Reassessing the Safety Concerns of Utilizing Blood Donations from Patients with Hemochromatosis
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Abbreviations
HH- Hereditary hemochromatosis
RBC- Red blood cell
NTBI- Non-transferrin bound iron

Abstract

Hereditary hemochromatosis (HH) is a genetic disorder of iron metabolism which may lead to iron overload. Clinical penetrance is low, however those afflicted may develop cirrhosis, hepatocellular carcinoma, diabetes mellitus and cardiomyopathy. Treatment involves regular phlebotomy to reduce the systemic iron burden. In many countries—including the United States—numerous blood centers do not accept donated blood obtained from HH patients during therapeutic phlebotomy and there are inconsistent positions regarding this globally. This refusal is borne out of a few concerns. First, there is a theoretical increase in the infectious risk of these blood products, particularly by siderophilic organisms such as *Yersinia enterocolitica.* Second, given the increased incidence of hepatitis C infection from non-voluntary donors in the 1970s, there is a concern that blood from HH donors may harbor additional risk given the non-voluntary nature of their presentation. In this review, we examine the existing biologic and clinical data concerning infectious risk and summarize clinical experience from centers allowing HH donors, and demonstrate that blood from HH patients is safe and should be allowed into the donor pool. We conclude that there is no convincing evidence to exclude this population from serving as blood donors.

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive genetic disease characterized by the inappropriate absorption of dietary iron from the small intestine. In a majority of cases, it is the end result of mutations in genes regulating the synthesis of hepcidin, a molecule integral to iron homeostasis. Hepcidin deficiency is associated with increased expression of ferroportin, a molecule expressed on the cell surface vital for the exit of iron from cells, most notably macrophages responsible for erythrophagocytosis—recycling iron from senescent red blood cells (RBC)—as well as intestinal cells (1, 2) . This resulting increase in plasma iron overwhelms transferrin, resulting in excess circulating non-transferrin bound iron (NTBI) (3). The most commonly affected gene is *HFE*, which is mutated in about 80% of cases (4). The mutation is present in about 10% of northern Europeans, with those homozygous at risk of developing the clinical syndrome (1). The prevalence of homozygous C282Y and H63D mutations in the United States —the two most common mutations of the *HFE* gene—has been estimated to be 0.26% and 1.89%, respectively (5). The clinical syndrome is due to uptake of excess iron in plasma by hepatic, pancreatic, cardiac and endocrine cells resulting in parenchymal excess. Although clinical penetrance is low--estimated between 1%-28% (6, 7)--the pathologic state can be characterized by cirrhosis, hepatocellular carcinoma, diabetes mellitus, and cardiomyopathy.

The mainstay of HH treatment is phlebotomy. There are no randomized controlled trials to establish the efficacy of phlebotomy and current treatment guidelines are based solely on expert opinion. Much of the data regarding phlebotomy is limited to patients diagnosed clinically with hemochromatosis and are not entirely reflective of patients with HH (8). In one study of 163 patients diagnosed with hemochromatosis, mortality was similar to age and gender matched normal controls when phlebotomy was initiated before the development of diabetes or cirrhosis (9). In another observational study of Danish patients with clinically overt hemochromatosis, 66 were adequately treated with phlebotomy (median amount of iron removed 14 grams) and 62 patients were inadequately treated (median amount of iron removed 4.4 grams) due to poor compliance. Patients with hemochromatosis who were adequately phlebotomized had

a significantly longer median survival (16 versus 4.5 years) as well as lower rates of cirrhosis (68% versus 93%) (10).

Therapeutic phlebotomy is initiated until a goal serum ferritin of <50 ng/mL is obtained. (11) Additionally, some experts recommend phlebotomy if there is evidence of liver iron deposition on magnetic resonance imaging, although the most recent guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (8, 12), do not explicitly comment upon this. Once this induction level is met, patients undergo regular screening to ensure that a goal ferritin of 50-100 ng/mL is maintained. If this level is exceeded, patients will require additional maintenance phlebotomy, often every two to four months (12). RBC collection can either be performed via whole blood donation or apheresis. Phlebotomy is often done in the office by an experienced physician but may also be performed by a blood center or medical laboratory, the latter two requiring a physician prescription. It is unknown what percentage of HH patients receive therapy in a physician's office or present to a blood center for treatment.

The blood obtained during phlebotomy of patients with HH is often discarded, eliminating a potentially rich source of blood products. The European Federation of Associations of Patients with Hemochromatosis' 2010 survey of phlebotomy practices by country highlight the variation that exists worldwide (8). According to their respondents, Ireland and France allow patients with HH to donate blood, while Austria, Hungary, Iceland, Italy, the Netherlands and Spain forbid donation. A survey-based study of blood banks from 2013, found 31% of responding centers, primarily from European countries, did not accept blood donation from HH patients, including patients with *HFE* gene mutation but without increased iron stores. An additional 17% of those responding accepted donations from asymptomatic patients with HH but not patients with clinical evidence of HH (i.e. end-organ damage from iron overload such as cirrhosis or diabetes mellitus) (13). Often, it is up to the patient to disclose their HH status. One 2001 survey-based study found that up to 89% of patients with HH have donated blood at centers that

specifically prohibited donation from these patients, owing to either a lack of patient education or targeted screening at these facilities (14).

According to a 1999 report from the National Blood Data Resource Center, blood shortages have caused 9% of United States (US) hospitals to postpone elective procedures at least one day per month, and more troublingly in 25% of hospitals non-surgical blood needs went unmet at least one day per month. The latter number has been reduced to 10.3% as of the 2011 survey (15); however, clearly shortages still exist. Therefore, the use of this potentially under-utilized resource is essential to consider. In this review, we will first detail the theoretical risks of blood donations with HH, most notably infection, iron toxicity and ethical considerations. We will then examine the available data and clinical experience of HH blood donation, demonstrating its safety despite these concerns. Finally, we will review existing guidelines on HH blood donation and highlight specific examples of successful HH blood donation programs, and propose the universal acceptance and use of blood donated by individuals having HH.

Concerns Over HH Donation

Infection

One of the concerns cited most frequently is the increased risk of infection in RBC products with high iron content. Clinical evidence of blood contamination by bacteria is exceedingly rare given current RBC storage practices, which includes storage at 1 to 6 degrees Celsius and transportation at 1 to 10 degrees Celsius. However, there have been examples of post-transfusion sepsis, including siderophilic organisms such as *Yersinia enterocolitica* (16, 17) and Babesosis (18). Given that platelets are stored at room temperature, transfusion-associated sepsis is far more common in platelet transfusions than RBCs. *Yersinia* is the most common organism and is responsible for about 46% of sepsis from contaminated RBCs.

There are a number of proposed mechanisms for increased bacterial virulence in states of iron overload. For example, bacteria synthesize and release enterobactin to obtain iron from their environment, where it serves as a redox catalyst intracellularly. When serum iron levels are elevated, bacteria can use this vital nutrient for proliferation (19, 20). Additionally, the iron overloaded state can impair the activity of phagocytic cells by altering the pH of lysosomes allowing engulfed organisms to proliferate freely (21). Lastly, hepcidin, an acute phase antimicrobial peptide secreted by the liver, becomes dysregulated in states of iron overload(22). Normally hepcidin has a role in disrupting bacterial membranes, however in states of liver compromise and iron overload hepcidin production is impaired.

Given the necessity of iron for growth and survival, specific bacteria have evolved strategies to compete for iron in the tissues and serum (23). As mentioned, iron may impair phagocytic function of granulocytes and monocytes, making hosts susceptible to *Listeria monocytogenes* infection (24). Further, many bacteria, including *Listeria monocytogenes,* may have increased virulence in iron overload states (25). Siderophilic organisms such as *Yersinia enterocolitica* have iron-dependent growth pathways (26). *In vitro* studies have suggested that *Vibrio vulnificus*, another siderophilic organism, has been shown to grow in blood from HH patients but not in unaffected blood (27). However, it would be exceedingly unlikely for patients with bacteremia to present to a donation site and satisfy the initial healthy donor screen (**Appendix 1**). Together with stringent RBC storage practices, the concerns for an increased risk of infection remain only theoretical.

Excess Non-Transferrin Bound Iron

Another concern regarding blood donation from HH patients is the potential toxicity of NTBI. Iron becomes dangerous as it readily undergoes oxidation-reduction reaction, converting between Fe^{2+} and Fe^{3+} (and even Fe^{4+}). In unaffected humans, this threat is minimized by having iron chaperoned by multiple molecules, most notably transferrin. However in HH, the amount of iron exceeds the binding capacity of transferrin and forms loose complexes with the components of plasma (28). This NTBI is

theorized to cause cytotoxic effects through oxidative stress, an observation demonstrated in stored RBCs (29). While it has been demonstrated that donated blood from HH patients has a higher concentration of NTBI, this difference is negligible. For instance, one study found that after 35 days of storage there was no significant difference between the iron concentration of HH blood and that of healthy donors. At 42 days, the difference was approximately 2μmol/L (30), a margin unlikely to be clinically significant.

Typically, a unit of whole blood from a healthy donor contains 200 mg to 250 mg of elemental iron. This is likely similar to HH blood given the findings of the above study. In comparison, the amount of elemental iron in one dose of intravenous ferric gluconate is 125 mg to 187.5 mg. A single dose of IV ferumoxytol can provide up to 1,020 mg of elemental iron (31). Given that the amount of iron in HH blood is similar or, in some cases, less than that used in Federal Drug Administration (FDA) approved parenteral iron, concerns about iron toxicity are unlikely to be of clinical concern.

Ethical Considerations

Finally, ethical concerns have been raised about HH patients donating phlebotomized blood. As HH patients receive therapeutic phlebotomy as part of treatment, they are not providing the blood donation as a truly altruistic donor and have a self-serving goal, namely their health. What's more, blood donation is free for patients while therapeutic phlebotomy may actually require payment from patients. One 1999 survey-based study of 2,362 patients with HH found that mean charges for one phlebotomy session at a hospital, physician's office, or blood center were $90, $69, and $52, respectively (32). There is concern that this will create a financial incentive for patients to donate rather than potentially pay for therapeutic phlebotomy, which may reward withholding histories of behavior that would qualify as deferrable risk in order to receive free care. (33) This is suggested by studies done in the 1970s showing decreased rates of transmission of hepatitis C after excluding commercial donors (34, 35). These studies were performed in a population receiving purely financial benefit from donation rather than medical therapy, and there is no existing clinical evidence demonstrating increased risk from HH donors. To counteract these concerns,

the FDA prohibits blood centers from charging patients for phlebotomy, even if their blood is not considered suitable for allogenic donation. As long as a patient has a valid prescription from a physician, they may receive free phlebotomy at blood centers that have applied for an FDA variance. A complete list of blood centers who have applied for this variance can be found at: https://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/regulationofthebloodsupply/variances/ucm164649.htm.

Interested blood centers may apply for the FDA variance under the provisions of Title 21, Code of Federal Regulations, Section 640.120 (21 CFR 640.120). The center must include a written request to the FDA to omit labeling of blood from HH donors and stipulate that donated blood will meet allogeneic donor suitability criteria. A copy of the donor acknowledgement form—which includes a statement that no fees will be charged—must also be included. Finally, a separate written request is required allowing the center to collect blood more frequently than every 8 weeks without examination by a physician at the time of donation (36).

Evidence Regarding Safety

Despite the above concerns, there is countering clinical data to suggest that HH blood is suitable and safe for donation.

Biophysical and biochemical safety

Several biophysical metrics are used in both in research and clinical settings to determine the quality of RBC units. For instance, hemolysis results in a decrease in the amount of functioning intact RBCs. The longer a RBC unit is stored, the more hemolysis that occurs which degrades its quality—typically defined as >1% of hemolysis. Additionally, a decrease in glucose and adenosine 5′-triphosphate (ATP) levels implies metabolic depletion of RBCs (37). A Dutch study set to determine differences in these and other measures in blood from eight HH patients with transferrin saturation greater than 50% and a ferritin greater than 700 μg/L and fifteen healthy controls. Weekly samples were collected for hematologic and

biophysical quality testing. In the HH donated blood, hemolysis remained well below the required 0.8% and was not significantly different from healthy controls. Additionally, glucose and ATP levels remained above required levels and were not different between HH blood and unaffected controls. The only difference detected was a significantly elevated mean corpuscular volume in HH patients which was attributed to the younger cell age of the HH population (38).

In a similar French study involving blood donation from 10 HH patients, leukoreduced RBCs from whole blood underwent more extensive testing for bioactive chemokines and cytokines to investigate if HH donated blood was more pro-inflammatory. At day 35 of storage, hemolysis in blood from healthy controls was significantly elevated compared to HH patients, although still within the acceptable range for donation. Again observed was an increased mean corpuscular volume in HH blood. No differences in other biochemical variables were detected. Using a cytokine assay, investigators effectively demonstrated no significant difference in levels of multiple soluble chemokines suggesting that there is no added risk of endothelial cell inflammation. Furthermore, *in vitro* functional testing on endothelial cells using the RBC supernatant showed no difference in bioactivity of immune modulators, such as interleukin-1, tumor necrosis factor-α, and interferon-γ (30). These studies suggest that from a biophysical standpoint, HH blood is safe. Additionally, hematologic and biochemical safety parameters were met and were not significantly different than healthy controls.

Infectious Risk

Donated blood is screened for many transmissible infectious diseases, specifically human immunodeficiency virus-1, human immunodeficiency virus-2, human T-lymphotropic virus-I, human T-lymphotropic virus-II, hepatitis B virus, hepatitis C virus, West Nile virus, *Treponema pallidum* (syphilis), *Trypanosoma cruzi* (Chagas disease) and Zika virus (39). However, there is also the competing risk of bacterial contamination of donated RBC. In general, bacterial contamination of RBC transfusion is much rarer than with that of platelets. The estimated fatality rate from bacterially contaminated RBCs is

approximately 1 per 500,000 transfusions (40, 41). As mentioned previously, concerns have been raised that HH blood may have an increased rate of transmissible infections as well as a propensity towards bacterial growth given the presence of excess iron.

There are a number of studies that provide compelling evidence to contradict the theoretical transmissible infection risk of blood donated by HH patients. In a prospective US study looking at blood donation from 130 participants with HH, it was found that after excluding donor blood with a verified history of transmissible disease or strong risk factors conferring the possibility, none of the tested products demonstrated seroconversion for a transfusion-transmissible viral infection among the 1,402 donations over the course of the study (42). In another US based study of 52,650 blood donors, 197 of whom reported a history of HH, no statistically significant difference in the rates of positive screening tests for syphilis (the only bacterial infection screened), hepatitis B, hepatitis C, human immunodeficiency virus or human T-lymphotropic virus between donors with and without a reported history of hemochromatosis was found(14). A study by a group in France examined the serum for antibodies against various serotypes of *Yersinia pseudotuberculosis* and *Yersinia enterocolitica* in 539 men, 303 healthy controls and 236 patients with HH. They found no significant difference in the presence of anti-*Yersinia* antibodies amongst these groups (43).

In an attempt to examine the potency of immune response in patients with HH, the same French group assessed *in vitro* serum anti-bacterial activity in HH patients. Patients were divided into three groups, HH patients with either biochemical or radiological evidence of iron overload, HH patients who completed iron-depletion therapy, and healthy controls. Each group had their serum incubated with *Salmonella enterica* Typhimurium LT2 strain. They found no statistically significant difference between antibacterial activity in the serum of iron-depleted patients from that of the healthy controls (44). The serum from iron overloaded patients, however, did show a significant reduction in antibacterial activity. A comparison of normal, healthy blood and iron-overloaded blood from five HH patients showed that *Vibrio vulnificus* had

increased survival in the latter group. However, of the HH patients, only those with an elevated transferrin saturation (ranging from 85-95%) showed increased *Vibrio* survival time, while the one patient with a normal transferrin saturation (49%) had similar results as the healthy controls (27). These findings suggest that while grossly iron-overloaded blood may harbor additional risk *in vitro*, blood from HH patients whose transferrin saturation is brought near the normal range confer no additional risk as compared to blood from normal, healthy donors, especially with the use of one unit of blood at a time.

Guidelines

Several major societies have published guidelines allowing the use of HH blood donated for therapeutic purposes, although many have not expressed a position (**Table 1**). In the US, the FDA has released a guidance document for industry stating that HH patients should be allowed to donate blood free of charge, as long they meet standard suitability requirements. Historically, blood from HH donors had been labeled as such to allow providers and patients the choice of whether or not to accept it. Under this 2001 FDA variance, blood centers may forego this labeling requirement if therapeutic phlebotomy is performed free of charge for all HH patients (45). Incentives for donors to be untruthful in responding to standardized health history screening questions are thus minimized. If phlebotomy is performed more frequently than every 8 weeks, either a prescription from a physician must be provided or a physical exam is required on the day of donation demonstrating that the donor is in good health (36). Furthermore, the FDA guidance requires collection and submission of safety data from donations meeting allogeneic donor suitability requirements to compare with the general donor population. In accordance, the AABB, formerly the American Association of Blood Banks, recently amended their Standards for Blood Bank and Transfusion Services to allow donation from HH patients in accordance with the FDA variance (46).

Clinical Experience with HH Donation

Many centers across the globe currently accept HH donor blood and have programs to recruit these donors. In a 2013 survey-based study of 35 blood centers from 33 different countries, it was found that

69% accept blood from individuals homozygous for C282Y without clinical evidence of expanded iron stores. (13). Of those surveyed, only 20% accepted blood from patients with homozygous mutations and evidence of clinical disease. Many other centers do not allow HH blood donation despite the convincing safety evidence, including those centers operated by the American Red Cross (13), the largest blood collection organization in the US. The American Red Cross has no official position paper, however according to an opinion article from the late-1990s, the collecting, labeling and testing of therapeutically drawn blood was deemed to be cost-ineffective (47). Of note, this opinion was offered prior to the issuance of the FDA variance.

A study from a blood bank in Maryland prospectively examined the outcome of 130 patients with confirmed HH who were recruited as blood donors (42). Those 130 patients yielded 1,120 units of packed RBCs deemed suitable for transfusion. Over the 27-month study period, HH donors were responsible for about 9% of total blood donations for the center, which rose to 14% in the last quarter of the study. HH donors kept their scheduled appointments 89% of the time compared to 75% for non-HH donors, attesting to the reliability of therapeutic donation. Of note, no seroconversions for transfusion-transmissible diseases occurred during the study. This study also calculated the number of additional RBCs that could potentially be available if similar HH donor programs were implemented across the US. This could increase the total annual yield by 16%, almost 2.3 million units **(Figure 1)**. Elsewhere, it has been estimated by the AABB that allowing HH donors could increase the annual US blood supply by 200,000-3 million units (45).

Other centers, like Kaiser Permanente in San Diego, receive as much as 40% of their transfusable blood from HH donors (45). These examples suggest that HH donors can reliably and safely be utilized to augment the supply of transfusable blood products. Currently, 114 blood centers in the US have applied for and are approved to accept blood from HH patients under the FDA variance (48). As a comparison, there are currently well over 1,000 blood centers accredited by the AABB in the United States, suggesting

the under-utilization of donated HH blood (49). There are theoretic logistic hurdles that may preclude blood centers from accepting HH blood donation. Prior to the 2001 FDA variance, HH donor blood would need to be separately labeled and require physician clearance if donation occurred more than every 8 weeks. However, this is no longer a required if a center applies for the FDA variance for blood collection from patients with HH. There are considerable financial incentives to accept HH blood donation. One study of a 398-bed hospital identified 17 HH patients who were eligible for donation. Over the course of 1 year, their phlebotomized blood total 60 units, of which 55 units were eligible for donation. This represented $23,595 of potential gross revenue. Even after removing cost of infectious disease testing, units from HH donors would have yielded $20,345 (50).

Conclusion

Hereditary hemochromatosis is a genetic condition causing those affected to develop an iron overload syndrome. The most effective therapy is frequent therapeutic phlebotomy to reduce the iron burden in these patients. Many blood banking organizations around the world—including in the United States—often do not accept HH donors, eliminating a potentially rich source of blood products. The two concerns most frequently cited are an increased risk of infection and these donations not being performed in a voluntary nature.

In this review, we've shown that there is no compelling evidence that blood from HH patients confers any additional infectious risk than that from normal, healthy donors. Furthermore, the data on non-voluntary donation hails from the 1970s and those patients were not receiving a medical treatment, merely compensation for their donation. In published data from a center accepting HH patients as blood donors, there is no evidence of transfusion-transmissible disease arising from these donations. In addition, over 100 US blood centers currently allow HH donations under the FDA variance.

Despite an increasing number of blood centers in the US that accept donations from HH patients, a majority do not—most notably those affiliated with the American Red Cross. In our review, we've found no evidence that supports blood donation from HH patients confers additional infectious risk. There is similarly no data to suggest that the non-voluntary nature of these donations compromises the safety of the products. In fact, many patients express dissatisfaction that their blood does not enter the donor pool (32). Given the existing evidence and perceived benefit, we conclude that there is no reason to exclude blood donations from patients with HH. We encourage the adoption of universal acceptance of blood donated from individuals having HH.

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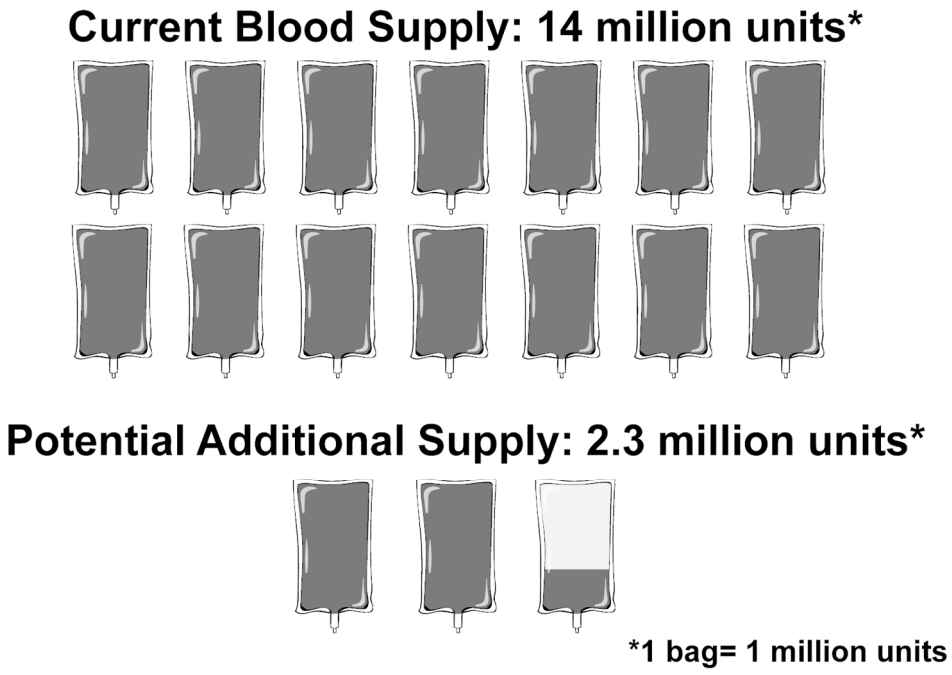
Figure 1. Estimates of potential addition to current blood supply with widespread adoption of blood from hemochromatosis (HH) donors. Adoption of the HH blood donation would introduce up to 2.3 million units of packed red blood cells to the current population of 14 million units (45).



140x97mm (300 x 300 DPI)

Professional Organization	Guideline
AABB	Allows HH donations. Does not specify donation intervals, fees, or eligibility requirements(49)
United States Food and Drug Administration	Allows HH donations every 56 days or more frequently with physician provided prescription or examination day of donation. Donation is free of charge. Must meet all other donor eligibility requirements.(48)
World Health Organization	Allows HH donations. Must meet all other donor eligibility requirements.(54)
Canadian Blood Services	Allows HH donations every 56 days for males and every 84 days for females. Must meet all other donor eligibility requirements.(55)
Irish Blood Transfusion Service	Allows HH donations at limited sites with physician provided prescription. Must meet all other donor eligibility requirements(56)
American Red Cross	Does not allow HH donations.(57)
Australian Red Cross	Does not allow HH donations, but does phlebotomize HH blood.(58)
Hong Kong Red Cross Blood Transfusion	Does not allow HH donations.(17)

International Society of Blood Transfusion	No specific position.(59)
International Federation of Red Cross and Red Crescent Societies	No specific position.(60)
European Blood Alliance	No specific position.(61)
Asian Association of Transfusion Medicine	No specific position.(62)

Table 1. Existing Guidelines for Hemochromatosis Donation

Appendix 1: Donor History Questionnaire (55)

Full-Length Donor History Questionnaire (DHQ)

	Yes	No
Are you		
1. Feeling healthy and well today?		
2. Currently taking an antibiotic?		
3. Currently taking any other medication for an infection?		
4. Have you taken any medications on the Medication Deferral List in the time frames indicated? (Review the Medication Deferral List.)		
5. Have you read the educational materials today?		
In the past **48 hours,**		
6. Have you taken aspirin or anything that has aspirin in it?		
In the past **8 weeks,** have you		
7. Donated blood, platelets or plasma?		
8. Had any vaccinations or other shots?		
9. Had contact with someone who was vaccinated for smallpox in the past 8 weeks?		
In the past **16 weeks,**		
10. Have you donated a double unit of red cells using an apheresis machine?		
In the past **12 months,** have you		
11. Had a blood transfusion?		
12. Had a transplant such as organ, tissue, or bone marrow?		
13. Had a graft such as bone or skin?		
14. Come into contact with someone else's blood?		
15. Had an accidental needle-stick?		
16. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?		
17. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?		
18. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?		
19. Male donors: Had sexual contact with another male?		
20. Female donors: Had sexual contact with a male who had sexual contact with another male in the past 12 months?		
21. Had sexual contact with a person who has hepatitis?		
22. Lived with a person who has hepatitis?		
23. Had a tattoo?		
24. Had ear or body piercing?		
25. Had or been treated for syphilis or gonorrhea?		
26. Been in juvenile detention, lockup, jail, or prison for more than 72 consecutive hours?		

Appendix 1: Donor History Questionnaire (55)

Full-Length Donor History Questionnaire (DHQ)

In the past **three years,** have you		
27. Been outside the United States or Canada?		
From **1980 through 1996,**		
28. Did you spend time that adds up to 3 months or more in the United Kingdom? (Review list of countries in the UK)		
29. Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?		
From **1980 to the present**, did you		
30. Spend time that adds up to 5 years or more in Europe? (Review list of countries in Europe.)		
31. Receive a blood transfusion in the United Kingdom or France? (Review country lists.)		
Have you **EVER**		
32. Female donors: Been pregnant or are you pregnant now?		
33. Had a positive test for the HIV/AIDS virus?		
34. Used needles to take drugs, steroids, or anything not prescribed by your doctor?		
35. Received money, drugs, or other payment for sex?		
36. Had malaria?		
37. Had Chagas disease?		
38. Had babesiosis?		
39. Received a dura mater (or brain covering) graft or xenotransplantation product?		
40. Had any type of cancer, including leukemia?		
41. Had any problems with your heart or lungs?		
42. Had a bleeding condition or a blood disease?		
43. Have any of your relatives had Creutzfeldt-Jakob disease?		