Evolving Evidence on Anemia, Transfusion, Intravenous Iron and Patient Outcomes

A Need for Updated Intravenous Iron Coverage

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Overview

• Requested changes in the Policy Article
• Defining anemia, the “at risk” population and why they are at risk
• Prevalence of anemia – an epidemic
• Current attitude (practice)
• Anemia and the surgical patient
  – Risks
  – Management
NGS Limitations on IV Iron Use

• Requirement that patients first fail a trial of oral iron (due to intolerance or lack of efficacy) before IV iron will be covered
  – IV iron has superior efficacy and fewer ADE’s

• IV iron will not be reimbursed if co-administered with an ESA regardless of transferrin saturation or ferritin results, comorbidities such as CKD, or prior attempts to increase the TSAT to > 20%
  – Co-administration of IV iron reduces ESA use by 30% or more and may reduce number of clinic visits

• Not all IV iron preparations available in the U.S. are covered by the Policy Article

• The existence of iron deficiency independent of anemia is not recognized
Requested Changes:  
**Expanded Inclusion Criteria for Coverage**

- Eliminate requirement of “failure to respond to oral iron”
- Provide coverage for:
  - Both elective and non-elective surgery
  - Inflammatory process if documented by an hs-CRP > 4 or TSAT < 20% with elevated ferritin
  - Known IBD or RA regardless of disease activity
  - CKD, Stage 3 or higher (eGFR < 60 ml/min)
  - Chronic heart failure with ferritin <100 ng/ml or TSAT <20% regardless of hemoglobin level\(^1\)
  - Iron deficiency **without anemia** (TSAT less than 20% and ferritin < 100 ng/ml)

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\(^1\) Anker NEJM 2011
Requested Changes:

**Expanded Inclusion Criteria for Coverage of IV Iron**

- Provide coverage for:
  - TSAT <20% and malignancy
  - Ferritin <100 and TSAT <20% and total iron deficit ≥ 1,000 mg
  - Iron deficiency (TSAT < 20% and ferritin <100 and pregnancy or within 8 weeks after delivery)
  - Any patient being treated with an ESA, if transferrin saturation < 35% and ferritin < 1,200 ng/ml, including coverage for iron administered on same day as ESA
  - Obesity
  - Status post bariatric surgery
Current Qualifying ICD – 9 Codes

Diagnoses for Iron Therapy:
- Iron deficiency anemia secondary chronic blood loss [280.0]
- Iron deficiency anemia, unspecified [280.9]
- Iron deficiency anemia due to inadequate iron dietary intake [280.1]
- Personal hx of other specified digestive system diseases [V12.79]
- Postsurgical non-absorption, other and unspecified [579.3]
- Unspecified adverse effect of other drug, medicinal, and biological substance [995.29]

Renal failure unspecified [586.0]
Other:_________________________
- Chemotherapy related anemia [285.22]
- CKD, Stage 3: (mod) GFR 30 to 59 [585.3]
- CKD, Stage 4: (severe) GFR 15 to 29 [585.4]
- CKD, Stage 5: GFR less than 15 [585.5]
- Intestinal malabsorption, unspecified [579.9]
- Iron deficiency anemias, other specified [280].
Additional Qualifying Diagnosis Codes Requested

- Functional iron deficiency
- Inflammatory states, unspecified, acute and chronic
- Chronic heart failure
- Obesity
- Malignancy
- Dysfunctional uterine bleeding and related codes
- Pregnancy
- Bariatric surgery
- Iron deficiency as defined by ferritin or TSAT who do NOT have anemia
Prevalence of Anemia and Why We Need to Treat It
Age, Anemia and Iron Deficiency

- 35% of adults over the age of 65 have unexplained anemia (defined as Hgb less than 12 g/dl)
- 17% of adults over the age of 65 have iron deficiency
  - Of those with iron deficiency anemia, only 50% normalized their hemoglobin with oral iron therapy

Blood Cells Mol Dis. 2011;46(2):159
Prevalence of Iron Deficiency Anemia

• Walsh TS et al. - 35% of patients have red cell indices consistent with functional iron deficiency at ICU admission

• Lasocki S et al. Iron deficiency may affect up to 40% of critically ill patients

• Rodriguez RM et al. 9% of ICU patients were iron deficient, 2% B12 deficient, and 2% folic acid deficient

1. Walsh TS. Br J Anaesth. 2006
2. Lasocki S. Anesthesiology, 2011
Prevalence of Iron Deficiency Anemia

- 30-60% of patients with RA have anemia
- 30-80% of patients with IBD have anemia
- 30-50% of patients with CHF have anemia
- 20-40% of diabetics *without* overt renal failure have anemia
- 40-60% of patients with chronic kidney disease have anemia

All of these are related to iron absorption and metabolism
10 hospitals, from 1/09 to 08/11 188,447 Hospitalizations
Endpoints: Mortality, Charges and LOS

<table>
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<th></th>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Definition</td>
<td>&gt;11 – 12F &gt;11-13M</td>
<td>9.1 - ≤ 11</td>
<td>≤ 9.0</td>
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<tr>
<td>HAA (74%)</td>
<td>29%</td>
<td>41%</td>
<td>30%</td>
</tr>
<tr>
<td>Mort RR</td>
<td>1.0</td>
<td>1.51</td>
<td>3.28</td>
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<tr>
<td>LOS</td>
<td>1.08</td>
<td>1.28</td>
<td>1.88</td>
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<tr>
<td>Charges</td>
<td>1.06</td>
<td>1.18</td>
<td>1.80</td>
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Anemia is often “accepted” or ignored

• A long tradition of accepting anemia as a “harmless” problem that can be easily corrected with transfusion
• For the medical community transfusion as treatment for anemia remains a default position
• New paradigm: Anemia is an independent risk of morbidity and mortality regardless of the level of hemoglobin
• Transfusion as a treatment of anemia compounds the problem and increases costs
  – Cost of transfusion range from $800 to over $1200 per transfusion done through activity-based costing, excluding ANY complications of transfusion

Isbister J. Shander A. TMR 2011
Shander Transfusion 2010
Anemia—A Potent Multiplier of Mortality

Preoperative Anemia Is Associated With Postoperative Mortality

Hb < 12 g/dL for women and < 13 g/dL for men

Does Preoperative Anemia Adversely Affect Colorectal Surgery Outcomes?

- 2005-2008 - NSQIP (251 hospitals)
- CO – MI, CVA, AKI, Mortality and HLOS
- N – 23,348 – 47.4 % Anemic
- Uni, multi, logistic regression and propensity scoring

<table>
<thead>
<tr>
<th>Anemia</th>
<th>HCT</th>
<th>N</th>
<th>CO - OR</th>
<th>HLOS</th>
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<tr>
<td>None</td>
<td>(&gt;38%)</td>
<td>12,281</td>
<td>1.0</td>
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<tr>
<td>Mild</td>
<td>(30-37%)</td>
<td>9037</td>
<td>1.47</td>
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<tr>
<td>Moderate</td>
<td>(26-29%)</td>
<td>1726</td>
<td>1.87</td>
<td>1.2</td>
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<tr>
<td>Severe</td>
<td>(21-25%)</td>
<td>304</td>
<td>2.1</td>
<td>1.6</td>
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Who Gets Transfused?

• 94% of transfusions in **surgical** patients can be attributed to:
  – Low preoperative hemoglobin levels
  – Excessive (uncontrolled) surgical blood loss, and/or
  – Inappropriate transfusion practices

ALL MODIFIABLE RISKS

Anemia Management in Surgical Patients – Published Clinical Pathway

1. Surgical patients have a Hb level determination as close to 28 - 30 days before the scheduled surgical procedure

2. Patient’s target Hb be within the normal range (female ≥ 12 g/dL, male ≥ 13 g/dL) before surgery

3. Laboratory testing take place to further evaluate for nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease

4. Nutritional deficiencies be treated - including iron deficiency!

5. ESA therapy be used for anemic patients in whom nutritional deficiencies have been ruled out and/or corrected

Goodnough LT, et al. BJA 2011
Safety and Efficacy of Iron Preparations
Side Effects with Oral Iron

- Constipation and Diarrhea
- Gastric Cramping
- Metallic Taste
- Thick, green tenacious stool
- Leads to significant non-compliance!
- Oral iron is low cost but ineffective in many patients and delays effective anemia treatment

FDA MedWatch reports (2001-2003) show HMWID was associated with a 3.4-fold increase in odds of life-threatening AEs.

This analysis likely overestimates AEs with LMWID (all AEs reported by generic name only where attributed to LMWID).

In tens of thousands of patients in prospective studies SAEs with IV iron are vanishingly rare.

# Maintenance Therapy With IV vs Oral Iron in EPO-Treated Patients

<table>
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<th></th>
<th>Baseline</th>
<th>2 Months</th>
<th>4 Months</th>
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<tbody>
<tr>
<td><strong>Hct, %</strong></td>
<td></td>
<td></td>
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<tr>
<td>IV Iron</td>
<td>32.5 ±0.6</td>
<td>36.3 ±0.9*</td>
<td>34.4 ±0.7*</td>
</tr>
<tr>
<td>PO Iron</td>
<td>31.8 ±0.3</td>
<td>32.1 ±0.3</td>
<td>31.8 ±0.4</td>
</tr>
<tr>
<td><strong>EPO, U/Rx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Iron</td>
<td>7100 ±571</td>
<td>3350 ±689*</td>
<td>4050 ±634*</td>
</tr>
<tr>
<td>PO Iron</td>
<td>6750 ±419</td>
<td>7250 ±409</td>
<td>7563 ±378</td>
</tr>
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</table>

PO Iron = 200-300 mg/d; IV Iron = 200 mg/wk.  
*P<.05 compared to PO iron group.

IV Iron Improves Anemia in Women with Menorrhagia

Proportion of 477 Patients Achieving an Hgb Increase of 2 g/dL or 3 g/dL after Ferric Carboxymaltose

Proportion of patients achieving an Hgb increase of more than 2.0 g/dL or 3.0 g/dL according to treatment assignment; significant between-group differences.

*P<0.05. **P<0.01. ***P<0.001.

**DOSING**  
**Ferric carboxymaltose:** The median calculated iron deficit was 1405.5 mg (range 937–2102 mg), requiring 1–3 administrations on an individual basis at 1 week intervals.

**Ferrous sulfate:** 2x100 mg/day for 12 weeks (total 16,800 mg). Non-inferiority of ferric carboxymaltose confirmed in primary endpoint.

Treatment comparison log-rank test 0.009.

*P=0.0051; **P=0.0346.

Addition of IV Iron to EPO Increases Hgb Response in Cancer-associated Anemia

Increase in Hgb of ≥2 g/dL during the study without transfusion.

Significant difference ($P=0.0012$) between treatment arms.
Summary of Literature Review

• Superiority of IV iron over enteric iron in the management of IDA and functional IDA (iron sequestration syndromes) in multiple disease states
• Requiring a failed course of enteric iron before IV iron unnecessarily delays needed treatment and increased ADEs
• Clinical and economic benefits of concomitant use of IV iron and ESAs is demonstrated