

COMMITTEE REPORT

Use of blood therapeutically drawn from hemochromatosis patients

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EXECUTIVE SUMMARY

Objective

To assess the feasibility of the unrestricted and unlabeled use of blood drawn therapeutically from patients with hereditary hemochromatosis (HH) in the United States, via a review of the scientific literature, current media reports, and governmental regulations.

Data Sources

Literature searches on the terms "hemochromatosis," "blood donation," and "voluntary blood donation" were conducted in the MEDLINE database from 1966 through 1998. Lexis/Nexis news databases were searched for developments in the last 2 years by using the same terms. The World Wide Web was searched by using the key terms "blood donation" and "hemochromatosis" and was employed to access the Code of Federal Regulations and the Food and Drug Administration (FDA) to determine regulatory actions. Additional information was obtained through direct consultation with leading experts in the field of transfusion medicine.

Data Extraction

English-language articles were selected according to their ability to provide information pertinent to assessment of the feasibility of the unrestricted and unlabeled use of blood drawn therapeutically from patients with HH in the United States.

ABBREVIATIONS: AMA = American Medical Association; CDC = Centers for Disease Control and Prevention; CFR = Code of Federal Regulations; FDA = Food and Drug Administration; HH = hereditary hemochromatosis; HTLV-I = human T-lymphotropic virus type I.

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Results

HH is an autosomal genetic disorder that cannot be transmitted via blood transfusion. However, treatment for persons with this disease involves frequent, lifelong therapeutic venesections that may cost up to \$200 per phlebotomy. Thus, persons with HH undergoing therapeutic phlebotomy cannot be classified as voluntary donors by the FDA's current definition, because there is the potential for significant personal monetary benefit to patients with HH from their blood "donation." The highest level of safety of the United States blood supply depends on the use of volunteer blood donors who give blood solely on the basis of altruistic intent. This is documented by several studies that have shown an increase in the prevalence of bloodborne viral pathogens in blood obtained from compensated, directed, or autologous donors as compared to the prevalence in blood drawn from volunteer donors. In contrast, there have been few studies demonstrating that blood drawn from HH patients is at least as safe as blood from volunteer donors with respect to bloodborne viral pathogens. In addition, there are other technical, ethical, and legal issues that may obstruct the unrestricted, unlabeled use of therapeutically drawn blood from HH patients for direct transfusion.

Conclusion

The highest level of safety for the US blood supply is required by the National Blood Policy of 1974. To ensure this level of safety, the concept of an all-volunteer blood donation system based entirely on the altruistic intent of the donor cannot be compromised. Until a system exists whereby the altruistic intent of the blood donor with HH can be guaranteed, the prudent medical position remains recommendation against the unrestricted, unlabeled use of therapeutically drawn blood for direct transfusion.

Resolution 504, introduced by the Medical Students Section at the 1998 Annual Meeting and referred to the Board of Trustees for study, asks

That the American Medical Association (AMA) advocate the acceptance of blood

drawn therapeutically from patients with hemochromatosis as a measure to correct the shortage in the blood supply, provided that methods are in place to ensure the donor's altruistic intent that the blood be used for transfusion.

This report provides an introduction to HH, examines the concept of altruistic intent in blood donation and how it may be ensured, discusses the feasibility of accepting blood drawn from HH patients as a measure to correct the shortage in the United States blood supply, and provides some recommendations.

METHODS

Literature searches were conducted in the MEDLINE and PREMEDLINE databases for English-language articles between the years 1966 to 1998 using the search terms "hemochromatosis," "blood donation," and "voluntary blood donation."

Lexis/Nexis news databases were searched for current developments in "hemochromatosis," "blood donation," and "voluntary blood donation." Leading experts in the field of transfusion medicine were consulted via telephone and e-mail.

The World Wide Web was used to access the Code of Federal Regulations (CFR) (<http://www.access.gpo.gov/nara/cfr/>). The World Wide Web was searched for information using the search words "blood donation" and "hemochromatosis" and was used to access memoranda and guidance and regulatory manuals issued by the FDA (<http://www.fda.gov/>).

HH

HH is an autosomal recessive disease that is fairly common in the white population.¹⁻³ Progressive accumulation of iron in the tissues of homozygotes potentially leads to life-threatening clinical manifestations, such as liver failure, heart failure, and diabetes.⁴ Generally, as much as 40 to 60 years may elapse before these clinical symptoms are apparent, but a minority of individuals present with significant symptoms by age 20. The diagnosis of hemochromatosis is often missed because the disease is usually asymptomatic until irreversible tissue damage has occurred.^{1,3} Symptoms, when present, lack specificity.¹ Today, HH patients with all levels of iron stores are being identified via family studies, screening programs, and incidental findings through abnormal blood tests. Despite this, delays of several years in diagnosing HH still occur, and only 27 percent of affected individuals are being identified before the appearance of clinical symptoms.^{5,6}

There has been some debate about the terminology used to describe HH, because the clinical condition of iron overload can occur in various ways. The original term

"hemochromatosis" was coined to denote the presence of iron overload and iron-related organ injury.³ Because of the nonspecific nature of this term, attempts have been made to distinguish the genetic disorder from other forms of iron overload by using terms such as "hereditary" or "genetic" hemochromatosis. The College of American Pathologists adopted the term "hereditary hemochromatosis" in recent practice guidelines for the genetic condition, and that term or its abbreviation HH is used in this report.⁷

Genetics of HH

In 1996, Feder et al.⁸ proposed the HLA-linked iron-loading gene, or *HFE*, as the candidate gene for HH. The gene is located more than 3 Mb from *HLA-A* and encodes an HLA class I-like molecule.^{8,9} It is speculated that the *HFE* protein may behave as a receptor for an iron-binding ligand, that it may play a role in signal transduction, that it may act indirectly by affecting components of the immune system that may influence iron metabolism, or that it may even directly play a role in iron absorption in the intestines.^{3,8,10} Two mutations that result in loss of cell surface expression of the *HFE* protein have been described for *HFE*.^{11,12} In general, persons who possess these mutations in both the maternally and paternally inherited *HFE* alleles (i.e., homozygotes) are particularly vulnerable to developing overt HH. Persons with just one mutation in either allele (i.e., heterozygotes) are susceptible to developing clinical HH but do not necessarily do so. However, several studies have demonstrated that, while these mutations in the *HFE* gene are the primary genetic basis for HH, iron overload can occasionally occur as a result of other, as-yet-unidentified genetic and/or environmental factors.^{8,13,14}

Since the *HFE* gene was identified, only small-scale studies have been done to determine the prevalence rate of the genetic mutations in the population. These studies indicated a heterozygote prevalence rate of either 6 percent³ or 15 percent⁸ in the United States, 11 percent in the United Kingdom,¹⁵ and 6 percent in France.¹³ These figures translate to a disease frequency of between 1 and 5 per 1000 population. However, studies in asymptomatic persons with HH have shown that about 43 to 50 percent of affected males and 12 to 28 percent of affected females will eventually become clinically ill; these figures translate to clinical disease frequency rates of about 0.5 to 2.5 per 1000 for males and significantly less for females.^{1,16} As a result of uncertainty about prevalence and penetrance of the *HFE* mutations, and also about the optimal care of asymptomatic persons carrying these mutations, an expert consensus panel recently convened by the Centers for Disease Control and Prevention recommended that population-based research to define the penetrance of the *HFE* mutations be accorded high priority and that the social and economic consequences of genetic testing for HH be thoroughly evaluated before DNA testing is incorporated into population-based screening techniques.¹⁷

External factors that affect expression of HH

Several external factors play a role in the expression of HH. The most important are blood loss, diet content, and alcohol abuse. In women, positive iron balance, which eventually results in iron overload, is lower because of blood lost during menstruation and pregnancy.¹⁸ Thus, clinical expression of HH in women is about one-fourth that in men.¹⁶

In countries where iron-deficient diets are prevalent, iron overload is rare, even in individuals who are homozygous for the *HFE* mutations.³ On the other hand, HH expression is enhanced by diets such as the mixed, meat-containing diets of the industrialized nations. These diets also contain significant amounts of heme iron, which is readily absorbed. In Australia, for example, where meat consumption is extremely high, there is also a high rate of HH expression.^{3,19}

While the abuse of alcohol itself may not lead to iron overload, it is associated with the development and severity of the clinical manifestations of HH.³ In fact, patients with HH who are severe abusers of alcohol have a higher prevalence of cirrhosis and shorter survival times than HH patients who do not drink excessive amounts of alcohol.^{20,21}

Clinical features and diagnosis of HH

The results of a long-term study of 251 patients with HH identified the most common symptoms of HH as weakness, lethargy, abdominal pain, arthralgia, and gonadal dysfunction.²² More striking clinical presentations included skin pigmentation (characteristic "bronzing" of the skin), diabetes, hepatomegaly, and cirrhosis.²² In the past 10 years, there has been an increase in the number of persons diagnosed with HH, even though they presented without symptoms or cirrhosis, as a result of growing awareness of the genetic nature of the disease.³ However, it still takes an average of 4 years after the development of symptoms in women and 7 years in men for a diagnosis of HH to be reached.⁵ Thus, abnormal iron study results, abnormal skin pigmentation, diabetes, impotence, abdominal pain, weakness, or unexplained increases in liver enzyme levels should prompt consideration of the diagnosis of HH; otherwise, it will be missed. Physicians who specialize in hepatology, rheumatology, diabetes, endocrinology, and cardiology should always be alert for HH, and observations that are compatible with HH should prompt further investigation, even when a patient's complaints may not necessarily indicate iron overload.

Once a diagnosis of HH is considered, definitive diagnosis is straightforward by a determination of fasting transferrin saturation and ferritin levels.²³ Finally, the diagnosis can be confirmed in three ways: 1) a therapeutic trial phlebotomy removing at least 3 g of iron in females and 5 g in males; 2) a liver biopsy showing characteristic histopathologic patterns of excess iron in hepatocytes⁷; and 3) a simple polymerase chain reaction-based genetic test to demon-

strate the presence of the *HFE* mutations.^{3,8,14} While this genetic test may be helpful, it must be carefully interpreted.^{17,24,25}

Treatment of HH

Management of the major clinical manifestations, such as diabetes and hepatic and cardiac failure, follows conventional guidelines for these conditions. Once such therapy is ongoing, it is essential to begin definitive therapy for HH via the removal of excess iron. The best method is repeated venesection, or therapeutic phlebotomy. Detailed guidelines for such treatment have been published by the College of American Pathologists.⁷ About 200 to 225 mg of iron is removed with every 500 mL of blood. In response to the blood loss, the rate of erythropoiesis is increased, mobilizing iron from the tissues to replace the iron lost via the phlebotomy. Most HH patients can tolerate the removal of as much as 500 to 1000 mL of blood weekly.

In the initial phases of treatment, the goal of venesection is to reduce the transferrin saturation and serum ferritin levels, which would indicate a depletion of the body's stores of iron. Weekly phlebotomies are performed as long as the hematocrit value is above 36 percent.⁷ Each phlebotomy will reduce the level of serum ferritin; however, the level of transferrin saturation will generally stay constant until the body's stores are depleted.³ When hematocrit values can no longer be maintained, serum ferritin levels are examined. If the serum ferritin concentration is less than 20 µg per L, maintenance therapy can begin; this generally involves one phlebotomy every 3 months, and this schedule is continued for life. This maintenance therapy is individualized to maintain serum ferritin levels below 100 µg per L, although levels below 50 µg per L are also acceptable.⁷ In certain countries, in the absence of other criteria prohibiting blood donation by the HH patient, such as clinical disease, the phlebotomized blood is used for transfusion.^{3,26}

VOLUNTARY BLOOD DONATION: THE "ALTRUISTIC INTENT"

The motivation for a volunteer donor system

Less than 30 years after the virtual elimination of compensation to donors, the current US blood supply is remarkably safe. Perhaps no other measure has improved blood safety more than the elimination of paid individuals as donors of blood for transfusion.²⁷ In addition, before the availability of tests for HIV, the AIDS epidemic was handled entirely at the transfusion level on the basis of donor selection criteria, such as the use of volunteer donors (Alter H, e-mail communication, October 1998). Similarly, before the availability of a test for hepatitis C virus, posttransfusion hepatitis C infection was managed via similar donor selection criteria. Coincident with the move to the use of volunteer whole-blood donors was the rise of the commercial plasma

donor sector (paid donors), but because of the use of virus-inactivation procedures in the production of plasma products (procedures that cannot be applied to whole blood), the plasma supply is also remarkably safe.^{28,29}

Almost all blood collected in the United States now comes from volunteer donors. The move to an all-volunteer system came after studies in the 1970s indicated that blood from paid donors was far more likely to harbor hepatitis viruses than was blood obtained from nonpaid donors.^{27,30,31} With the exclusion of paid donors, there was a dramatic decrease in the incidence of posttransfusion hepatitis B in recipients of transfused blood.^{32,33} In addition, the rates of HIV incidence in persons with hemophilia who were treated in the early 1980s with multiple single-donor components from volunteer donors were much lower than the rates in those receiving components of pooled pharmaceuticals from paid donors.^{34,35} Accordingly, existing AMA Policy H-50.995³⁶ directs attention to the need for adequate donor selection and reaffirms previous AMA policy supporting the use of volunteer donors.

Until recently, paid plasma donations used to make pharmaceuticals had at least a twofold risk of harboring hepatitis B virus, HIV, and human T-lymphotropic virus type I, and as much as a 20-fold risk of harboring hepatitis C virus than did plasma from volunteer whole-blood donors.^{30,31,37} To address this situation, the commercial plasma industry has implemented several new initiatives.³⁸ One such initiative directly reflects the importance of donor selection: plasma from a paid donor who does not return for another phlebotomy is not used.³⁸ Additionally, the plasma centers now hold donations for 60 days until these donors return, which significantly reduces the possibility that any plasma drawn during a window period, when tests will not detect recent infection of the donor, will enter the pharmaceutical plasma supply.³⁸ Unfortunately, this practice is not practical for whole blood or platelet donations. Even with these added measures, the paid donor pool is still one-and-a-half times more likely to harbor bloodborne pathogens than the volunteer-donor pool.³⁸

In addition, a prospective study in Italy has demonstrated that cardiac surgery patients who received blood only from volunteer donors were far less likely to have posttransfusion hepatitis C than patients who also received blood obtained from paid donors.³⁹ Starkey and coworkers⁴⁰ showed that blood drawn from directed donors (donations that are given for a specific person, usually a relative) have higher viral marker rates than blood obtained from volunteer donors. Studies have also shown that autologous donors (i.e., donors who give blood for themselves in advance of planned surgery) have an increased incidence of a hepatitis B virus marker.^{40,41}

Finally, despite the comprehensive bloodborne pathogen testing of the US blood supply, the continued presence of a window period for several of these pathogens makes it

imperative that the US blood supply continue to be derived from volunteer blood donors—that is, persons giving blood solely out of altruism.⁴² The potential for new, as yet unidentified bloodborne pathogens for which no tests exist, such as hepatitis C was before the 1990s, requires that stringent donor-selection criteria, such as the exclusive use of volunteer whole-blood donors, remain firmly in place. Without doubt, the use of volunteer donors for whole blood plays an invaluable role in maintaining the safety of the US blood supply. Recently, recognition of this important fact has led the People's Republic of China to switch to an all-volunteer blood donation system in an attempt to reduce the incidence of posttransfusion HIV and hepatitis infection.⁴³

FDA regulations

To support the intent of voluntary blood donation, the FDA implemented regulations in 1978 requiring that any blood that is used for transfusion in the United States be labeled with the source of the blood, whether a volunteer or a paid donor.⁴⁴ The FDA has defined “paid” and “volunteer” donors:

A paid donor is a person who receives monetary payment for a blood donation.

A voluntary donor is a person who does not receive monetary payment for a blood donation. Benefits, such as time off from work, membership in blood assurance programs, and cancellation of non-replacement fees that are not readily convertible to cash, do not constitute monetary payment....⁴⁴

Thus, almost all donated blood used for transfusion today is derived from voluntary donors and is specifically labeled as such. The FDA requires that persons who give blood for other than altruistic reasons must have their blood labeled accordingly. Thus, blood donated for autologous use is so labeled⁴⁴ and blood donated for family or friends is accordingly labeled so that it may be properly tracked. Blood from donors who are motivated to give blood for monetary reasons is also labeled accordingly. This regulation has played an important role in eliminating paid donor blood and associated components from direct transfusions, because blood that is labeled as being from paid donors is voluntarily not considered as a source for direct transfusions by physicians, patients, and transfusion centers.^{26,42,45} As mentioned earlier, these paid donors now make up the bulk of the sources for plasma products, which undergo virus-inactivation procedures that enhance their safety.

Furthermore, the FDA introduced regulations that state: “Blood withdrawn in order to promote the health of a donor. . . shall *not* (emphasis added) be used as a source of whole blood unless the container label conspicuously in-

dicates the donor's disease that necessitated withdrawal of blood."⁴⁶ This regulation places the burden on the physician transfusing the blood to approve the use of the blood and to explain to the recipient the significance of this labeling difference as part of the informed-consent process.^{26,42} Thus, while blood drawn for therapeutic reasons may theoretically be used for direct transfusion, the donated blood must be labeled accordingly, and, for whatever reason, justified or otherwise, blood labeled as such is not considered by physicians, patients and hospitals for transfusion.^{42,45} Finally, in its current Policy H-50-995,³⁶ the AMA has endorsed the FDA's existing blood policy as the best approach to ensuring the safety and adequacy of the US blood supply.

The American Red Cross, which draws over 45 percent of the 14 million units of whole blood donated in the United States annually, states that collecting, testing, and labeling therapeutically drawn blood is cost-ineffective and not a prudent use of the Red Cross's resources.⁴⁵ This is because specifically labeled blood is usually returned to blood centers or allowed to expire as a result of widespread poor acceptance by practitioners in the transfusion centers.²⁶ Because this practice is coupled with standards from the American Association of Blood Banks, which recommend that blood drawn for therapeutic reasons not be used for direct allogeneic transfusion,⁴⁷ asymptomatic persons with a diagnosis of HH have, in effect, been excluded from donating blood, even though there is no national policy that prevents the use of such blood for direct transfusion.²⁶

Ensuring altruistic intent

This resolution, number 504, asks that altruistic intent be ensured before the blood of HH patients is used for transfusion. Such a requirement would recognize the importance of the concepts of voluntary blood donation and altruistic intent. However, as previously discussed, whenever any form of monetary incentive is in place, it is extremely difficult to guarantee the altruistic intent of any donor and the consequent safety of the donated blood. A 1993 study in Los Angeles has documented that when even small, non-monetary incentives such as tee-shirts are provided to increase donor numbers, there is a corresponding increase in the donated blood's rates of serologic markers for bloodborne viral diseases, medical deferrals, and self-deferrals.⁴⁸

It is not certain why blood from paid donors is less safe than blood from volunteer donors.²⁶ It has been suggested that the monetary compensation may make the donors less honest about their specific risk factors, but there are few data to support this hypothesis.²⁶ It is interesting that, even among volunteers who have been approved to donate blood after screening, a small number (0.4%) have admitted to engaging in high-risk behavior within 3 months before their donation and not revealing this information prior

to donating blood.⁴⁹ A significant reason for these high-risk donations is a population of test-seeking individuals—that is, people donating blood for the purpose of obtaining a free test for bloodborne pathogens such as HIV.^{49,50}

Finally, the National Blood Policy (published in 1974 by the federal government) requires that blood for transfusion be as safe as possible. As such, the "burden of proof is not to demonstrate that blood from a given source is less safe, but to demonstrate that it is as safe as the current supply."²⁶ Thus, donated blood in which the volunteer-donor principle and the concept of altruistic intent have been compromised cannot be demonstrated to be as safe as the current whole-blood supply, which is derived entirely from voluntary donors.

Perhaps the most satisfactory way to ensure the altruistic intent of a blood donor is to remove any form of potential monetary benefit attached to the blood donation.²⁷ This, of course, is the principle behind the volunteer-donor system. If blood resulting from therapeutic phlebotomy is used for transfusion, the potential monetary incentive to the person undergoing the phlebotomy would be his or her direct cost savings for the treatment, because the person would no longer have to pay the fee for the therapeutic bleeding (ranging from \$20-\$200/phlebotomy; the Red Cross charges an average of \$32 to recoup the cost of the blood bag and the phlebotomist's time^{45,51}). Logically, the only way to remove this monetary incentive would be to eliminate the cost of the phlebotomy for the person undergoing the therapy.⁴² This is the case in Sweden, Canada, Australia, and the United Kingdom, where HH patients undergoing therapeutic phlebotomies incur no cost for the treatment.²⁶ However, while Sweden, Canada, and Australia will use the blood from such therapeutic bleedings for direct transfusion, the United Kingdom still classifies the persons "donating" the blood as "nonvolunteers" and will not allow the use of their blood for direct transfusion.²⁶

In the United States, complete reimbursement by health insurance for therapeutic bleeding would not adequately remove the monetary incentive, because of the large number of persons in this country who do not have health insurance and would therefore still be required to pay for their treatment on their own. If therapeutic phlebotomies were available at no cost to the patient in the United States, the "monetary incentive" to persons receiving therapeutic phlebotomies would be removed, thereby ensuring altruistic intent.⁴²

USE OF BLOOD DRAWN FROM HH PATIENTS

Given the estimated prevalence of the *HFE* gene defect in the white population, HH is underdiagnosed in the United States.⁵² Thus, it is highly probable that persons with undiagnosed HH are among the more than 8 million annual volunteer blood donors. However, regardless of the issues

of safety of the blood supply that have been discussed above, there would be many other problems should blood from persons with HH be used for direct transfusion. Technical issues include the current FDA labeling requirements for therapeutically drawn blood, the requirement for informed consent by the recipient of the blood transfusion, the lack of universal acceptance of blood labeled as such for transfusion, and the special operational requirements for handling units of blood from persons with HH, leading to increased margins of error.²⁶

Should persons with HH be allowed to donate blood as part of their therapeutic regimen, these patients must still meet all the requirements that a volunteer donor meets. These include general good health and submission to a predonation screening process, which includes a detailed medical history. Many exclusionary criteria such as jaundice, liver disease, diabetes, cirrhosis, and malignancy have higher incidences in persons with HH, especially those of more advanced age.^{3,6} As mentioned earlier, 27 percent of persons with HH are asymptomatic at the time of diagnosis.⁶ Thus, there will have to be more stringent screening by physicians at blood centers to ensure the discovery of medical details that may not be immediately reported by the HH donor or detected by the interviewer. There are few available studies that examine the rates of incidence of bloodborne pathogens in the blood of HH patients, and the few that exist conflict. One retrospective study examined persons with chronic hepatitis and discovered that none of them had HH. However, the sample size of 200 was too small (assuming a disease incidence rate of 1-5/1000) to yield useful results.⁶ A French study examining 272 HH patients for serology against hepatitis B virus revealed a significant increase in the incidence of a hepatitis B marker in this population over that in a control population of volunteer blood donors.⁵³ However, all these patients were already symptomatic, and it is possible that asymptomatic HH patients may have very different hepatitis B incidence rates. Patients with HH also have a higher likelihood of bacteremia due to siderophilic organisms such as *Yersinia enterocolitica* or *Vibrio vulnificus*.^{54,55} Thus, there is at least the theoretical possibility that units from HH patients could more frequently contain bacteria. Because the transmission rate for all infectious diseases through blood is low, a very expensive, lengthy, and technically difficult study would be required to prove that the blood of asymptomatic persons with HH is as safe as the blood from volunteer donors with regard to the transmission of bloodborne pathogens.²⁶ A less satisfactory alternative might be the study of viral markers in a large unselected pool of persons with HH, comparing those who already donate and those who do not with first-time and repeat volunteer blood donors. In this situation, the data generated would be inferential and would only allow estimation of whether a higher rate of viral markers existed in the HH population as a whole (Klein H, e-mail communication, October 1998).

However, the quality of the blood from asymptomatic HH patients is generally excellent. Because of the greater frequency of phlebotomy, there is a higher frequency of younger red cells in the blood taken from the HH patient. This could potentially make the blood more desirable for transfusion, although there is still some debate about this matter²⁶ (Haley NR, written communication, December 1998). Arguments that the blood of persons with HH may contain red cells with compromised cell membrane function due to the higher iron level or that the transfusion of blood containing high levels of iron may be detrimental to the health of the recipient are usually less compelling, because it is unlikely that a transfusion recipient will be given several units of HH blood consecutively.²⁶

The necessity for informed consent would require physicians transfusing blood derived from HH patients to explain to the recipients the difference between such blood and that from volunteer donors.⁴⁷ It also might be prudent to offer the recipient a choice between units obtained from the therapeutic bleeding of an HH patient and those from a volunteer donor, unless such a choice is not available.²⁶ All these legal and ethical issues may prove to be roadblocks to the use of therapeutically drawn blood for direct transfusion.

There is much discussion about the potential increase in the US blood supply should blood from HH patients be used for transfusion.^{51,56} In a recent, elegant analysis, Conry-Cantilena and Klein²⁶ suggest that if eligible (i.e., asymptomatic) persons with HH were added to the donor supply, it would increase the number of donors in the system by 202,500. Taking into account various factors, such as age eligibility and frequency of phlebotomy, the authors say that these new "donors" would add about another 53,000 units of blood annually to the US blood supply, an increase of about 0.4 percent over the current 14 million units obtained annually from volunteer donors.²⁶ While this increase is desirable, it is uncertain what impact such a small increase would make on the total blood supply. Conry-Cantilena and Klein believe that this increase would not affect the US blood supply greatly, as they state that annual red cell usage has been stable over the last several years, and new biologics, such as erythropoietin, have been developed that are more desirable than allogeneic transfusion.²⁶

Evidence that the US blood supply is adequate to meet patients' demands can be found in the latest national survey of US collections and transfusions of blood and blood derivatives, performed in 1994.⁵⁷ On the other hand, in the last 2 years, several areas of the United States have reported a 3- to 5-percent increase in annualized red cell usage (Macpherson J, written communication, December 1998), and the United States still imports at least 220,000 units of red cells from Europe annually.⁵⁷ Thus, the United States is by no means self-sufficient in terms of its supply of red cells, and there may be a real shortage of blood in parts of this

country. Consequently, the potential augmentation of the US blood supply remains an influential argument for allowing the unrestricted, unlabeled use of blood drawn therapeutically from HH patients.^{26,51}

It is interesting that, in Canada, there has not been a dramatic increase in the blood supply since the decision to accept therapeutically drawn HH blood for transfusion. However, this could be due to a failure to accept eligible HH patients at the Canadian blood centers because of a general lack of awareness.⁵⁸ Alternatively, it could be due to the political and operational problems that have enveloped the Canadian blood donation system administered by the Canadian Red Cross, leading to the establishment on September 28, 1998, of Canadian Blood Services as the blood-collecting agency of Canada.^{59,60} In other countries, estimates made with criteria different from those used in the studies mentioned above suggest that potential donations might be increased by as much as 30 percent if therapeutically drawn HH blood were used for transfusion.^{26,61}

SUMMARY AND ANALYSIS

HH is an autosomal genetic disorder that cannot be transmitted via blood transfusion. However, treatment for persons with this disease involves frequent, lifelong therapeutic venesection that may cost up to \$200 per phlebotomy. Thus, persons with HH undergoing therapeutic phlebotomy cannot be classified as voluntary donors by the FDA's current criteria because there is significant personal monetary benefit to be gained by the HH patient "donating" blood. The highest level of safety of the US blood supply depends on the use of volunteer blood donors who give blood solely on the basis of altruistic intent. This is documented by several studies showing an increase in the prevalence of bloodborne viral pathogens in blood obtained from compensated donors as compared to the prevalence in blood drawn from volunteer donors. In contrast, there have been few studies demonstrating that blood drawn from HH patients is at least as safe as blood from volunteer donors with respect to bloodborne viral pathogens. In fact, there is some uncertainty about the incidence of hepatitis B markers in a population of HH patients and about the potential health detriment of receiving blood drawn from a person with HH.

In addition, there are other technical, ethical, and legal issues that may obstruct the use for direct transfusion of blood therapeutically drawn from HH patients. Thus, until a system exists whereby the altruistic intent of the HH donor can be ensured, perhaps by offering free therapeutic phlebotomies, the prudent medical position remains a recommendation against the unlabeled use of therapeutically drawn blood for direct transfusion.

RECOMMENDATIONS

The following statements, recommended by the Council on Scientific Affairs, were adopted as AMA policy in June 1999. The AMA

1. Encourages physicians to explain to their patients that HH has a genetic basis, that the disease is not transmissible via blood transfusions, and that the blood from persons with HH is not necessarily unsuitable for direct transfusion;
2. Reaffirms existing Policy H-50.995 and support the concepts of altruistic intent and the use of volunteer blood donors as fundamental to ensuring the highest safety of the United States blood supply; and
3. Recommends against the unlabeled use for direct transfusion of blood drawn therapeutically from persons with HH until a means to ensure their altruistic intent is available, such as when therapeutic phlebotomies are available at no charge to persons requiring them.

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REFERENCES

1. Adams PC, Gregor JC, Kertesz AE, Valberg LS. Screening blood donors for hereditary hemochromatosis: decision analysis model based on a 30-year database. *Gastroenterology* 1995;109:177-88.
2. Little DR. Hemochromatosis: diagnosis and management. *Am Fam Physician* 1996;53:2623-8, 2631-2.
3. Bothwell TH, MacPhail AP. Hereditary hemochromatosis: etiologic, pathologic, and clinical aspects. *Semin Hematol* 1998;35:55-71.
4. Bacon BR. Diagnosis and management of hemochromatosis. *Gastroenterology* 1997;113:995-9.
5. Adams PC, Valberg LS. Evolving expression of hereditary hemochromatosis. *Semin Liver Dis* 1996;16:47-54.
6. Adams PC, Deugnier Y, Moirand R, Brissot P. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology* 1997;25:162-6.

7. Witte DL, Crosby WH, Edwards CQ, et al. Practice guideline development task force of the College of American Pathologists. Hereditary hemochromatosis. *Clin Chim Acta* 1996;245:139-200.
8. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399-408.
9. Ruddy DA, Kronmal GS, Lee VK, et al. A 1.1-Mb transcript map of the hereditary hemochromatosis locus. *Genome Res* 1997;7:441-56.
10. Parkkila S, Waheed A, Britton RS, et al. Immunohistochemistry of HLA-H, the protein defective in patients with hereditary hemochromatosis, reveals unique pattern of expression in gastrointestinal tract. *Proc Natl Acad Sci U S A* 1997;94:2534-9.
11. Waheed A, Parkkila S, Zhou XY, et al. Hereditary hemochromatosis: effects of C282Y and H63D mutations on association with β_2 -microglobulin, intracellular processing, and cell surface expression of the HFE protein in COS-7 cells. *Proc Natl Acad Sci U S A* 1997;94:12384-9.
12. Feder JN, Tsuchihashi Z, Irrinki A, et al. The hemochromatosis founder mutation in HLA-H disrupts β_2 -microglobulin interaction and cell surface expression. *J Biol Chem* 1997;272:14025-8.
13. Jouanolle AM, Gandon G, Jezequel P, et al. Haemochromatosis and HLA-H (letter). *Nat Genet* 1996;14:251-2.
14. Jazwinska EC, Cullen LM, Busfield F, et al. Haemochromatosis and HLA-H (letter). *Nat Genet* 1996;14:249-51.
15. Roberts AG, Whatley SD, Morgan RR, et al. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet* 1997;349:321-3.
16. Edwards CQ, Griffen LM, Kushner JP. The morbidity of hemochromatosis among clinically unselected homozygotes: preliminary report. *Adv Exp Med Biol* 1994;356:303-8.
17. Burke W, Thomson E, Khoury MJ, et al. Hereditary hemochromatosis: gene discovery and its implications for population-based screening. *JAMA* 1998;280:172-8.
18. Edwards CQ, Dadone MM, Skolnick MH, Kushner JP. Hereditary haemochromatosis. *Clin Haematol* 1982;11:411-35.
19. Leggett BA, Brown NN, Bryant SJ, et al. Factors affecting the concentrations of ferritin in serum in a healthy Australian population. *Clin Chem* 1990;36:1350-5.
20. Niederau C, Fischer R, Sonnenberg A, et al. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985;313:1256-62.
21. Adams PC, Agnew S. Alcoholism in hereditary hemochromatosis revisited: prevalence and clinical consequences among homozygous siblings. *Hepatology* 1996;23:724-7.
22. Niederau C, Fischer R, Purschel A, et al. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107-19.
23. Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. *Am J Gastroenterol* 1997;92:784-9.
24. Mura C, Nousbaum JB, Verger P, et al. Phenotype-genotype correlation in haemochromatosis subjects. *Hum Genet* 1997;101:271-6.
25. Shaheen NJ, Bacon BR, Grimm IS. Clinical characteristics of hereditary hemochromatosis patients who lack the C282Y mutation. *Hepatology* 1998;28:526-9.
26. Conry-Cantilena C, Klein HG. Hemochromatosis subjects as blood and tissue donors. In: Edwards CQ, Barton JC, eds. *Hemochromatosis*. Cambridge: Cambridge University Press (in press).
27. MacPherson J. On volunteer donors and the pursuit of a safe blood supply. *ABC Newsletter* 1998;38(Oct 2):15-8.
28. Horowitz B, Bonomo R, Prince AM, et al. Solvent/detergent-treated plasma: a virus-inactivated substitute for fresh frozen plasma. *Blood* 1992;79:826-31.
29. Mannucci PM. Clinical evaluation of viral safety of coagulation factor VIII and IX concentrates. *Vox Sang* 1993;64:197-203.
30. Alter HJ, Holland PV, Purcell RH, et al. Posttransfusion hepatitis after exclusion of commercial and hepatitis-B antigen-positive donors. *Ann Intern Med* 1972;77:691-9.
31. Aach RD, Kahn RA. Post-transfusion hepatitis: current perspectives. *Ann Intern Med* 1980;92:539-46.
32. Alter HJ, Holland PV, Purcell RH. The emerging pattern of post-transfusion hepatitis. *Am J Med Sci* 1975;270:329-34.
33. Seeff LB. Transfusion-associated hepatitis B: past and present. *Transfus Med Rev* 1988;2:204-14.
34. Colvin BT, Collier LH, Craske J. A prospective study of cryoprecipitate administration: absence of evidence of virus infection. *Clin Lab Haematol* 1987;9:13-5.
35. Evensen SA, Ulstrup J, Skaug K, et al. HIV infection in Norwegian haemophiliacs: the prevalence of antibodies against HIV in haemophiliacs treated with lyophilized cryoprecipitate from volunteer donors. *Eur J Haematol* 1987;39:44-8.
36. American Medical Association Council on Long Range Planning: Policy compendium. Chicago: American Medical Association, 1998.
37. General Accounting Office. Blood supply: transfusion-associated risks. Washington: Government Printing Office, February 1997.
38. General Accounting Office. Blood plasma safety: plasma product risks are low if good manufacturing practices are followed. Washington: Government Printing Office, September 1998.
39. Tremolada F, Chiappetta F, Noventa F, et al. Prospective study of posttransfusion hepatitis in cardiac surgery patients receiving only blood or also blood products. *Vox Sang* 1983;44:25-30.
40. Starkey JM, MacPherson JL, Bolgiano DC, et al. Markers for transfusion-transmitted disease in different groups of blood donors. *JAMA* 1989;262:3452-4.

41. Grossman BJ, Stewart NC, Grindon AJ. Increased risk of a positive test for antibody to hepatitis B core antigen (anti-HB) in autologous blood donors. *Transfusion* 1988;28:283-5.
42. Friedrich C. Blood donation by patients with hemochromatosis (letter). *JAMA* 1993;270:2928-9.
43. Poole T. China bans sale of blood. *The Independent*; 1998 Oct 1 (news section):14.
44. 21 CFR 606; April 1997.
45. Davey RJ. Throwing out good blood: the American Red Cross Response. *U S News and World Report*. Available at <http://www.usnews.com/usnews/issue/970922/22lett.htm>. Accessed March 1999.
46. 21 CFR 640; April 1997.
47. Menitove JE, ed. Standards for blood banks and transfusion services, 18th ed. Bethesda: American Association of Blood Banks, 1997.
48. Read EJ, Herron RM, Hughes DM. Effect of non-monetary incentives on safety of blood donations (abstract). *Transfusion* 1993;33(Suppl):45S.
49. Williams AE, Thomson RA, Schreiber GB, et al. Estimates of infectious disease risk factors in US blood donors. Retrovirus Epidemiology Donor Study. *JAMA* 1997;277:967-72.
50. Doll LS, Petersen LR, White CR, Ward JW. Human immunodeficiency virus type 1-infected blood donors: behavioral characteristics and reasons for donation. The HIV Blood Donor Study Group. *Transfusion* 1991;31:704-9.
51. Hawkins D. Throwing out good blood. *U S News and World Report*. Available at: <http://www.usnews.com/usnews/issue/970901/1bloo.htm>. Accessed March 1999.
52. Edwards CQ, Griffen LM, Goldgar D, et al. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med* 1988;318:1355-62.
53. Deugnier Y, Battistelli D, Jouanolle H, et al. Hepatitis B virus infection markers in genetic haemochromatosis. A study of 272 patients. *J Hepatol* 1991;13:286-90.
54. Vadillo M, Corbella X, Pac V, et al. Multiple liver abscesses due to *Yersinia enterocolitica* discloses primary hemochromatosis: three case reports and review. *Clin Infect Dis* 1994;18:938-41.
55. Bullen JJ, Spalding PB, Ward CG, Gutteridge JM. Hemochromatosis, iron and septicemia caused by *Vibrio vulnificus*. *Arch Intern Med* 1991;151:1606-9.
56. Penning HL. Blood donation by patients with hemochromatosis (letter). *JAMA* 1993;270:2929.
57. Wallace EL, Churchill WH, Surgenor DM, et al. Collection and transfusion of blood and blood components in the United States, 1994. *Transfusion* 1998;38:625-36.
58. Levstik M, Adams PC. Eligibility and exclusion of hemochromatosis patients as voluntary blood donors. *Can J Gastroenterol* 1998;12:61-3.
59. Krever H. Report of the Commission of Inquiry on the Blood System in Canada. Ottawa: Canadian Government Publishing, November 26, 1997.
60. Canadian Red Cross. Red Cross says goodbye to blood program. Available at: <http://www.redcross.ca/news/1998-09-28ge1.htm>. Accessed September 1998.
61. Worwood M, Darke C, Trenchard P. Hereditary haemochromatosis and blood donation (letter). *BMJ* 1991;302:593. □