New Insights about Anemia from Studies of Blood Donors

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Disclosure

• Receiving an honorarium for this educational presentation
Blood Donation - 2008

- 17,159,000 units of blood were donated
- 10,877,000 individual donors
- 3,165,000 (29%) were first time donors
- ~1,000,000 were deferred for low hemoglobin

The United States Department of Health and Human Services 2009 National Blood Collection and Utilization Survey was conducted under contract with the AABB.

What happens during blood donation?

- ~50,000 people are screened for anemia each day at blood centers
- Those with Hgb ≥12.5 are allowed to donate blood
  - Men with anemia are allowed to donate!
What happens to the donors?

- They become iron deficient
- If they have Hgb < 12.5:
  - They receive a pamphlet about eating iron rich foods.
  - They are deferred (typically for 1 day).

Talk Outline

- Iron deficiency in blood donors
- Anemia in blood donors
- Epidemiology of low Hgb in blood donors
- Donors that never get deferred
You lose lots of iron when you donate blood

Iron lost in one donation

- Male stores
- Female stores
- Iron lost in one donation

Iron deficiency in blood donors: analysis of enrollment data from the HEED-II Haem Iron Stores Evaluation (HISE) study

Absent Iron Stores = ferritin < 12ng/mL
- 16.4% of males
- 27.1% of females

Iron-Deficient Erythropoiesis = $\frac{\text{Log(sTfR/ferritin)}}{2.07}$
- 48.7% of males
- 66.1% of females

769 females with ≥2 donations in previous 12 months
768 males with ≥3 donations in Previous 12 months
Iron deficiency causes:

Fatigue/Decreased exercise capacity
Decreased cognitive function
Restless leg syndrome
Pica

Blood Donation by 16 year olds

- Many teenagers have poor nutrition and are undergoing cognitive development.
- 20% of US blood supply is collected from 16-24 year olds.
- High school donation starting at age 16 will allow them to donate 4-6 times before graduation.
- Iron deficiency induced by blood donation in 16-year old donors should be a major concern of blood collection agencies.
With the increasing knowledge of the prevalence of iron deficiency in blood donors that is a direct consequence of blood donation and the adverse health effects of iron deficiency, it is a problem that can no longer be ignored by blood centers.

**Strategies To Reduce Iron DEficiency**

- Multi-center study conducted at BCW, ITxM and New England Red Cross
- R01 study funded by NHLBI

**Goal:** To develop and test methods for replacement of iron lost during blood donation that can be readily implemented in community blood centers
Strategies to Reduce Iron Deficiency Study

Study Group 1: Letters
- “thanks for donating!”
- “your iron status is normal”
- “your iron status is low”

Study Group 2: Iron Tablets
- 0 mg iron = placebo
- 19 mg iron = 1x
- 38 mg iron = 2x

660 donors are now enrolled and are approximately one year through the two year longitudinal phase of follow-up.

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Definition of Anemia

- WHO Criteria (1960s)
  - 13.0 g/dL for men
  - 12.0 g/dL for women
- Beutler & Waalen, Blood 2005 107:1747
  - 13.7 and 12.9 g/dL for White and Black men
  - 12.2 and 11.5 g/dL for White and Black women
- Blood Donation
  - 12.5 for everyone (anemic men can donate, some non-anemic women can not)

Low Hemoglobin Deferral

Most common deferral – 10% of all donation attempts
- 17.7% of females
- 1.6% of males
  - Transfusion (2010) 50:1794
Anemia is an early indicator of many diseases, yet blood donors found to have anemia often receive inadequate information about its medical importance.

GI bleeding including Colon Cancer
Vitamin Deficiency
Leukemia
Chronic Inflammation

Most blood centers reassure the donor that a HCT can vary from day to day and tell the donor that they should eat iron rich foods and return to try to donate again the next day!!!
Healthier Wisconsin Partnership Program Study

• Collaborative effort between the Blood Center of Wisconsin, the Medical College of Wisconsin and the National Anemia Action Council.

• The primary goal is to develop new educational materials and test their efficacy in getting the correct donors to seek further care for diagnosis and treatment of their anemia.

• www.anemia.org

Survey of 75 blood centers in US -52 responded

• 38 (73%) defer all donors for 1 day
• 3 more have graded deferral periods starting at 1 day
• American Red Cross defers for 1 day

Delaney et al., Transfusion 2011
The 1 day deferral is probably based on blood centers not wanting to lose donations from donors with a borderline hemoglobin value who may qualify for donation the following day solely due to random variation in test results.

Only 35% of centers have a cut-off value where donors with very low hemoglobin are contacted and advised to seek medical attention.

Delaney et al., Transfusion 2011

Is anemia identified in otherwise “healthy” blood donors a big deal?

A survey of 104 deferred donors (women <50 excluded) found 2 donors with serious disease diagnosed within 3 months of their deferral.

Acute lymphocytic Leukemia
Metastatic lung cancer
Both had hematocrit of 35%

Delaney et al., Transfusion 2011
BLOOD DONORS AND BLOOD COLLECTION

Community blood donors’ knowledge of anemia and design of a literacy-appropriate educational intervention

Staci Young, Arlene Fink, Susan Geiger, Anne Marbella, Alan E. Mast, and Kenneth G. Schellhase

TRANSFUSION 2010;50:75-79.

Thank you so much for coming to donate blood today. It is a very important service that you help others in need of a transfusion. We are very grateful to have you here today and invite you to fill out the questionnaire to help us determine whether you are eligible to donate blood.

You are not a donor if you:

1. Are under age 18 and are not a registered donor
2. Are pregnant
3. Are on a medication that affects your blood levels
4. Have had a blood transfusion in the past 10 years
5. Have a fever or are feeling unwell

What is a blood donor:

The blood donor is the percentage of your blood that is red blood cells. These red blood cells carry oxygen to your tissues and organs, and prevent the body from storing too much iron. Your blood donor may be a male or a female, and you may choose to donate blood two or three times a year. You may be able to donate blood again in the future.

Blood donor programs:

- Blood donor programs are designed to help people in need of blood.
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What are the consequences of low blood pressure and anemia?

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Did you know that men have anemia?

You may not have heard of this disease, but it is common. It is often referred to as "iron-deficiency anemia." Other causes of anemia include:

- Blood loss from a gastrointestinal tract
- Iron deficiency from frequent blood donation or other causes
- Iron deficiency from menorrhagia or other causes
- Iron deficiency from the use of iron supplements

If you have low blood pressure or anemia, it is important to see a doctor as soon as possible. A doctor can help you determine whether you are eligible to donate blood, or if you are already a blood donor, they can help you determine whether you are eligible to donate blood again.

Learn more online:

The National Anemia Action Council is a nonprofit organization that can provide more information about anemia. Visit www.anemia.org for more information.
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About 50,000 people attempt to donate blood each day in the United States.

All are screened for anemia.

Although most are White, there are large numbers of donors from other ethnic groups.
Population-based screening for anemia using first-time blood donors
Alan E. Mast,1,2 Whitney R. Steele,3 Bryce Johnson,3 David J. Wright,3 Richard G. Cable,4 Patricia Carey,5 Jerome L. Gottschall1 Joseph E. Kiss,6 Toby L. Simon,7 and Edward L. Murphy5,8; for the NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II) Investigators

• Blood donor data compares well with that collected in the National Health and Nutrition Examination Survey (NHANES)
• Cigarette smoking increases hemoglobin by 0.26 g/dL in those smoking <10 per day and 0.59 g/dL in those smoking >10 per day.
• Can be used as a public health resource for ongoing anemia surveillance.

Mast et al, Am J Hematology 2012

BLOOD DONORS AND BLOOD COLLECTION

Demographic correlates of low hemoglobin deferral among prospective whole blood donors
Alan E. Mast, Karen S. Schlumpf, David J. Wright, Brian Custer, Bryan Spencer, Edward L. Murphy, and Toby L. Simon for the NHLBI Retrovirus Epidemiology Donor Study-II

715,000 donors tracked for low Hgb deferral over 24 months

A multivariable logistic regression model was developed to comprehensively assess demographic correlates for low Hgb deferral.
Odds for deferral

- Women have 11 times greater odds than men.
- Blacks have 2-2.5 greater odds than Whites.
- Hispanic women have 1.3 times greater odds than White women.

The odds for low hemoglobin increase with age

Mast, Transfusion 2010
Perhaps most surprisingly, the odds for low Hgb deferral decrease with increasing donation intensity.

Women with 6 donations in the previous 12 months have 0.45 the odds for deferral compared to women with 1 donation.

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Superdonors

- These individuals donate whole blood every 56 days over 2 year period.
- They are losing a lot of blood.
- Why don’t they get iron deficiency anemia?

Daily Iron Absorption
Biochemical Characteristics of Superdonors

Most superdonors have low serum hepcidin, in over 50% it is undetectable.
Genetic Characteristics of Superdonors

- None were homozygous for the major HFE mutation.
- HFE mutations are present at the same frequency as in the normal population.
- None of the donors had the JAK-2 mutation associated with polycythemia.
- TMPRSS6???

The Serine Protease TMPRSS6 Is Required to Sense Iron Deficiency

Hepcidin restricts enteric Fe absorption and is the key regulator of body Fe content.

Mask mice lack body but not facial hair, and have microcytic anemia.

TMPRSS6 deficiency produces the mask phenotype.

The promoter of the hepcidin gene is suppressed TMPRSS6.

Conclusion of paper: TMPRSS6 is an essential component of a pathway that detects iron deficiency and blocks hepcidin production, permitting increased dietary iron absorption.
My recommendations

• Do not treat all blood donors the same
  ▫ Do not collect blood from 16-year old girls
  ▫ Do not collect double red blood cells from donors over 70.

• Screen donors for iron deficiency
  ▫ Low intensity donors (1-2 times/year) are ok
  ▫ Develop “VIP” programs for our best donors
    • Ferritin monitoring
    • Other tests to predict impending deferral?
      • Hepcidin, CBC/reticulocyte parameters

Conclusions

• Blood donation causes iron deficiency
  ▫ Programs to assess iron status and prevent/treat it in blood donors are needed.

• The diagnosis of anemia in blood donors may be a indicator of significant underlying disease.
  ▫ Donors with anemia should be provided with improved and consistent educational information.

• Lots of people donate blood and all are screened for anemia
  ▫ Blood donors are a rich source of available information for study of anemia in the United States.