- RCT of 1432 patients
- Compared target hemoglobin 13.5 g/dl to 11.3 g/dl
- Primary endpoint was composite of death, AMI, hospitalization for CHF, and stroke

Kaplan-Meier Estimates of the Probability of the Primary Composite End Point and Secondary End Points of Individual Components -- Hospitalization for Congestive Heart Failure (CHF) without Renal Replacement Therapy (RRT), Myocardial Infarction, Stroke, and Death
ESA and Cancer: Venous Thromboembolism and Mortality Risk in Cancer-Associated Anemia

- Meta-analysis of mortality in 51 trials involving 13,611 patients and VTE in 38 trials involving 8172 patients
- Overall odds ratio for VTE risk was 1.57
- 8 studies from 2003 - 2007 showed increased mortality or tumor progression among patients treated with ESA
  - Variety of tumors: breast, head and neck squamous cell, cervix, lung
  - All targeted hemoglobin > 13 g/dL (3 targeted Hgb > 15 g/dL)

Bennett CL et al, JAMA. 2008;299 (8): 914-924
ESA and Cancer: Venous Thromboembolism and Mortality Risk Cancer-Associated Anemia

- Meta-analysis of 60 controlled ESA trials (15,323 patients) involving cancer patients with anemia undergoing chemo and/or RT
- Included studies not in the Bennett analysis
- ESA use did not significantly affect mortality (60 studies: OR = 1.06) or disease progression (26 studies: OR = 1.01)
- VTE risk was increased (44 studies: OR = 1.48)
- Future randomized trials recommended

Glaspy J et al British Journal of Cancer 2010;102, 301-315
Conclusions: Perioperative use of ESAs, Cancer, Renal Disease, and Thrombosis

• Conclusions:
  – ESAs should be used conservatively in preoperative management of anemia in patients with malignancy or CKD
  – Use lowest dose and shortest administration period needed to avoid allogeneic transfusion
  – Consider thromboprophylaxis in patients at higher risk for thrombosis, especially oncology patients
  – Conservative use of ESAs in cardiovascular surgery
    • Use in CV surgery NOT a labeled indication
Reimbursement by CMS for ESA

• Reimbursement is governed by a National (and corresponding local) Coverage Determination (NCD)

• ESA will NOT be covered if the patient’s ferritin is < 100 ng/ml or transferrin saturation (TSat) is < 20%
  – Be sure your patients are iron replete before treating with an ESA
    • Best practice
    • Required for reimbursement
  – Give I.V. iron concomitantly with an ESA
    • Improves response rate
    • **Lower** ESA dose needed to achieve same response
CMS Requirements for Perisurgical Use of ESAs

- Anemic surgical patients must meet ALL of the following:
  - Surgery is elective; patient is iron replete
  - Surgery is non-cardiac, non-vascular
  - Patient is “at risk” for perioperative transfusions due to significant, anticipated blood loss
  - Includes patients “expected to require allogeneic transfusion, and who are not able or willing to participate in an autologous blood donation program”
  - Typical dose (600 units epoetin alfa/kg weekly on days -21, -14, -7 and 0)
  - Refer to the NCD/LCD for terms of coverage
Iron “Essentials”

- To be discussed:
  - Impact of inflammation on iron absorption, transport and metabolism
  - Intravenous iron as an adjuvant or alternative to ESA

Ferritin Molecule
What inflammation means for iron absorption and bioavailability

- Enteric iron absorption is impaired
- Release of iron from storage is impaired
- Transferrin saturation will be decreased
- Ferritin may be increased
- Erythroid (and other) cells are deprived of adequate iron and become functionally iron deficient
  - Iron deficient erythropoiesis (IDE) and anemia results
  - FID is the most common cause of “anemia of chronic inflammation”
- I.V. iron circumvents hepcidin blockade

Ganz T, Blood 2011 117: 4425-4433
The Role of Intravenous Iron in ESA Therapy

• Response to ESAs improved with concomitant intravenous iron in CKD and chemotherapy-associated anemia
  – Shorter time to response
  – Higher percentage of responders
  – 30% reduction in ESA dose to achieve same response
  – Independent of serum ferritin up to 1000 - 1200 ng/ml and transferrin saturation up to 25-30%

Enteric vs. Parenteral Iron

• Enteric iron
  – Lower cost, but slower response
  – 30-40% of patients have gastrointestinal intolerance
  – Poor absorption in many patients even if tolerated
    • H2-blockers, PPI’s atrophic gastritis, intestinal malabsorption

• If there is inflammation:
  – Enteric iron absorption is significantly impaired
  – Release of storage iron is significantly impaired
  – Erythropoietic cells become functionally iron deficient
Use of Intravenous Iron in Preoperative Anemia Management

- Intravenous iron is our most common intervention in management of preoperative anemia
  - Less expensive than ESAs
  - Few adverse events
  - Effective, even in inflammation
  - In patients with true iron deficiency, better tolerated and much faster than enteric iron replacement
    - If adequate time, no ongoing blood loss, and enteric iron is tolerated, enteric iron can be considered because of lower cost
Options for Intravenous Iron Replacement

- Formulations available in U.S. include
  - Low molecular weight iron dextran (InFeD)
  - High molecular weight iron dextran (Dexferrum)
  - Iron sucrose (Venofer) and iron gluconate (Ferrlecit)
  - Ferumoxytol (Feraheme)
    - superparamagnetic nanoparticle surround by a polyglucose sorbitol carboxymethyl ether coat, in colloidal suspension
Intravenous Iron: “Per Dose” Maximum

• Iron sucrose and iron gluconate: per infusion dose is limited
  – We limit Iron sucrose to no more than 300 mg/infusion

• Iron dextran: can be used for “total dose” iron replacement (up to 1,500 mg/infusion)
  – May be more cost effective – single clinic visit
  – Test dose recommended per FDA labeling
  – 1,000 mg can be given safely over one hour (Auerbach, ASH 2011)

• Ferumoxytol: dose (510 mg) may be given IV push over 20 seconds
Intravenous Iron: Calculating Required Dose

• Usual dose:
  – 150 - 200 mg of iron for each gm/dL deficit in hemoglobin
  – Add 500 – 800 mg to replace depleted iron stores in patients with true iron deficiency (TID)
    • TSAT < 10% regardless of ferritin OR
    • TSAT < 20% AND ferritin < 100 ng/dL
    • Alternative: \[100 – \text{ferritin (ng/ml)}\] x 10

• In patients with normal hemoglobin and decreased ferritin
  – \[100 – \text{ferritin (ng/ml)}\] x 10
Safety of IV Iron

• We generally DO NOT premedicate
• Most common reactions include allergic (flushing, pruritis, urticaria, rash) and hypotension
  – Hypotension usually associated with rapid infusion
• Few serious adverse drug events
  – Overall ADE rate reported as 3.8 per million doses (100 mg = dose)
  – Life-threatening ADE rate reported as 0.6 / million doses of iron sucrose compared to 11.3 / million doses HMW iron dextran
  – Life-threatening ADEs appear to be more common with HMW iron dextran

When Treating with Iron

• For patients with iron deficiency, expect increase in hemoglobin of 0.5 – 1.0 g/dL/week
  – Assumes adequate marrow reserve and erythropoietic “drive”
  – Iron repletion, then ESA plus iron if decreased EPO or EPO responsiveness

• Always evaluate patient for possible sources of chronic blood loss if true iron deficiency

• We usually add 1 mg oral folate daily

• We usually add 500 mg Vitamin C twice daily
  – Some data suggests improved bioavailability of administered iron by favoring pathway that keeps iron as ferritin rather than hemosiderin
Summary

• Preoperative anemia is
  – Common
  – Associated with increased perioperative morbidity and mortality
  – Associated with increased risk of transfusion

• Preoperative anemia screening and treatment
  – Identifies anemic patients
  – Allows optimization of hemoglobin before surgery
    • Use of ESAs and intravenous iron is safe and effective
  – Decreases perioperative transfusion rates
Pearls

- Iron deficiency anemia may be normocytic, not microcytic while anemia secondary to B12 deficiency may be normocytic, not macrocytic

- Anemia of chronic disease (anemia of inflammation) is due, in part, to interference with iron absorption, transport, and release, and responds to intravenous iron infusion

- When using an ESA, most patients should also receive intravenous iron. This increases the response rate and decreases the dose of ESA required
Selected References

- Bennett CL et al, JAMA. 2008;299 (8): 914-924
- Glaspy J et al, British Journal of Cancer 2010;102, 301-315
- Brookhart Ma et al JAMA. 2010;303(9): 857-864
- Transfusion 2003; 43: 459-69
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