Review

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Is blood of uncomplicated hemochromatosis patients safe and effective for blood transfusion? A systematic review

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Summary

Hemochromatosis is a disorder of the iron metabolism, characterized by high body iron content, necessitating frequent phlebotomies to remove excess iron. In some countries, this blood is discarded and not used for blood transfusion because of the non-voluntary character of this donation, and because a potential risk of microbial contamination of the donor blood is assumed.

A systematic review was performed in order to collect and critically examine solid evidence with regard to the effectiveness and safety of blood for transfusion when derived from hemochromatosis patients who do not suffer from complications or organ damage. Using three databases (The Cochrane Library, MEDLINE, and Embase) we searched for studies from date of inception until January 2012.

Out of 3470 articles, 80 references that were relevant to our question were selected, including many opinion pieces, comments, letters, and narrative reviews. Based on our selection criteria, we finally retained only six observational studies, so evidence on this subject is scarce and furthermore, the strength of the available evidence is low to very low, due to poor study designs. We found no evidence that red blood cell concentrates from hemochromatosis patients without complications of iron overload do not comply with the physiological quality requirements for transfusion, nor that their blood would present a greater risk to recipient safety than blood from non-hemochromatosis donors. However, *in vitro* findings from two studies suggest that iron-overloaded patients would be more susceptible to bacterial growth, but future *in vivo* studies are warranted to confirm this.

Based on this, we call for harmonization of the blood donor selection policy among countries allowing hemochromatosis patients who do not suffer from complications of iron overload to donate blood, once iron levels are normalized.

Keywords: Hemochromatosis; Blood donation; Viral infections; Bacterial infections; Evidence-based.

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Introduction

Hemochromatosis is characterized by entry of iron into the blood stream in excess of that required for erythropoiesis. The excess iron can accumulate in parenchymal cells of liver, heart, endocrine glands, and other tissues, and result in organ damage. Hemochromatosis is in most cases inherited ('primary or hereditary hemochromatosis') as an autosomal recessive disorder, but can also be acquired. It arises from alterations in genes that regulate the synthesis of hepcidin, the latter downregulating the entry of iron into the blood stream, and many genotypes exist. Approximately 12.5% of individuals of Northern European descent are heterozygous for a mutation in the *HFE* gene (High Fe) and almost one in two to three hundred white people are homozygous. Based on genetic testing, it became clear that although homozygotes most often display abnormally high iron levels (high biochemical penetrance, 'biochemical hemochromatosis'), only a small number of them develop complications and organ damage (low clinical penetrance, 'clinical hemochromatosis') [1–3].

The standard medical treatment for hemochromatosis is removal of iron by regular therapeutic phlebotomy, either weekly to return to safe blood levels of iron (iron depletion therapy) or 1–4 times a year (maintenance therapy) [4].

For many years, there has been a debate whether blood from patients with hemochromatosis can be accepted for transfusion. The two frequently raised arguments against the use of blood from hemochromatosis patients are that: (1) the blood would be unsafe and (2) the donation is not voluntary [5,6]. Concerning the safety of the blood, there is fear of possible contamination with siderophilic bacteria, such as *Vibrio* sp., *Salmonella* sp., and *Yersinia* sp. [7–10], especially as *Yersinia enterocolitica* has been identified with increased frequency as a causative agent of post-transfusion septic shock with possible fatal outcome [11]. Because iron overload can impair the host immune system, and viruses can interact with the iron metabolism to cause infection (e.g., by altering the expression of proteins involved in iron homeostasis), there is also a potential higher susceptibility for viral infections [12–14]. The second argument deals with the fact that hemochromatosis patients that donate blood are not considered to be voluntary non-remunerated donors because they benefit from the donation. Since the phlebotomy is free of charge, becoming blood donor may be a cheap alternative for physician visits thus providing a financial incentive. In addition, the necessity of phlebotomy does not qualify this donation as "voluntary" [15].

The management and cost of hemochromatosis treatment and the use of blood obtained via phlebotomy vary strongly throughout the Western world [16]. In many countries, mainly Europe, blood from hemochromatosis patients is drawn only for therapeutic reasons and cannot be used for blood transfusion because of both arguments described above. The concern with regard to the voluntary nature of the donation however, can be addressed by rigorous use of the donor medical questionnaire, rejecting the blood for further use if the criteria applicable to any other donor are not met. In addition, making all phlebotomies free to hemochromatosis patients could eliminate any financial incentives and thus the non-voluntary character of the donation.

Because it is not clear whether the assumed risk for contamination of blood from hemochromatosis patients is based on scientific evidence and the Belgian Red Cross-Flanders Blood Service seeks to improve a qualitative blood supply based on evidence-based policies, we focused on this argument and addressed the question whether blood of uncomplicated hemochromatosis patients is safe and effective for blood transfusion. Furthermore, this question is also relevant for the convenience of therapy and the satisfaction/sense of contribution of hemochromatosis patients. Therefore, a systematic review of the literature was performed. The rationale for performing this systematic review is summarized in Key Points 1.

Key Points 1
Rationale for reviewing this question

- Relevant existing blood transfusion guidelines are not uniform and are based on opinion and consensus rather than on solid evidence
- Available red blood cell units are often limited
- This question is also relevant for the quality and convenience of therapy and a sense of contribution of hemochromatosis patients
- The Belgian Red Cross-Flanders Blood Service seeks to improve a qualitative blood supply based on evidence-based policies

Materials and methods

Search strategy

All searches for evidence were performed between December 2011 and January 2012. The following sources were searched: The Cochrane Database of Systematic Reviews, The Database of Abstracts of Reviews of Effects, The Cochrane Central Register of Controlled Trials, MEDLINE (using the PubMed interface), and Embase (using the Embase.com interface).

The following search formula was used for searching MEDLINE:

1. "Hemochromatosis" [Mesh] OR "hemochromatosis" [TIAB] OR "haemochromatosis" [TIAB]
2. "Blood Donors" [Mesh] OR "Blood Transfusion" [Mesh]
3. "Blood Safety" [Mesh] OR "Blood-Borne pathogens" [Mesh] OR "infection" [TIAB] OR "safety" [TIAB]
4. "Virus Diseases" [Mesh] OR "transfusion transmissible" [TIAB]
5. "Bacterial Infections" [Mesh] OR "Bacteremia" [Mesh]
6. "Erythrocytes" [Mesh] OR "Erythrocyte Indices" [Mesh] OR "Erythrocyte Count" [Mesh] OR "quality" [TIAB] OR "mean corpuscular volume" [TIAB] OR "mean cell volume" [TIAB] OR "cell count" [TIAB] OR "mean cell hemoglobin" [TIAB] OR "MCV" [TIAB] OR "MCH" [TIAB]
7. 2–6 OR
8. 1 AND 7

The following search formula was used in Embase:

1. 'hemochromatosis'/exp OR hemochromatosis:ab:ti OR haemochromatosis:ab:ti
2. 'blood donor'/exp OR 'blood transfusion'/exp
3. 'blood safety'/exp OR infection:ab:ti OR safety:ab:ti
4. 'virus infection'/exp OR 'transfusion transmissible':ab:ti
5. 'bloodborne bacterium'/exp OR 'bacterial infection'/exp OR 'bacteremia'/exp
6. 'erythrocyte'/exp OR 'mean corpuscular volume'/exp OR 'erythrocyte count'/exp OR quality:ab:ti OR 'mean corpuscular volume':ab:ti OR 'mean cell volume':ab:ti OR 'cell count':ab:ti OR 'mean cell hemoglobin':ab:ti OR 'MCV':ab:ti OR 'MCH':ab:ti
7. 2–6 OR
8. 1 AND 7

Selection of the studies was performed in parallel by two independent reviewers (E.D.B., N.S.P.). Titles and abstracts of the studies identified by the search were scanned. When a study met the eligibility criteria, full text articles were obtained. Studies that did not meet the in- and exclusion criteria were excluded. The citation lists of included studies were searched for additional related articles, the first 20 related items in PubMed were scanned for other potentially relevant studies, and the references by which the included studies were cited were screened. The final selection of articles was compared among the two reviewers. Disagreement on the selection of studies was resolved by discussion or by involving a third reviewer (T.D.).

Study selection/inclusion and exclusion criteria

Language
Studies in English and French were included.

Types of studies
Randomized controlled trials, controlled clinical trials, cohort studies, case–control studies, and case-series were included. *In vitro* studies were included if a control group was used and if the blood or serum sample was tested in unprocessed form (no incubation or cultivation of specific cell types). Excluded study designs were narrative reviews, commentaries, letters and opinions.

Types of participants
We included studies with a population that represents our target population: hemochromatosis patients without complications of iron overload that need phlebotomies to treat or maintain their condition and that are eligible as a blood donor. In detail, the included population consists of hereditary hemochromatosis patients without organ damage but having abnormal serum ferritin levels or undergoing iron depletion or maintenance therapy ('biochemical hemochromatosis'). Excluded population: patients with complications of iron overload or organ damage ('clinical

hemochromatosis'); people with positive genetic testing for hemochromatosis, but without any indication of increased iron levels; patients with secondary, neonatal or juvenile hemochromatosis.

Intervention and comparison
Intervention: Blood from hemochromatosis patients; Comparison: Blood from healthy donors; blood from hemochromatosis patients at different time points.

Types of outcome measures
Primary outcomes: (1) safety: markers of transfusion-transmissible diseases or viral or bacterial infections in blood from persons who receive blood from a hemochromatosis patient; (2) effectiveness: erythrocyte properties/hematologic variables in blood from blood acceptors who receive blood from a hemochromatosis patient. Secondary outcomes: (1) safety: markers of transfusion-transmissible diseases or viral or bacterial infections in blood from hemochromatosis patients; (2) effectiveness: erythrocyte properties/hematologic variables in blood or serum samples from hemochromatosis patients.

Data collection

Data concerning study design, study population, outcome measures and study findings were extracted and tabulated in addition to the limitations in study design by two independent reviewers (E.D.B., N.S.P.). In case of disagreement a third reviewer was involved (T.D.).

Quality of evidence

The GRADE approach was used to grade the overall quality of evidence included in this review. GRADE considers limitations in study design of the included studies, inconsistency between the different studies (due to differences in populations, interventions or outcomes), indirectness (of population, intervention or outcome), imprecision and publication bias. Limitations in study design were analyzed by evaluating the presence of eligibility criteria, adequate control of confounding, design-specific sources of bias and correct measurement of exposure and outcome. The quality of evidence can be downgraded for each of the previous quality criteria and finally results in high, moderate, low or very low grade of evidence [17].

Results

Study characteristics

Fig. 1 provides a flowchart of the identification and selection of studies. The reviewers screened 3470 citations, including 164 duplicates and one triplicate. Evaluation of titles and abstracts resulted in 80 references. After full text evaluation, 74 studies were excluded because selection criteria were not met. It is remarkable that half of the studies that were selected for full text evaluation did not meet the criteria because of the study design. Many reviews, comments, letters and case reports are published on this subject, but very few studies exist to support them. Table 1 displays an overview of all studies that were excluded based on the criteria for population, intervention or outcome, with the reason for exclusion [18–43]. Only six references [44–49] met the inclusion criteria and were available for analysis (Table 2). All included studies were observational studies, three of them were performed in the United States, two in France and one in The Netherlands. One study measured blood effectiveness by determining hematologic variables [44]. Five studies measured safety (agents of viral or bacterial transfusion-transmissible disease). Among the latter, two studies investigated the prevalence of viral infections [45,46], including one screening 52,650 blood donors (hemochromatosis patients and regular donors) and another investigating 130 hemochromatosis patients before and after blood donation (without control group). Furthermore, three studies were included evaluating the prevalence of bacterial infections in hemochromatosis patients and healthy people (not donating blood) [47–49]. Study characteristics and a detailed description of the populations can be found in Table 2.

Quality of evidence

All included studies were observational studies, including one case-series, which results in an initial 'low level of evidence'. In three out of the six studies, risk of bias was found because of lim-

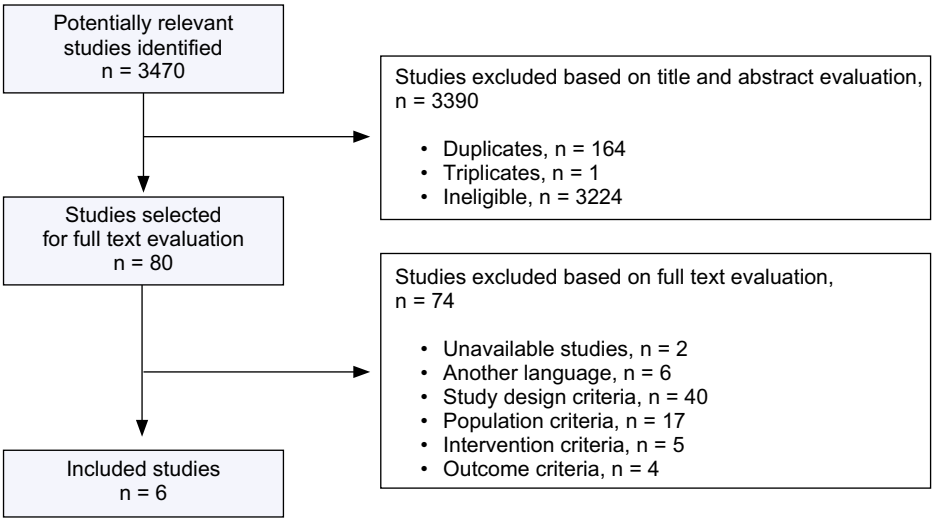

Fig. 1. Flowchart of identification and selection of studies.

Table 1. Excluded studies based on the selection criteria for population (P), intervention (I) or outcome (O), with the reason for exclusion.

Reference	Reason for exclusion	
Adams *et al.,* 1997 [18]	O	prevalence of symptoms; serum ferritin level
Barton *et al.,* 1999 [19]	O	eligibility for being blood donor; reasons for ineligibility are only given for the patient group and not for the control group
Barton *et al.,* 2000 [20]	P	patients with complications of iron overload were not excluded
Bell *et al.,* 1997 [21]	P	the population is based on genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
Beutler *et al.,* 2006 [22]	P	the population is based on a genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
Blacklock *et al.,* 2000 [23]	I	no control group
Bove *et al.,* 2011 [24]	P	the population is based on genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
Brandão *et al.,* 2005 [25]	P	mixed population, patients with liver cirrhosis and persons with normal ferritin concentrations are included
De Filippi *et al.,* 1998 [26]	P	only 8% have a normal liver
De Gobbi *et al.,* 2004 [27]	P	the population is based on genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
Del Castillo *et al.,* 2009 [28]	I	no control group
Deugnier *et al.,* 1991 [29]	P	in probands [n = 224] GH diagnosis was based on the following data: [a] absence of anemia and hemolytic disease; [b] classical clinical signs of genetic hemochromatosis; and [c] liver iron overload assessed on liver biopsy
Edwards *et al.,* 1988 [30]	P	the population is based on genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
Feeney *et al.,* 2005 [31]	P	mixed population, persons with normal ferritin levels are included
Levstik *et al.,* 1998 [32]	I	no control group
Mah *et al.,* 2005 [33]	P	patients with chronic hepatitis B and C
McLaren *et al.,* 2007 [34]	P	the population is based on genetic screening and is a mixed population [with normal and increased ferritin levels, patients with complications of iron overload are not excluded]
McDonnell *et al., 1*999 [35]	O	prevalence of symptoms
Olakanmi *et al.,* 2007 [36]	P	no information on the population
Lee *et al., 1999* [37]	P	patients with clinical hemochromatosis
Power *et al.,* 2004 [38]	I	no control group
Røsvik *et al.,* 2010 [39]	O	serum ferritin level
Sendi *et al.,* 2005 [40]	P	no proven ferritin increase
Shan *et al.,* 2005 [41]	P	hemochromatosis patients excluded
Silva *et al.,* 2005 [42]	I	no control group
Wise *et al.,* 2010 [43]	P	not clear

itations in design: one study had high risk of recall bias [46], another had lack of clearly defined in-/exclusion criteria [49], and a third study did not include a control group (case-series) [45]. We did find consistency across the different studies. We also addressed indirectness: all studies included the study population of interest, but two of the six studies were *in vitro* studies, and all studies included secondary outcomes. Due to the limited number of included studies, it was difficult to evaluate publication bias. Because of limitations in design in three out of the six studies and the case-series design in one study, we did not upgrade the strength of the body of evidence. Overall, the strength of the body of evidence, based on the GRADE approach, is low to very low. An overview of the limitations in design of the individual studies is summarized in Table 2.

Synthesis of findings

One study evaluated parameters that give an indication of the effectiveness of blood of hemochromatosis patients for the purpose of blood transfusion [44]. In this study, cell concentrates from hemochromatosis patients and regular donors were collected and stored up to 50 days. Samples were taken for analysis at the beginning and weekly thereafter. The outcome of interest was the mean cell volume (MCV): it was shown that red blood cells (RBCs) of hemochromatosis patients at time of collection had a larger MCV (mean, 99.4 fL; range, 87.4–105.6 fL) than the RBCs of regular donors (MCV; mean, 92.3 fL; range, 86.1–98.1 fL). This is probably due to the overall younger cell age of RBCs of hemochromatosis patients. In addition, during storage,

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Table 2. Characteristics and main results of included studies.

Study (country) [Ref.]	Design	Patient characteristics	Outcome	Findings	Limitations in design
Luten *et al.*, 2008 (The Netherlands) [44]	Observational study	Eight hemochromatosis patients with proven iron-overload and 15 regular donors; patient characteristics: transferrin saturation ≥50%; serum ferritin level ≥700 μg/L	Several hematologic, biophysical, and biochemical variables in red blood cell concentrates, from the first week of storage and weekly thereafter during the storage period of 50 days	No significant differences between hemochromatosis and regular donors	None
Sanchez *et al.*, 2001 (United States) [46]	Observational study	52,650 blood donors from eight different US blood centres, including 197 hemochromatosis patients; patient characteristics: patients are suitable as blood donors according to the deferral criteria used by eight large US blood centers; patients are not in a period during which they require phlebotomy to treat their condition; ferritin levels are not available	Unreported deferrable risks based on anonymous mail survey. Screening for antibody to hepatitis B core antigen (anti-HBc), syphilis, human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg) and human T-lymphotropic virus (HTV) in blood samples	No statistically significant differences between hemochromatosis and regular donors	Recall bias in anonymous mail survey. No limitations in the screening
Leitman *et al.*, 2003 (United States) [45]	Observational study (case-series)	130 hemochromatosis patients; patient characteristics: laboratory evidence of iron overload; ferritin >50 μg/L; patients are suitable as blood donors according to the FDA eligibility criteria	Seroconversions for agents of transfusion-transmissible disease (not specified) during serial donations (weekly to every 8 weeks, based on ferritin levels), during the study period of 27 months	No incident seroconversions for agents of transfusion-transmissible disease occurred	No control group
Jolivet-Gougeon *et al.*, 2008 (France) [47]	*In vitro* study	26 iron-overloaded (homozygous C282Y mutation), 35 iron-depleted hemochromatosis patients and 33 healthy control subjects; patient characteristics: no included subjects exhibited diabetes, cardiomyopathy, non-specific inflammatory states, and concomitant infection or immune deficiency, and none received any antimicrobial treatment; ferritin: iron-overloaded group: 1118.38 μg/L ± 1096.75 μg/L; iron-depleted group: 21.29 μg/L ± 11.85 μg/L; control group: 108.03 μg/L ± 82.36 μg/L	Antibacterial activity of serum samples against *Salmonella typhimurium* LT2	Statistically significant decrease for iron-overloaded hemochromatosis patients compared to iron-depleted patients and controls. No difference for iron-depleted patients versus controls	None
Jolivet-Gougeon *et al.*, 2007 (France) [48]	Observational study	236 male hemochromatosis patients (C282Y/C282Y) and 303 blood donors; patient characteristics: average of iron and ferritin serum concentrations was 25 ± 10 μmol/L (5.2-48) and 235 ± 581 μg/L (6-4520), respectively. None of the hemochromatosis patients exhibited diabetes, cardiomyopathy, inflammatory state, concomitant infection or immunity deficiency and none received antimicrobial treatment (to preclude false-positive and -negative serological reactions)	Antibodies against several serogroups of *Yersinia pseudotuberculosis* (I to V) and *Yersinia enterocolitica* (O:3, O:9 O:5.27) in serum samples	No significant increase for hemochromatosis patients compared to control blood donors	None
Bullen *et al.*, 1991 (United states) [49]	*In vitro* study	Five iron-overloaded hemochromatosis patients and five healthy people; patient characteristics: five patients with hemochromatosis who were undergoing phlebotomy for therapeutic reasons	Survival of *Vibrio vulnificus* in the blood samples, measured by mixing the blood with a suspension of *V. vulnificus* bacteria	Statistically significant difference in survival: no survival in normal blood for inoculum 10^3/ml or less, while bacteria grew rapidly in blood samples from iron-overloaded hemochromatosis patients	Lack of inclusion and exclusion criteria

the MCV of RBCs increased in both groups in a similar way with 10–15%. No clinically relevant significant differences could be found between the two groups for a large number of biochemical and biophysical variables including extracellular glucose concentration, extracellular concentration of sodium and potassium ions, intracellular 2,3-DPG levels, cellular ATP concentration, total adenylate content, pO_2, pCO_2, pH, and bicarbonate. Based on this study, it can be concluded that there is no evidence that blood derived from hemochromatosis patients does not comply with the quality requirements, and therefore is suitable for the purpose of blood transfusion from a hemato-physiological point of view.

With regard to the safety of the blood, two studies evaluated transfusion-transmissible viral infections, one study measured antibacterial antibodies and two other *in vitro* studies tested sus-

ceptibility of the blood against bacteria. Based on an email survey filled in by blood donors from eight different US blood centers [46], it was concluded that there is no statistically significant different prevalence of unreported deferrable risks (risk factors for transfusion-transmissible viral infections that should result in deferral if reported during donor screening) between hemochromatosis donors (during maintenance therapy) and donors reporting no medical conditions necessitating phlebotomy (prevalence 2.0% versus 3.1%, respectively). Based on laboratory screening tests, including screening for antibody to hepatitis B core antigen, syphilis, human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen, and human T-lymphotropic virus, no statistically significant difference could be found for hemochromatosis donors versus regular donors (overall prevalence of positive screening test results of 1.3% versus 1.6%, respectively).

A second study analyzed 130 hemochromatosis patients with laboratory evidence of iron overload. Of these, 76% met FDA eligibility criteria applied for blood donation. Based on the ferritin level, phlebotomy was performed weekly to every 8 weeks, during a study period of 27 months. In every blood sample, serologic testing for (not specified) agents of transfusion-transmissible disease was performed and no incident seroconversions for agents of transfusion-transmissible disease occurred during this period [45]. The findings from the latter two studies suggest that hemochromatosis patients do not present a greater risk to blood safety than other donors, at least with regard to viral infections.

In three observational studies, including two *in vitro* studies, antibacterial activity of blood of hemochromatosis patients was compared with blood of regular donors. No significant increase in antibodies against several serogroups of *Yersinia pseudotuberculosis* (I to V) and *Yersinia enterocolitica* (O:3, O:9, O:5.27) could be found in the serum of hemochromatosis patients without complications (average iron concentration of 25 μmol/L (5.2–48) and ferritin 235 μg/L (6–4520), absence of diabetes, cardiomyopathy, inflammatory state, concomitant infection or immunity deficiency) as compared to control blood donors [48]. Furthermore, in blood samples from iron-depleted hemochromatosis patients, antibacterial activity against *Salmonella typhimurium* LT2 was shown to be the same as in samples from healthy donors [47]. In contrast, it was shown that there is a statistically significant decreased antibacterial activity against *S. typhimurium* LT2 and a better survival of *Vibrio vulnificus* in blood from iron-overloaded hemochromatosis patients when compared with samples from healthy people [47–49].

In summary, there is no evidence showing that blood from uncomplicated hemochromatosis patients would be unsafe to use as donor blood. Moreover, the available evidence supports the use of blood from hemochromatosis patients for blood transfusions, at least after normalization of their ferritin status. Since two *in vitro* studies suggest that blood obtained from iron-overloaded patients would be more susceptible for bacterial growth, further studies are warranted here. An overview of the findings per study can be found in Table 2.

Discussion

Hemochromatosis patients need frequent therapeutic phlebotomies. In some countries, this blood is discarded and not used for transfusions because of the non-voluntary character of the donation and the assumption that this blood would be less safe with regard to the possible presence of viral or bacterial contaminations. In this article, we show that there is no evidence that this blood after normalization of the iron level is not safe for blood transfusion. Study selection was limited to studies describing the target population, i.e. hemochromatosis patients that apart from their known diagnosis, would otherwise be eligible to donate blood based on the other exclusion criteria for donors in general. Since irreversible organ damage is such an exclusion criterion, we did not take this subgroup of hemochromatosis patients into account.

Evidence is scarce concerning this subject: from 3470 potentially relevant studies, we selected 80 studies that were relevant to the question, and retained only six studies that met the selection criteria. The reason for the low number of published studies may be (1) the low prevalence of transfusion-related infections, which necessitates large scale and long term studies, (2) logistic problems, implicating the follow-up of patients receiving the blood, or may be (3) ethical, because potentially unsafe blood should be transfused.

Furthermore, the quality of the evidence available in the six included studies is low to very low. We downgraded the level of evidence due to indirectness, because all studies measured secondary outcomes. It would have been of greater interest to measure outcomes in patients receiving the blood (which we defined as primary outcome), however, such studies are lacking in the literature. One study measured blood effectiveness by determining hematologic variables, and for this study there were no limitations in design [44]. Two studies measured the prevalence of viral infections [45,46], including a study without control group (case-series), testing blood samples from 130 hemochromatosis patients [45]. Taking into account the very low incidence of transfusion-transmissible viral infections, this represents a very low number of test persons, which is a serious limitation in design. The other three selected studies evaluated the prevalence of bacterial infections, and at first sight the results of these studies were not consistent. In two *in vitro* studies it was shown that a higher risk for bacterial contamination is present in blood from iron-overloaded, but not from iron-depleted patients [47,49]. In a third study, the presence of anti-*Yersinia* antibodies in the blood of uncomplicated hemochromatosis patients was compared to control blood donors, and no significant difference could be found [48]. In this study, it is not clearly stated whether the included patients where iron-overloaded or iron-depleted. Because none of them had complications, presumably only a minority of the study group is in the iron-overloaded stage, and thus the results are in agreement with these of the other studies. Based on *in vitro* findings with iron-overloaded patients, and in the absence of more solid evidence concerning the risk of viral and bacterial infections in this subset of hemochromatosis patients, conclusions about accepting hemochromatosis patients as blood donors should be cautious and take into account the normalization of the iron level.

In addition to the evidence, current practice also seems to support this finding. Because of the high prevalence of hereditary hemochromatosis in the general population, there is no doubt that in current practice of blood donations (with no routine testing of hemochromatosis parameters, as ferritin and transferrin saturation, nor of genetic testing), a substantial number of donations originate from carriers of the hemochromatosis gene. Until now, this practice has never resulted in documented serious adverse events in patients transfused with these blood products.

Apart from concerns with regard to the safety of the blood of hemochromatosis patients, the non-altruistic character of the

donation remains a potential argument for exclusion of hemochromatosis patients [5,6]. However, using the donor medical questionnaire in a rigorous way, rejecting the blood for further use if all donor criteria are not met, should address this concern. One way to eliminate potential financial incentives is by making all phlebotomies free to hemochromatosis patients, a measure that is already taken in some countries [15].

In recent years, the British, French, German, and Swedish transfusion services already changed their policy with regard to hemochromatosis patients who require continued phlebotomies. In France, a multidisciplinary working group studied the subject in 2001, and re-evaluated the eligibility criteria for hemochromatosis patients as blood donors, because the discovery of the *HFE* gene in 1996 made it clear that hemochromatosis exists in many different variants [50]. Similar measures have been taken, outside Europe, in the US, Canada, and Australia [4,51–54], where hemochromatosis donor blood is being used for transfusion. However, increased hemovigilance is required in their operating policies and because of these logistical consequences, collection of hemochromatosis donor blood is still not implemented worldwide [55].

Combining the available evidence and experiences from daily practice, we conclude that there is no reason supporting the exclusion of these patients, after normalization of their ferritin status and in the absence of organ damage, from the donor pool. Although not decisive in donor acceptance policy, accepting these patients into the donor pool is also relevant for the quality and convenience of therapy, and for the satisfaction or sense of contribution of these patients as advocated by hemochromatosis patient groups. In Key Points 2, we summarize how we used the principles of Evidence-Based Practice (evidence, practice experience and preferences) to address our initial question [56].

Key Points 2
Addressing this question using the three principles of Evidence-Based Practice

- Best available evidence: a systematic review of evidence resulted in only six (all of them observational, including two *in vitro* studies) studies amongst 3470 potentially relevant studies identified. None of these studies contained any evidence showing that blood from uncomplicated iron-depleted hemochromatosis patients, would be unsafe to use as donor blood
- Practical experience and expert opinion: in several countries hemochromatosis blood is being used for transfusion, and many unknown hemochromatosis patients are blood donors anyway. No adverse effects have been reported so far
- Patient's values and expectations: including these patients into the donor pool is also relevant to the quality and convenience of therapy of hemochromatosis patients and for the satisfaction or sense of contribution of these patients as advocated by hemochromatosis patient groups
- Based on these three pillars, a call for harmonization of the use of blood of uncomplicated iron-depleted hemochromatosis patients as donor blood is warranted

In conclusion, the variance in policy that exists in and between many countries today calls for a harmonization of the use of the blood of hemochromatosis patients that have no complications of iron overload and have normalized iron levels, allowing them to be accepted as blood donors. However, taking into account that only a limited number of studies are available, future research is necessary. In particular, the susceptibility to infections of iron-overloaded patients should be addressed as this would reveal whether we can also use blood from uncomplicated patients who still have high ferritin levels, i.e., who are still in the iron removal stage and need more frequent phlebotomies. Follow-up studies on patients who received blood from hemochromatosis donors hence is a priority; furthermore, studying other blood products such as platelets and plasma from hemochromatosis donors would be interesting (Key Points 3).

Key Points 3
Gaps in evidence and future research

- Solid evidence is scarce concerning this subject. Reasons could be: the low prevalence of transfusion-related infections (which would result in large scale and long term studies); ethical reasons (transfusing potentially unsafe blood); logistic problems (follow-up of patients receiving the blood)
- Studies evaluating safety and effectiveness of blood transfusions with blood from hemochromatosis patients are lacking. Future research should fill this gap in by follow-up studies from patients who received blood from hemochromatosis patients
- The evidence obtained was retrieved from *in vitro* and observational studies, so more robust study types are needed. For example, future studies should confirm, *in vivo*, the *in vitro* findings of increased susceptibility to infections of iron-overloaded patients
- The available evidence does only provide evidence on transfusion with red blood cells and not other blood products. Therefore, future research should also focus on other blood products such as platelets and plasma preparations

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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P.V. and V.C. proposed the concept and question of the literature review and critically revised the manuscript. E.D.B. and N.S.P. performed the literature review and drafted the manuscript. T.D. was the third reviewer in case of disagreements and wrote the

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