Iron Metabolism and the Treatment of Anemia in Chronic Kidney Disease

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Microcytic, hypochromic red cells
Learning Objectives

• Describe the role of inflammation in limiting enteric iron absorption

• Discuss the possible role of intravenous iron and transfusion in infection

• Discuss recent trends in the use of erythropoietic stimulating agents and IV iron in the treatment of anemia associated with chronic kidney disease
Major Players in Iron Absorption and Metabolism
Hepcidin

Ferroportin 1

Fe lost by shedding of epithelial cells
Enteric Iron Doesn’t Work in Inflammation
The Central Role of Hepcidin

- Hepcidin up-regulated by inflammation
- Enteric iron absorption and release of iron from storage is impaired
- Erythroid (and other) cells are deprived of adequate iron and become functionally iron deficient – hepcidin “blockade”
  - Iron-deficient erythropoiesis even with adequate “stainable hemosiderin”

I.V. iron circumvents hepcidin blockade
Possible Mechanism for Efficacy of Parenteral Iron in Inflammation: Hepcidin, Inflammation and Iron Metabolism

J Am Soc Nephrol
18: 394-400, 2007
Iron – It’s Not Just for Hemoglobin!

- Physiologic functions of iron
  - Oxygen transport (hemoglobin)
  - Oxygen transfer (myoglobin)
    - During periods of oxygen deprivation, oxymyoglobin releases its oxygen for metabolic use
  - Numerous proteins and enzymes are iron-containing
  - Cellular respiration is iron-dependent
    - Electron transfer
    - ATP production
Classification of major iron-containing proteins

Clinical Manifestations of ID
(Not just IDA)

- Signs and symptoms are non-specific
  - Impaired myocardial function
  - Increased mortality?
  - Impaired immune function?
  - Weakness, fatigue, lethargy
  - Headache
  - Irritability
  - Exercise intolerance
  - Cognitive dysfunction
  - Pica, especially for ice (pagophagia)
  - Poor feeding
  - Restless leg syndrome
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, in some degree, to iron absorption and metabolism*
Anemia—A Potent Multiplier of Mortality


N = 1.1 million (5% Medicare sample, 1996-1997)
Anemia is often “accepted” or ignored

- A long tradition of accepting anemia as a “harmless” problem that can be easily corrected with transfusion
- For providers, transfusion as treatment for anemia remains a default position

**New paradigm**

Anemia (and possibly iron deficiency) is an independent risk factor for morbidity and mortality regardless of the level of hemoglobin

Isbister J., Shander A. TMR 2011
Shander. Transfusion 2010
Avoiding Transfusion Dependency in CKD
Prevalence of Anemia in CKD

Stage 3A: GFR 45-59
Stage 3B: GFR 30-44
Stage 4: GFR 14-29

Avoiding Transfusion Dependency in CKD

• Traditional approach has been erythropoietic stimulating agents (ESAs) with iron supplementation (often enteral)
  – Concerns have been raised: ESAs have been associated with adverse events (CHOIR, CREATE, TREAT)

• IV Iron has been underutilized
  – Iron supplementation often inadequate

• Questions:
  – What are the data on adverse events with ESA use?
  – What are the data on response to IV iron?
  – What are the data on adverse events with IV iron?
  – Can IV iron replace or reduce ESA use?
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Four Major RCTs, Published in NEJM Created Doubts on the Safety of ESAs in CKD/ESRD

- Normal Hematocrit Study (1998 – target 14 g/dl)
- CHOIR (2006 – target 13.5 g/dl)
- CREATE (2006 – target 13-15 g/dl)
- TREAT (2009 – target 13 g/dl)

- These studies may have been structured in a way that increased risks:
  - Higher target hemoglobin (> 13 g/dL)
  - Higher ESA doses
  - Inadequate iron replacement
TREAT - 2009
(Trial to Reduce Cardiovascular Events with Aranesp Therapy)

Fatal and Non-fatal Stroke (at 48 months)

HR = 1.92 (P <0.001)  Target Hgb 13.0 g/dl

Increase in hemoglobin in placebo group of > 1 g/dl

Iron supplementation?
Many of the patients in TREAT may have been iron deficient at the start of the study
– 25% had ferritin < 66 ng/dl; TSAT < 18% = iron def.

Darbepoetin may have exacerbated iron deficiency
– Can iron deficiency cause reactive thrombocytosis and an increased risk of stroke?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Darbepoetin Alfa (N=2012)</th>
<th>Placebo (N=2026)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>18–29</td>
<td>18–28</td>
</tr>
<tr>
<td>Serum ferritin (µg/liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>131</td>
<td>137</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>66–254</td>
<td>68–263</td>
</tr>
</tbody>
</table>

### Table 1. Changes in platelet count upon iron treatment (primary dataset n=307): Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th></th>
<th>Pre iron</th>
<th>Post iron</th>
<th>N</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets G/L</td>
<td>425 (153)</td>
<td>320 (101)</td>
<td>308</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>8.8 (1.4)</td>
<td>12.2 (1.7)</td>
<td>308</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocytes G/L</td>
<td>8.9 (3.3)</td>
<td>8.7 (3.2)</td>
<td>121</td>
<td>0.577</td>
</tr>
<tr>
<td>C-reactive protein mg/dL*</td>
<td>0.8 (0–15.2)</td>
<td>0.7 (0–24)</td>
<td>303</td>
<td>0.735</td>
</tr>
<tr>
<td>Ferritin μg/L*</td>
<td>6 (0–407)</td>
<td>68 (1–1920)</td>
<td>301</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin saturation %*</td>
<td>3 (0.5–49)</td>
<td>16.1 (1–98)</td>
<td>302</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Cerebrovascular Events in Congenital Heart Disease

• 162 patients
• 140 without CVA; 22 with CVA
• 41 patients had iron deficiency anemia secondary to phlebotomy, GI hemorrhage or menorrhagia
• 26% (11/41) in the iron deficiency group vs. 9% (11/121) in the non-iron deficiency group had a CVA (p = 0.004)
• Very strong association between iron deficiency and a history of cerebrovascular event

Ammash et al. JACC Vol 28, No.3 1996: 768-772
Ischaemic Strokes in Patients with Pulmonary Arteriovenous Malformations and Hereditary Hemorrhagic Telangiectasia: Associations with Iron Deficiency and Platelets (Shovlin et al, 2014)

Lower stroke-free survival in iron deficiency group

Serum iron > 19 umol/L

Serum iron < 8 umol/L

doi:10.1371/journal.pone.0088812.g002
What Can We Conclude from TREAT?

- Hgb target of 9-11.5 gm/dl does not increase CV events or deaths. *(placebo group received rescue darbepoetin for Hgb < 9 g/dl)*
- The natural history of anemia in CKD is not inexorable worsening
- Iron deficiency in CKD is common and plays a significant role in anemia
- Many patients in TREAT were *overtly iron deficient*
- Iron deficiency may relate to thrombosis (arterial and venous)
- Use lowest ESA dose possible to avoid transfusion
- **Treatment with iron can raise Hgb and delay, defer, or reduce ESA requirements**
But We Knew that Intravenous Iron Could Help Before the TREAT Trial!
Dialysis Patients’ Response to IV Iron with Elevated Ferritin: The DRIVE Study

- Included patients with **Hgb <11 g/dl, TSAT <25%** and **Ferritin 500-1200 ng/ml (n=134)**
  - Remember: interquartile TSAT range in *TREAT* was 18-29%
  - All patients on stable EPO dose of > 225 IU/kg/week
- Randomized to no iron vs. ferric gluconate 125 mg I.V. for eight dialysis sessions + 25% increase in EPO dose in both arms
- **Faster response and greater magnitude of response with I.V. iron**
- **Response similar for Ferritin ≤ 800 or > 800 ng/ml**
- **Response similar for TSAT above or below 19%**
- **Reticulocyte hemoglobin content fell in control group suggesting worsening iron deficient erythropoiesis**

*J Am Soc Nephrol 18: 975-984, 2007*
DRIVE Study Results

Patients in the IV iron group had a larger and more rapid hemoglobin response and required less ESA after the fixed dose period.
• **Questions:**
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  – **What are the data on adverse events with IV iron?**
  – Can IV iron replace or reduce ESA use?
Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

- Reported on **IV iron dose and clinical outcomes** in 32,435 HD patients from 2002-2011
- **Evaluated mortality as it related to average iron dose/month over first 4 months**
- Case mix adjusted mortality was assessed
  - Higher mortality for ave. dose > 300 mg monthly if Hgb > 10 g/dl
  - Higher mortality for ave. dose > 400 mg monthly regardless of Hgb
- **Patients who received higher iron dose also received higher average ESA dose** – approximately 50% higher ESA dose

HR for mortality. Median (interquartile range) follow-up time was 1.7 years (1.0-2.4)
The importance of iron in long-term survival of maintenance hemodialysis patients treated with epoetin-alfa and intravenous iron: analysis of 9.5 years of prospectively collected data

Best Survival:
Low EPO
High TSAT

Worst Survival:
High EPO
Low TSAT

Iron Administration and Infection: Data

- **EPIBACDIAL Study:** No association between IV iron and bacteremia or between ferritin level and bacteremia in 988 dialysis patients (Hoen).

- **RCT of effects of enteral iron on risk of infection in surgical critical illness:** No increased risk but reduction in transfusion (Pieracci).

- **Non-randomized study comparing 302 CT surgery patients receiving IV iron vs. 561 receiving no IV iron:** No difference in infection rates (Hoen et al., J Am Soc Nephrol 1998; 9: 869-876; Pieracci FM et al. Surgical Infections 10:1, 2009; Torres S et al. Surgical Infections 7:4, 2006*)
HR for mortality. Median (interquartile range) follow-up time was 1.7 years (1.0-2.4)
DOPPS did not report on, nor adjust for, transfusion

Could those patients receiving higher iron doses and more ESA be those patients who were refractory to therapy and had greater exposure to red cell transfusion?
Proposed mechanistic pathway (the “iron hypothesis”) explaining how transfusion of older stored RBCs may induce adverse effects in patients. Transfusion of stored, but not fresh, RBCs delivers an acute bolus of RBCs and RBC-derived iron to the monocyte/macrophage system, resulting in oxidative stress and inflammatory cytokine secretion. Some of the macrophage-ingested iron is also released back into the circulation (ie, NTBI), where it can also cause oxidative damage and enhance bacterial proliferation. SIRS, systemic inflammatory response syndrome. Reprinted from Hod et al6 with permission.

The pooled risk of all serious infections was **11.8% in the restrictive group** and **16.9% in the liberal group**.

For trials with a restrictive **hemoglobin threshold < 7 g/dl**, the RR was 0.82 with **NNT of 20 to prevent one hospital acquired infection**.
• **Questions:**
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Response to I.V. Iron in CKD

- 100 non-dialysis patients treated with **1,000 mg iron sucrose alone – no ESA**
- 70% of patients with initial Hgb <10 gm/dl
- **Hgb increased by > 1 gm/dl in 48% of patients**
  - 63% response w/o marrow Fe
  - 30% response w/marrow Fe
  - 26% attained Hgb > 11 gm/dl
  - PPV was 76% for TSAT < 15%
- Chance of response increased **7% for each 1% decrease in TSAT**
- **Recommendation by authors: therapeutic intravenous iron trial for non-dialysis CKD with anemia**

Trends in Anemia Care in Older Patients Approaching End-Stage Renal Disease in The United States (1995-2010)

Iron Therapy

Trends in Anemia Care in Older Patients Approaching End-Stage Renal Disease in The United States (1995-2010)
Trends in Anemia Care in Older Patients Approaching End-Stage Renal Disease in The United States (1995-2010)

- 39% received no treatment
- 72% of patients receiving an ESA received no iron
- 57% of transfused patients received no anemia treatment other than transfusion!
- Overall, 87.7% received no iron
We Must Do Better!