Advancing Transfusion and
Cellular Therapies Worldwide

Association Bulletin #17-02

Date:	March 16, 2017 **UPDATED JULY 2022**
To:	AABB Members
From:	Zbigniew Szczepiorkowski, MD, PhD – President Thomas Hopkins, MBA – Interim Chief Executive Officer
Re:	Updated Strategies to Limit or Prevent Iron Deficiency in Blood Donors

This bulletin, developed by the AABB Donor Health and Safety Committee and approved by the AABB Board of Directors, contains information for all establishments that collect Whole Blood (WB) or apheresis component donations. It supersedes Association Bulletin #12-03 "Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors" and recommends action(s) to limit or help prevent iron deficiency in blood donors.

Summary

Association Bulletin #12-03 recommended that blood collection establishments take voluntary action(s) to monitor, limit, or prevent iron deficiency in blood donors. AABB's current version of the *Standards for Blood Banks and Transfusion Services* require procedures to ensure donors are given, and acknowledge reading, educational materials that include the risks of postdonation iron deficiency.[1] Mounting evidence indicates that frequent donors require iron supplementation to prevent significant iron depletion that may have deleterious health consequences. Blood collection establishments should therefore take action(s) with all donors or selected subpopulations at risk for, or from, iron deficiency (listed below) to include at least one of the following interventions/strategies: 1) development of programs to provide replacement iron in the absence of ferritin measurements, 2) evidence-based lengthening of the interdonation interval and/or restriction of the number of donations per year, or 3) measurement of serum or plasma ferritin leading to recommended actions (including iron supplementation) for donors with low ferritin levels.

Association Bulletins, which are approved by the AABB Board of Directors, may include

announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations.

Background

Iron deficiency is observed in blood donors, with rates ranging from 49 percent in men to 66 percent in women, who donate frequently.[2,3] Premenopausal women are at particular risk for developing iron deficiency. As iron deficiency progresses, it eventually results in anemia, but the potential for adverse health consequences exists before anemia occurs.[4,5] Iron deficiency (particularly in the presence of anemia) can affect several physiological and health parameters. Adverse effects include: cognitive dysfunction, fatigue, pregnancy-related complications (perinatal mortality, preterm delivery, low birthweight, newborn cognitive abnormalities), decreased exercise endurance, pica (the desire to compulsively ingest non-food substances such as ice or clay), and the less-clearly associated restless legs syndrome.[6-23]

Subgroups at Risk
The following donors are at risk for developing iron deficiency and/or at increased risk for adverse effects of iron deficiency:
- Young donors.
- Premenopausal females.
- Frequent donors.
- Donors with hemoglobin values near the minimum for eligibility.

Pertinent Studies
Many of the studies reporting adverse effects are more suggestive than definitive, particularly in non-anemic iron deficiency (NAID).[4] Most iron-deficient blood donors have NAID, and a growing body of literature identifies the effect of NAID in impaired quality-of-life measures.[9,19,23] Frank iron deficiency anemia occurs occasionally in blood donors and is more clearly and consistently associated with adverse outcomes. Although more randomized, controlled trials are needed, our current understanding of the potential harms associated with NAID resulting from blood donation demands thoughtful clinical and ethical attention.[24]

Since Association Bulletin #12-03 was published, two important randomized, controlled trials investigating iron balance and iron recovery in frequent blood donors have been published. The first study, conducted as part of the National Heart, Lung, and Blood Institute (NHLBI)-supported Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) was the

HEmoglobin Iron and Recovery Study (HEIRS). The second study, also funded by the NHLBI, was the Strategies To Reduce Iron DEficiency (STRIDE) study.[25,26] Preliminary data from another NHLBI-funded study, the Comparison of the History of Donation and Iron LeveLs in Teen Blood Donors (CHILL) study, have also been reported.[27]

- HEIRS
  Important aims of HEIRS were to determine the time to postdonation hemoglobin and ferritin recovery with and without oral iron supplementation.[25] HEIRS enrolled 136 female and 79 male blood donors ≥18 years old at four US blood centers. None of the donors had donated blood in the prior 4 months. Donors were separated into two groups by storage iron level at enrollment: a lower ferritin group (≤26 ng/mL; iron-depleted) and a higher ferritin group (>26 ng/mL; not iron-depleted). At their next study visit (3-8 days after donation), subjects were randomly assigned to receive either 37.5 mg of elemental iron as oral ferrous gluconate daily for 24 weeks, or no supplementation within strata based upon initial ferritin level, gender, and age. Hemoglobin and ferritin levels were measured seven times during the study, with the final measurement 24 weeks after donation. Approximately 90 percent of subjects completed at least six of the seven scheduled visits.

  Primary results of the study are as follows. Compared to those who did not take iron, donors taking supplements returned to 80 percent of predonation hemoglobin levels faster in both the lower ferritin group (median of 5 weeks vs 23 weeks) and higher ferritin group (median of 4 weeks vs 11 weeks). Similarly, donors taking iron supplements recovered lost iron (as determined by ferritin measurements) more rapidly than those not receiving supplements (11 weeks vs >24 weeks for return to baseline ferritin). At 24 weeks after donation, two-thirds of the donors who did not take supplements still had not recovered the iron lost at donation. Thus, in addition to showing the efficacy of iron supplementation, HEIRS demonstrated that extending the interdonation interval to 12 or 16 weeks is not sufficient for the average donor to recover iron stores without supplementation.

  In a second analysis, the investigators calculated the total body iron, the sum of storage iron and iron in hemoglobin.[28] They identified a statistically significant effect of iron supplementation on total body iron recovery in the first 8 of the 24 weeks of iron administration. This effect was demonstrable (but weakly) in the second 8 weeks only in those with iron deficiency, and not in any donors by the third 8-week period. Taken together, these findings suggest that the majority of iron's beneficial effect is achieved within the first 8 weeks of supplementation. Thus, daily intake of low-dose oral iron for 8 weeks is likely to be an effective way to remedy donation-related iron depletion.

- STRIDE
  The STRIDE study was a multicenter, randomized, blinded, and placebo-controlled study investigating several readily implemented approaches to mitigate donor iron deficiency.[26] Frequent blood donors from three blood centers were randomly assigned to one of five study arms. Donors in two intervention arms received either 19 mg or 38 mg of elemental iron as ferrous gluconate for 60 days after each donation. The third intervention arm was informational; in this arm (designated as the "Iron Status Information" arm), donors received a letter informing them of their ferritin level. The letter recommended continued frequent donation for donors with ferritin levels ≥26 ng/mL, while donors with ferritin levels <26 ng/mL were advised to take self-purchased iron supplements and/or delay donation for 6 months. In the two control arms, donors received a letter encouraging frequent donation or administration of a placebo in lieu of iron supplements. Donors were evaluated at multiple follow-up visits over a 2-year period. Ferritin, soluble transferrin receptor, and a complete blood count were measured at each donation. Of 692 enrolled donors, 57 percent completed the study. There was a higher dropout rate in the three groups receiving pills, including the group taking placebo, unrelated to side effects that occurred equally in all three groups.

  Ferritin level and hemoglobin concentration at the end of the study were statistically equivalent among subjects randomly assigned to the 19- and 38-mg iron groups and the Iron Status Information arm. Values in the placebo and no-information-letter study arms were significantly lower. This finding held true for other iron deficiency measurement cutoffs. Reductions of 30-80 percent in the prevalence of iron deficiency from enrollment occurred only in the iron and Iron Status Information study arms. Additional analyses of absolute changes in iron and hemoglobin status from enrollment to final visit and models incorporating data from all visits by all enrolled subjects (not just those completing the study) showed that donors in the Iron Status Information group did not improve their iron status and hemoglobin concentration quite as much as those who were directly provided iron pills. Differences between the primary and secondary analyses can be attributed to the diverse responses of Iron Status Information donors, some of whom took iron and/or lengthened their interdonation intervals, while others did neither, particularly those with ferritin levels ≥26 ng/mL. Taken as a whole, STRIDE results demonstrated that providing 19 or 38 mg of daily iron or iron status information after ferritin testing was effective and mostly equivalent in mitigating postdonation iron deficiency.

- CHILL

  Recently, the REDS-III program completed the CHILL study.[27] Two blood centers enrolled donors at high school blood drives during 2015-2016 and measured donor ferritin levels at their first and any subsequent donations during the school year. In total, 4,265 donors making 6,219 donations were enrolled. Of those, 3,714 donors making 5,439 donations were aged 16-18 (defined as teen donors) while the remainder were adult donors, aged 19-49, who served as controls.

  Preliminary data analysis indicated that at study outset, the mean ferritin levels of first-time donors (at each age and gender) did not differ from national population data obtained in the 2001-2002 National Health and Nutrition Examination Survey (NHANES) but that the prevalence of iron deficiency was greater in teen donors than in the adult control donors. Further, with repeat donation, the prevalence of iron deficiency was also greater in female and male teen donors than in gender-matched adults. CHILL investigators concluded that the baseline prevalence of iron deficiency is higher in teenagers before donation and may be exacerbated to a greater extent by blood donation when compared to adult donors; this latter preliminary finding is undergoing further evaluation by statistical modeling.

Recommendations

In light of 1) the possibility that some donors may develop iron deficiency anemia after donation, 2) the known progression of iron deficiency that occurs with ongoing frequent blood donation, and 3) the potential for adverse effects of iron deficiency, blood collection establishments should develop policies to limit or help prevent iron deficiency in their donors. These policies should go beyond the current AABB standard requiring development of educational materials for all donors on the risk of postdonation iron deficiency.

Recommendation #1: Blood Collection Establishments Should Prepare Comprehensive Educational Materials to Assist Donors in Better Understanding the Need for Specific Interventions.
Blood collection establishments should provide all donors with comprehensive information that not only includes information on the risks of iron deficiency resulting from blood donation and their applicability to particular at-risk donor subgroups (as described below), but also discusses the benefits of iron supplementation following donation. This information should include recommendations on the type of iron, dosage, and length of supplementation required to replace

an equivalent amount of iron lost at donation. Because iron supplements may be harmful in some individuals or mask conditions associated with gastrointestinal blood loss, donors with a personal or family history of hereditary hemochromatosis, familial polyposis, or colorectal cancer should be advised to check with their health-care provider before commencing iron supplementation. Donors should also be advised to consult with their health-care provider or pharmacist about the effect of iron on absorption of other medications.

Recommendation #2: Facilities Should Implement One or More of the Following Interventions/Strategies in All Blood Donors or in Subgroups of At-Risk Blood Donors (described below).
If blood collection establishments choose to implement one of the following interventions/strategies in only a single select donor subgroup, it is recommended that they begin with young donors (described below). However, it is anticipated that blood centers will progressively extend actions to all other at-risk groups.

- Subgroups at Risk
  The following donors are at risk for developing iron deficiency and/or at increased risk for adverse effects of iron deficiency. In the absence of efforts to prevent iron deficiency in all donors, the following donors should be the target of interventions/strategies to mitigate iron deficiency:

  o *Young donors.*
    At a minimum, this applies to donors 16-18 years of age. It could also include donors through their early 20s, because substantive, measurable brain maturation and cognitive development can continue in that age group.[29-31]

  o *Premenopausal females.*

  o *Frequent donors, defined as:*
    – Males donating three or more times within a 12-month period.
    – Females donating two or more times within a 12-month period.

  o *Donors with hemoglobin values near the minimum for eligibility (eg, males with hemoglobin levels between 13.0 and 13.5 g/dL and females with hemoglobin levels between 12.5 and 13.0 g/dL).[32]*

- Interventions/Strategies

These may include one or more of the following actions:

o *Donor iron supplementation.*
Blood collection establishments may choose to dispense iron supplements or multivitamins with iron directly to donors or provide vouchers exchangeable for iron to facilitate their obtaining iron supplements. Data from the HEIRS and STRIDE studies can be used to determine the minimal iron dose and duration of administration. As shown in HEIRS, a 38-mg supplement resulted in the majority of iron being replaced within the first 8 weeks; in the STRIDE study, 19- and 38-mg doses were equally effective in replacing iron lost from blood donation. Therefore, to replace the iron lost in a WB donation, a minimum of 18 mg of elemental iron [as a multivitamin with iron (18 mg being the most commonly available dosage) or an iron supplement] is recommended daily for 60 days.

Based on the amount of red cells removed at donation, it seems logical that 2-unit Red Blood Cell (RBC) donors should take iron for twice as long as single-unit donors. However, iron absorption is quite dependent on donor iron status; ie, donors with a greater degree of iron deficiency will absorb more iron. Therefore, 2-unit RBC donors may also get the maximal benefit from supplemental iron in the first 8 weeks after donation when they have their lowest ferritin levels. Currently, in the absence of data that address this issue, blood centers should provide 2-unit RBC donors with supplements or vouchers for a minimum of 18 mg of elemental iron daily for either 60 or 120 days following donation, at the discretion of the facility's medical director.

Blood centers should define the number of apheresis procedures (platelets and plasma) that result in red cell losses (including incomplete procedures and blood samples) that approximate the red cell loss in one WB donation. Based upon kit residuals and testing tube losses, this is likely to be four to five plateletpheresis or plasmapheresis donations.[33,34] Donors reaching red cell losses equivalent to those of frequent blood donors should be informed about iron loss and provided with supplements or vouchers for a minimum of 18 mg of elemental iron daily for 60 days; this same regimen should be repeated at intervals approximating each subsequent equivalent WB unit loss. With the introduction of iron supplementation programs, it is expected that blood collection establishments will experience a reduction in low hemoglobin deferrals. A 2014 Cochrane meta-analysis of four studies of iron supplementation in blood donors describes a 66% reduction in deferrals with iron use (95% confidence interval 45% - 79%).[35]

o *Lengthening the interdonational interval and/or decreasing the number of donations*

per year.
Blood collection establishments may choose to increase interdonation intervals and/or decrease the maximal permissible number of donations per year. There is clear evidence from observational studies that the number of donations in the previous 1-2 years is the foremost determinant of iron deficiency in blood donors.[2] Furthermore, it is well-documented that a 56-day interdonation interval, without iron supplementation, produces a negative iron balance.[36] Even countries with an interdonation interval greater than the 56 days permitted in North America have reported high rates of hemoglobin deferral due to iron deficiency in the absence of iron supplementation.[37] In the HEIRS study, two-thirds of subjects receiving no iron supplementation had not recovered lost iron by 24 weeks after donation.[25] Based upon these and other data,[36] it is increasingly clear that lengthening the interdonation interval is highly unlikely to be fully effective as a solitary intervention to mitigate donor iron deficiency unless the interval is lengthened to ≥26 weeks. In other words, if no other interventions in addition to extended interdonation interval or limitations on donation frequency are utilized as a strategy to protect blood donors from iron deficiency, then limiting WB donations to two times in a 12-month period or one 2-unit RBC donation in a 12-month period appears to be the maximal collection schedule that can be employed. Because of higher documented rates of iron deficiency in young donors, it is recommended that in the absence of any other intervention for such donors (ages 16-18) of both genders, blood collection establishments should limit collections to the red cell loss from one WB donation in a 12-month period. Collections from premenopausal women may similarly be limited to one donation in a 12-month period at the discretion of the facility's medical director.

Limiting the number of donations per year to this extent is likely to have a significant impact on the adequacy of the blood supply in the absence of a significantly expanded donor base.[38,39] Therefore, blood collection establishments may choose to combine a lesser limitation on donation intervals or frequency with other strategies listed in this Association Bulletin.

o *Donor ferritin testing as a basis for advising donors about further actions.*
Blood collection establishments may choose to test ferritin levels for all donors or donor subgroups to provide those donors whose values are low with personalized recommendations for iron supplementation and/or delaying subsequent donation. This allows for a targeted approach to donors demonstrated to be iron deficient rather than

targeting donors presumed to be iron deficient by a demographic characteristic or prior donation activity. Based upon findings from the STRIDE study, it appears that donors may be highly motivated to follow blood center iron supplementation recommendations or self-extend interdonation intervals when their ferritin value documents iron deficiency. Canadian data outside the more carefully controlled STRIDE environment highlight the need for especially clear communication.[40]

Ferritin testing should be performed on a sample collected at the time of blood donation. A low ferritin result would apply to management of the donor before any subsequent donation. Clear recommendations for iron supplementation and/or for interdonation interval extension should be provided in writing to donors along with their ferritin test results. Repeat ferritin testing should be determined by prior test results and operational capabilities of the blood collection establishment.

Recommendation #3: Blood Collection Establishments Should Consider Postimplementation Monitoring
Blood collection establishments are encouraged to collect, track, tabulate, and publish data on any interventions they conduct. AABB also encourages blood collection establishments to design their interventions in such a way that endpoints are clear and the derived data can be readily compared to interventions implemented at other facilities.

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41. **AABB DONOR IRON DEFICIENCY RISK-BASED DECISION-MAKING ASSESSMENT REPORT**