The Importance of Pre-Surgical Identification and Management of Anemia for the CV Surgery Patient

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Credentials and Conflicts of Interest

• Pathologist (AP/CP/Tx. Med) and Director of Patient Blood Management and Pre-OP Anemia Clinic, Fairview Southdale Hospital
• AABB Standards Committee: Patient Blood Management
• Society for the Advancement of Blood Management (SABM) “Iron Corner” Expert Panel.

• Medtronic Speakers Bureau for “Rethinking Blood Conservation”
• Chief Medical Officer, Patient Readiness Institute.
Disclaimer

No off-label use of medications or commercial products will be discussed in this presentation.
What % of red cell use is believed to be avoidable?

• 20%
• 30%
• 40%
• 50%
For the patient having non-emergent high blood loss surgery there should be:

• An adequate red cell mass prior to surgery

• High predictability for bone marrow resilience/red cell regeneration capability
Objectives

• Recognize prevalence of pre-operative anemia
• Recognize impact of pre-operative anemia on post-operative outcomes
• Understand causes and diagnosis of anemia
• Understand the medical treatments for anemia
• Understand the safety of the medical treatments
• Prevalence of pre-operative anemia
Anemia

• WHO definition - Hgb < 12g/dL (f, pre-menopausal), < 13 g/dL (m)
• 20% of world population, iron deficiency most common cause
• Surgical patients US- 5-75% of patients, varies by surgery type
• Orthopedic joint replacement 25 %
• CV Surgery patients overall 40%, CABG @ 20-30 %, Valve replacement 50-65%, TAVR greater than this
Incidence of Anemia Increases With Age


N = 65,788
1980–2000
WHO anemia definition

Patients (%)

Age (years)

Men
Women

20-30
31-40
41-50
51-60
61-70
71-80
81-90
> 90

0
5
10
15
20
25
30
Pre-Operative Anemia Scope

- 5-75% of surgical patients
- 25% Joint replacement
- 20-30 % CABG
- 65% Valve replacement
- High blood loss surgeries: > 3 gm
- Transfusion variability: often 3 fold difference in surgeons doing same procedure (can be 5-95% of patients)
- Ex. elective Joint replacement Tx rate nationwide 40%, best practice @ 5%

- Overall a real, but modifiable, problem
Anemia in CV Surgery Patients:
overall 30%, CABG @ 20%, Valve replacement 50-65%

• Numbers may be even higher if using > 12 g/dL for females (STS < 13 for M and F)
• Women disadvantaged by lower Hgb cutoff in addition to lower body mass, red cell mass and blood volume
Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs

Abdullah A. Alghamdi, Aileen Davis, Stephanie Brister, Paul Corey, and Alexander Logan

TABLE 4. Statistical details of the final model (Model B)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>df</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Odds ratio</th>
<th>95% LCL</th>
<th>95% UCL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>1</td>
<td>1.15</td>
<td>0.06</td>
<td>3.15</td>
<td>2.81</td>
<td>3.53</td>
<td>&lt;0.0001</td>
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<tr>
<td>Female sex</td>
<td>1</td>
<td>0.84</td>
<td>0.07</td>
<td>2.42</td>
<td>2.02</td>
<td>2.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>1</td>
<td>0.64</td>
<td>0.11</td>
<td>2.32</td>
<td>1.53</td>
<td>2.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>1</td>
<td>0.63</td>
<td>0.09</td>
<td>1.88</td>
<td>1.58</td>
<td>2.24</td>
<td>&lt;0.0001</td>
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<tr>
<td>Nonelective surgery</td>
<td>1</td>
<td>0.64</td>
<td>0.06</td>
<td>1.90</td>
<td>1.70</td>
<td>2.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.76</td>
<td>0.06</td>
<td>2.14</td>
<td>1.91</td>
<td>2.38</td>
<td>&lt;0.0001</td>
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<tr>
<td>Body weight</td>
<td>1</td>
<td>0.93</td>
<td>0.06</td>
<td>2.53</td>
<td>2.26</td>
<td>2.83</td>
<td>&lt;0.0001</td>
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<tr>
<td>Nonislated surgery</td>
<td>1</td>
<td>0.52</td>
<td>0.07</td>
<td>1.67</td>
<td>1.46</td>
<td>1.92</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

df = degrees of freedom; LCL = lower confidence limit; UCL = upper confidence limit.

Fig. 1. Predicted probabilities with their 95 percent confidence limits.
Impact of Pre-Operative Anemia on Post-Operative Outcomes
Effect of Preoperative Anemia on CV Patients

• Pre-Surgical anemia alone is associated with increased morbidity and mortality
• Pre-Surgical anemia is the strongest predictor of need for blood transfusion
• Blood Transfusion is also associated with increased morbidity and mortality in a dose dependent manner
Risk Associated with Preoperative Anemia in Cardiac Surgery: A Multicenter Cohort Study

Keyvan Karkouti, et al; Circulation, Jan 2, 2008

Pre-Operative anemia independently associated with adverse outcomes (n= 3500, Hgb < 12.5, 7 hosp, 500 pts each, retrospective)

Association independent of transfusions

Propensity matched:
- Death = 51% increase
- Stroke = 60% increase
- Acute kidney injury\(^1\) = 80% increase
- Second most predictive variable after CPB time.

\(^1\) > 100% increase in Creatinine above normal or dialysis
Pre-op Anemia Outcomes in Non CV Surgery

Even mild preoperative anemia is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.

Incidence of Postoperative AE’s vs. Preoperative Hb Levels

AE=adverse event; Hb=hemoglobin.

Dose-Response for Transfusion & Infection in Cardiac Surgery

Effect of blood transfusion on long term survival after CV surgery

- Retrospective study; primary CABG (N=1915)
- Patients transfused and not transfused in hospital matched by propensity score
- 5-year mortality: 2x higher in transfused group
- 5-year mortality (comorbidity correction): remained 70% higher in transfused group (p<.001)

Understand causes and diagnosis of anemia
Pre-Surgical Anemia Causes

- Iron deficiency (30%)- poor diet, blood loss, impaired absorption
- Anemia of Chronic Disease (functional iron deficiency) (25%)
- Chronic Kidney Disease (15-20%)
- B 12 deficiency
- Folate deficiency
- Medication related (inhibited erythropoiesis and/or anticoagulant-associated bleeding)
- Blood loss- Recent Invasive Procedure (ex. Angiogram can have 1-2 gm Hgb loss into soft tissues *****)
- Unexplained Anemia of the elderly (UAE)

MULTIFACTORIAL
(ex. CKD + IDA + Medication components)
Anemia of Inflammation:
Functional Iron Deficiency
(decreased iron absorption and bioavailability)

- Interleukin 6, increases hepcidin production
- Impaired enteric absorption
- Impaired release of storage iron (constipated)
- Decreased transferrin, increased ferrititin
- Iron containing cells (red cells, muscle, etc)
- Iron deficient erythropoiesis
- Patients: CHF, DM, obese, autoimmune, etc...
Iron Restricted Erythropoiesis

**Figure 1.** Iron deficiency syndromes. The relationships between absolute iron deficiency, iron sequestration, and functional iron deficiency are illustrated. Patients can have ≥1 combinations that all result in iron-restricted erythropoiesis. Adapted from Goodnough LT.61

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expected hepcidin levels</th>
<th>Iron parameters</th>
<th>Iron therapy strategies</th>
<th>Potential hepcidin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute iron deficiency anemia (IDA)</td>
<td>Low</td>
<td>Low Tsat and ferritin</td>
<td>Orally or IV if poorly tolerated or malabsorbed</td>
<td>No</td>
</tr>
<tr>
<td>Functional iron deficiency (ESA therapy, CKD)</td>
<td>Variable, depending on ± CKD</td>
<td>Low Tsat, variable ferritin</td>
<td>IV</td>
<td>Antagonist (if hepcidin levels not low)</td>
</tr>
<tr>
<td>Iron sequestration (anemia of inflammation[AI], mixed anemia [AI/IDA, or AI/functional iron deficiency anemia])</td>
<td>High</td>
<td>Low Tsat, normal-to-elevated ferritin</td>
<td>IV</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Variable</td>
<td>Low Tsat, low-to-normal ferritin</td>
<td>IV</td>
<td>IV</td>
<td>Antagonist (if hepcidin levels not low)</td>
</tr>
</tbody>
</table>

Tsat = transferrin saturation; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent.

*Mixed anemia is a diagnosis of exclusion without a therapeutic trial of iron.

Adapted from Goodnough LT.61

Kathrine Frey, MD  Fairview Southdale Hospital, May 2014
Iron Deficiency - Anemia is Late Stage

• Iron depletion: near absent storage iron, no anemia, asymptomatic
• Iron deficiency without anemia - stored and blood borne iron below normal, can be asymptomatic or symptomatic (fatigue)
• Iron deficiency anemia - initially normocytic, as severity increased, microcytic...
Iron Deficiency in CV Surgery Patients

Preoperative iron deficiency increases transfusion requirements and fatigue in cardiac surgery patients: a prospective observational study.


- Iron deficiency searched for in anemic and non-anemic patients
- 100 consecutive patients, iron studies done day of surgery, 37 with iron deficiency
- IDA patients WITHOUT anemia received more blood than iron replete non-anemic patients
Iron Matters: Beyond Anemia

• Iron deplete and deficient patients will have difficulty making new red cells to replenish surgical and hospital blood loss
• Good to know who these patients are so iron stores can be replenished, pre and post OP.
• Iron important in 200+ in vivo chemical reactions, including in muscle in ATP production and oxygen storage (myoglobin)
• Iron deplete and deficient, non anemic CHF patients have improved function and QOL when iron levels restored.
Lab Testing

Initial Panel
- CBC (need more than just Hgb)
- Reticulocyte count, Reticulocyte Hgb
- Creatinine with GFR
- Serum Iron, % saturation TIBC
- Ferritin

Add on tests as needed
- CRP (i)
- Red cell folate
- Serum B12
- Soluble transferrin receptor
- LDH
- Haptoglobin
- DAT
- Differential
- blood morphology
Hb<12 g dl⁻¹ for females
Hb<13 g dl⁻¹ for males

No action required

Evaluation necessary

Iron status?

SF<30 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 tomeline before surgery

SF 30–100 μg litre⁻¹ and/or TSAT<20%

SF>100 μg litre⁻¹ and/or TSAT>20%

Serum creatinine
Glomerular filtration rate

Abnormal

Vitamin B₁₂ and/or folic acid

Normal

Chronic kidney disease

Consider referral to nephrologist

Anaemia of chronic disease

No response

Folic acid and/or vitamin B₁₂ therapy

Erythropoiesis-stimulating agent therapy

Anemias

• Iron deficiency- normocytic or microcytic, Ferritin < 100, % saturation < 20%, increased RDW, increased plts (sometimes)

• Functional Iron deficiency- normocytic, % sat < 20 %, Ferritin > 100, CRP (i) increased, medical history chronic disease/inflammation

• Renal failure associated, normocytic, Cr > 1.2, GFR 59 or <

• Thalassemia-microcytic, erythrocytosis, nl iron studies or increased iron
• Understand the medical treatments for anemia
Anemia Treatment
Safely increase Hgb 0.5-1 gm/week

• Treatment Options: IV iron, enteric iron, Erythropoietin stimulating agents (ESA’s), Vitamin B-12, folate, treat co-morbidities, delay and defer

• IV iron, effect at 1 week, max effect at 2 weeks, several doses needed (1 gram divided dose common)

• ESA action onset 4-6 days, max at 10 days, must give with iron
Conditions treated and agents:

• IDA- IV iron effect at 1 week, Iron effect, max at 2 weeks, several doses needed (1 gram divided dose common)

• Anemia of chronic disease/inflammation- IV iron and sub Q erythropoietin, EPO action onset 4-6 days, max at 10 days

• Renal failure associated- Sub Q Epo and IV iron
IRON

- **Enteric** - lower cost, slow response, 30-40% of patients have GI intolerance, poor absorption in tolerant patients (antacids, gastritis, other malabsorption, inflammatory conditions), short timeframe to surgery

- **Parenteral** - few adverse drug events. Overall 3/1M doses, life threatening 0.6/1M doses, common reactions are urticarial, flushing and hypotension
# Currently Available Intravenous Iron Preparations

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Dexferrum</th>
<th>INFeD</th>
<th>Ferrlecit</th>
<th>Venofer</th>
<th>Ferumoxytol</th>
<th>Injectafer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>American Regent, Inc</td>
<td>Watson Pharmaceuticals, Inc</td>
<td>Watson Pharmaceuticals, Inc</td>
<td>American Regent, Inc</td>
<td>AMAG Pharmaceuticals</td>
<td>American Regent, Inc</td>
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<tr>
<td>Carbohydrate</td>
<td>High-molecular-weight dextran</td>
<td>Low-molecular-weight dextran</td>
<td>Gluconate</td>
<td>Sucrose</td>
<td>Polyglucose sorbitol carboxymethyl ether</td>
<td>Carboxymaltose</td>
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<tr>
<td>Molecular weight by manufacturer (Da)</td>
<td>265,000</td>
<td>165,000</td>
<td>289,000-440,000</td>
<td>34,000-60,000</td>
<td>750,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Total-dose or &gt; 500 mg infusion</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Premedication</td>
<td>TDI only</td>
<td>TDI only</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Test dose required</td>
<td>Yes (0.5 ml)</td>
<td>Yes (25 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Iron concentration (mg/mL)</td>
<td>50</td>
<td>50</td>
<td>12.5</td>
<td>20</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Vial volume (mL)</td>
<td>1-2</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>17</td>
<td>2 or 10</td>
</tr>
<tr>
<td>Black box warning</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Preservative</td>
<td>None</td>
<td>None</td>
<td>Benzyl alcohol</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

NA = not applicable; TDI = total dose infusion

* = not approved in the United States.

Effects of Preoperative Intravenous Erythropoietin Plus Iron on Outcome in Anemic Patients After Cardiac Valve Replacement

- 75 consecutive patients- EPO + IV iron x 5 doses (2006-2011)
- 59 observational cohort

- Decreased Post op morbidity OR 0.13  p = 0.008
- Decreased in hospital mortality OR 0.16  p = 0.04
- Decreased postop renal failure OR 0.23  p = 0.03
- Decreased Transfusion rate 67 v 93%  p=0.01
- LOS (median) 10 v 15  p= 0.01

- Adjusted for Operative Risk Score, type of intervention, time on CPB, year of surgery

ESA Use

• Effective
• Check CMS guidelines -
  – Elective Hips and Knees HCTS < 39
  – Not on label for CV or vascular surgery
  – CKD Stage 3 and > and HCTS < 30 or symptomatic
  – Ending Hcts 36
  – Patient can’t be Iron deficient
  – Labs within 1 week of first treatment

• Give iron with ESA

Goodnough Transfusion 34:66-71, 1994
J Thorac Cardiovasc Surg 2001;122:741-745
Sowade Blood 1997 89: 411-418
On “warnings”

• ESA- black box
  - Increased mortality,
  - Serious cardiovascular and thrombo-embolic events
  - Increased mortality and/or
  - Increased risk of tumor progression or recurrence

• If there were a “black box” for red cell transfusion
  - Increased mortality,
  - Lung injury,
  - Circulatory overload,
  - Tumor progression or recurrence,
  - Infection
  - Thrombo-embolic events,
  - Hemolysis,
  - Renal failure and
  - Allergic reactions.
Anemia Treatment

• Standardized order sets, including coding for pharmacy approval and reimbursement

• IV iron is the most commonly used agent

• ESA use: Non CV or vascular surgery, anemia's with inflammatory or renal components, no autologous blood donation

• Patients getting ESA need DVT prophylaxis in hospital
Is anemia treatable, including in a short timeframe?

Yes – BUT!

• Requires knowing the cause
• Requires knowing the absolute surgical timeframe (flexibility to delay surgery in select cases)
• Requires evaluating the patient as early as possible
• Requires knowing more than just lab values
• Requires understanding the treatment/medication options including risks, benefits, effectiveness and reimbursement rules
• Requires a standardized approach that integrates this information and reliably outputs treatment plans, gets patients treated quickly and safely and measures the results
Patient Example

• 52 y/o female, 3 vessel CABG
• AMI 1 year ago, stents x 2, EF 20-25%, new onset angina with progression of CAD, DM
• BMI 26
• Meds: **Iron, Prilosec**, sublingual nitroglycerine, **aspirin, Plavix**, Lantus, Novolog, Humulin, digoxin, Lasix, Zocor, **metoprolol, enalpril**, isosorbide
Iron deficiency anemia, patient on oral iron, takes 5 medications inhibiting erythropoiesis. 14 days from surgery. Treated with IV iron, 3 300 mg doses.
Results

Hgb Day of surgery- 12.3 (11.7), retic % 3.7 (2.3)

Hgb Day of discharge (POD 3) 11.2
Patient Example

- 81 y/o female
- 5’2”, 140 lbs
- Primary AVR
- On Coumadin and Metprolol
- Abnormal Lab Values: Hgb 11.1, GFR 59, Ferritin 73, % saturation 11%, CRP-I 16.8
- Diagnosis: Iron deficiency anemia, stage 3 renal failure, increased inflammatory activity
Treatment, Timeframe and results

• 3 weeks to surgery
• 1 dose Erythropoietin, 3 doses Iron sucrose
• Pre- Hgb 11.1, post Tx Hgb 13.1
Patient Example 3

- 64 y/o male
- 5’8”, 180 lbs, s/p gastric bypass 14 years
- Surgery: AVR 2 endocarditis, MVR and CABG
- On Plavix, H2 blocker, 2 beta blockers, B12, oral iron and Aspirin
- AMI X 1 month with bare metal stent, chronic anemia 2 malabsorption
Patient Example

• Hgb 10.1, MCV 79, Ferritin 66, % saturation 26, retic 2.6%, had received IV iron in the hospital (3 doses)
• Treated: 4 doses Iron Sucrose over 3 weeks
• Pre-surgical Hgb 10.9
Patient Blood Management Performance Measures

- PBM-01 Transfusion Consent
- PBM-02 RBC Transfusion Indication
- PBM-03 Plasma Transfusion Indication
- PBM-04 Platelet Transfusion Indication
- PBM-05 Blood Administration Indication
- PBM-06 Preoperative Anemia Screening
- PBM-07 Preoperative Blood Type Testing and Antibody Screening
Costs

- Red cell transfusion 700-1100 $ cost/unit transfused
- Iron therapy safe and reimbursed
- ESA therapy on label safe and reimbursed
What I hoped to have you “see”

• There is a Need for Pre-Op **Blood Health** check (clearance) for non-emergent patients (3 weeks to surgery) to plan peri-operative anemia care

• Includes assuring: 1) patient’s red cell mass maximized and 2) ability to make new red cells after blood is lost (hospital anemia plan)

• Blood Health Preparedness akin to dental exam clearance for valve or PFT need for lobectomy patients- don’t go to surgery without it.
“Blood Utilization Represents the 8th highest savings opportunity for hospitals”

- Report by Premier, Oct 9, 2012
- 7.4 M case mix adjusted patients, common DRGs d/c’d from 474 hospitals
- Compared blood use in top quartile against the rest, top 10 blood use DRG’s
- If all performed as the top 25%, 1.06 M $ savings/hosp/year
- 165 M $ annually combined