Iron Deficiency in Donors: How to Assess and Prevent it?

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Blood Systems

Established in Phoenix, Arizona USA in 1943
Provides blood to ~800 hospitals in 24 states
In 2015 collected ~1.25 million RBCs and ~310K apheresis platelets
US Statistics & Information

- 6.85M volunteer blood donors
  - 67.6% repeat donors
  - ~35% may be iron deficient

- 13.6M allogenic whole blood or RBCs
  - ~1999 transfusion levels due to PBM

- With each donation 200-250mg of iron is lost.
US Statistics & Information

• ~13% potential donors deferred for <12.5g/dL Hb standard
  – Low Hb = 51.8% of deferrals
  – Low ferritin = 1.2% of deferrals

• Deferrals:
  – 8wks whole blood
  – 16wks 2RBC
RESULTS:

• Post Hb varies with pre-donation Hb & EBV - 1.3 to 2.7 g/dL

• Hb levels dip for 1-2 wks

• Hb levels return 3-4 wks after bleeding

**Solid lines** = bled about a pint

**Dotted line** = not bleed control
Hemoglobin concentration in a 47yo repeat O+ male donor

Ferritin = 10
Iron = 49
TIBC = 346
%Sat = 14
Global Burden of Anemia

- According to WHO, global anemia prevalence is 33%
  - Highest in young children, women, elderly
  - Most common malnutrition, affecting >2 billion.

- Anemia is common, symptoms are vague and often overlooked or neglected
  - Even mild anemia can associated with increased risk of morbidity and mortality

- Anemia is often considered a “normal reaction to aging”
Iron Deficiency Anemia

Development of IDA depends on:
- dietary availability
- altered iron absorption due to dietary composition (e.g. phytate or phenolic compounds)
- age and gender
- environmental factors (e.g. oxygen levels)
- blood loss

WHO Definition (healthy persons):
- <13 g/dL in men
- <12.0 g/dL in women
- <11.0 g/dL in pregnant women

Prevalence of Anemia in the General Population Worldwide

50% IDA
Iron deficiency anemia

42% ACD
Anemia of Chronic Disease

Development of ACD depends on:
- acute infection (e.g. malaria)
- chronic infection (e.g. tuberculosis, HIV)
- inflammation (e.g. rheumatoid arthritis)
- cancer

Development of other anemia subtypes depends on:
- micronutrient deficiencies (e.g. Vit A, Vit B12, folate, riboflavin or copper)
- genetic alterations (e.g. iRIDA)
Body Iron Storage

Duodenum (average, 1 - 2 mg per day)

Dietary iron

Plasma transferrin (3 mg)
Body Iron Storage

- Heme-like enzymes & Iron-sulfur proteins

- Duodenum (average, 1 - 2 mg per day)
- Dietary iron: <2%
- Plasma transferrin (3 mg)
Body Iron Storage

- **Heme-like enzymes & Iron-sulfur proteins**
- **Duodenum (average, 1-2 mg per day)**
  - **Utilization**
  - **Dietary iron** <2%
  - **Utilization**
- **Muscle (myoglobin) (300 mg)** ~72%
- **Plasma transferrin (3 mg)** ~6%
- **Circulating erythrocytes (hemoglobin) (1,800 mg)** ~66%
- **Bone marrow (300 mg)**
Body Iron Storage

~72%
Active Reserve

Muscle (myoglobin) (300 mg)

~6%
Duodenum (average, 1 - 2 mg per day)

~25%
Storage iron

~6%
Plasma transferrin (3 mg)

~66%
Circulating erythrocytes (hemoglobin) (1,800 mg)

<2%
Dietary iron

~66%
Utilization

Bone marrow (300 mg)

~72%
Utilization

Liver
Male ~750mg
Female ~300mg

Blood Systems
Iron – Daily iron need

• 90% of daily iron needs obtained from endogenous sources

• Increased in infants, children, adolescents, & during pregnancy

• WHO recommends 60mg iron per day in adults due to anemia prevalence

Hurrell R et al. AJCN 2010.
Iron – Daily iron loss

• No physiologic mechanism for iron excretion

• Obligatory iron loss in skin, intestines, urinary tract, airways

• Other blood loss: menstruation, pathology, iatrogenic, & blood donation

Iron – Dietary support

• Average iron absorption is 2-3mg/day
  – The daily iron intake is 11-18mg in a typical western diet (10-20% ingested and used)

• Two types of dietary iron:
  – **nonheme iron**: absorption a balance between inhibitors v enhancers, iron status
  – **heme iron**: 10-15% of total iron intake, but >40% total absorbed iron & up to 2/3 average person’s total body iron stores. Iron status has less effect on absorption.

• Iron bioavailability depends on many factors
  – 14-18% mixed diet, 5-12% vegetarian diet
  – Inhibitors and enhancers can affect absorption >10x

Hurrell R et al. AJCN 2010.
Iron Absorption Co-factors
dose dependent, starting at low conc (2-10mg/meal)

Inhibitors
- Phytate (plant, legumes, cereals)
- Polyphenols (tea -black & herbal, coffee, wine, cocoa)
- Proteins (casein, whey, albumin, soybean)
- Calcium ? limited effect with mixed diet
- Spices (e.g. oregano)
- Infection/Inflammation
- Fortified elemental iron < native food iron
- Food preparation (time and temperature)
Iron Absorption Co-factors
dose dependent, starting at low conc (2-10mg/meal)

Enhancers

• Ascorbic acid & Citrate (chelation overcomes inhibitors)
• Muscle tissue (↑ nonheme uptake 2-3x)
• Fermented vegetables and soy sauce
• Iron status affects non-heme > heme

• Vitamin A and riboflavin deficiencies
A. Enterocyte

- Fe-reductase
- DMT1
- Fe-oxidase
- Ferroportin
- Ferritin
- Hemosiderin

Liver

Intestine

Transferrin

Fe-TF

Ferritin

Bone marrow

Erythrocytes

Blood Systems
Ferritin
Hemosiderin
Transferrin
Hepcidin
Erythroferrone

Blood Systems
What we now know

Non-Anemic Iron deficiency

Fatigue
Decreased exercise capacity
Non-Anemic Iron deficiency

Fatigue
Decreased exercise capacity

PICA
When what you crave is not fit for human consumption
Non-Anemic Iron deficiency

Fatigue
Decreased exercise capacity

PICA
When what you crave is not fit for human consumption

Restless leg syndrome
Non-Anemic Iron deficiency

Fatigue
Decreased exercise capacity

Decreased cognitive function
And school performance

PICA
When what you crave is not fit for human consumption

Restless leg syndrome
Non-Anemic Iron deficiency

Fatigue
Decreased exercise capacity

Decreased cognitive function
And school performance

Restless leg syndrome

75% teenage F
17% teenage M
DO NOT MEET RDA FOR IRON

PICA
When what you crave is not fit for human consumption
Many preparations of oral iron are used to treat anemia. No evidence one is better than the other.

<table>
<thead>
<tr>
<th>Ferric pyrophosphate</th>
<th>Ferrous fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous bisglycinate</td>
<td>Ferrous carbonate, anhydrous</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Carbonyl iron</td>
</tr>
<tr>
<td>Ferrous sulfate (cost effective)</td>
<td>HIP: Heme-iron polypeptide</td>
</tr>
<tr>
<td>Ferrous sulfate, dried</td>
<td>(well-tolerated, high cost, ?? effectiveness)</td>
</tr>
</tbody>
</table>

Iron absorption occurs at the duodenum and proximal jejunum:

- Extended release capsules or enteric coated capsules get absorbed lower parts of the GI tract and are not very effective.
- Iron salts should not be given with food because the salts bind the iron and impair absorption.
Ironically…
a word about multivitamins in US

• Available since early 1940s
  – > 1/3 of all Americans take them ($5.7B in 2014).
• The RDA for iron is 18mg
  – Not all multivitamins contain iron (children toxicity concern)

https://ods.od.nih.gov/factsheets/MVMS-HealthProfessional/
Summary so far

• Iron deficiency anemia is the most prevalent anemia worldwide.
  – Diet, genetics/demographics, and physical attributes influence iron absorption greatly.

• During donation 200-250mg iron is removed.
  – 25% of male iron stores (700mg) but 75% for female iron stores (300mg)
  – lost iron may not be restored during normal deferral periods.
Summary so far

• Since anemia is a late manifestation of iron deficiency, Hb is not sensitive enough to predict the early stages of iron depletion.

• How can donors be protected against becoming iron depleted?

• Are there tests we can use to better predict iron deficient and those with true iron deficiency anemia?
How to Assess?

Laboratory tests

- Newer RBC indices (CHr, HYPOm, %HYPOm) *6hr window*

- Serum Iron, TIBC, & % Transferrin Saturation
  - Lack specificity and some assays lack standardization

- Traditional RBC Indices (low MCV, MCH, MCHC) *occur late*

- Hemoglobin values

- Liver biopsy

Kiss JE. Clin Lan Med. 2015
How to Assess? Laboratory tests

- Soluble Transferrin Receptor (sTfR) & Soluble Transferrin Receptor/Ferritin ratio ("R/F" ratio)

- Serum (or Plasma) Ferritin – good sens/spec
  - ? Role of Hepcidin
  - Hb1c versus glucose testing in Diabetes

- Zinc Protoporphyrin (ZPP)

- Hepcidin??
How to Assess? “Red Cell-omics”

- **HFE polymorphisms** (C282Y, H63D): affects hepcidin regulation and are common (~34%) in Caucasian population and may be enriched in blood donor population in US (including in African American donors)

- **Transferrin**: Affects TIBC. Polymorphism (G227S) may predispose to iron deficiency
How to Assess? “Red Cell-omics”

- **TMPRSS6** (A736V, SNPs rs855791): membrane associated serine protease that mediates changes in hepcidin expression
  - A736V associated with higher Hb levels in repeat donors

- **Hypoxia inducible factor [HIF]-1-alpha**: increases erythropoietin and suppresses hepcidin. Polymorphism (P-582-S) maybe protective.
Summary so far

- There are many potential tests for predicting iron depletion and iron deficiency anemia.
  - There is overlap in normal and affected populations.
  - Combining assays ↑specificity, but ↓sensitivity.
  - Hepcidin, ZPP, & ferritin show promise.

- Red cell-omic studies are interesting, but may not be realistic donor screening tools at this time.

- How to protect donors against iron depletion?
Iron deficiency in blood donors has been of international interest for ≥21yrs

- Many donors have low iron stores (P-ferritin ≤30 mg/L and lower).
  - 10% of first time donors already had subclinical iron deficiency.

- Many of the assays have been used to evaluate donors.

- Fe supplements have been used to improve iron stores
  - Maximal iron absorption ~4.1 mg/day male, ~3.55 mg/day female
Iron balance in first time blood donors shows a predictable decline following subsequent donations

- 54 newly recruited donors
- ≥4 donations (450mL each) ≥10wk apart in 1yr.
- Hb, reticulocyte Hb content (CHr), serum ferritin, soluble transferrin receptor, & CRP
- Majority also tested for serum hepcidin and serum EPO.
Iron balance in first time blood donors shows a predictable decline following subsequent donations.
Iron balance in first time blood donors shows a predictable decline following subsequent donations.

Figure 2: Changes of Serum Hepcidin following repetitive Blood Donation

REDS-II Donor Iron Status Evaluation

DESIGN: Prospective study evaluating AIS, IDE, and Hb deferral

• Evaluate effects of donation intensity on Fe & Hb
• 2425 ≥18yo Successful whole blood or RBC donors
• For 2yrs, first time & reactivated (no donations in 2 years) donors compared v frequent donors
  – (M ≥3, F ≥2 donations in past year)
• Baseline & final questionnaires plus ferritin, soluble transferrin receptor (sTfR) and Hb determined.
• Selected interim additional testing was performed based on available funds.
• HFE C282Y and H63D and transferrin G277S mutations also determined
REDS-II Donor Iron Status Evaluation

AIS (P-ferritin <12ng/mL), IDE ([log (sTfR/Ferritin)] ≥ 2.07)

<table>
<thead>
<tr>
<th>Donor Cohorts</th>
<th>AIS % Initial/Final</th>
<th>IDE % Initial/Final</th>
<th>Hb deferral % (&lt;12.5g/dL) Initial/Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>181 FT/RA women</td>
<td>5/20</td>
<td>22/51</td>
<td>11/25</td>
</tr>
<tr>
<td>149 FT/RA men</td>
<td>0/8</td>
<td>3/20</td>
<td>1/5</td>
</tr>
<tr>
<td>486 Frequent women</td>
<td>27/28</td>
<td>66/62</td>
<td>22/25</td>
</tr>
<tr>
<td>512 Frequent men</td>
<td>16/18.5</td>
<td>49/47</td>
<td>5/10</td>
</tr>
</tbody>
</table>

- % donors returned: 75% FT/RA and 97% frequent donors
- Ave F/M donations: 2.6/2.9 FT/RA & 4.4/5.2 frequent donors
- OR of 5-9x for AIS or IDE if donated >4 red cells in last 2 years
- Reduced risk of iron depletion in smokers
Predicting blood donors with absent iron stores (Hb, Age, RBC donation, ferritin <12ug/L)

<table>
<thead>
<tr>
<th>Donor and Donation Characteristics</th>
<th>MALE (n=1155) OR (95% CI)</th>
<th>FEMALE (n=1074) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL) (Reference: 15.5-26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.5-13.4</td>
<td>80.8(31.1-209.7)</td>
<td>65.3(15.6-273.3)</td>
</tr>
<tr>
<td>13.5-14.4</td>
<td>12.6(6.5-24.4)</td>
<td>15.4(3.7-64.4)</td>
</tr>
<tr>
<td>14.5-15.4</td>
<td>4.2(2.2-8)</td>
<td>8.1(1.9-34.3)</td>
</tr>
<tr>
<td>Age (years) (Reference: 50-64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-18</td>
<td>3.2(1.1-9.6)</td>
<td>2.8(1.2-6.4)</td>
</tr>
<tr>
<td>19-22</td>
<td>1.6(0.5-5)</td>
<td>3.3(1.7-6.6)</td>
</tr>
<tr>
<td>23-49</td>
<td>1.4(0.8-2.5)</td>
<td>2.4(1.5-3.6)</td>
</tr>
<tr>
<td>=&gt;65</td>
<td>0.4(0.2-0.98)</td>
<td>1.5(0.8-2.7)</td>
</tr>
<tr>
<td># of Prior RBC donation in the past 2 years (Reference: 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.4(0.04-3.7)</td>
<td>1(0.4-2.1)</td>
</tr>
<tr>
<td>2-3</td>
<td>4.2(1.4-13.1)</td>
<td>3.1(1.6-5.7)</td>
</tr>
<tr>
<td>4-5</td>
<td>4.6(1.5-13.9)</td>
<td>4.5(2.4-8.5)</td>
</tr>
<tr>
<td>6-9</td>
<td>7.8(2.7-22.3)</td>
<td>5.5(2.9-10.6)</td>
</tr>
<tr>
<td>10+</td>
<td>12(3.6-40.7)</td>
<td>13(3.2-52.8)</td>
</tr>
</tbody>
</table>

Table: Multivariable logistic regression analysis on factors associated with absent iron stores

22% v 52%
Predictors of Hb recovery or deferral in blood donors after an initial successful donation

DESIGN:

• 135,0040 FT successful donors who donated at least one more time over a 3yr period.
• Looked at factors associated with Hb recovery that blood center routinely collects already
  – (Hb, age, sex, donation interval, donation type)

RESULTS:

• Whole blood 83%, 2RBC 16%, MC (+RBC) 1%
• 5% deferred for low Hb on next presentation
• Males (45-49%) > Females (31-40%) recovered
Donors with low Hb recover faster than donors with high Hb

BSI data August 2009 to July 2012
## Hemoglobin recovery proportion and median recovery time by gender and donation type

<table>
<thead>
<tr>
<th></th>
<th>WB</th>
<th>Multi-Component</th>
<th>2RBC</th>
<th>All Firsttime Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Total Donors (N)</td>
<td>48,106</td>
<td>64,241</td>
<td>726</td>
<td>516</td>
</tr>
<tr>
<td>Did not recover (n)</td>
<td>24,411</td>
<td>38,371</td>
<td>368</td>
<td>339</td>
</tr>
<tr>
<td>Recovered (n)</td>
<td>23,695</td>
<td>25,870</td>
<td>358</td>
<td>177</td>
</tr>
<tr>
<td>Donors who recovered (%)</td>
<td>49</td>
<td>40</td>
<td>49</td>
<td>34</td>
</tr>
<tr>
<td>Median recovery time (days)</td>
<td>140</td>
<td>147</td>
<td>119</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>126</td>
<td></td>
<td>182</td>
</tr>
<tr>
<td>Median recovery time (weeks)</td>
<td></td>
<td></td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>18</td>
<td></td>
<td>26</td>
</tr>
</tbody>
</table>
Factors associated with not recovering

- Interdonation interval <24wks
- Female
- African American
- Native American
- Age 16-18 & ≥65
- BMI ≥40kg/m2

**TABLE 2. Factors associated with Hb recovery by collection type**

<table>
<thead>
<tr>
<th>Donor and donation characteristics (reference group)</th>
<th>WB</th>
<th>2RBC</th>
<th>MC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Male</td>
<td>5.1 (4.9-5.3)†</td>
<td>5.3 (4.8-6.0)†</td>
<td>5.7 (3.9-8.4)†</td>
</tr>
<tr>
<td>Interdonation interval (24 to &lt;36 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>0.8 (0.78-0.84)‡</td>
<td>0.2 (0.09-0.35)†</td>
<td>0.8 (0.52-1.16)‡</td>
</tr>
<tr>
<td>8 to &lt;16</td>
<td>0.9 (0.67-0.95)†</td>
<td>0.8 (0.47-1.27)</td>
<td>0.8 (0.47-1.27)</td>
</tr>
<tr>
<td>16 to &lt;20</td>
<td>0.8 (0.80-0.88)‡</td>
<td>0.8 (0.76-0.91)‡</td>
<td>1.0 (0.58-1.72)</td>
</tr>
<tr>
<td>20 to &lt;24</td>
<td>1.2 (1.1-1.22)†</td>
<td>1.2 (1.12-1.36)†</td>
<td>1.3 (0.75-2.26)</td>
</tr>
<tr>
<td>36 to &lt;52</td>
<td>1.3 (1.21-1.33)†</td>
<td>1.4 (1.27-1.53)†</td>
<td>1.1 (0.70-1.81)</td>
</tr>
<tr>
<td>≥52</td>
<td>1.4 (13.4-14.9)†</td>
<td>6.6 (5.4-6.9)†</td>
<td>6.5 (5.9-7.2)†</td>
</tr>
<tr>
<td>Index Hb (≥15 g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.5-13.2</td>
<td>14.1 (13.4-14.9)†</td>
<td>9.9 (5.8-17.0)†</td>
<td>1.1 (1.1-1.2)†</td>
</tr>
<tr>
<td>13.3-14.4</td>
<td>6.6 (6.3-6.9)†</td>
<td>4.8 (3.1-7.2)†</td>
<td>1.1 (1.0-1.2)†</td>
</tr>
<tr>
<td>14.5-15.4</td>
<td>3.0 (2.9-3.1)†</td>
<td>2.3 (1.7-3.3)†</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>1.1 (1.1-1.2)†</td>
<td>1.1 (1.0-1.2)†</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>Race (white)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black-African American</td>
<td>0.6 (0.59-0.67)‡</td>
<td>0.7 (0.57-0.75)‡</td>
<td>0.5 (0.25-0.91)†</td>
</tr>
<tr>
<td>Native Indian-Alaskan</td>
<td>0.8 (0.75-0.88)‡</td>
<td>0.9 (0.71-1.07)</td>
<td>0.5 (0.19-1.17)</td>
</tr>
<tr>
<td>Asian-Pacific Islander</td>
<td>0.9 (0.88-1.01)†</td>
<td>1.0 (0.85-1.25)</td>
<td>0.5 (0.23-1.29)</td>
</tr>
<tr>
<td>Other</td>
<td>1.0 (0.93-1.02)</td>
<td>1.0 (0.91-1.11)</td>
<td>1.07 (0.7-1.6)</td>
</tr>
<tr>
<td>Age (23-49 years old)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-18</td>
<td>0.9 (0.9-0.95)‡</td>
<td>0.96 (0.89-1.03)</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>19-22</td>
<td>0.95 (0.90-0.99)‡</td>
<td>0.89 (0.83-1.04)</td>
<td>1.3 (0.8-1.9)</td>
</tr>
<tr>
<td>25-29.99</td>
<td>1.06 (1.01-1.11)†</td>
<td>0.9 (0.8-0.98)‡</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>50-64</td>
<td>1.0 (0.9-1.11)</td>
<td>0.7 (0.6-0.9)‡</td>
<td>0.7 (0.2-1.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>0.8 (0.76-0.90)‡</td>
<td>0.8 (0.6-0.9)‡</td>
<td>0.7 (0.2-1.9)</td>
</tr>
</tbody>
</table>

* The OR for each reference group is 1.0. Final model for WB and 2RBC included blood center as a significant factor (results not shown).
† Significantly increased odds of recovery.
‡ Significantly decreased odds of recovery relative to each listed reference group.
HEmoglobin and Iron Recovery Study
(Oral Iron Supplementation After Blood Donation)

DESIGN:

• 203 successful whole blood & red cell repeat 18-79yo
  – Randomized to receive 37.5mg elemental iron (Fe gluconate) daily or not for 24wks.
  – Stratified by low (<26ng/mL) or high (>26ng/mL) ferritin levels
  – Paid 25$ per visit

• Outcome determined by time to recovery of 80% of postdonation decrease in Hb
**HEmoglobin and Iron Recovery Study**
(Oral Iron Supplementation After Blood Donation)

**RESULTS:**

- Baseline Hb similar in both groups with similar post-donation decline in Hb
  - Low ferritin = 13.4 to 12.0 g/dL
  - High ferritin = 14.2 to 12.9 g/dL

- Those who received iron had shortened recovery: 76 v 168 days
  - 68% of participants who didn’t receive iron did not recover in 168 days

HEmoglobin and Iron Recovery Study (Oral Iron Supplementation After Blood Donation)

RESULTS:

- Ferritin decreases by about 30ng/mL over 30 days following 500mL donation
  - Reconstitution of storage iron did not occur till after recovery of Hb (~84 days in no-iron higher ferritin group)
  - Without supplementation, there is wide variation in the rate of Hb and ferritin recovery
  - Even in iron replete donors, mean recovery was only 70% at 8 weeks, the current deferral period for US and Canada.

Mean Time to 80% of Recovery by Quartile of Ferritin and Treatment Assignment

Figure 4. Mean Time to 80% Hemoglobin Recovery by Quartile of Ferritin and Treatment Assignment

- **No iron**
  - Ferritin quartile, ng/mL
    - 51-192: 24
    - 29-50: 22
    - 16-28: 23
    - 4-15: 29

- **Received iron supplements**
  - Ferritin quartile, ng/mL
    - 51-192: 24
    - 29-50: 22
    - 16-28: 27
    - 4-15: 24

Strategies To Reduce Iron Deficiency (STRIDE)

DESIGN:
• Randomly assigned to one of five arms for 2yrs of follow-up. Interventions were performed after each donation;
  – 3 double-blinded arms provided 60 once-daily pills (38/19/0 mg elemental Fe).
  – 2 single-blinded arms provided iron status (Ferritin) and information on how to proceed with donation vs non-specific letters encouraging donors to donate frequently
  – Ferritin, soluble transferrin receptor, & complete blood count measure

Strategies To Reduce Iron Deficiency (STRIDE)

RESULTS

- 692 subjects enrolled, 393 completed study
  - $\geq$18yo Males with $\geq$3 and Females with $\geq$2 RBC equivalent donations in prior 12 months.
  - Asked to continue donating 2 (Female) or 3 (Male) RBC equivalent donations/yr x2yrs
- Pill groups de-enrolled more than letter groups (39% v 7%)
- Adverse events occurred equally across placebo or iron pills

Strategies To Reduce Iron Deficiency (STRIDE)

RESULTS

• Iron Status
  – 50% decline in low ferritins (<12 or <26ng/mL) in 3 intervention groups

• Venous Hb
  – Improved equally in all iron pill groups
  – Worsened in placebo and non-informative letter
  – Iron status letter showed intermediate improvement to 38mg v 19mg Fe

Percentage study subjects with laboratory measures of iron status or Hb beyond clinical cutoff values for iron deficiency or anemia
Summary so far

• How should donors be protected against becoming iron depleted?

• There are several risk factors for developing low iron.
  – Baseline Hb and donation intensity show highest association.
  – Female gender, young and old age show 10x less association.

• Iron stores appear to be of secondary concern to the body, since Hb recovery appears to precede increases in ferritin.

• Iron supplementation OR letters containing specific information about a particular donor’s iron status helpful.
  – Iron supplementation decreases Hb recovery 20wks to 5wks
  – There is a wide range of recovery in the absence of iron
Factors influencing Iron Stores in blood donors

SUMMARY: Not all donors have the same behavior. Donation interval and donation frequency are different. Not all donors have the same physiology. There is variation in the rate of iron absorption, in the dietary iron intake, in the nature of the dietary iron, erythropoietin response, etc.
Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors

1. Measurement of serum or plasma ferritin

2. Prolong the **interdonation interval** or restrict the **total number of allowable donations** in a 12-month period for whole blood and red cells
   a) Switch between RBCE and platelet apheresis donations
   b) Problem remains in European countries where Hb acceptance criteria are higher, Interdonation intervals are longer, WB Collection volume is smaller

3. Specific & targeted education with easy to read metrics

Updated from AABB Association Bulletin #12-03
O’Meara et al. 2012
# Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors

## Universal or Targeted Strategies

| Age (lower & upper limits?) | Gender | Race | Frequency | Low but acceptable Hb | Drop in Hb, relative anemia? |

## Optimize deferrals

- Following recent pregnancy
- Following low Hct/Hb during donation attempt (> 1 day)
- Increase Male Hb cutoff (13.5g/dL)
- Identify “vulnerable” and/or “protected” donors

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Updated from AABB Association Bulletin #12-03
O’Meara et al. 2012
Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors

Optimize Iron Supplementation

- Daily 20mg elemental Fe compensates for donation:
  - 40mg needed for positive iron balance
  - >60mg FeSO4 increases hepcidin for up to a day, lowering iron absorption the following day.

- ? Role for heme-derived supplements, iron sprinkles, blood donor formulated multivitamin

Updated from AABB Association Bulletin #12-03
Ratke et al, TRFN 2004
Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors

Iron replacement to prevent iron depletion:

a) Either in the form of medication provided by the blood center, or

b) Specific donor instructions use of over-the-counter iron supplements along with current iron status

Iron Supplements

At Collection facility’s expense:
- Provide at time of donation
- Mail to donor
- Provide a voucher for donor to buy

At donor’s expense:
- Advise donor to buy

Updated from AABB Association Bulletin #12-03
Ratke et al, TRFN 2004
### Current Challenges

<table>
<thead>
<tr>
<th>Decreasing Donations</th>
<th>Changing Donor base</th>
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<tbody>
<tr>
<td>• Decrease in collections.</td>
<td>• “A donor deferred is a donor deterred”</td>
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<tr>
<td>– A perfect storm with TRALI mitigation?</td>
<td>• Changing donor demographics</td>
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<td>• Fragility of O Neg supply</td>
<td>• Increased pressures on O neg donors</td>
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<table>
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<tr>
<th>Increasing Logistics Complexity</th>
<th>• Differential recruiting/messaging</th>
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<tr>
<td>• Training</td>
<td>• Adherence to pill regimen</td>
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<tr>
<td>• Complexity of SOPs</td>
<td>• Nausea, constipation</td>
</tr>
<tr>
<td>• Computer systems support</td>
<td></td>
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</tbody>
</table>
1) do no harm to patient or donor
2) maintain a safe & adequate blood supply
3) keep asking and answering critical questions with research
4) use objective data to drive policy
Special Acknowledgement

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Thank you!

kland@bloodsystems.org
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